Development and validation of the Living with Medicines Questionnaire; a generic measure of patients' experiences of medicine use and associated burden.

Barbra Katusiime

A thesis submitted in partial fulfilment of the requirements of the University of Kent and the University of Greenwich for the Degree of Doctor of Philosophy

August 2017

DECLARATION

I certify that this work has not been accepted in substance for any degree, and is not concurrently being submitted for any degree other than that of Doctor of Philosophy being studied at the Universities of Greenwich and Kent. I also declare that this work is the result of my own investigations except where otherwise identified by references and acknowledgement of work undertaken jointly with others. In the latter circumstances I have clarified my own contributions. I have not plagiarised the work of others.

Bkatusiime

Barbra Katusiime

Supervised by Prof. Janet Krska & Dr Sarah Corlett

ACKNOWLDEGEMENTS

Firstly, I acknowledge financial support from the Medway School of Pharmacy and the prestigious award from the Commonwealth Scholarship Commission (CSC), funded by the UK government, which sustained my three-year PhD research programme.

Heartfelt gratitude is extended to my supervisors, Professor Janet Krska and Dr Sarah Corlett, for their continuous support, guidance, and mentorship throughout this PhD journey, and for the patience in reading and commenting on several drafts of this work. Thanks to Dr Joanne Reeve and Dr Trudy Thomas for providing guidance in early phases of my research. I thank all my departmental colleagues for the peer support, humour and motivation.

This research was made possible by voluntary participation of patients and members of the general public who took part in different phases of my research programme. I am more than grateful for sharing your views and experiences that greatly shaped this thesis. Special thanks to the members of the Public Involvement in Pharmacy Studies (PIPs) and the Kent Adult Research Unit (KARU) for supporting part of my research. To all managers and personnel in-charge of Community Pharmacies, General Practices, and Hospital outpatient clinics that granted permission and access to research participants, I really appreciate. For patient organisations, health websites/fora, and public organisations that provided valuable platforms to enable participant recruitment, thank you. Many thanks, to the Quintiles Inc. and the EuroQoL group for granting me permission to use copyrighted tools in my PhD. I also appreciate the efforts of the MPharm undergraduate students who helped with data collection during different phases of my research programme.

I remain indebted to my wonderful family in Uganda (Mr & Mrs Rwangire, Marvin, Jeanne, Gerald, Vincent, Denis, Josephine, Martin, Cleo, and Christine) for the moral support and encouragement while enduring my absence without objection. To my confidant, Fran, thank you for listening to my endless PhD 'stories' and for being the shoulder to cry on. To my Grannie- it is a shame I did not get to say goodbye while presenting part of this research at an international conference, but your blessings and wishes will always be treasured. To my sister, Angela, you inspired me to explore the world of medicines - I know you are happy to see how far I have gone. Thanks again to all my friends for being there when I needed to talk about my ups and downs - you know yourselves! Above all, 'I will give thanks to You, Lord, with all my heart, I will tell of all your wonderful deeds.' Psalm 9:1. It is not my strength, but your grace that sustained this journey -Thank you Jesus!

ABSTRACT

Background: Prescription medicines are a common healthcare intervention. Although medicines are often beneficial in controlling effects of disease and preventing mortality, some people have negative experiences with medicines use. Health professionals often prioritise actual or anticipated treatment benefits above any associated psychosocial or practical burdens patients may experience when using medicines. There is a need for generic, valid and reliable patient-reported tools to evaluate varying experiences of using medicines and associated burden.

Aim: This thesis focusses on instrument development, revision and validation of a novel generic patient-reported measure of prescription medicine burden, the Living with Medicines Questionnaire (LMQ).

Methods: A systematic literature review was conducted to confirm the suitability of the LMQ-1 as a relevant measure for development. This was followed by a pragmatic, iterative, mixed methodological approach, including qualitative interviews and surveys that were used in further development and validation of this instrument. Across all studies, participants were adults, using long-term prescription medicines, and were recruited face-to-face from community pharmacies, general practices, outpatient clinics and public areas in south-east England, or on-line across England. Principal components analysis of responses to the LMQ-1 enabled preliminary item reduction, and revealed gaps in the resulting 42-item version (the LMQ-2). To cover missing domains, new item generation and semi-structured, cognitive interviews led to an interim, 58-item, LMQ-2.1 ensuring that meanings of all statements were as intended. Final item reduction and confirmatory factor analyses of responses to the LMQ-2.1 established the 41-item LMQ-3 as the final agreed instrument. Criterion-related validation of the LMQ-3 ascertained relationships among medicine burden concepts, treatment satisfaction and health-related quality of life (HRQoL). Internal consistency (Cronbach's alpha) and test-retest reliability (intraclass correlation coefficients, ICCs) were also examined. LMQ-3 composite scores were used to define levels of burden, while regression analyses assessed predictors of medicine burden.

Results: The systematic review identified the original 60-item LMQ-1 as a relevant measure based on patient-generated concepts, but which required extensive modification and testing, including content addition. The final 41-item LMQ-3 instrument covers eight domains, under an overarching construct of medicine burden: interferences with day-to-day life; patient-doctor relationships and communication about medicines; lack of effectiveness; general concerns; side effects; practical difficulties; cost-related burden, and lack of autonomy/control over medicines use. Cronbach's alpha (0.61-0.90) and ICC values (0.73-0.93) were satisfactory for most subscales. Medicine burden was established as a distinct concept negatively associated with treatment satisfaction and HRQoL. Higher-level medicine burden, estimated at 10% prevalence for the English adult population, was associated with age < 65 years, unemployment, residence in areas with higher relative level of deprivation, more frequent medicine use and combinations of formulations, but was not clearly related to the number of medicines.

Conclusion: The LMQ-3 is a relatively comprehensive, valid, reliable, and interpretable measure of medicines burden suitable for use among adults using long-term medicines for any disease/condition (s) in England. The instrument could be used to identify those with high

medicines burden or in studies of healthcare interventions aimed at the prevention, and/or reduction of medicine burden.

CONTENTS

TABLES

FIGURES

ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AMOS	Analysis of Moment Structures (statistical software)
ANOVA	Analysis of Variance
BMQ	Beliefs about Medicines Questionnaire
BoT	Burden of Treatment
CCM	Cumulative Complexity Model
CFA	Confirmatory Factor Analysis
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPPQ	Community Pharmacy Patient Questionnaire
CTT	Classical Test Theory
DTC	Drug Therapy Concerns
EFA	Exploratory Factor Analysis
EQ-VAS	EuroQol Visual Analogue Scale
EQ-5D-	EuroQol five dimensions questionnaire
GP	General Practitioner
HRQoL	Health-related Quality of Life
IRT	Item Response Theory
KARU	Kent Adult Research Unit
KMO	Kaiser-Meyer-Olkin (measure of sampling adequacy)
LMQ	Living with Medicines Questionnaire
MAI	Medication Appropriateness Index
MDM	Minimally Disruptive Medicine
MO	Medicines Optimisation
MRB	Medicine-related Burden
MUR	Medicines Use Review
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

ABBREVIATIONS AND ACRONYMS

NMS	New Medicine Service
OTC	Over-the-Counter
PAF	Principal Axis Factoring
PATD	Patients' Attitudes Towards Deprescribing
PCA	Principal Components Analysis
PIPS	Public Involvement in Pharmacy Studies
PPCs	Prepayment Certificates
PREM	Patient Reported Experience Measure
PROM	Patient Reported Outcome Measure
PROMPT-QoL	Patient-Reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life
PSM	Perceived Sensitivity to Medicines Questionnaire
PSMM	Patient Satisfaction with Medication Management
PTRQoL	Pharmaceutical Therapy-Related Quality of Life
QOF	Quality and Outcomes Framework
QOL	Quality of Life
RPS	Royal Pharmaceutical Society
SATMED-Q	Treatment Satisfaction with Medicines Questionnaire
SF-36	Short Form (36-item) Health Survey
SIMS	Satisfaction with Information about Medicines Scale
SPSS	Statistical Package for the Social Sciences
START/	Screening Tool to Alert to Right Treatment/
STOPP	Screening Tool of Older People's Prescriptions
TBQ	Treatment Burden Questionnaire
TSQM	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organisation

GLOSSARY

Autonomy	The perceived ability to control, cope with and make personal decisions about how one lives on a daily basis, according to one's own rules and preferences'. In the context of this thesis, autonomy/control over medicines use relates to ability to vary medicine regimes (e.g. dosing and timing) without influence from a healthcare professional.
Cognitive interview	A qualitative research method used to determine whether concepts and items (questions) in an instrument are understood in the same way that instrument developers intend.
Construct	The specific measurement attribute (i.e. the concept or 'thing' that is to be measured).
Construct validity	The extent to which an instrument measures the intended concepts and the inferences that can therefore be made from the scores.
Content validity	Qualitative evidence demonstrating that the instrument covers the concepts of interest including judgements that the items are appropriate, relevant, and comprehensive relative to the instrument's intended measurement construct, population, and use.
Convergent validity	The extent to which questionnaire scores correlate with scores on another (concurrently administered) measure of the same construct.
Criterion validity	The extent to which the scores of an instrument are related to a known 'gold standard' measure of the same concept. When there is no 'gold standard' comparison, criterion-related validity refers to the extent to which questionnaire scores are related to scores obtained by other relevant measures.
Divergent/ discriminant validity	The extent to which questionnaire scores do not correlate (strongly) with scores on another (concurrently administered) measure of a different construct. It provides evidence that an instrument measures a distinct construct.
Face validity	A judgement that an instrument and its items, on the face of it, appears to be assessing the intended construct.
Item	An individual question or statement (and its response options) that is intended to measure a particular concept.
Known- groups validity	The extent to which questionnaire scores differ between groups of persons known or expected to differ on the variable of interest.
Medicine burden	In this thesis, medicine burden refers to negative experiences associated with using long-term prescription medicines.
Multimorbidity	The existence of two or more chronic conditions in the same patient.
Patient capacity	Ability to manage own health, including ability to engage with prescribed healthcare activities (e.g. diet, exercise, using medicines).
Patient workload	The set of tasks that patients must carry out to manage their own health.

GLOSSARY

Patient-reported outcome	A measurement based on a self-report that comes directly from the patient about his/her status without amendment or interpretation of the patient's response by a clinician or anyone else.
Provider	An individual healthcare professional or an institution that delivers care services.
Psychometric properties	Attributes relevant to the application of an instrument (questionnaire) including the different forms of validity (e.g. content validity, construct validity) and reliability. The term 'psychometric properties' is used synonymously with 'measurement properties'.
Reliability	Evidence that an instrument yields consistent (or reproducible) estimates, producing the same or similar results, when used to measure a given construct.
Scale	The system of numbers or verbal anchors by which a value (or score) is derived for an item. For example, Likert-type scales may use a scale of 1 to 5 to reflect the level of agreement with a statement. A visual analogue scale (VAS) may have verbal anchors to reflect levels of an attribute.
Score	A number derived from a patient's response to items in a questionnaire.
Treatment burden	Self-care practices that patients with chronic illness must perform to respond to the requirements of their healthcare providers (e.g. doctor visits, blood tests) and the impact of these practices on patient functioning and well-being.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS RESEARCH PROGRAMME

Full papers

1. B. Katusiime, S. Corlett, J. Reeve, J. Krska (2016) Measuring medicine-related experiences from the patient perspective: a systematic review. *Patient Related Outcome Measures* 2016: 7; 1-15.

2. J.Krska, B.Katusiime, S. Corlett (2017). Validation of an instrument to measure patients' experiences of medicines use- the Living with Medicines Questionnaire (LMQ-2). *Patient Preference and Adherence* 2017: 11; 671-679

Oral presentations/published abstracts

1. B. Katusiime, S.Corlett, J.Krska (2017). Criterion validation of the Living with Medicines Questionnaire Version 3 (LMQ-3). *Abstract presented as an oral communication at PCNE 2017 conference held in Bled, Slovenia. 1-4 February 2017.*

2. B. Katusiime, S. Corlett, J. Krska (2016). Validation of a revised Living with Medicines Questionnaire (LMQ© version 3). *International Journal of Pharmacy Practice* 2016, Supplement 2: 4–32. *Abstract presented as an oral communication at the ISPW 2016 conference held in Aberdeen, Scotland. 19-22 July 2016.*

3. B. Katusiime, M O'Grady, C Vaghji, R Rubasayone, T, Ojikutu, S.A. Corlett and J. Krska (2014). Patients' experiences of using regular medicines - A Quantitative Survey. *Pharmacoepidemiology and Drug Safety.* Available at: http://on-linelibrary.wiley.com/doi/10.1002/pds.3682/pdf (Accessed 26/09/2014). *Abstract presented as an oral communication at the Prescribing and Research in Medicines Management (UK) conference held in London, England. 2nd May 2014.*

Poster presentations/published abstracts

1. B. Katusiime, M. O' Grady, C. Vaghji, R. Rubaseyone, T. Ojikutu, S. Corlett, J Krska (2015). Experiences of using prescription medicines among the general public in the UK- a comparison of paper- and on-line-reported experiences. *International Journal of Clinical Pharmacy,* 37:403-425
   Abstract presented as a poster at the 9th Pharmaceutical Care Network Europe (PCNE) working conference in Mechelen, Belgium. 4-6 February 2015.

2. B. Katusiime, M. O'Grady, S. Corlett, J. Krska (2014). Experiences of using prescription medicines in day-to-day living – a web-based survey among the general population. *International Journal of Pharmacy Practice,* 22 (Suppl. 2), pp. 23–106. Available at: http://on-linelibrary.wiley.com/doi/10.1111/ijpp.12146/pdf (Accessed: 26/09/2014). *Abstract presented as a poster at the Royal Pharmaceutical Society (RPS) conference held in Birmingham, England. 7–8 September 2014.*

3. G. Bulanadi, B. Katusiime, TF. Chen, S. Corlett, J. Krska, SR. Carter (2014). Measuring patients' subjective experiences of living with medicines. *Abstract presented the APSA conference, by G. Bulanadi in Brisbane, Australia. 5-7 December 2014*

Relevant workshops attended

1. Developing indicators to measure pharmaceutical care across nations. PCNE 2017.
2. The challenges of polypharmacy: rhetoric to reality. RPS & RCGP conference 2016.
3. Patient specific evaluation measures for medication review. PCNE 2015

1.1 The use of medicines

Within modern medical practice, prescribing medicines is one of the common therapeutic interventions following a patient consultation.[1] Both prescription medicines and over-the-counter (OTC) medicines contribute to the total medicine consumption,[2] but there is a growing interest in the long-term use of prescription medicines by various stakeholders.[3,4] Prescription medicines are those sold or supplied only in accordance with a valid prescription from an appropriate practitioner.[5] Medicines are not only used for alleviating symptoms, but increasingly are prescribed prophylactically for primary or secondary prevention of different health conditions (e.g. for cardiovascular disease risk protection).[4]

1.2 Defining polypharmacy

Over the years, the interest in polypharmacy has rapidly grown. Both the World Health Organisation (WHO)[6] and the Kings Fund[4], an independent organisation seeking to improve healthcare in England, define polypharmacy as the concurrent use of 'multiple' or 'excessive' medicines by an individual. Numerous studies have researched different aspects of this subject. To illustrate this, combined literature searches for the term 'polypharmacy', in multiple databases (Medline, CINAHL Plus, and PsychInfo) revealed an estimated seven-fold increase in publications citing the term 'polypharmacy' within their titles, over the periods 1988-1998 to 2010-2014 (See Figure 1-1).

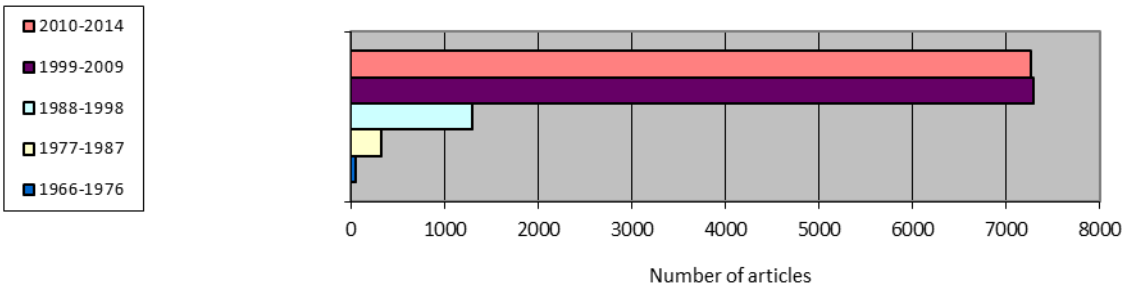


Figure 1-1 Articles citing the term 'polypharmacy' in their titles from 1966 to 2014

In spite of the decadal use of the term 'polypharmacy' and the cumulative literature on polypharmacy, there are definitional problems, for researchers, with an apparent lack of consensus in definitions. Nevertheless, there are two major approaches to defining polypharmacy; use of a specific numeric threshold/cut-off value for the number of medicines used, or the appropriateness of medicines used according to pre-defined criteria.[4,7,8]

Consensus regarding what number of medicines (or threshold) defines polypharmacy is also lacking. Using at least five medicines appears the most cited threshold for defining polypharmacy,[4,7,9] but Bjerrum et al (1997)[10] justified subdivisions (e.g. minor polypharmacy for 2-4 medicines and major polypharmacy for ≥ 5 medicines) or higher thresholds. In a recent Cochrane review, Cooper et al (2015)[11] used ≥ 4 regular medicines as their cut-off for polypharmacy. Bushardt et al (2008)[12] considers a threshold of six medicines or over, while Steinman et al (2006)[13] proposed eight or more medicines as a potential threshold for polypharmacy.

Owing to the shifting population demographics over the years, patients continue to receive a rising number of medicines, and polypharmacy thresholds may change.[14] Current propositions suggest 10 or more medicines as a more suitable threshold for defining polypharmacy (hyperpolypharmacy),[4,15] while 20 or more is currently considered 'excessive'.[9] Although often arbitrary, using numeric cut-off values to define polypharmacy is a simple way, which is commonly used. As the number of prescription medicines increases, the number of medicine-related problems and adverse effects (e.g. falls, hospitalisation) also increases.[4,7] Nonetheless, a recent Cochrane's review indicated that '…polypharmacy is not just about the…numbers of drugs but rather the prescription of medication appropriate to the needs of patients.'[16]

While there has been much research about the appropriateness of medicines, there are definition problems here too. Recent definitions by the Kings Fund[4] describe polypharmacy as either 'appropriate' or 'inappropriate' (problematic). Problematic polypharmacy includes the use of a potentially inappropriate medicine or the prescription of more medicines than are warranted clinically.[4,8] From the prescribers' perspective, inappropriate polypharmacy involves using more medicines

than are needed for an individual's clinical condition or where the anticipated therapeutic benefits are not attained.[4] However, multiple medicines may be appropriate if they are beneficial to the patient, especially in cases of multiple complex illnesses (multimorbidity).[4,16]

However, the concept of 'appropriateness' of medicines has different meanings for prescribers and patients. Prescribers' views of what constitutes an appropriate medicine differ from patients' views.[17,18] From the prescriber's perspective, medicines are deemed 'appropriate' if they have evidence of efficacy and safety, and are of minimal cost to the health system, according to some predefined 'scientific' criteria.[19] For a patient, medication appropriateness relates to broader issues including psychosocial aspects, day-to-day experiences of managing medicines, effectiveness (if medicines are working), side effects, choice, anxieties and concerns about medicines, relationships with health providers, and consequences of treatment, among many other factors.[17,20,21] Some patients look to general practitioners (GPs) to decide/assess if their medication is 'correct' and effective,[17] and feel they lack sufficient medical knowledge and expertise to evaluate the appropriateness of their medication. Many others seek clear and simplified information to enable themselves to assess their medication's appropriateness.[22,23] More recently, a person-centred perspective of defining and understanding inappropriate/problematic polypharmacy is recommended by Heaton and colleagues (2016).[24]

In this research programme, participants were included in the different studies if they used at least one long-term prescription medicine and investigations of patients' experiences were not restricted to multiple medicine users. This is in recognition of the fact that some patients may feel burdened by just one medicine while others cope with many perceiving no burden. In fact, Zarowitz suggests that 'for some patients, one medication may be too much, and for others, 15 medications may be too few'.[8] Thus the programme concerns patients' perceived burden of medicines use, regardless of the number of medicines used, and does not only focus on those using multiple medicines. Nonetheless, the association between the number of medicines used and medicine burden was examined in Chapter 9.

1.3 Epidemiology of polypharmacy- the rising prevalence

Globally, there is an increasing prevalence of polypharmacy, with more and more individuals taking multiple medicines.[14,25–27] There are international variations in medicines use. In a 2008/2009 comparative study (updated to 2012/2013) into variations in medicines usage across high income countries, the UK ranked 8th/9th out of the 13-14 countries studied; usage per head of population rose in 11 of 16 medicine categories used for managing or preventing different long-term conditions, including cancer, heart disease, stroke, dementia.[28,29]

The increasing consumption of medicines in the UK is even more vivid, and reportedly reflects 'a nation of pill poppers'.[30] This follows the findings of the 2013 Health Survey for England on prescription medicines use, which revealed that about 50% of all adults used one or more prescribed medicines in the week prior to the survey.[31] In England alone, the average number of prescription items dispensed (including medicines) is estimated to have risen by 55.2% over the last decade (the period 2004 to 2014)[32] and prescribing data indicates yearly increments in the number of medicines dispensed in primary care.[32] One large Scottish study indicates that the proportion of patients receiving five or more dispensed medicines rose from 12% in 1995 to 22% in 2010.[14] This study further indicates that the number of patients receiving 10 or more dispensed medicines tripled (from 1.9% to 5.8%) over the same period, highlighting the substantial rise in prevalence of 'hyperpolypharmacy'.[14] Comparative data for polypharmacy trends in England is limited, but similar patterns are likely. The polypharmacy problem is not just confined to primary care, as some studies indicate that many patients leave hospital taking more medicines than they went in with.[33]

1.4 Factors associated with polypharmacy

Several factors are associated with the rising prevalence of polypharmacy in the UK, encompassing changing demographics, the impact of health technology assessments and evidence-based medicine, clinical guidelines and health policies and systems, and changing societal attitudes and expectations towards treatments.

Changing demographics – aging and multimorbidity

The prevalence of polypharmacy increases with both age and multi-morbidity.[4,9,14] The UK's population is increasingly aging and more people are living longer with at least two or more chronic conditions (termed multimorbidity) for which multiple medicines are prescribed.[34] With the population aged 85 years and over projected to more than double by 2035, polypharmacy is projected to continue growing.[4] Multimorbidity is more common among the elderly (age 65 years or over).[34,35] For instance, most elderly patients with diabetes have, on average, six or more co-existing long-term conditions when compared those under 65 years of age with approximately three conditions (See Figure 1-2).[25]

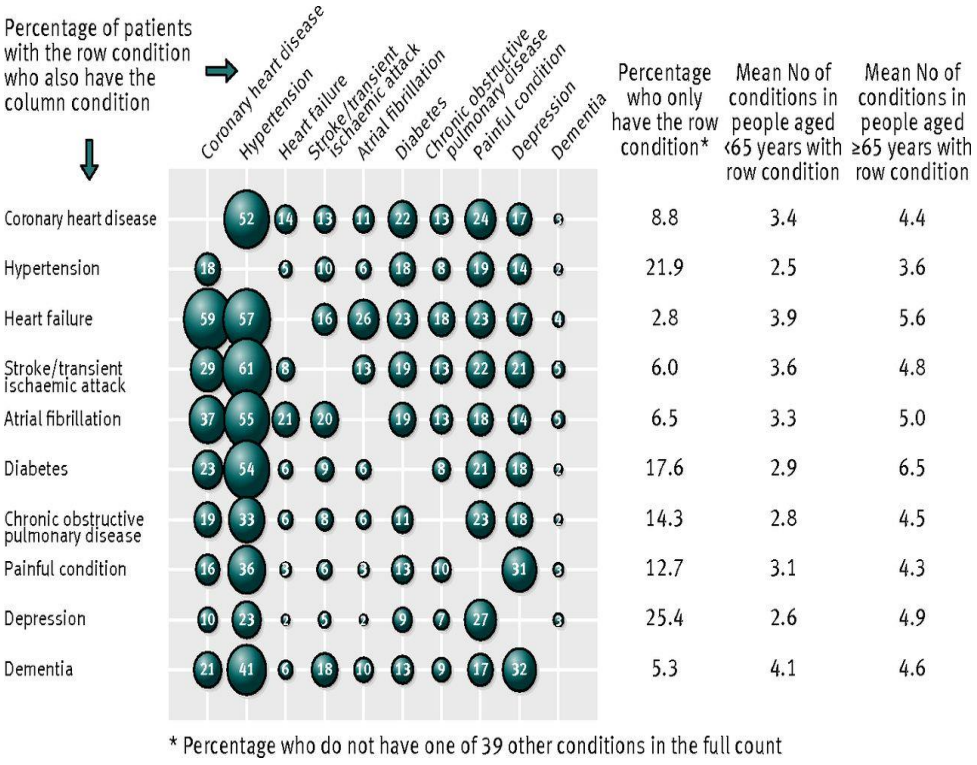


Figure 1-2 Comorbidity among patients in the UK Primary care

Source: Guthrie B et al (2012)[35]

The impact of health technology assessments, clinical guidelines and health policies

There has been a trend towards greater use of evidence-based practice both in the UK and internationally, with more prescribers feeling compelled to adhere to clinical guidelines, such as those developed by the National Institute for Healthcare Excellence (NICE). NICE is responsible for appraising new and existing medicines and recommending their use within the National Health Service (NHS) in England. Existing clinical guidelines are largely criticised for having a single-disease focus, and less consideration of medicines use in the context of multimorbidity.[35,36] For patients with multiple disease conditions, prescribing based on disease-specific clinical guidelines, if used in isolation for each condition, contributes to polypharmacy.[36] Moreover, most evidence-based guidance is derived from studies conducted in atypical patient populations that lack complex multimorbidities encountered in real-life settings. Guidelines are also described as limiting to professional judgment and person-centred practice, and impact on patient preferences.[36,37] Some professionals may have more difficulties than others in considering patient wishes, concerns or obtaining detailed accounts, and enacting patient preferences may be viewed as out-of-protocol and against evidence-based guidelines.[37] Another significant consequence of adhering to clinical guidelines is a rise in the use of prophylactic medicines for disease- and mortality-prevention, especially among asymptomatic patients. This results in many 'well' individuals increasingly prescribed medicines, particularly for the prevention of cardiovascular disease and stroke, and contributes to the growing levels of polypharmacy.[4]

Furthermore, prescribing targets set out by incentivised initiatives, particularly the Quality and Outcomes Framework (QOF) for general practice in the UK, may contribute to polypharmacy.[37] The QOF initiative, as a 'national primary care pay-for-performance (P4P) scheme… designed to improve evidence-based quality targets', awards practices for managing and preventing common chronic conditions.[38] For instance, one QOF indicator is the percentage of patients treated with statins of those with cardiovascular risk assessment scores ≥ 20% in the previous one-year, and practices prescribing more of these lipid-lowering medicines would be rewarded for primary prevention of cardiovascular disease.[39] A recent systematic review into the impact of the QOF revealed negative effects on the degree of person-centredness of doctor consultations

and on continuity of care, all of which may cause inappropriate polypharmacy and dissatisfaction with care.[38]

Health systems

The rise in polypharmacy may also be related to prescribing systems. In England, the use of repeat prescriptions, among patients with chronic conditions, has gradually increased over the years.[40] It is estimated that repeat prescriptions contribute 80% of all dispensed prescription items in primary care.[4] Patients (or their representatives) can request repeat prescriptions through wide-ranging methods depending on the practice: in person, telephone, on-line, by post or fax.[41] This enables patients with long-term conditions to have easier access to medicines, but systems may not provide adequate control over the extent of repeat prescribing,[42] which could contribute to polypharmacy. More recently, electronic prescribing, which enables prescriptions to be sent electronically to a patient-chosen community pharmacy,[43] is further easing access to repeat medicines, but with even greater possibility of minimal communication between the patient and the prescriber.

With about a third of patients in England paying for their prescriptions, the cost of prescription medicines is another health-system-related challenge for some users of long-term prescription medicines. Within the English NHS, regulations set out prescription charges and arrangements for exemptions among specific groups of people (e.g. based on age, disease/condition state, and income brackets) or for specific medicines.[44] Different cost-sharing mechanisms, including a fixed co-payment (a prescription charge of £8.40 per item as of April 2016[45]), are applicable in England. Also in use are quarterly (£29.10) or annual (£104) prepayment certificates (PPCs) that are intended to put a ceiling on patient charges, among those in need of regular medicines.[45] However, previous studies have indicated low levels of awareness of the existence of PPCs as cost-saving strategies.[46] All these cost-related issues may affect access to prescription medicines. In their 2014 report, a coalition of patient organisations against prescription charges for patients in need of long-term prescriptions in England, revealed that cost-related non-adherence affects about a third of non-exempt patients, particularly the younger and those with lower income.[47]

1.5 Consequences of polypharmacy

Whereas polypharmacy may be beneficial, it also poses several challenges and has wide-ranging impacts on the healthcare system, society, and patients. For health systems, including the NHS, polypharmacy has financial implications associated with costs of medicines (over £14.4bn per annum) and related pharmaceutical services, and expenditure and wastage resulting from patient non-adherence and medicine-related problems (e.g. medication errors).[4] For society, polypharmacy may influence caregiver burden or strain/family relationships among those needing to care for patients unable to manage their own medicines.[48,49] For patients using multiple or inappropriate medicines, the consequences are well documented. Non-adherence, one of the most common implications for the patient, is very common; up to 50% of medicines are not taken as prescribed.[3] Other polypharmacy-related problems include pill burden, time and effort related to organising multiple regimens, self-monitoring demands,[48–50] adverse drug reactions (ADRs), drug-drug or drug-food interactions.[7,14,15] All these may contribute to poor clinical outcomes, including symptom occurrence, relapse, and exacerbation of disease/condition or hospitalization. For patients without an exemption from prescription fees, polypharmacy can lead to direct financial burden associated with out-of-pocket payments for their medicines.[44,51,52] Overall, the use of multiple or inappropriate medicines may impact on patients' quality of life, physical health, psychological wellbeing, and social functioning, and can be a burden to some patients.

1.6 Initiatives designed to address the polypharmacy problem in the UK

Over the years, there have been several national recommendations for supporting medicines management schemes within primary and secondary care in the UK.[53,54] These promote improved access to medicines, rational prescribing, and reduction of costs and medicine wastage within the NHS. Several researchers have devised interventions/methods to promote identification and reduction of polypharmacy, which are discussed in this section.

1.6.1 Prescribing guidelines, indicators, and tools

As part of interventions to solve the global problem of polypharmacy, a number of guidelines, prescribing indicators, and risk assessment/screening tools to identify medicine-related-problems and inappropriate prescriptions have been developed.
In the UK, key guidelines targeting polypharmacy include:

a) the 2014 'Polypharmacy: Guidance for Prescribing' for Scotland and Wales that targets the frail and elderly, those using multiple medicines, high-risk medicines and those with shortened life expectancy;[55]
b) the 2015 'Polypharmacy Guidance' published by the Scottish Government, which describes a 7-step approach to reviewing medicine use among adult patients encompassing aims, need, effectiveness, safety, cost-effectiveness, adherence or patient-centredness;[56]
c) the 2015 NICE guideline on 'Medicines Optimisation: the safe and effective use of medicines to enable the best possible outcomes', whose key priorities relate to medicine-related communication and methods to identify patient safety issues.[57] Most of the guidance appears prescriber-focussed and centred on the appropriateness of medicines from the health professional perspective.

Common indicators (and measures) of appropriateness of medicines use predefined criteria, such as the Beer's criteria (and its adaptations),[58] and the Medication Appropriateness Index (MAI).[59] The START/ STOPP tools (Screening Tool to Alert to Right Treatment and Screening Tool of Older People's Prescriptions),[60] are recommended by the NICE Guidelines in the identification of medicine-related problems among older people with polypharmacy, but neither has been routinely used in practice.

Within the UK, other prescribing indicators include those tested in the PINCER trial, a pharmacist-led information technology intervention that provided feedback and education to GPs to minimise medication errors.[61] Other prescribing indicators for UK general practice were developed by the Royal College of General Practitioners,[62] while Oborne's[63] prescribing indicators were intended for elderly medical inpatients. Although validated for use in various settings, prescribing indicators are largely prescriber-led, require healthcare professional judgement, and require little or no input from patients. They are also medicine-centred, and applicable to specific patient populations with less consideration of multi-morbidity. Other recent guidance on strategies designed to tackle polypharmacy considers the selection of appropriate formulations with minimal regimen complexity.[16]

Deprescribing algorithms, which involve tapering or cessation of undesirable medicines,[64–67] are also proposed to guide clinical decisions in reducing polypharmacy but are also clinician-driven and tend to focus on reducing medicine usage and costs. Deprescribing has also been criticised for general lack of effectiveness, sustainability, and insufficient validation.[65]

1.6.2 Medicine use reviews

Other interventions aimed at reducing polypharmacy, include pharmacist-led medicine use reviews.[68] In England and Wales, the Medicine Use Reviews and Prescription Intervention (MUR) service was initiated in 2005, under the Community Pharmacy Contractual Framework, as one of the Government strategies to improve patients' adherence and reduce medicine costs and waste. Provided by the vast majority of community pharmacies in England, MUR services are increasingly targeted to people using high-risk medicines (e.g. anticoagulants for stroke prevention), those recently discharged from secondary care and had altered regimens during admission, those in need of medicines with respiratory conditions (e.g. corticosteroids), diabetes, and the elderly. Tools to guide or document MURs vary, but comprise questions around knowledge, adherence and actual use of medicines.[69]

The New Medicine Service (NMS), which is also provided by most community pharmacies in England, specifically offers support to using newly-prescribed medicines in the context of long-term illness, but also aims to improve adherence.[70] Despite evidence to support MURs, particularly the achievement of prescribing process outcomes (and reducing polypharmacy),[71] from the patients' perspective, these services have been criticised to have minimal impact regarding how patients use their medicines or even less with improving knowledge of medicines, and not addressing patients' needs fully.[72,73]

1.6.3 Drive towards patient-centred strategies

Most recently, improving the quality of patient care has been placed at the heart of the NHS. In their 2014/15-2018/19 report, 'Everyone counts: planning for patients', NHS England prioritises delivering and measuring patient-centred outcomes against five major domains; two of these relate to 'enhancing quality of life for people with long-term conditions' and 'ensuring that people have a positive experience of care'.[74]

Other recent developments within the UK include the concept of medicines optimisation, an agenda originally developed and promoted by the Royal Pharmaceutical Society (RPS),[1] the professional body for pharmacists and pharmacy in Great Britain. Figure 1-3 illustrates the RPS definition of medicines optimisation.

> '…ensuring that the right patients get the right choice of medicine, at the right time.. It represents a paradigm shift to a more holistic, patient-focused approach to health care. By focusing on patients and their experiences, the goal of medicines optimisation is to: help improve patient outcomes, encourage patients to take their medicines as prescribed, avoid use of unnecessary medicines, reduce wastage of medicines, and improve medicines safety.'[1]

Figure 1-3 Definition of medicines optimisation

The medicines optimisation agenda has four guiding principles, with the foremost aiming 'to understand the patient's experience, encouraging 'ongoing, open dialogue with the patient…'.[1] The medicines optimisation agenda is supported by other organisations in the UK, such as NHS England.[75] In their call for research on polypharmacy from the patient's perspective, Heaton et al (2016)[24] reviewed five recent policy reports and guidelines in England, including those published by Exemplar organisations (e.g. NICE, The Kings Fund, RPS). The authors found minimal documentary guidance considering the patient experience of medicines use in the reviewed policy documents, and they proposed further research into the patients' perspectives of polypharmacy.[24]

In an updated Cochrane review on interventions to improve the appropriate use of medicines in older people (≥65 years using ≥4 regular medicines), Cooper et al (2015)[11] highlighted a dearth of effective interventions. These findings which were similar to the preceding Cochrane review, which concluded that 'it is unclear if interventions... such as pharmaceutical care [interventions], resulted in a clinically significant improvement; however, they appear beneficial in terms of reducing inappropriate prescribing and medication-related problems'.[68] A range of interventions were described, including medication reviews, screening tools (e.g. the START/STOPP), computerised-decision support to prescribers, and patient consultation or education. Most interventions described in Cooper's review[11] did not consider certain patient outcomes in depth, particularly adherence and quality of life, and were tested in populations outside of the UK. This may indicate a need for UK-based interventions.

Another Cochrane review included 18 randomised-controlled trials testing interventions for improving outcomes in patients with multimorbidity in primary care and community settings.[76] Smith et al (2016)[76] reported that most trials incorporated changes to the organisation of care delivery though multidisciplinary teams, while a few others were patient-oriented and considered education or self-management interventions delivered directly to participants. There were 'no clear positive improvements in…adherence and patient-related health behaviours'.[76]

Despite mixed findings in terms of the effectiveness of interventions, the review indicated that '...Interventions that focus on difficulties that people experience with daily functioning…may be more effective'.[76]

Indeed, an earlier synthesis of Cochrane reviews[77] exploring the consumer-perspective, on strategies to encourage safe and effective use of medicines, found that patient-centred strategies (e.g. self-management programmes) were most promising, compared to other interventions (e.g. pharmacist-led medicine reviews).[77] Other useful interventions were aimed at promoting medicine-related communication, education/information provision, and behavioural support (including adherence).[77]

1.7 Patient perspectives of medicines use

In their recent debate and analysis, exploring solutions to problematic polypharmacy, Reeve and colleagues indicated the lack of an evidence base that considers the patient's perspective on polypharmacy.[78] The authors emphasise that, despite the decision-making role by health professionals who determine what medicines to use, patients (or consumers of healthcare) have the ultimate responsibility in 'translating a medical decision into the best decision [for them]'.[78] In 2012, NICE published guidelines, titled 'patient experience in adult NHS services: improving the experience of care for people using adult NHS services', to encourage health professionals to deliver patient-centred care.[79] The report highlighted the need to 'recognise that individual patients are living with their condition … and how the person's circumstances and experiences affect their condition and treatment' need to be taken into consideration.[79] The report's emphasis relates to patient involvement and active participation in healthcare, recognising self-management as fundamental to people with long-term conditions.

For people using long-term medicines, the demands of therapies (or the health condition) dictate that they devise ways of incorporating medicines into their day-to-day life.[80] Subsequently, decisions about using medicines (or not) often depend on 'real world considerations'.[81] Some individuals value the ability to live a normal life that allows them to meet personal and social obligations over controlling symptoms or disease risks. Although qualitative research into lay perspectives and experiences of

medicines use is increasingly reported, relatively little research has been done to assess the impact of medicines and how they fit into routine lives of people on long-term medicines. Put simply, Reeve and colleagues (2015) suggest that while some people using long-term medicines are able to cope, ' ...many become overwhelmed and confused….'.[78]There is an increasing recognition that self-care activities, including prescription medicines use, can be burdensome for some individuals. The Oxford dictionary defines the noun burden as 'a duty that causes worry, hardship, or distress'.[82]

1.8 Existing theories of treatment burden

The burden associated with managing chronic disease has been the subject of several studies. Definitions of treatment burden vary but a more explicit definition by Tran et al (2012)[83] considers 'the impact of healthcare on patients' functioning and well-being, apart from specific treatment side effects. It takes into account everything patients do to take care of their health: visits to the doctor, medical tests, treatment management, and lifestyle changes.'[83]

For others, the concept of treatment burden relates to patient workload of healthcare activities and capacity to manage this. Shippee and colleagues (2012),[84] in their literature review on patient complexity, shed more light on the concepts of patient workload and capacity. The authors view patient workload as a broader concept that covers 'all the demands in patients' lives, including everyday responsibilities alongside the demands of patient-hood' that require time, effort and attention, including non-healthcare activities (such as jobs and family).[84] It also encompasses healthcare activities, such as the workload associated with travel, attending clinical appointments, preventative care, self-education, self-care, and organising/using medicines. Treatment burden is imposed by investments into healthcare in the form of time, money and effort. Patient capacity relates to ability or readiness to handle the workload demands, including the physical and mental functioning.[84] Other factors that impact on patient capacity include socioeconomic, psychological issues, literacy and language, and social support.[84]

In the UK, Gallacher et al (2013)[85] have identified components of treatment burden after reviewing 69 qualitative studies exploring experiences of stroke management of adult patients: making sense of management and care plans, demands of social interactions with family, other patients and healthcare professionals, and implementing management strategies (e.g. managing the condition in the community). Although Gallachers'review was disease-specific, it highlighted challenges of managing long-term conditions and problems relating to information provision and communication with health professionals.[85]

In another review attempting to identify how treatment burden can be 'normalised', Gallacher et al (2011)[86] also identified specific aspects of patient workload using data from 47 patients managed for chronic heart failure in primary care. These were: adherence to treatment and lifestyle changes, which was the most prominently identified component of treatment burden; learning about treatments and their consequences; monitoring and appraisal of treatments; and engaging with others to seek social support. Similar findings have been reported by research into everyday experiences of long-term medicines, suggesting that many practical, organisational, logistic, and financial efforts are made by patients in order to cope with their treatment.[23,87,88]

In their concept analysis, Sav et al (2013)[48] indicated that treatment burden is multifactorial identified by five major antecedents: treatment characteristics, the healthcare system, patient characteristics, the disease condition (s), and the family or support network.[48] These factors were further elaborated in their seminal paper, 'You say treatment, I say hard work', in which Sav and colleagues revealed inter-related constituents of treatment burden: medication burden, healthcare access burden, financial burden (including costs of medicines and consultations), time and travel burden.[49] Many of these efforts are described as laborious, troublesome, and time- and energy-consuming. Eton et al (2015)[89] proposed similar factors in their updated conceptual framework of burden of treatment (See Figure 1-4). Healthcare access burdens were associated with poor unhelpful relationships with individual providers or system barriers relating to continuity and coordination of care.[89]

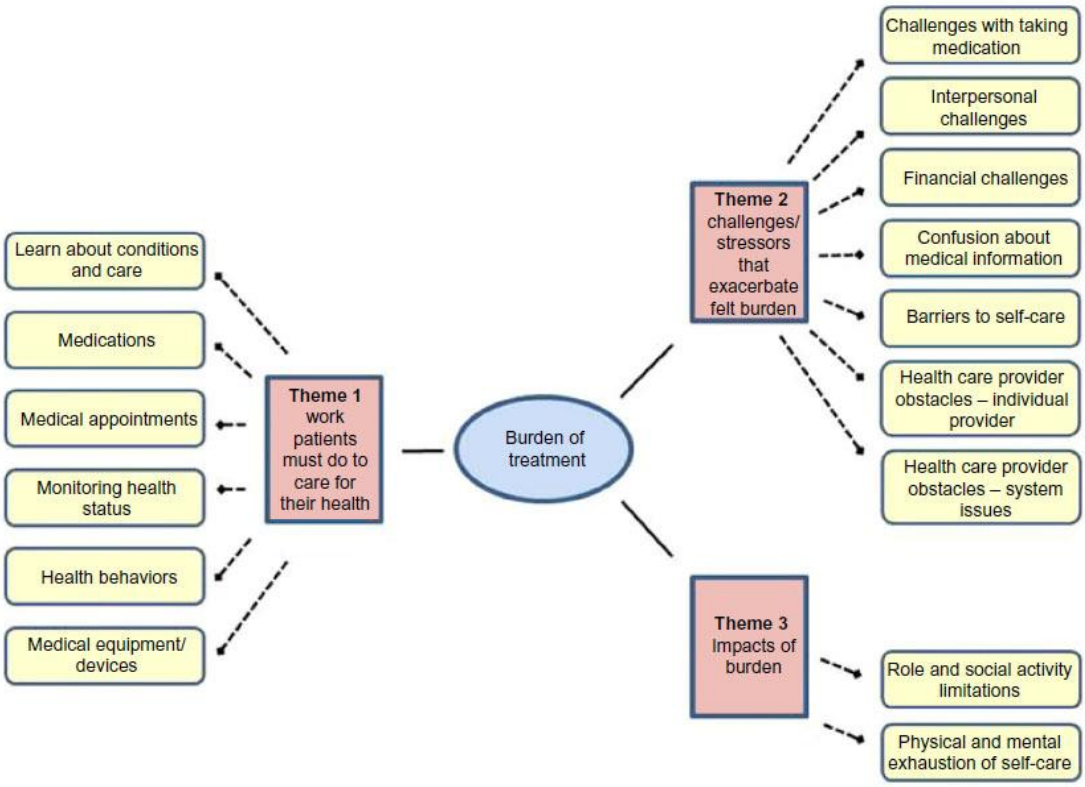


Figure 1-4 A conceptual framework of the burden of treatment

Source: Eton et al (2015)[89]

The Burden of Treatment Theory

More recently, May et al (2014)[90] proposed the burden of treatment theory (BoT) as a contemporary model that 'aims to facilitate a new understanding of the interaction between capacity for action and the work that healthcare systems pass on to patients and their relational networks.'[90] As a structural model, the BoT model illustrates the impact of patient 'workload', including all tasks delegated by the healthcare system that patients and their social networks must do to manage long-term conditions. The BoT model attempts to explain relationships between workload and patient capacity, which relates to the ability to perform different healthcare tasks (e.g. cognitive and informational tasks relating to learning about disease or its treatments, and organisational demands of accessing care e.g. seeking appointments). It suggests redesigning of healthcare services so they are geared towards improving patients' experiences, and providing better co-ordinated and more-patient-centred care that equips patients better to handle their problems.

The work involved in learning/understanding various aspects treatments (or medicines), including differentiating various formulations, and understanding the rationale for using medicines, can be burdensome. In their BoT concept, May and colleagues suggest that supporting patients can help them improve capability to perform delegated healthcare tasks. This in turn may result in better patient experiences, and confidence in performing these tasks. Though this requires further validation and is mostly broad and theoretical, the BoT concept appears to have a patient-focus and calls for interventions to improve patients' experiences of care.

The Cumulative Model of Patient Complexity

The Cumulative Complexity Model (CCM), also known as the cumulative model of patient complexity, is a more elaborative model that also considers patient experiences of long-term care.[84] The CCM is a 'patient-centred framework that emphasises the workload-capacity balance and incorporates treatment and illness burdens'.[84] The developers of the CCM indicate that experiences of care become burdensome when workload demands exceed capacity.[84] Eton and colleagues (2015),[89] who indicate that 'capacity determines whether work will be perceived as manageable and routine or unmanageable and excessively burdensome', support this finding. In the CCM framework, burden of treatment is theorized as 'a feedback loop, connecting poor outcomes with further erosion of patient capacity and intensified demands, such that patient complexity may build through cumulative cycles.'[84] The CCM encourages using treatments that minimise burden while avoiding workload-capacity imbalances. The authors recommend patient-provider partnerships and research to identify workload-capacity difficulties, solutions for reducing patient burden, and 'development of a decision-support tool to help ascertain problems during clinical encounters'.[84] Though relevant in the context of chronic illness and long-term care, both the BoT and CCM frameworks consider treatment burden as a broader concept including treatment modalities other than prescription medicines (e.g. diet, exercise).

The MDM Care Model

The Minimally Disruptive Medicine (MDM) care model is another framework that covers both treatment burden and patient complexity.[91] It has recently been proposed as 'a theory-based, patient-centred, context-sensitive approach to care' for managing multiple chronic illnesses, and is focussed on 'on achieving patient goals for life and health while imposing the smallest possible treatment burden on patients' lives'.[91] The MDM framework is founded on two key strategies, including identification of the 'right care' for patients and making the 'right care' happen in the context of multimorbidity. By 'right care', the authors imply 'care that is needed and wanted by patients and feasible for them to enact'.[91] They acknowledge a need for workload-capacity balances, similar to other treatment burden theories, and the need to integrate healthcare activities into patients' day-to-day routines.[91] Although the authors recognise the need for further validation and refinement of the MDM care model, they uniquely propose tools to identify and implement right care, for instance, through workload and capacity assessments and systematically tracking patient-reported outcomes.[91] Nonetheless, a notable challenge across most models is the use of terminology that is prone to patient aversion (e.g. capacity, burden); further validation may involve different patient cohorts to assess the likelihood of this.

1.9 Conceptualising medicine-related burden

To inform the development of interventions or measures of medicine-related burden, there is a need to understand existing theoretical/conceptual frameworks, including potential causative factors, how they relate to each other, and consequences of excessive burden.

Prescription medicine burden is a relatively new concept relating to medicine-only therapies and little research has defined or focussed on this construct. As previously described, there have been several attempts to conceptualise treatment burden. Relevant theories looking at the burden of treatment are rather broad and explore the general burden of healthcare activities, with less focus on prescription medicine use. Nonetheless, treatment burden is depicted as a broader concept that encompasses medicine burden as one of its key components.[48,89]

A few researchers have proposed theoretical frameworks specifically looking at the burden of medicines or pharmaceutical products from the patient's perspective. The earliest research by Murawski and Bentley (2001)[92] described the 'inherent burden of drug treatment' that was conceptualised in terms of health-related quality of life (HRQoL). Specifically, the inherent burden of medicines (termed pharmaceutical-therapy related quality of life) was conceptualised as the difference or gap between the theoretically maximum possible HRQoL obtained after drug therapy and that actually observed/experienced post-treatment (See Figure1-5).[92]

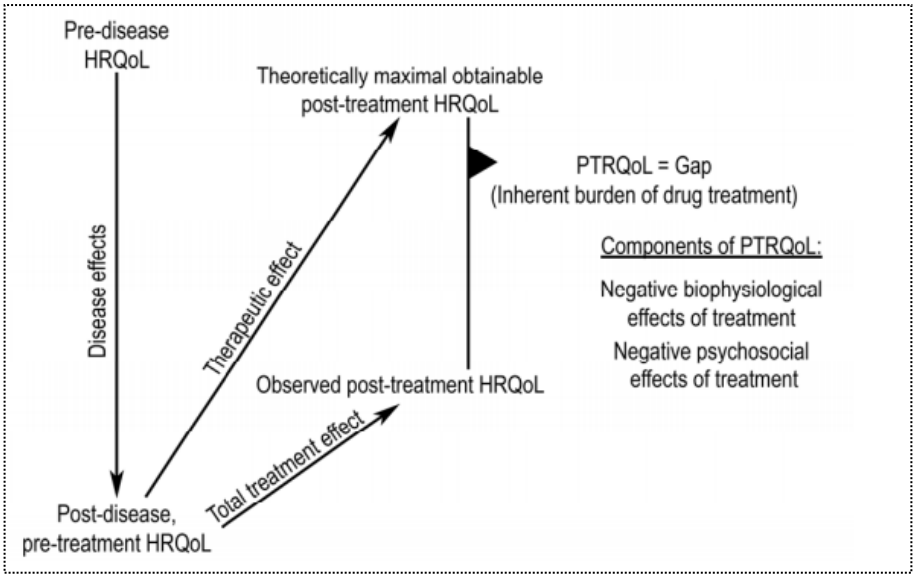


Figure 1-5 The concept of 'inherent burden' of medicines

Source: Murawski & Bentley (2001),[92] simplified by Renberg (2009)[93]

Negative consequences or burden were thought to arise from biophysiological effects of medicines (e.g. side effects). Despite the quantitative and somewhat biomedical definitions used within Murawski and Bentley's framework, psychosocial factors and subjective experiences of medicine use were considered by the authors to relate to the inherent burden. Issues around practicalities and logistics of managing medicine regimens, including administration and scheduling difficulties, indicating that complex regimens are associated with greater burden on the patient, were highlighted.[92] Inconveniences that can be burdensome to patients were also considered, for instance challenges around carrying and storing medicines (e.g. from home to school/work).

Psychosocial factors were also highlighted, including social stigma around using medicines, and interferences to social activities or impairment of social skills as a side effect of certain medicines.[92] Stress, fear or anxiety related to medicine use were also considered, as well as worries and concerns about the negative effects of medicines, including fears of addiction, dependence, tolerance and ineffectiveness. The negative impact of medicines on personal control and anxieties related to missing or changing doses were also superficially considered.

Although the authors described factors that reflect the burden of medicines, their theoretical framework covered all forms of pharmaceutical agents and services and was not limited to prescription only medicines. Moreover, the authors deliberately omitted the financial burden of using medicines use, relating to the cost of prescription medicines, citing that it not part of conceptualisations of HRQoL; the general context used to define medicine burden. What is clear from the Murawski and Bentley's (2001) model[92] is that the burden associated with medicine therapies, just like other treatment modalities, is a multidimensional concept. Despite covering relevant domains, further empirical work on the model, reported by Renberg et al (2008),[94] revealed conceptual problems.

In a recent metasynthesis of qualitative studies,[88] medicine-related burden (MRB) was conceptualised as one of the three interrelated components of patients' lived experience with medicines (PLEM), alongside medicine-related beliefs and medicine use practices (See Figure 1-6).

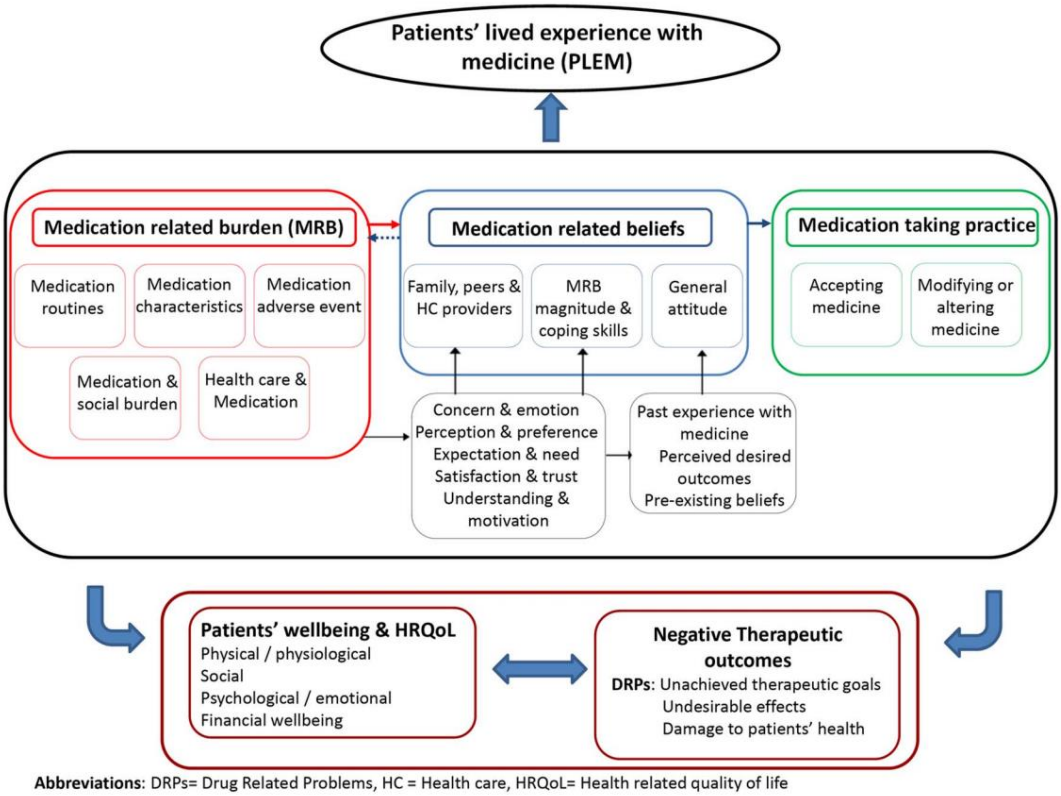


Figure 1-6 Recent conceptualisation of medicine-related burden

Source: Mohammed et al (2016)[88]

In this conceptual framework, five aspects of medicine-related burden are described: routines of medicines use, characteristics of medicines, adverse events relating to medicines, social burden, and healthcare system-related burden.[88] Most of these aspects of medicine-related burden are similar to those described in earlier conceptualisations of treatment burden. Although it considers key aspects that are burdensome to users of prescription medicines in detail, Mohammed and colleagues' conceptual framework[88] seems to be rather restrictive or perhaps overly structured. For instance, the framework deliberately considers the experience of 'medicine-taking' and medicine-related beliefs, attitudes, concerns and emotions as external to the burden construct. The authors[88] acknowledge that empirical testing of this framework is necessary to understand this construct further. Nonetheless, the issues covered in the framework are supported by Demain and colleagues (2015)[95] whose view of treatment burden considers aspects of medicine-related disruptions.

Social burden, denoted as relational disruptions, considers strains to family and social relationships as a result of treatment; biological disruptions in the form of side effects are a burden; and biographical disruptions relating to restrictions to day-to-day activities, impact on personal identity, freedom and independence, and social stigma can be burdensome among those using routine treatments.[95]

1.10 A summary of factors associated with medicine burden

As noted in the previous sections, treatment (and medicine burden) are disruptive and there is a need to understand associated factors. This section summarises factors or issues that may affect medicine burden and likely consequeces, based on collated findings from the aforenamed theoretical frameworks and related literature (See Figure 1-7).

Patients' experiences with using prescription medicines vary. Numerous studies in many countries show that most patients would prefer not to take medicines, particularly those with chronic conditions, that some patients are resistant towards using medicines,[21] and that there is a desire among some patients to stop some or all of their medicines.[96]

Managing medicines routines can be burdensome to some individuals whose overall goal is to maintain health and perform normal activities of daily living.[88] Some patients struggle to fit medicine use routines into their day-to-day lives and may utilise different coping strategies, including the use of practical tools (e.g. reminders, dossette boxes/pill organisers). Others may fail to manage demands relating to accessing prescriptions and medicines. Self-administration of medicines(e.g. that which requires multiple steps in premixing formulations), and self-monitoring medicine use may also exacerbate medicine-related burden and impact on behaviours, including non-adherence. Some patients rely on family, friends or health providers to support medicine routines, and inadequate social support may further exacerbate the felt burden.

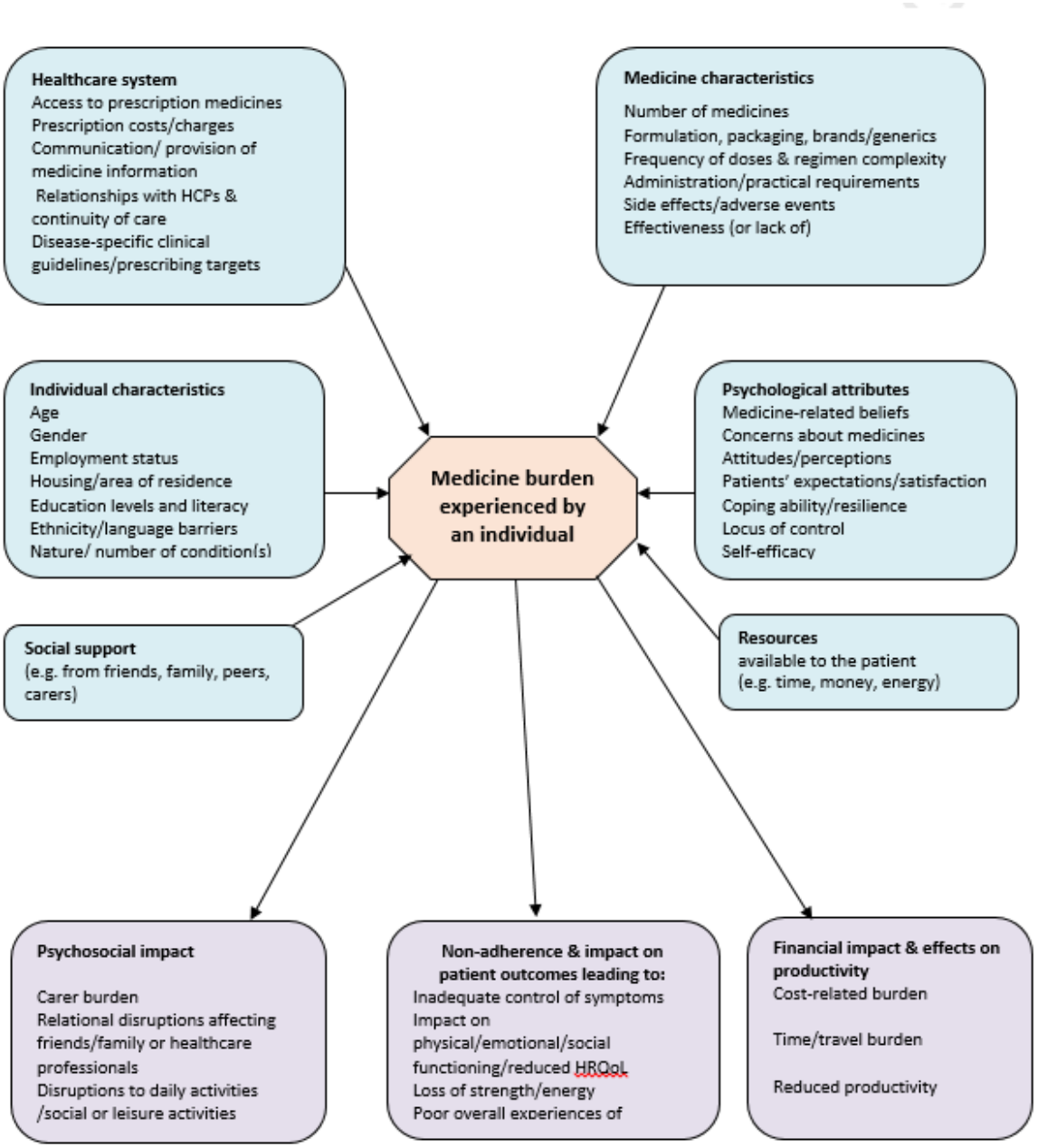


Figure 1-7 A conceptual framework of medicine burden and likely consequences

Notes: The top half of the figure (in blue) reflects factors associated with medicine burden while the lower half (in lilac) reflects the likely consequences.

Medicine characteristics

Medicine-specific characteristics including the number of medicines, formulation (e.g. smell, taste, size of tablet, ease of swallowing/use), route of administration (e.g. oral versus injections), the dosing frequency, may all affect medicines use experiences and perceived burden.[83,88,97] As the complexity of medicine regimes increases, including the number of doses, number of dosage units per dose or dosing schedules and frequency of use or self- monitoring, medicine burden may increase.[16,98,99] Complexity of regimes may be augmented by strict food requirements, for example some medicines need to be used a few hours before or after food, while certain foods/drinks may need to be avoided when using certain medicines (e.g. no grapefruit juice when using atorvastatin). This may subsequently impact on daily routines and having to adjust life to suit medicine use. Issues around generic brand switching may also cause worries or concerns about efficacy/tolerability of different brands,[100] which may, in turn, exacerbate the burden of medicines. Practical difficulties (and discomfort) associated with opening certain medicine packaging may be burdensome to individuals, especially the elderly, as with the time taken in organising medicines use.[23,89]

Medicine-related adverse events

Concerns about potential harm from medicines (and adverse events) and experiences of side effects may contribute to medicine burden. Patients experiencing side effects may perceive more burden than those who do not.[83] Patients are more likely to alter medicine use (or even stop) or request changes to medicines if they are dissatisfied with the experience of side effects.

Healthcare system factors

As previously discussed, healthcare systems contribute, indirectly or directly, to treatment burden.[48,86,89] Medicine-related burden could arise from poor access to prescriptions and medicines. Difficulties may be associated with arranging doctor appointments, asking for prescriptions, long waiting times and effort in accessing medicines. Patient-provider relationships and communication difficulties and/or information burden[23,88] and lack of continuity of care (and multiplicity of providers) can exacerbate actual or perceived medicine burden. Studies suggest that patients' experiences of medicine use may be neglected during consultations with providers, and thus issues influencing medicine burden are often not discussed.[101] Some patients desire convenient, flexible regimes (dosing and timing) that can 'mirror' their personal life situations.[99] Interruption to medication routine may be caused by changes in prescriptions and could be burdensome to some patients.

Cost of prescription medicines

The financial burden of prescription medicines, for individuals that have to pay out-of-pocket or co-pay to access their long-term medicines is well documented. Prescription medicine costs influence how some patients manage their condition,[46] and can be particularly burdensome to chronically ill patients.[51] Some patients may reduce or alter using their essential medicines due to costs (cost-related non-adherence), while others may forego basic needs to pay for their medicines,[47,51] which may ultimately impact negatively on health outcomes. Cost reduction strategies employed by patients have encompassed: not getting items dispensed, delay in cashing prescriptions, reducing or spreading out the dose, or buying cheaper alternatives.[46,47,102]

Cost-related non-adherence is not uncommon, and is associated with several patient factors such as income levels, age, ethnicity, attitudes and beliefs about medicines (including low perceived need and side-effect-related concerns), type of medicines, health status, or low educational level.[51,103,104] A recently published measure of patients' cost-related medicine burden (and non-adherence) has assessed this construct in isolation, and in health settings dissimilar to the UK.[52]

Different countries and health systems have varying mechanisms for paying for prescriptions[105] and different policy strategies to reduce cost-related burden among patients using long-term prescription medicines.[44] Despite the various cost-reduction strategies, prescription charges may pose an access barrier for some patients in need of long-term prescription medicines in England.[46]

Patient-related attributes

Certain patient-related attributes and socio-demographic characteristics may be associated with medication burden. The nature/type, severity, and duration of illness (e.g. chronic versus acute, mental health condition versus physical condition, multimorbidity versus single disease states) may be associated with differing perceptions and levels of medicine burden.[48] Patients who have symptomatic illness (e.g. chronic/severe pain) may perceive less (or no) burden of medicines, as they are likely to experience immediate benefits of medicines (e.g. symptom relief) more than treatment-related inconveniences. On the other hand, asymptomatic patients, who may not perceive an immediate burden of illness, may perceive greater medicine burden if the need for their regimens, or their immediate benefits, is not realised.

Aging, which is associated with multiple medicines use, may affect perceptions of medicine burden. Although elderly patients may experience greater treatment burden when compared to younger people,[48] this may vary across different populations. Nonetheless, elderly people may experience practical difficulties with accessing their medication and with opening packages, especially those with problems relating to physical functioning and dexterity. However, increasing age is associated with fewer expectations of healthcare and greater satisfaction,[106] which could manifest as less medicine burden.

Gender has also been associated with treatment burden,[48] with females more likely to experience higher burden when compared to males. Women are more likely to seek medical care and be more evaluative of their medicines.[21] Women are also more likely to perceive themselves as sensitive to the negative effects of medicines, and thus report more medication burden. Socioeconomic factors, particularly unemployment may also be associated with treatment (and medication) burden,[48] possibly due to greater financial burden.

Psychological attributes

The burden of medicines may be influenced by patients' beliefs, attitudes and perceptions about medicines. Efficacy-related beliefs are a major basis for health-related actions, including medicines use.[107] Decisions which affect using medicines 'are influenced by the weighted judgment of [the] positive value of medicine, and negative value of medicine' harms and inconveniences.[108,109] Patients are likely to persist or follow prescribed medicine regimes if they believe that perceived benefits (e.g. relief or control of symptoms, avoidance of relapse), outweigh the negatives of potential harm.[110] Research into adherence and persistence with medicine use has demonstrated the role of medicine-related beliefs.[111–114]

Stronger beliefs about the necessity of medicines,[110] may translate into lower perceived medicine burden. People evaluate their medicine in terms of effectiveness (if the medicine is doing what it is intended to do); experiences or concerns about side effects (and their impact on physical health and functioning, mood or emotions, mental function); and convenience of medicine use, including ease of administration.[17,108,109] Perceived effectiveness is the greatest valued attribute and determinant of treatment success among most, if not all, patient groups.[108,109] If effectiveness is achieved, tolerating side effects or medicine-related discomforts/inconveniences becomes less weighted.[108,109] Patient satisfaction and dissatisfaction with treatment can be predicted by people's expectations versus their actual experiences of treatment.[106,115] Expectations include beliefs about the likelihood of achieving a successful outcome and are in the form of anticipations, wants, hopes and desires.[106] Unmet/met expectations with healthcare services affect patient satisfaction,[106,115] and could contribute to perceived burden. Greater satisfaction with medicines could be associated with lower medication burden.[83]

Higher levels of self-efficacy, which relates to '…beliefs in one's capabilities to organise and execute the courses of action required to produce given attainments',[107] may be associated with lower perceived medication burden. Beliefs of self-efficacy are cited to influence an individual's knowledge acquisition (necessary in learning about medicines or their effects), course of action, and behavior.[107] Although inherent, self-efficacy also requires mastery of knowledge and skills.[107] This can be achieved by investment of

time, efforts, and resources. With practice and routinisation, skills become easily executed, and may not need higher cognitive effort.[107] The latter concepts are akin to Gallacher's theory of 'normalising' treatment burden.[86] Self-efficacy also affects motivation, perseverance and resilience, the nature of thought patterns, and the amount of stress experienced in coping with challenging demands.[107] All these factors may influence perceptions of burden.

Locus of control, which is a personality belief that certain outcomes are as a result of self (internal), others (external), or chance,[107] may also affect perceptions of medicine burden. External locus of control is associated with less ability to cope with difficult situations.[116] On the other hand, internal locus of control is associated with more positive experiences, such as active engagement in activities, better relationships, information seeking, independent decision making, and a better sense of wellbeing.[116] In terms of medicines use, patients with a high internal locus of control may report more positive experiences of medicines use, thus are likely to report lower burden of medicines.

Consequences of medicine burden from the patient perspective

Like treatment burden, medication burden may affect an individual in multiple ways. The consequences could be physical (e.g. poor clinical outcomes), psychological (e.g. dissatisfaction with medicines), social (e.g. transfer of burden to carers) or take the form of financial burden. Medicine burden is associated with non-adherence, with some patients cited to manipulate their own regimens, 'particularly when intolerable burden was experienced', without consulting their healthcare providers.[88] More recently, Demain et al[95] has described the latter as 'rationalised non-adherence', a secret coping strategy, as a consequence of treatment burden.[95] It is possible that consequences of medicine burden are likely to exacerbate the felt burden. For instance, the resulting non-adherence may not only contribute to sub-optimal clinical outcomes (e.g. poor symptom control, disease progression or relapse, deterioration of health and quality of life), but could also trigger another prescribing cascade to manage new symptoms which may cause further burden.[48]

Besides impacting on physical health and psychosocial wellbeing, the burden of medicines may affect a patient's work and productivity (including employment), as well as activities of daily living. Medicine-related absenteeism from work may be associated with the need to seek repeat prescriptions and refills, or experience of side effects. Treatment-related absence from work could lead to a loss of annual leave or sick days per month, or feelings of guilt about lost productivity and burdening their co-workers; .[48] this can in turn worsen existing burden. Psychologically, medication burden may lead to dissatisfaction with medicines (including concerns), affect patient choice, and lead to refusal of medicines.

Using certain medicines may also disrupt individual lifestyles and social lives, including planning leisure or social activities, holding conversations with friends and family.[81,92,95] All this, coupled with the demands of fitting medicine regimes into usual life and social stigma may worsen medicine burden and affect relationships with family and friends. Some individuals may face social isolation with the aim of adhering to discreet regimes, all of which could exacerbate perceived or actual burden.[21,81] Moreover, disruptions to medicine use routines (and non-adherence) are associated with changes in day-to-day schedules.[88]

On the other hand, social networks and support may reduce medicine burden. The role of spouses/partners or caregivers, in supporting patients to cope with practicalities involved in using medicines, has been cited[117] and those living alone may have real difficulties. However, treatment-related demands can lead to caregiver burden (including fatigue and distress),[48,49] which in turn may affect the patient and his/her social or family structure. Paradoxically, loss of independence (in form of assistance provided by a caregiver) may also lead to treatment burden for some patients.[48]

1.11 General aim and objectives of this doctoral thesis

Aim

The series of studies in this thesis aimed to identify, develop and test a generic measure of patients' experiences of long-term prescription medicine use and associated burden in the English adult population.

Research question

This thesis explores the specific research question: Is the Living with Medicines Questionnaire (LMQ) (or its adaptations) a comprehensive, valid, reliable, and interpretable measure of medicines burden?

Specific research objectives were:

1. To identify a suitable measure of prescription medicine burden and assess its content coverage in relation to existing measures.
2. To assess the original version of the measure (LMQ-1) so as to identify areas of improvement and revise and test its interim versions (LMQ-2 and LMQ-2.1) for face and content validity, by obtaining patients' perspectives of the content coverage, concepts measured, and item readability.
3. To evaluate psychometric properties of the LMQ (version 3) including:
   - Construct validity, by exploring and confirming underlying domains or concepts measured;
   - Criterion-related validity by comparing LMQ concepts to those in relevant standard questionnaires;
   - Reliability (internal consistency and test-retest) of the questionnaire;
   - Interpretation of questionnaire scores.
4. To determine the prevalence of medicine-related problems uncovered by the LMQ, and to assess potential predictors of prescription medicine burden.

1.12 Overview of study phases in this research programme

To help clarify the roadmap for this research programme, and show how the different chapters within this thesis meet the objectives defined above, I will provide an overview of all phases of research conducted. Figure 1-8 illustrates the iterative procedures involved in LMQ instrument development and validation. The LMQ was developed and validated through iterative processes (See Figure 1-8), which are described within this thesis and are summarised below.

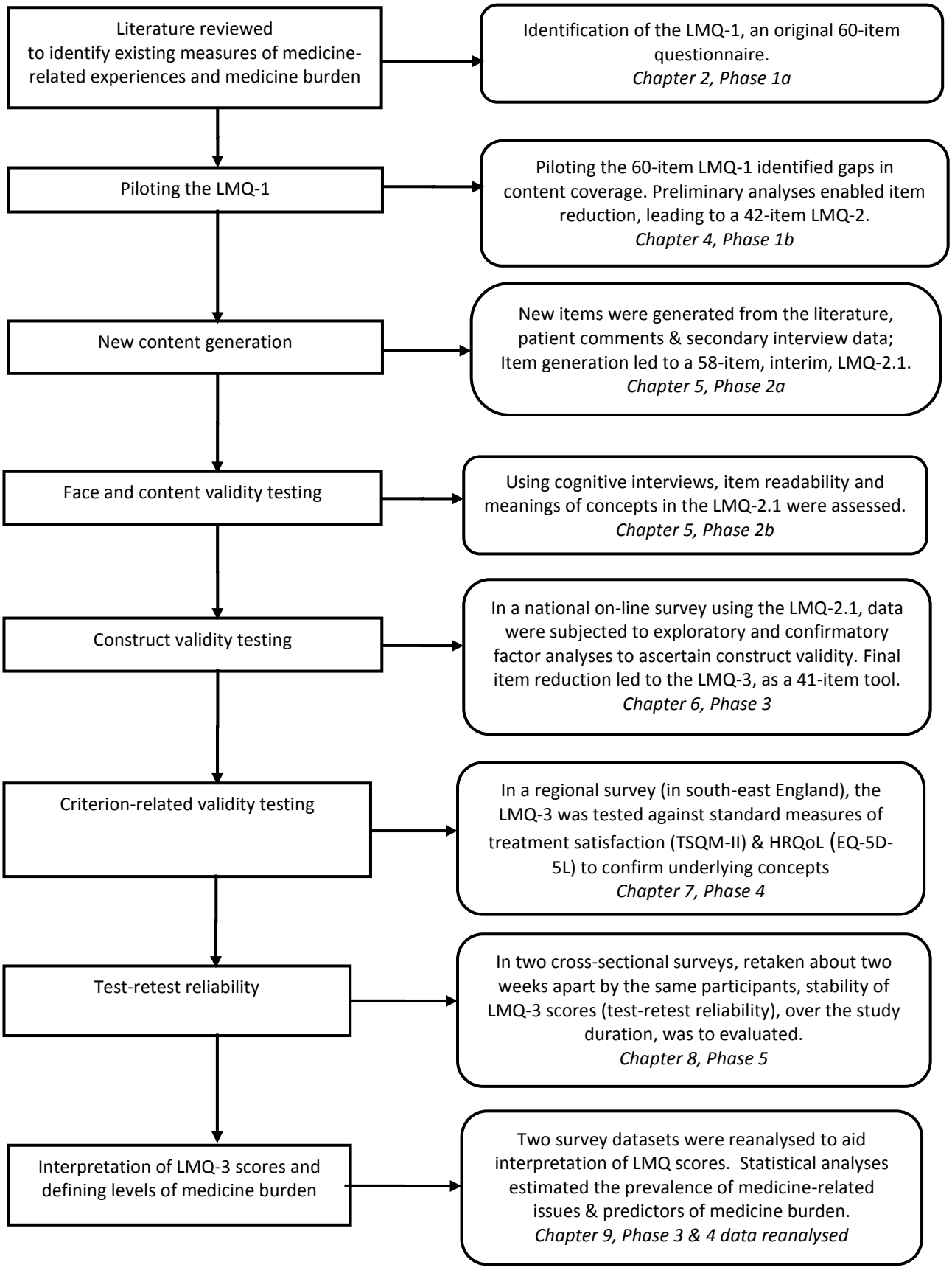


Figure 1-8 Overview of the present research programme

Phase 1- Instrument identification and preliminary item reduction

Phase 1a involved a systematic literature review described in Chapter 2. A critical literature review is a fundamental step in instrument development.[118] In this case, it enabled identification and comparison of existing measures of medicine-related experiences, while examining their relevance to this research programme. This phase identified a relevant questionnaire, the LMQ-1 as the original 60-item instrument, which was reported to measure medicine burden in the adult English population, but which required further development;[119] preliminary analyses of the LMQ-1 did not identify meaningful item-groupings in the questionnaire.

Phase 1b involved a large cross-sectional survey undertaken to pilot the LMQ-1 among people on long-term medicines recruited from community pharmacies and from public areas. This enabled preliminary item reduction to produce a 42-item interim version of the questionnaire (LMQ-2) reported in Chapter 4. However, this phase also identified gaps in the LMQ-2 instrument, which was found to be deficient of explicit statements on cost-related burden, and also had inadequate coverage of side effects and the social impact of medicine use. Therefore, subsequent work was needed to address these problems.

Phase 2 – Generation of new content and review of existing statements

Phase 2a involved generation of new statements to address the gaps identified from the analyses of phase 1b and review of the existing statements in the LMQ-2. New content was based on reanalysis of patient interview data, originally used to elicit concepts in the LMQ-1.[23] Alongside qualitative literature, free-text comments from survey participants in Phase 1b were also used for new item generation. Following new item addition and revisions, the interim instrument (a 58-item LMQ-2.1) was assessed qualitatively. Phase 2b comprised a qualitative study using cognitive interviews with the general public using long-term medicines. It was designed to evaluate face and content validity of the LMQ-2.1, enabling early identification and resolving potential questionnaire problems (such as misinterpretation of statements). The findings of phase 2 study are reported in Chapter 5.

Phase 3 - Final item reduction and construct validation

The remaining phases constituted a series of studies designed to assess different aspects of questionnaire validity and reliability (altogether referred to as psychometric testing). In Phase 3 (described in Chapter 6), final item reduction was conducted using on-line survey responses to the 58-item interim version (LMQ-2.1) completed by the UK general public on long-term medicines. Poorly performing items were eliminated which resulted in the final 41-item instrument (the LMQ-3). The LMQ-3 was statistically tested (by factor analyses) to verify and confirm underlying concepts (domains) to ascertain construct validity. Internal consistency of the LMQ-3 was also assessed in Phase 3.

Phase 4 -Criterion-related validation

In Phase 4 (described in Chapter 7), a criterion-related validation study was conducted using survey responses from patients on long-term medicines recruited via community pharmacies, GP practices, and outpatient clinics in south-east England. Criterion-related validation involved comparison of LMQ-3 scores with reference measures of treatment satisfaction (the TSQM-II) and health-related quality of life (EQ-5D-5L) respectively. Although criterion-related studies are traditionally used to validate a new questionnaire against a 'gold standard' measure of the same construct, the lack of a 'gold standard' measure of prescription medicine burden explains the use of alternative comparisons. Streiner and colleagues (2015) support verification of a new instrument against existing ones that are deemed 'maximally different',[118] but Chapter 2 highlighted possible relationships between the three constructs. This study phase was used to ascertain relationships between medicine burden and satisfaction with medicines and health-related quality of life, thus indirectly contributing to construct validation of the final questionnaire (LMQ-3).

Additionally, data from the Phase 4 (Chapter 7) study was reanalysed, together with data from Phase 3 (Chapter 6), to aid interpretation of LMQ scores, determine prevalence of medicine-related issues, and to understand predictors of medicine burden (described in Chapter 9). Known-groups validity of the LMQ-3, testing its ability to differentiate cohorts of patients with well-known treatment characteristics [118,120](e.g. number of medicines or formulation), was established, also reported in

Chapter 9. Known-groups analyses shed light on potential predictive validity of the LMQ-3, which relates to an instrument's ability to reveal associations or differences in certain variables in the hypothesised direction.

Phase 5- Stability testing (test-retest reliability)

To examine stability of scores and whether the LMQ-3 measures underlying concepts in a reproducible manner, Phase 5 studied the questionnaire's test-retest reliability (described in Chapter 8). The same participants completed the questionnaire on two different occasions with an average retest interval of two weeks to minimise recall of initial responses and to limit variations in participants' medicine use experiences over the study period.

Table 1-1 details characteristics of all study phases in this research programme.

	Phase	Timeline	Objective	Questionnaire property investigated/activities	Instrument (s) used (no. of items)	Instrument derived (no. of items)	Study design	Participants/ Setting	Thesis Chapter
Phase 1: Development phase (Instrument identification)	Phase 1a	Feb 2014-June 2014	To identify a measure of medicine burden	Instrument identification	NA	LMQ-1 (60 items)	Systematic literature review	15 studies included	Chapter 2
	Phase 1b	June 2014-December 2014	To assess the LMQ-1 and identify areas of improvement	- Preliminary item reduction (n=18 items) - Content coverage assessed & initial construct validity	LMQ-1 used (60 items)	LMQ-2 derived (42 items)	Cross-sectional survey (pilot study)	Adult members of the general public/ on-line recruitment across the UK/ face-to-face recruitment in Kent & Medway	Chapter 4
Phase 2: Development phase (New content generation)	Phase 2a	Mar 2015-May 2015	To revise the LMQ-2	-New item generation & review of existing items	LMQ-2 used (42 items)	LMQ-2.1 derived (58-items)	Secondary data & review of literature	Secondary data based on 21 patient interview transcripts, which informed LMQ-1 content, was reanalysed.[23]	Chapter 5
	Phase 2b	Jun 2015-Jul 2015	To assess face and content validity of an interim questionnaire version	- Readability & interpretability of new items & existing ones - Review of all items & rewording of some statements.	LMQ-2.1 used (58 items)	LMQ-2.1 derived (58 items)	Semi-structured cognitive interviews	Adult members of a public engagement group at the Medway School of Pharmacy/ face-to-face recruitment in Medway.	Chapter 5
Phase 3: Validation phase		Aug 2015-October 2015	To explore and confirm domains underlying the LMQ-3.	-Construct validity -Final item reduction	LMQ-2.1 used (58 items)	LMQ-3 derived (41 items)	Cross-sectional survey	Adult members of the general public/ on-line recruitment across the UK	Chapter 6
Phase 4: Validation phase		October 2015-Dec 2015	To examine the criterion-related validity of the LMQ-3.	-Criterion-related validity	-LMQ-3 (41-item) -TSQM-II (11 items) - EQ-5D-5L (5 items)	NA	Cross-sectional survey	Adults attending community pharmacies, GP practices & hospital outpatient clinics/ face-to-face recruitment in Kent & Medway	Chapter 7
Phase 5: Validation phase		Jun 2016-Aug 2016	To assess test-retest reliability of the LMQ-3.	Test-retest reliability	LMQ-3 used (41 items)	NA	Cross-sectional surveys	Adult public engagement group at the University of Kent/ on-line recruitment	Chapter 8

Table 1-1 Summary road map for my doctoral thesis

Chapter 2 Measuring medicine-related experiences from the patient perspective - a systematic review

Acknowledgments

The work presented in this chapter was published in Patient-Related Outcomes, and permission to reproduce it in this thesis was granted by the Journal on 21/11/2016. As the first author, I conducted all literature searches, synthesised and critically reviewed all primary data, and drafted early versions, compiled responses to the reviewers, and proofread the final published paper. The supervision team (JK and SC) and an external advisor (JR) reviewed and commented on early versions, and read and approved the final paper.

2.1 Introduction

In order to identify a patient-reported measure of medicine-related burden for use in the present research programme, a thorough, systematic, search of the literature was necessary. This chapter aimed to identify all potential generic measures of medicine-related experiences and to identify the most appropriate to measure medicine-related burden. By assessing content domains, comparing and summarising the development and/or validation processes across all instruments, the original Living with Medicines Questionnaire (LMQ-1) was identified, in this Chapter, as the only tool reported to assess medicine burden in the context of chronic illness and long-term medicine-only therapies. This work addressed the first research objective. Standard methodology was used to systematically search for relevant instruments across a range of databases using pre-defined inclusion criteria. Data abstraction was conducted by myself (BK) and double-checked by the supervision team. This chapter contributed to understanding of the literature on measurement of prescription medicine-related experiences, and highlighted the LMQ-1 instrument identifying its unique application, limitations and opportunities for further development.

2.2 Methods

2.2.1 Database search and search strategy

Multiple electronic databases were searched: Medline, Embase, PsycINFO, PsycARTICLES, the Cumulative Index to Nursing and Allied Health Literature (CINHAL Plus), and Google Scholar. A manual, free-text, search of the PROQOLID® (http://www.proqolid.org), a specific database that houses several patient-related measures was also conducted. Hand searching of bibliographies of relevant articles was undertaken to identify related articles. A 20-year search period, January 1995 to April 2015, was selected, based on the publication date of an early landmark measure of lay representations and beliefs about prescription medicines, the Beliefs about Medicines Questionnaire (BMQ).[110] This timeframe ensured relevant measures developed in the five years before publication of the BMQ[110] were included. A broad, but sensitive, key-word search strategy was employed to identify studies describing the development and/or validation of measures used to assess adults' medicine-related experiences. Categories of search terms were combined in a stepwise fashion and relevant search filters applied to specific publication dates. Sample categories and search terms used include [1] 'medicine' or 'medication' or 'drug' or 'prescription' [2] 'patient experiences' or 'experienc*' or 'view*' or 'perception*' or 'attitude*' or 'belief' or 'concern*'. Categories [1] and [2] were crossed with search terms in category [3]: 'questionnaire' or 'instrument' or 'tool' or 'scale' or 'measure' or 'survey*' or 'self-report' or 'patient reported measure' or 'develop*' or 'valid*'. Neither disease-conditions nor medicine-types were specified. Appendix 1 provides the full search strategy.

2.2.2 Inclusion and exclusion criteria

Studies which involved adults (age 18 years and over) using prescription medicines were reviewed, as children's ability to self-report their own experiences differ and instrument development processes may also vary.[121] Primary research studies using a generic (not disease- or treatment-specific), self-completion instrument on any aspect relating to medicine use experiences and describing questionnaire development and/or validation in a target population were included. Articles were published in

English. We excluded studies that: involved only children or adolescents; primarily reported use of over-the counter medicines or other therapies (e.g. diet, exercise, or any other aspect of self-care); described disease-, product- and/or device- specific measures; used clinician- or pharmacist-reported tools for drug-related problems; used tools assessing patients' ability to manage their medicines; described screening tools for assessing inappropriate prescribing; used side effects and ADR rating scales; satisfaction with pharmaceutical services; measures primarily assessing adherence; secondary validation studies, except if they reported a revised version of the instrument; cross-cultural (and language) adaptations of eligible questionnaires; and protocols for research.

2.2.3 Article retrieval, data extraction and analysis

All study titles and abstracts were reviewed, discarding duplicates. If eligible, the full-text article was scrutinised to check for the questionnaire and/or its items (questions). Additional searches were conducted if the questionnaire was not included in the primary article. Potentially relevant studies were screened for inclusion suitability and discussed among the research team (BK, SC, JK). Data extraction (by BK) from eligible articles was checked and supervised (by SC, JK) and regular discussions among all authors were held to resolve any issues. The initial literature search was conducted in April 2015, first updated in November 2015, and then in March 2017.

A data extraction form was used to collect the following study-specific information: sample size, study population and setting, country and language of origin; and questionnaire-specific information: name and purpose, number of items, content domain(s) and/or subscales, type of response scale, mode of administration and recall period (if specified). Questionnaire derivation (and the extent of direct patient involvement in item generation and testing) and validation methods were reviewed and psychometric properties, such as reliability and different forms of validity, assessed, in relation to published criteria.[122] Comparison of instruments included: domain coverage, development history, particularly patient involvement in item

generation, reliability and validity. Practical properties, such as completion time, were also examined where available.

Standards and guidance state that documentation of an instrument's development history is fundamental.[123,124] This includes item generation and testing of how well patients understand questionnaire items and response options and the appropriateness of the measure to the patient group,[125,126] helping to assess face and content validity, alongside researchers and expert panels.[122] Records of measurement (or psychometric) properties, particularly reliability and validity, also provide evidence that an instrument measures what it claims.[122–124] Other characteristics, such as mode of questionnaire administration and the time period over which a participant is requested to reflect (recall period), content domains, the number of items and their response options and the population and setting used also impact on instrument validity.[124]

Construct validation of underlying theoretical concepts and domains in a questionnaire can be conducted using different methods: scale analysis (through exploratory and/or confirmatory factor analysis, item-total correlations (adequate if > 0.20)[118,127] and floor-ceiling effects that explore lowest or highest possible scores); convergent- and discriminant (or divergent) validation, which explore relationships with conceptually similar and dissimilar reference instrument(s) respectively.[118,122,127] Correlations ≥ 0.3 may support convergent validity, whereas a trend of low correlations may infer discriminant validity.[118,127] Both convergent and discriminant validations are aspects of criterion-related validation, in which scores of new questionnaires (or those undergoing development) are compared with established ones (or 'gold standards'); correlations of at least 0.70 with a 'gold standard' measure may confirm criterion-related validity.[122] Other aspects of criterion-related validity, such as predictive validation, test an instrument's ability to predict associations or differences in certain variables in the expected direction.[128] Known groups validity examines an instrument's ability to differentiate cohorts of patients with well-known characteristics.[118,127]

2.3 Results

2.3.1 Identified generic measures of medicine use experiences

Fifteen articles described the development and/or validation of generic measures relating to the experience of using prescription medicines among adult patients. Of these, nine were multi-domain (3-10 domains), five of which examined satisfaction with different aspects of using medicines: three versions of the Treatment Satisfaction Questionnaire for Medication-TSQM (TSQM version 1.4,[108] TSQM II,[109] and TSQM-9[129]); the Treatment Satisfaction with Medicines Questionnaire (SATMED-Q[130]); and the Patient Satisfaction with Medication Management instrument (PSMM[131]). Other multi-domain instruments were: the Drug Therapy Concerns Questionnaire (DTC[132]); the Okere-Reiner Survey;[133] the Living with Medicines Questionnaire (the LMQ[119]); and the Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life (PROMPT-QOL[134]).

Six instruments covered only one domain, although some of these were divided into subscales by statistical analyses: a unidimensional measure of treatment burden (the TBQ[83]), a questionnaire assessing patients' attitudes to deprescribing or medicine cessation (PATD[64]), the Beliefs about Medicines Questionnaire (BMQ[110]), a measure of perceived sensitivity to medicines (PSM[135]), the Satisfaction with Information about Medicines Scale (SIMS[136]) and questionnaires looking at doctor-patient communication about medicines.[137]

Most of the questionnaires identified are self-administered on 3- to 10-point Likert-type scales. All instruments were multi-item, ranging from 5 to 60 items per questionnaire. The majority were developed in English, originating from the UK, USA and Australia, with only three[83,130,134] from non-English speaking countries: Spain, France and Thailand. Table 2-1 summarises the characteristics of the 15 instruments

Instrument	Focus	Study population / setting	No. of items and subscales	Response scale	Administration mode / Recall period	Original language/ Country
BMQ[110]	Patients' beliefs about medicines	Chronically ill patients, aged 45-64 years , using ≥ 1 regular prescription medicine / hospital clinics	18 items in 4 subscales	5-point Likert-type scale (strongly agree to strongly disagree)	Self-completion	English/ UK
SIMS[136]	Patient satisfaction with medicine information	Chronically ill patients, aged 46-68 years, using ≥ 1 regular prescription medicine / hospital clinics & wards	17 items in 2 subscales	5-point Likert-type scale (too much, about right, too little, none received & none needed)	Self-completion	English/ UK
Jenkins et al[137]	Doctor-patient communication about medicines	Patients with a doctor consultation / general practice	12-20 items for pre- and post-consultation questionnaires.	3-point Likert type scale (agree, disagree, uncertain/no response)	Self-completion	English/ UK
DTC[132]	Patients' perceptions of medicine-related problems	Adults, average age 69 years, using 5 (± 3.4) prescription medicines / community pharmacies & general public	25 items in 5 subscales	5-point Likert-type scale (strongly agree to strongly disagree)	Self-completion	English/ USA
TSQM (v. 1.4)[108]	Patient satisfaction with medicines	Chronically ill adults, mean age 50 years, using regular medicines / general public	14 items in 4 subscales	5- and 7-point Likert-type scales & a yes/no response	Self-completion / 2-3 weeks, or since last use	English/ USA

Table 2-1 Characteristics of reviewed generic measures of medicine-related experiences

Instrument	Focus	Study population/ setting	No. of items and subscales	Response scale	Administration mode / Recall period	Original language/ Country
TSQM II[109]	Patient satisfaction with medicines	Adult outpatients, using new prescription medicine(s)/ Community pharmacy	11 items in 4 subscales	5- and 7-point Likert-type scales (e.g. Extremely Dissatisfied to Extremely Satisfied) & a yes/no response	Self-completion / 2-3 weeks, or since last use.	English/ USA
TSQM-9[129]	Patient satisfaction with medicines	Adult hypertensive patients, average age 55 years, on prescribed medicines/ general public	9 items in 3 subscales	7-point Likert-type scale (extremely dissatisfied to extremely satisfied)	Self-completion /2 -3 weeks, or since last use	English/ USA
SATMED-Q[130]	Patient satisfaction with long-term medicines	Adult outpatients, with chronic condition, in receipt of ≥ 2 months of treatment/ hospital & general public	17 items in 6 subscales	5-point Likert-type scale (Not at all, a little bit, somewhat, quite a bit, very much)	Self-completion / one month	Spanish/ Spain
PSMM[131]	Patients' perceptions of medicine management	Adult inpatients/ hospital setting	9 items in 3 domains	Likert-type: poor to excellent, much worse to much better, or strongly disagree to strongly agree (number of options not given)	Self-completion	English/USA
TBQ[83]	Treatment burden among multi-morbid patients.	Adults, of mean age 59, using average of two medicines daily/ hospital & general practitioner clinic	14 items: an open question, & 13 items in one scale	0 to 10scale (ranging from no burden to considerable burden)	Self-completion	French/ France

Table 2-1 Characteristics of reviewed generic measures of medicine-related experiences

Instrument	Focus	Study population/ setting	No. of items and subscales	Response scale	Administration mode / Recall period	Original language/ Country
PATD[64]	Attitudes to deprescribing (desire, willingness, attempt to stop/reduce medicine use)	Adults with multiple chronic conditions, using ≥ 1medicine/ hospital	15 items (number of subscales not known)	10 items have a 5-point Likert-type scale (strongly agree to strongly disagree 4 MCQs & one item has pictorial response options.	Self-completion	English/ Australia
PSM[135]	Perceived sensitivity to medicines and their adverse effects	HIV & hypertension patients, those on travel vaccination & students /general practices, travel clinics & university	5 items in one scale	5-point Likert-type scale (strongly disagree to strongly agree)	Self-completion	English/ UK and New Zealand
The Okere-Reiner Survey[133]	Perceived medicine knowledge, and self-confidence in using medicines.	Adult inpatients, of mean age 48 years, using ≥ 1 prescription medicine / hospital	7 items in 3 subscales	5-point Likert-type scale (strongly disagree to strongly agree)	Self-completion & interviewer administered	English/ USA
LMQ[119]	Medicine-related burden.	Adults, using one or more long-term medicines/ hospital, community pharmacy, & general public	60 items in 8 domains	5-point Likert-type scale (strongly agree to strongly disagree)	Self-completion	English/ UK
PROMPT-QoL[134]	Pharmaceutical therapy-related quality of life	Adult outpatients, using regular medicines for ≥ 3 months/ hospital	43 items in 10 domains:	5- and 4-point Likert-type scales (range of options not clarified)	Self-completion	Thai/ Thailand

Table 2-1 Characteristics of reviewed generic measures of medicine-related experiences

Acronyms: BMQ, Beliefs about Medicines Questionnaire; SIMS, Satisfaction with Information about Medicines Scale; DTC, Drug Therapy Concerns Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication; SATMED-Q, Treatment Satisfaction with Medicines; PSMM, Patient Satisfaction with Medication Management instrument; TBQ, Treatment Burden Questionnaire; PATD, Patients' Attitudes Towards Deprescribing; PSM, Perceived Sensitivity to Medicines questionnaire; LMQ, Living with Medicines Questionnaire; PROMPT-QoL, Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life; MCQs, Multiple Choice Questions

Content domains

The 15 instruments covered a wide range of domains (Table 2-2), described by authors as: effectiveness; convenience, practicalities and/or managing medicines; information, knowledge and/or understanding; side effects; relationships and/or communication with health professionals; impact on daily living and/or social life; general satisfaction; attitudes; beliefs, concerns, and/or perceptions; medical follow-up and/or adherence-related issues; treatment- and/or medicine-related burden, perceived control or autonomy; self-confidence about medicine use; availability and accessibility; and medicine-related quality of life; these may reflect most issues that affect people using regular medicines.

Content area	BMQ[110]	SIMS[136]	Jenkins et al[137]	DTC[132]	TSQM (V 1.4)[108]	TSQM (V.II)[109]	TSQM-9[129]	SATMED-Q[130]	PSMM[131]	TBQ[83]	PATD[64]	PSM[135]	Okere-Reiner Survey[133]	LMQ[119]	PROMPT-QoL[134]	N
Effectiveness				✓	✓	✓	✓	✓						✓	✓	7
Convenience, practicalities and/or managing medicines					✓	✓	✓	✓	✓					✓	✓	7
Information, knowledge &/or understanding		✓		✓					✓				✓	✓	✓	6
Side effects					✓	✓		✓						✓	✓	5
Relationships and/or communication with HCPs about medicines			✓						✓					✓	✓	4
Impact on daily living								✓		✓				✓	✓	4
General satisfaction					✓	✓	✓	✓								4
Attitudes											✓			✓	✓	3
Beliefs, concerns and/or perceptions	✓			✓								✓				3
Medical follow-up, monitoring, or adherence issues				✓				✓		✓						3
Treatment or medicine-related burden										✓				✓		2
Perceived control/autonomy														✓		1
Self-confidence													✓			1
Availability & accessibility of therapy															✓	1
Medicine-related quality of life															✓	1

Table 2-2 Comparison of content areas covered by items in reviewed generic measures of medicine-related experiences

Abbreviations: BMQ, Beliefs about Medicines Questionnaire; SIMS, Satisfaction with Information about Medicines Scale; DTC, Drug Therapy Concerns Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication; SATMED-Q, Treatment Satisfaction with Medicines; PSMM, Patient Satisfaction with Medication Management instrument; TBQ, Treatment Burden Questionnaire; PATD, Patients' Attitudes Towards Deprescribing; PSM, Perceived Sensitivity to Medicines questionnaire; LMQ, Living with Medicines Questionnaire; PROMPT-QoL, Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life; N- No. of instruments covering domain or area. HCPs- healthcare providers

2.3.2 Patient involvement in item generation

For the majority of instruments, item generation was based on the literature. Some incorporated patients' views but indirectly. Only seven measures had evidence of being developed using direct patient input: five employed patient interviews as the primary source of questionnaire items (BMQ,[110] PSMM,[131] TBQ,[83] LMQ[119] and PROMPT-QOL[134]) and two focus groups (SATMED-Q[130] and TSQM version 1.4[108]). Several were judged to emphasise the perspective/opinions of researchers or health professionals over those of patients (Jenkins' instrument,[137] SIMS,[136] and DTC[132]). Table 2-3 compares the different methods employed in item generation and testing.

Method(s)	BMQ[110]	SIMS [136]	Jenkins [137]	DTC [132]	TSQM (V1.4) [108]	TSQM (V.II) [109]	TSQM -9[129]	SATMED-Q[130]	PSMM [131]	TBQ[83]	PATD [64]	PSM [135]	Okere-Reiner Survey [133]	LMQ [119]	PROMPT-QoL [134]
Item generation															
Literature	✓	✓		✓	✓			✓		✓	✓		✓		✓
Patient involvement (via interviews/ focus groups/ feedback /comments from consultations)	✓		✓		✓	✓		✓	✓	✓	✓	✓		✓	✓
Expert opinion, including health professionals or other care providers				✓				✓	✓	✓	✓	✓			
Developed from existing instrument (s).			✓			✓	✓								
Emphasis on researcher/health professional perspective		✓	✓	✓							✓				
Item clarification –face and/or content validation															
Patient involvement (via interviews/focus groups/surveys/comments from consultations)				✓	✓			✓			✓			✓	✓
Expert opinion, including health professionals or other care providers									✓	✓	✓		✓		✓

Table 2-3 Methods employed in item generation and testing of reviewed generic measures of medicine-related experiences

Note: ✓ indicates the method was used

Abbreviations: BMQ, Beliefs about Medicines Questionnaire; SIMS, Satisfaction with Information about Medicines Scale; DTC, Drug Therapy Concerns Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication; SATMED-Q, Treatment Satisfaction with Medicines; PSMM, Patient Satisfaction with Medication Management instrument; TBQ, Treatment Burden Questionnaire; PATD, Patients' Attitudes Towards Deprescribing; PSM, Perceived Sensitivity to Medicines questionnaire; LMQ, Living with Medicines Questionnaire; PROMPT-QoL, Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life.

2.3.3 Reliability

The vast majority of instruments were assessed for internal consistency (Table 2-4), mostly using Cronbach's alpha with some reporting test-retest reliability as intra-class correlation coefficient (ICC), and correlation coefficients (r); values ≥ 0.7, obtained from a sample size of at least 50 patients, are advisable.[122] One study[134] employed Rasch analysis to estimate person and item reliabilities (acceptable values > 0.8 and 0.9 respectively), which assess an instrument's ability to distinguish between high and low patient scores, and the level of item difficulty respectively.[138]

2.3.4 Scale analysis and construct validity

Most instruments employed exploratory techniques for scale analysis (Table 2-4). However, only a few employed confirmatory methods ascertaining underlying content domains and/or their relationships: TSQM II, TSQM-9, SATMED-Q, BMQ, and the Okere-Reiner Survey.

2.3.5 Criterion-related, convergence and/or discriminant validity

Criterion-related, convergence and/or discriminant validity were variably reported by only eight instruments: TSQM (version 1.4), TSQM II, SATMED-Q, TBQ, SIMS, BMQ, PSM, PATD (Table 2-4). The BMQ[110] and earlier versions of the TSQM[108,109] were the most commonly used criterion-referenced instruments. For instance, in validating the SIMS,[136] patients with stronger concerns about medicines as measured by the BMQ, were more likely to be less satisfied with their medicine information. Patients with more medicine-related concerns, or beliefs about harm, are reported to not only be less trustful of their medicines but also to desire alterations to their regimes or avoid them.[110] In the development of the PSM scale,[135] scores on the 'concerns' subscale of the BMQ indicating negative beliefs about medicines were significantly associated with perceived sensitivity to medicines ($r=0.5$, $p<0.001$). Negative moderate correlations ($r=-0.56$, $p<0.001$) were reported between scores on BMQ items relating to 'necessity of current medications' and scores on the PATD. However, the sample

size used in this study (n=51) was inadequate to validate the measure of patient attitudes to medicine cessation.[64]

Ruiz et al[130] examined associations between SATMED-Q scores and the Spanish version of the TSQM (v.1.4); significant correlations (range, 0.58-0.68, p<0.0005) were reported between subscales assessing similar domains: treatment effectiveness, side effects, convenience and global satisfaction.[130] During validation of the TBQ, Tran et al[83] established a negative relationship between treatment burden and treatment satisfaction assessed using the TSQM Version II; moderate negative correlations between TBQ scores and TSQM global satisfaction and convenience subscales (r=-0.41 and r=-0.53 respectively) and weak negative correlations (r=-0.26) between TBQ scores and TSQM efficacy subscale. Treatment burden was significantly higher among patients who had experienced side effects compared to those who had not.

Satisfaction with medicines is positively associated with adherence.[129] While validating the TSQM-9,[129] moderate correlations (range, 0.34-0.46) were reported between convenience, effectiveness and global satisfaction TSQM-9-subscale scores, and the Modified Morisky scale,[139] which measures adherence. Weak correlations (range 0.09-0.22) were reported between SATMED-Q scores and Morisky-Green adherence questionnaire scores,[140] several failing to reach statistical significance.

2.3.6 Known-groups and predictive validity

Known-groups validity was reported for six measures: BMQ, TSQM (v.1.4); TSQM II, TSQM-9, TBQ, and the Okere-Reiner Survey (Table 2-4). The Okere-Reiner Survey was reported to 'clearly distinguish between patients with good and poor perceived knowledge or confidence or satisfaction.'[133] Least reported was predictive validity (Table 2-4). The BMQ was reported to adequately distinguish patients with different illnesses and treatments[110] and to predict adherence to therapy.[112]

In validating the TSQM (v.1.4), Atkinson et al[108] tested associations between medicine types and routes of administration and satisfaction levels on all four subscales; patients using parenteral medicines were least satisfied with convenience and side

effects, while oral medicines were rated highly on overall satisfaction and convenience.[108] Similarly, Ruiz et al[130] reported significantly lower satisfaction for convenience for parenteral routes of administration compared to oral and inhalation routes. Treatment satisfaction assessed by TSQM-9 was significantly greater among 'medium compliers', measured by the modified Morisky scale,[139] compared to 'low compliers' ($p<0.0001$). Tran et al reported significantly higher scores among patients with high treatment burden, measured by the TBQ, compared to those with low or moderate treatment burden, on specific items relating to treatment workload.[83] Patients with 'high burden' needed an average of 43 minutes/week to organise their medicines compared to 17 minutes/week required by 'low burden' patients ($p<0.0001$).[83]

Instrument	Reliability Internal consistency (Cronbach's alpha/ r)	Test-retest reliability/ ICC or r (sample size)	Validity Criterion-related, convergence and/or discriminant validity/ reference instrument (s)	Scale analysis	Predictive validity	Known-groups validity
BMQ[110]	✓ Specific-Necessity (0.55 -0.86) Specific-Concerns (0.63 -0.80) General-Overuse (0.60 -0.80) General-Harm (0.47-.83)	✓ 0.60- 0.78 (n=31)	✓Illness Perception Questionnaire, the Reported Adherence to Medication scale, the Sensitive Soma Scale, and items on medication-related thoughts	✓ EFA & CFA confirmed two BMQ scales	✓ Reported else where[112]	✓
SIMS[136]	✓ 0.81-0.91	✓ 0.67-0.76 (n=72)	✓ BMQ The Medication Adherence Report Scale- MARS			
Jenkins et al[137]	NR		NR	NR	NR	NR
DTC[132]	✓ 0.76-0.82			✓EFA revealed 5 subscales; a revised, 9-item, version confirmed unidimensional structure.[115]		
TSQM (version 1.4)[108]	✓ 0.85-0.87		✓ Tested associations among medicine & illness characteristics with treatment satisfaction	✓ EFAs revealed a 4-dimensional structure.	✓	✓
TSQM II[109]	✓ 0.88-0.94		✓	✓ EFA & CFA -confirmed an overarching global satisfaction domain with three subdomains		✓
TSQM-9[129]	✓ 0.84-0.92	✓ Effectiveness ICC=0.784 [95% CI: 0.757-0.811] Convenience: 0.737 [0.704-0.768] Global satisfaction 0.759 [0.729, 0.788](n=396)	✓ Modified Morisky scale	✓ CFA/SEM confirmed relationships among 3 underlying constructs of the TSQM-9		✓

Table 2-4 Psychometric properties of questionnaires included in the review

	Reliability		Validity			
Instrument	**Internal consistency (Cronbach's alpha/ r)**	**Test-retest reliability/ICC or r (sample size)**	**Criterion-related, convergence and/or discriminant validity/ reference instrument (s)**	**Scale analysis**	**Predictive validity**	**Known-groups validity**
SATMED-Q[130]	✓ 0.813-0.912	✓r = 0.945 ICC= 0.943 [95% CI 0.928–0.957] (n=128)	✓ Spanish TSQM (version 1.4) Morisky- Green Questionnaire	✓ EFA & CFA revealed a six-dimensional structure		
PSMM[131]	✓ 0.63-0.87			✓EFA revealed a 3-factor structure		
TBQ[83]	✓ 0.7-0.95	✓ICC=0.75[95% CI 0.65-0.83] (n=182)	✓ TSQM II	✓EFA revealed a unidimensional structure		✓
PATD[64]	✓ r = -0.560 inverse correlation between 2 related items	✓ Percentage agreement of 60–93% (n=10)	✓ BMQ Specific-Necessity			
PSM[135]	✓ 0.79–0.94	✓ r = 0.89 (n=52)	✓ BMQ & HADS		✓	
Okere-Reiner Survey[135]	✓ 0.744-0.833			✓ EFA & CFA revealed & confirmed 3 subscales		✓
LMQ[119]	✓ Values NR	✓ Values NR		EFA & CFA revealed a 10-dimensional version[141]		
PROMPT-QoL[134]	✓Item & person separation reliabilities range 0.52-0.96			✓ Rasch analysis suggested 10 domains		

Table 2-4 Psychometric properties of questionnaires included in the review

Note: ✓ indicates the test was conducted. EFA – exploratory factor analysis and methods such as principal components analysis
Abbreviations: NR-Not reported; CFA—confirmatory factor Analysis; SEM- Structural Equation Modeling; BMQ, Beliefs about Medicines Questionnaire; SIMS, Satisfaction with Information about Medicines Scale; DTC, Drug Therapy Concerns Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication; SATMED-Q, Treatment Satisfaction with Medicines; PSMM, Patient Satisfaction with Medication Management instrument; TBQ, Treatment Burden Questionnaire; PATD, Patients' Attitudes Towards Deprescribing; PSM, Perceived Sensitivity to Medicines questionnaire; LMQ, Living with Medicines Questionnaire; PROMPT-QoL, Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life. HADS- Hospital Anxiety and Depression Scale.

2.3.7 Summary characteristics of measures of medicine-related experiences

Of the 15 generic measures of medicine-related experiences, six covered multiple domains and were developed with direct patient involvement, particularly in the item generation phase, tested for any forms of reliability (as internal consistency, test-test, and/or person/item reliability), and/or attempted to confirm construct validity by any means. These were: TSQM (including the 14-item, 11-item, and 9-item versions), SATMED-Q, PROMPT-QOL and LMQ. However, validity was reported using different methods and to different extents for all these measures, and most authors acknowledge the need for further developmental and/or validation work. None of the identified questionnaires covered all domains or considered potential financial burden of medicines in-depth.

The BMQ, one of the earliest, domain-specific, measure of beliefs about medicines,[110] has been used widely to understand many aspects of medicine use, especially adherence-related behavior.[142] The DTC questionnaire[132] serves as a potentially useful tool for eliciting patients' perceptions and concerns about of medicine-related problems; however, it lacked patient involvement in item generation phases of its development. The domain-specific PSM scale[135] may be useful for studies evaluating concerns about potential adverse effects of medicines. Measures of satisfaction with different aspects of medicine use,[108,109,129–131] including information needs,[136] are also predominant. The Okere-Reiner Survey[133] is a short measure of patients' knowledge and self-confidence with medicine use, the latter aspect not being included in other instruments, which play an important role in the medicine use experience; however, it was not derived directly from patients despite testing instrument reliability and validity. The PSMM,[131] an instrument reported to measure patients' perceptions of medicine management, is prescriber-centered and focused on service evaluation, despite being derived directly from patient interviews and including relevant issues. For instance, it considers the practicalities of managing regularly-used medicines while in hospital, medicine information, understanding and patient-provider communication about medicines. The latter aspect was the subject of the scale developed by Jenkins and colleagues.[137] The PATD questionnaire[64] considers deprescribing (medicine cessation), and may be used to gain insight into patient preferences or dissatisfaction

with medicine regimes; however, further validation of this instrument is also necessary, as it was developed from the perspective of health professionals and evaluated in only a few patients. Although domain-specific and not solely focused on medicine-therapeutic interventions, the TBQ[83] is potentially useful in assessing treatment burden among multi-morbid patients. Two broad, patient-generated, multi-domain measures, the PROMPT-QOL[134] and the LMQ,[119] may provide insight into measurement of multiple, albeit complex, issues surrounding regular medicine use; however, both require further psychometric testing (and/or cross-cultural adaptation) for potential use in research or practice.

2.4 Discussion

To my knowledge, this is the first review of generic measures of adult patients' experiences of using prescription medicines. Most of the 15 instruments identified could potentially be used in patients with multi-morbidity, using a wide range of medicines, allowing comparison of experiences across different patient groups. However, those which instruct respondents to focus only on one medicine[130] would require modification. Only a few directly involved patients in item generation and further validation work is needed, particularly for those instruments covering multi-dimensional aspects of medicine use.

Collectively, the domains covered probably reflect most issues that affect people using regular medicines. However, none covered all domains – an important omission if a whole patient-centered understanding of medicine experiences is to be quantified.

Notably, none of the instruments considered the potential financial burden of using prescription medicines in any depth. One of the broad instruments, PROMPT-QOL, includes one item on 'medication and travel expenses'[134] which is limited as an assessment of cost-related burden. An item in the PATD questionnaire: *'having to pay for less [fewer] medications would play a role in my willingness to stop one or more of my medications'*,[64] only focusses on cost-related cessation. One recently-developed, 10-item, domain-specific measure of cost-related medicine burden in the USA population[52] explores this issue in isolation. However, it was not included in this review as half the statements relate to non-adherence (e.g. cost-related delays in refilling

prescriptions and skipping or reducing doses).[52] There remains a need for instruments that incorporate and assess cost-related issues alongside other dimensions of the medicine use experience.

Overall satisfaction with medicines could be regarded as a potentially key, over-arching domain, which is influenced by many of the other domains covered by these instruments and was the main focus of several questionnaires. Of the generic instruments, TSQM (versions 1.4 and II)[108,109] and SATMED-Q[130] seem promising for evaluating aspects of medicine use which impact on satisfaction. However, both have been criticised as circumscribed and lacking in 'psychological domains, such as worry, fear, or concerns', relating to the medicine use experience.[134]

Patient satisfaction with treatment (and medicines) is positively associated with persistence and adherence to therapy,[143] but negatively associated with treatment burden.[83] Life-long medicine use can be burdensome to some patients,[23,49,144] and may impact negatively on health-related quality of life. As already noted in Chapter 1 (section 1.8), research attempting to describe the burden (or negative experience) of using medicines has done so under the 'umbrella' of treatment burden,[48,85,89] which may represent unshared patient experiences that are not fully addressed during consultations.[101] However, measures of treatment burden are currently limited, as reported in a review by Eton et al (2013).[120] In contrast to the present review, Eton focused on the overall burden of healthcare activities particularly patients' workload of self-care. An instrument addressing the need for such a measure, the TBQ,[83] includes some aspects of medicine-related burden, as well as impact or restriction of daily activities and social life. A potentially useful multi-domain measure of medicine burden is the LMQ,[119] which also requires further psychometric testing.

Communication and relationships with healthcare providers was an aspect of medicines use included in a number of the instruments, including the two broadest, patient-centered measures, PROMPT-QOL[134] and LMQ,[119] emphasising the potential contribution of this domain to satisfaction and treatment burden. The PSMM questionnaire[131] also includes patient-provider communication problems, for instance perceived patient-burden following repetitive questioning about medicine-history,

often by multiple providers, and ineffective flow of medicine-related information among health professionals. Most measures of patient satisfaction with consultations and patient-provider relationships[145–147] do not focus on medicine-related communication, hence the instrument developed by Jenkins et al (2003)[137] is potentially valuable. Two other instruments, the SIMS[136] and the Okere-Reiner Survey,[133] also cover medicines information transfer. The SIMS focuses on this exclusively and is founded on pharmaceutical industry literature, with minimal patient involvement, While the Okere-Reiner Survey measures medicine-related knowledge and understanding, but again had little patient involvement during its' development.

Many other instruments reviewed were essentially uni-dimensional, with variable patient involvement in development. As already noted, the BMQ, which assesses psychological beliefs and concerns about the necessity and safety of medicines,[110] has been extensively used in adherence-related studies.[113,142,148] The PSM scale covers only patient concerns about potential adverse effects of medicines,[135] while the PATD was developed to measure patients' attitudes to cessation of medicines,[64] thus seeks to predict behavior. Like most instruments assessing inappropriate prescribing,[19] PATD questionnaire development seemed to emphasise the clinician's perspective, rather than the patient perspective. Moreover, deprescribing itself is criticised as a clinician-driven agenda, which aims to reduce medicine usage and health-system costs.[65,67] The DTC questionnaire is broader, including concerns about adverse drug reactions, as well as regimen complexity, overmedication and use of prescription medicines,[132] but also based on the clinician perspective.

A further instrument, developed in Taiwan and published since the literature review was completed, claims to measure Medication-Related Quality of Life,[149] a term originally adopted for the LMQ.[150] This instrument was developed based on subjective well-being scales plus patient interviews and consists of 14 items, covering only three domains, role limitations, self-control and vitality.[149] Only the first of these relates directly to medicines burden, as discussed in this review, therefore this instrument too is limited.

Most instruments included in this review were developed and tested in a specific language and in specific demographic settings and, with some exceptions, have not been tested in other situations. Therefore cross-cultural adaptations and/or further testing may be required prior to use in particular clinical or research settings. Given the psychometric properties of the reviewed instruments, there is a need for further development and/or validation of the existing multi-dimensional, generic, patient-generated, measures of experiences of using prescription medicines among adult patients living with chronic illness.

Study strengths & limitations

Owing to the heterogeneity of studies and reported results, data could neither be evaluated methodologically (as with most systematic reviews) nor collated for meta-analysis. Although relevant guidelines were used to critique the reported measurement properties of questionnaires,[122] I did not set out to report an overall quality score for the instruments and their methodological study designs, particularly as many of the instruments were developed long before the recently recommended quality-scoring criteria.[151–153] Therefore, this review employed a descriptive style to compare characteristics, content areas, questionnaire-derivation and validation processes across reviewed measures. It excluded all disease-, product- and/or device-specific instruments, pharmaceutical service evaluations, clinician- and pharmacist-led screening tools for medicine-related problems, including ADRs, tools assessing patients' abilities to manage their medicines, adherence-focused tools, and cross-cultural (and language) adaptations of eligible questionnaires, even though they may have considered key aspects of the medicine use experience. It did include measures of satisfaction with various aspects of medicine use, despite concerns that measuring patients' experiences in terms of satisfaction may introduce acquiescence bias. Although an organised and broad literature search was conducted across multiple databases, it is possible that a few generic instruments reporting certain aspects of medicine-related experiences may have been missed. Appropriate search strategies were designed to minimise the likelihood of this.

2.5 Chapter summary

This chapter identified the LMQ (relabelled as LMQ-1 to clarify subsequent versions) as a potential measure of medicine burden, which however required further validation. This chapter also revealed a scarcity of generic, patient-generated, psychometrically sound, comprehensive measures of the medicine use experiences of adult patients. Moreover, there is insufficient evidence for the routine use of existing measures in clinical practice. Therefore, there is a need for further development and/or validation of existing patient-derived, multi-domain, instruments, particularly the LMQ-1.

Although the PROMPT-QOL was the broadest (10-domain), patient-generated, instrument reported in this Chapter, it was designed as an 'HRQOL measure for medication management'[134] which is a separate concept that may overlap with medicine burden,[92] at least on face value. Moreover, the PROMPT-QOL was developed and tested among adult outpatients in Thailand, where the health systems differ considerably from the English NHS. It would therefore require considerable cross-cultural adaptation for it to be used in the English sample populations included in this research programme. The only instrument reported to measure the intended construct, medicines burden, the LMQ (relabelled the LMQ-1), was adapted for use in this research programme. As a multi-dimensional instrument, the LMQ-1 is a generic patient-generated measure that was reported to evaluate the negative impact of medicine interventions. Such a measure could facilitate the identification of patients who find using long-term medicines a challenging experience. There is, therefore, a need to develop further and fully validate the LMQ-1 as the most suitable patient-generated instrument identified through this systematic review, to facilitate such use.

As the need to develop a new instrument is evident, adding key, albeit deficient, content domains to the existing multidimensional measure (i.e. the LMQ) may support a more comprehensive assessment of medicine use experiences (and associated burden) among those living with chronic illness. The next chapters constitute a series of studies designed to assess and validate the LMQ-1. Chapter 3, in particular, discusses the methodological approach to further development and validation of the LMQ-1, a brief synopsis of which was provided at the end of Chapter 1.

Chapter 3 Methodology, methods, and research design

3.1 Introduction

This chapter presents the research methodology (and paradigm), methods of data collection and analysis procedures, and their theoretical underpinning. Specific tools (and questionnaire versions) employed in the development and validation of the Living with Medicines Questionnaire (LMQ) are also clarified. Briefly, I provide a rationale for the relatively complex (and iterative) process of designing and evaluating a patient-reported measure specific to prescription medicine use experiences.

According to Streiner et al (2015) [118] and other guidelines,[123,124] new patient-reported measures intended for use in research or clinical settings should undergo rigorous development and validation processes. Some of these processes (including item generation and testing) were illustrated in the previous chapter (See Table 2-3), which indicated variations in pathways for questionnaire development and validation. There is standard guidance on patient-reported measures recommended by regulatory agencies, including that by the US Food and Drug Administration[124] and the European Medicines Agency (EMEA).[154] Though restricted to clinical trial contexts and drug development, this guidance emphasises thorough evaluation of the measurement properties of patient-reported tools including content and construct validation, and reliability assessment via qualitative and quantitative methodologies. Such evaluation may help avoid unintended outcomes arising from decisions based on the measure, e.g. where scores on the instrument may determine whether or not an individual receives a health intervention.[118] Thus, it was vital to carefully develop and validate the LMQ while drawing on recommendations from standard guidance and current practices in psychometrics.

The next subsection briefly outlines the methodological approach adopted.

3.2 Methodology

3.2.1 Pharmacy practice research

Pharmacy practice research, a speciality within the broader area of health services research,[155] aims to understand 'how and why people access pharmacy services, the costs of pharmacy services, and the outcomes of patients as a result of using these services'.[156] Besides clinical and economic outcomes, broader definitions encompass humanistic aspects of pharmacy practice research relating to patient beliefs, attitudes, values, experiences, and practices.[157] With a gradual paradigm shift to patient-centred care, there is a need to understand the patient's perspective, and within pharmacy practice research studies increasingly seek to elicit patient and societal perspectives of medicines use.[21,81,158] This doctoral programme is highly relevant to pharmacy practice research as it aimed to investigate the patient perspective on medicine use, by developing (and testing) a tool to evaluate medicine use experiences.

3.2.2 Traditional research paradigms

This subsection briefly discusses philosophical assumptions and approaches (paradigms) to research, so as to clarify the methodological positioning of my own research. Research philosophy in the context of pharmacy practice research is not well demarcated.[158] Nevertheless, it is surrounded by complex philosophical terminology rooted in social sciences, particularly epistemology that relates to knowledge theories (and justified beliefs) that inform research methodology and data generation.[158] Research paradigms can take on two contrasting assumptions on a continuum: positivism (or empiricism) on the far left, interpretivism (constructivism or phenomenology or anti-positivism) on the far right, and pragmatism (subtle realism) somewhere in the middle.[155,158,159] Although these paradigms cannot be exhaustively discussed here, their tenets are highlighted.

Positivists (empiricists) believe in objectivity and measurability of phenomena with notions that 'people and social structures can be studied scientifically…'.[156] Early pharmacy practice research assumed a positivistic perspective, in which predominant frameworks were used to derive 'universal laws',[155] akin to biomedical research, assuming generalisability of findings, through quantitative methods of data collection and analysis.

Interpretivists (and phenomenologists) recognise subjectivity of phenomena[156] and explore, in-depth, people's views, thoughts and lived experiences primarily through qualitative methods (such as interviews, document analysis).[157] Regardless, purely qualitative findings may not establish whether or not lived experiences are typical, possibly due to the small samples employed. Also, highly qualitative data may pose practical challenges for end-users other than researchers (e.g. patients or practitioners) in terms of presentation of data.

3.2.3 Rationale for choosing pragmatism and mixed-methods

For this research programme, pragmatism was considered the most suitable standpoint. Pragmatism is increasingly recognised as a valuable approach in health-related research, and has been embraced by recent pharmacy practice researchers.[158] Pragmatism is a more flexible research paradigm uncommitted to unidimensional viewpoints (and single-method designs) of positivists or interpretivists/phenomenologists. As a philosophical framework underpinning mixed-methods research, pragmatism employs both quantitative and qualitative methods (such as interviews and questionnaires) for data collection and analysis to understand the research problem.[157] As a practical, problem-centred, and outcome-oriented paradigm, pragmatists adapt methods suited for addressing research questions or objectives.[159]

This research programme aimed to develop and validate a tool for exploring medicine-related experiences (and burden) in adults using long-term medicines. As described in Chapter 1, the concept of medicine burden is relatively new, and adapting methodology to evaluate the hypothesised construct and to devise a suitable measure was relevant. In choosing a pragmatic approach, multiple techniques were used to generate, revise, and test items in the LMQ.

Qualitative interview data from patients using long-term medicines was used by the originators of the 60-item LMQ, which was reported in the previous chapter. [23,119] In this research programme, qualitative cognitive interviews helped to clarify meanings and interpretations of LMQ statements, from the patients' perspective.

Through other forms of qualitative data (free-text comments in surveys), the patient's voice (as views, experiences, or feelings) was captured and represented in a language used by and understood by people on long-term medicines.

Quantitative methods, by cross-sectional surveys, were predominantly used to evaluate the questionnaire's measurement properties (such as reliability and validity). For instance, construct validation used quantitative data to determine which items (or groups of items) were measuring specific aspects of medicines use (e.g. medicine-related interferences with day-to-day life), and to investigate whether all LMQ domains measured aspects of medicine burden and to what extent. A pragmatic and mixed-methods approach has been endorsed in the development of patient-reported measures, and is illustrated by Winit-Watjana[158] as the approach used in the development of a measure of medicine-related quality of life (the PROMPT-QoL).[134] Thus, a pragmatic stance helped achieve the aims of this doctoral research by triangulating multiple methods including data from literature reviews, surveys, and interviews.

3.3 Methods

3.3.1 Ethical considerations and approvals

Ethics approval was granted for each phase of study. Phases that involved the general public were approved by the Medway School of Pharmacy, which has its own ethics review committee. The National Research Ethics Service (NRES Committee South Central - Oxford C) approved the Phase 4 study (reported in Chapter 7) to allow access to patients in NHS sites in Kent and Medway areas. Relevant procedures for research governance at different research sites were followed, including obtaining letters of access. At all phases of research, explicit research protocols, compiled a priori, were adhered to.

While undertaking all the individual research studies, participant respect, confidentiality, information provision, and encouraging voluntary participation was guided by the International Conference on Harmonisation (ICH) guidelines for good clinical practice.[160] For studies requiring disclosure of personal information (e.g. prescription medicine use and health status), assurances of anonymity and

confidentiality of data may improve response rates. It is worth noting that this research programme encompassed non-interventional studies, and consent was implied for those participating in anonymous surveys; written consent was obtained for cognitive interviewees in Phase 2b (described in Chapter 5).

In terms of potential benefits to participants, this research programme may have offered platforms for sharing lived experiences, views, feelings, and thoughts about long-term medicines some of which remain 'unheard' in healthcare settings. Feedback reports were disseminated to all patient organisations/fora and recruitment sites that assisted at various phases of the research programme.

3.3.2 General rationale of methods used in this research programme

3.3.2.1 Survey methods

Questionnaires were predominantly used in this research programme. Surveys can gather large-scale data from wider geographic populations in a relatively short time.[128,161,162] They may enable generalisability of findings if response rates are adequate. With questionnaires, standardised data were collected on all variables – this was relevant to assess measurement properties of the LMQ (such as test-retest reliability).

All questionnaires were intended for self-completion, simulating real-life use of patient-reported tools enabling direct assessments of medicines use experiences. Self-completion allowed participants to understand and answer questions from their own perspective, unlike interviewer-administered surveys that are more resource-intensive. Anonymous self-reports can draw sensitive information from individuals, possibly due to a perceived sense of privacy. LMQ statements about personal impact of medicines on social and sexual life may have been answered truthfully with the anonymous surveys conducted in this research programme. Regardless, self-completed questionnaires impose cognitive demands on the participant, and necessitate a certain level of literacy (reading and language skills) present in the respondent sample. Also, participants with visual impairment or inadequate dexterity (of wrist and figures) may be unable to complete questionnaires.[161] Readability of the questionnaire had been assessed previously during development of the LMQ-1,[119] and was reassessed for the LMQ-2.1 in a study described in Chapter 5.

3.3.2.2 Modes of survey distribution

Two survey distribution methods were used at various phases of this research programme: face-to-face and on-line distribution. Mixed-mode surveys are advantageous in improving response rates, as well as attaining representative samples of participants.[162]

a) Face-to-face distribution

Face-to-face recruitment using paper questionnaires, as a traditional mode of data collection, was employed in two study phases (Phases 1b and 4 as shown in Figure 1-8). Participants who can read and write, regardless of computer literacy or access to the Internet, can use paper-based questionnaires. Postal mail was mostly used to return paper questionnaires with only a few participants completing and returning questionnaires directly, by hand, to researchers. Returning questionnaires by mail may offer ample time to participants to respond and submit their responses at leisure. It also requires minimal co-ordination by the researcher who picks up completed questionnaires from one address.[118] To increase the likelihood of returning mailed questionnaires, all paper questionnaires were supplemented by a cover letter, participant information sheet, and a pre-paid postage, self-addressed envelope. A cover letter impacts on attitudes and practices of questionnaire completion.[118] Using cover letters and information sheets, on the School's letterhead, informed potential participants about specific aspects of each study, including rationale, inclusion criteria, and ethical issues (See Appendices).

b) On-line distribution

With recent technological advances and increased access to computer devices, smart phones and the Internet, web-based questionnaires provide an alternative, faster and easier, means of collecting data. Software (such as Qualtrics© provided by Qualtrics LLC via https://www.qualtrics.com/) can be used to host a questionnaire on a web-site and provide a unique link (url), which can then be used to promote the questionnaire via health websites, social media sites of selected patient organisations, and by email invitation. Qualtrics© automatically records survey responses into a database, thus minimising data entry errors associated with transcribing paper-based data into a database.[118] Web-based surveys were used because they reach people from wider geographical locations and in hard-to-reach areas that may otherwise not

have been encountered during face-to-face recruitment. Besides simplifying questionnaire layout, formatting replicated the paper questionnaire into an electronic form with the same statements. A cover page, participant information, and screening questions on inclusion criteria were also embedded in the electronic format, which also had an 'alert' to remind participants of incomplete responses- this may have minimised missing data. A disadvantage of on-line surveys, besides excluding those without computers/internet or with lower levels of education, relates to accurately estimating response rates.[118] For instance, it is difficult to determine how many people receive an anonymous web-based survey promoted to an 'open' patient organisation, although using an email list may solve this problem. Email recruitment has its unique limitations, although it was used in the Phase 5 study (described in Chapter 8). It requires access to valid email addresses of potential participants, and their ability and willingness to regularly read and respond to emails.[118]

3.3.2.3 Cognitive interviews

Cognitive interviews were used in Phase 2b (See Figure 1-8) to gain patient feedback on questionnaire content, and to check interpretability of all items. This subsection provides a general rationale for using cognitive interview procedures reported in Chapter 5.

Derived from the field of social and cognitive psychology,[163,164] cognitive interviews explore respondents' approach to the task of answering questionnaire items.[127] There is no consensus about how to conduct cognitive interviews, but the most commonly used cognitive-interview methods are think-aloud and verbal probing.[127,165,166] The think-aloud technique involves respondents verbalizing their thoughts as they respond to questionnaire items.[127,166] It is appropriate for questions involving recall,[127] is open-ended and may elicit unexpected information from respondents.[167] Conversely, thinking aloud is respondent-controlled and imposes a 'thinking burden' on the participant, who may stray from the main task of questionnaire evaluation.[127,167,168] Moreover, think-aloud interviewing is somewhat dependent on how outspoken or articulate a respondent is; some respondents may simply answer the questions without much elaboration, while others may spend more time talking about one question, resulting in only a few questions being tested in a planned amount of time.[168]

Verbal probing, an altetrnative technique, is interviewer-led by asking follow-up questions (probes) during or after item completion to facilitate relevant discussions about the questionnaire.[168] Concurrent probing is preferable for using 'fresh' information (in the participant's mind) during item completion, unlike retrospective probing where participants may not remember what they were thinking in relation to a particular item when interviewed at the end of questionnaire completion.[168] Probing is an increasingly preferred technique,[166] as it helps to gather more information on questionnaire items (e.g. clarity and relevance), appropriateness of response options, and general comments about questionnaire length, item order, formatting and layout. Probing enabled a clear and precise understanding of participants' interpretation of each question they answered.[166] During verbal probing, the interviewer asks for more specific information about questionnaire items, and seeks explanation of the answers given by participants; thus assessing questionnaire interpretation even further.[168] The same probes may be used for all survey items (standardised), or may vary depending on a participant's answer to a specific item.[127] Spontaneous probes may assess what a participant thinks of an unanticipated questionnaire problem, while targeted probing majorly focuses on potentially problematic items (e.g. newly generated or revised items). For a relatively lengthy questionnaire, such as the LMQ-1, targeted-probing can minimise respondent burden while allowing quick evaluation of the questionnaire.

Nevertheless, adapting a method that elicits adequate and relevant information (pragmatism) is preferable to maintaining consistency during cognitive interviews.[127] In the Phase 2 study (described in Chapter 5), a triangulation of think-aloud and verbal probing techniques achieved relevant and sufficient information on the questionnaire's readability and potentially problematic items in the LMQ-2.1. A probing guide was used to conduct the cognitive interviews (see Appendix 2).

3.3.3 Sample population inclusion/exclusion criteria

The sample population involved in the development and validation of the LMQ was given consideration. Across all studies, participants were adults using at least one long-term prescription medicine for any disease/condition. The LMQ was intended to assess adults' experiences and all participants were 18 years or older. Participants using medicines contributed to generating, revising, and testing items in the LMQ, which covered issues relevant to them. Patient and public involvement is indispensable in the development of novel health interventions (and tools) to draw on their experiences and perspectives.[169]

Participants were excluded from the study if: self-reporting to be too unwell to complete the questionnaires (e.g. those reporting severe dexterity problems); unable to read English as the language used in all study tools; and if using prescription medicines only for acute illnesses (e.g. antibiotics for an short-term infection). Across all studies described in this thesis, the questionnaires/study tools were only available in English as time, costs, and human resource constraints precluded their translation to other languages.

3.3.4 Study setting

Recruitment for different phases of the research programme was conducted via multiple research settings: public places, community pharmacies, GP practices, and hospital outpatient clinics. In Phase 1b (Chapter 4), street surveys were conducted in busy areas of Kent and Medway (such as leisure centres, parks, bus/train stations, entrances of shopping centres, community libraries) aiming to access a socio-demographically diverse sample.[162] With nearly half of all adults using prescription medicines in England,[31] the general public provided a suitable pool of potential participants. The public was relatively more accessible than patients in NHS settings owing to relatively lengthy/bureaucratic procedures associated with participant recruitment (such as applications for research governance and NRES approvals).

Nonetheless, a purposive sample of community pharmacies and GP practices in Kent and Medway were engaged to ensure that questionnaire development and testing also involved NHS patients using long-term prescription medicines. Hospital outpatient

clinics at Medway NHS Foundation Trust, were selected, owing to their clinically diverse patient population. As the largest and busiest hospital in Kent, the hospital serves over 650,000 patients per annum within the NHS south-east coast region.[170] The relatively high footfall of patients was exploited to generate high response rates in a short space of time.

All research sites were closely located to the Medway School of Pharmacy (the Universities of Greenwich and Kent) and were convenient to access. Capturing experiences of primary- and secondary-care users and the public provided an initial test of usability and acceptability of the LMQ tool in different settings. Figure 3-1 locates the study sites.

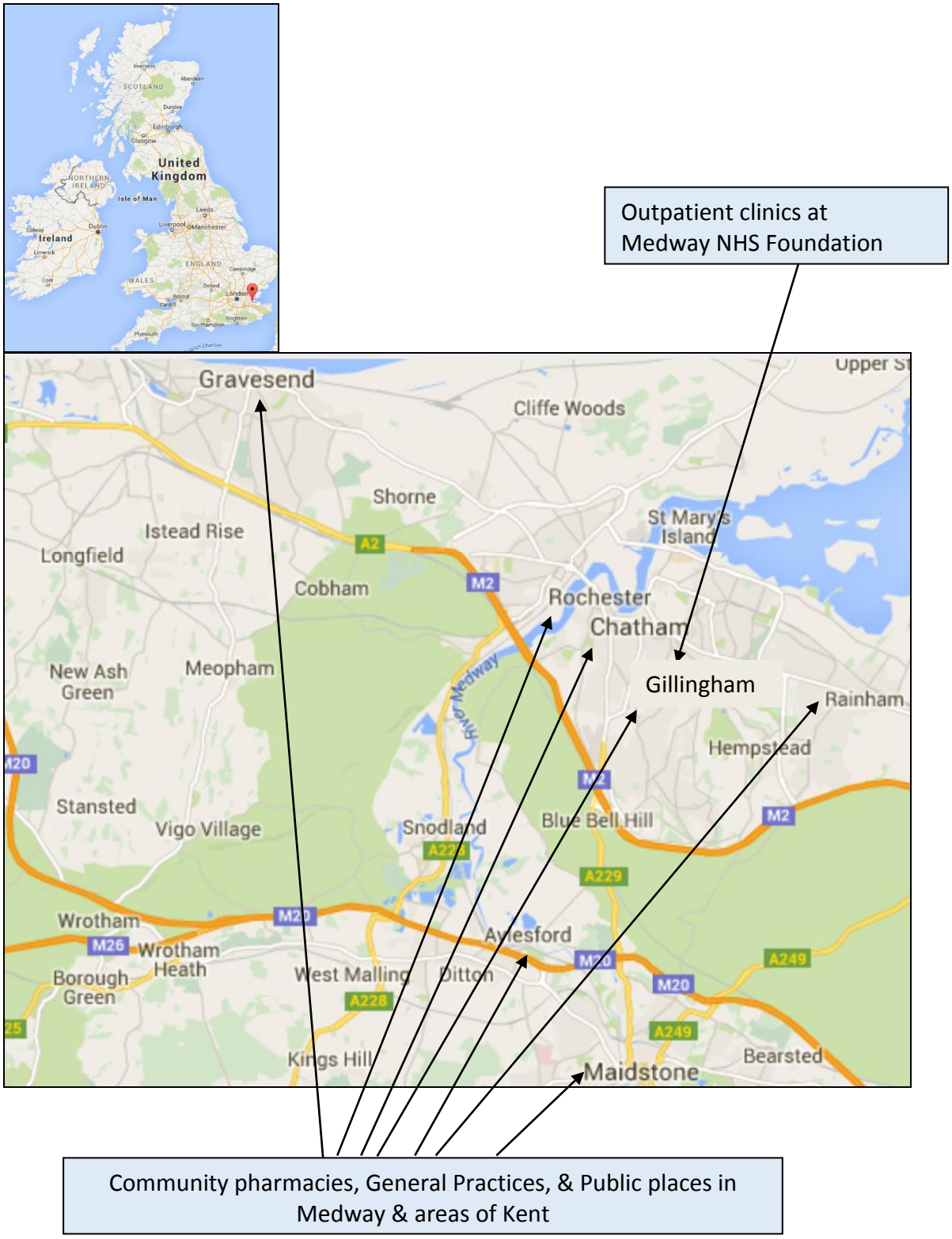


Figure 3-1 Location of research study sites in south-east England

3.3.5 Data management

Data analysis software

Quantitative data were manually entered (or downloaded from Qualtrics©) into IBM SPSS version 22 that was later upgraded to version 23 and then 24, within which most data were analysed. Analysis of Moment Structures (IBM AMOS ® version 22), was used in confirmatory factor analysis in Phase 3 (described in Chapter 6). All qualitative interview data were managed in NVIVO© version 10 (QSR International Pty Ltd), and Microsoft Excel 2013 spread sheets were used to manage participant feedback on an interim questionnaire reported in Chapter 5. Monte Carlo PCA, a specific web-based programme,[171] was used for parallel analyses in Chapters 4 and 6.

Quality assurance

a) Handling missing data

All data sets derived from questionnaires were screened for entry errors and missing data to minimise biased findings. The most traditional approaches for dealing with missing data include: a) Mean imputation. This involves replacing any missing values with estimated means scores, which may lead to misleading or biased results and is not commonly recommended.[172–174] b) Pairwise-deletion, which exploits all available data[175] by excluding only participants with missing values per analysis, may lead to distorted or inconsistent estimates owing to variations in sample sizes across studies. c) Listwise-deletion is a simple way of eliminating all participants with missing values on any variable to have complete datasets.[172,173,175] d) Other complex techniques (i.e. full information maximum likelihood and expectation maximization) require advanced software and are rarely used to handle missing data[176] despite producing the least biased results.[172,173] Of these techniques, listwise deletion was mostly selected as a simpler option to ensure consistency of sample sizes per study when sample sizes were not greatly reduced. Pairwise analyses were mainly used where sample sizes would be greatly affected by the listwise procedures.

b) Assessing normality of responses & presence of outliers

The distribution of responses was examined in all data sets by using histograms and normality Q-Q plots. Where tests for univariate normality (Kolmogorov-Smirnov test and Shapiro-Wilk test) were conducted, a non-significant p-value ($p > 0.05$) indicated normal distribution of variables. Skewness and kurtosis were estimated in some studies. The two indices of normality portray the score distribution and how tilted or peaked it is; values around one in absolute value support normal distribution of data.[177] Visual inspection of data for outliers, by means of scatter plots or box plots, was conducted in some studies; outliers are participants with scores differing markedly from those of others in the dataset.[173]

c) Reverse scoring of items

Although intended to measure a negative construct (medicine burden), the LMQ had a mixture of positively-phrased and negatively-phrased statements to minimise 'automatic' responding. Prior to reverse coding, each item response was coded as 1-2-3-4- or 5 to reflect strongly agree, agree, neutral, disagree, or strongly disagree respectively. To ensure that higher scores reflected worse experiences of medicine use (higher medicine burden), negatively-phrased items were re-coded to give higher weights to those in agreement with such statements. For instance, prior to reverse scoring a negatively-phrased item (e.g. I find getting my prescriptions from the doctor difficult) strongly agree was coded as 1, but after 'reverse scoring' a score of 5 indicated worse experience with that aspect of medicine use. Reverse scoring also aided interpretation of factor analysis results, and accurate estimation of internal consistency of LMQ subscales.

3.3.6 Qualitative data analysis

Qualitative data were obtained and used in various phases of the research programme. These comprised: original patient interviews from which the concepts and items in the LMQ-1 were derived;[23] cognitive interviews; and descriptive free-text comments from an open-ended question in the LMQ *('If you have any other views about how your medicines affect your day-to-day life, please describe them')*. Free-text comments were analysed thematically, and used for item generation in Chapter 5. In Chapter 9, free-text comments were also used to complement (and illustrate) quantitative findings on prevalence of medicine-related difficulties in the sample populations.

To identify new content for the LMQ, reanalysis of the original 21 qualitative interviews[23] was conducted thematically, using techniques akin to framework analysis. The 8-domain thematic framework proposed by Krska and colleagues[23] was used to code medicine use experiences into: impact on daily living, side effects, relationships with health providers, efficacy, attitudes, practicalities, information and control over medicines use. Any codes falling outside of these themes (e.g. about cost of medicines) were considered as potential gaps in the LMQ instrument. Codes about side effects and impact on daily living were reviewed, some of which were used to generate new items in these domains. As already described, new items and existing items in the questionnaire were tested using cognitive interviews. In Chapter 5, cognitive interview data were analysed descriptively, using procedures akin to constant comparison,[178] by grouping similar comments per LMQ statement and linking them, so as to identify potential questionnaire problems. Further descriptions of methods used to analyse cognitive interviews are included in Chapter 5 (See section 5.2.6). The interview comments were compiled for each item in specially designed Excel spreadsheets (Appendix 16), and analysed both on an item-by-item basis, and comparatively to assess potential questionnaire problems, including comprehension difficulties. Comments about each item were compared across all participant responses, and comprehension problems assessed and documented. The rationale for taking this analytical approach to analyse cognitive interviews was discussed in-depth in section 5.2.6 and was underpinned by the pragmatic methodological stance.

3.3.7 Choice of measurement framework –Classical Test Theory

There are two measurement frameworks, with different theoretical assumptions, that can be applied in questionnaire validation: classical test theory (CTT) and item response theory (IRT). Factor analysis is a typical application of CTT and will be described in a later section. This subsection explores the rationale for using CTT, as the most appropriate overarching measurement framework applied in Chapters 4 and 6.

CTT is a centurial, predominant, measurement theory in health services research, which has been widely used in questionnaire validation.[179] CTT simply proposes that 'any observation [or item score] is composed of two components: a true score and an error associated with the observation'.[118] In other words, observed item scores in a completed questionnaire (e.g. coded as 1-2-3-4- or 5 for the level of agreement with each LMQ statement) are the result of actual scores (indicating the level of attribute) and random error inflicted by external factors. Highly reliable instruments should produce observed scores that are closer to true scores, with lower measurement error.[179]

Summing up item scores to generate total scores is a common way of scoring questionnaires founded on CTT. However, there are methodological challenges with this method and its assumptions. One assumption is that each item contributes equally to the total score on a scale, and that summation may not account for weights of individual items and the extent to which they reflect the underlying construct.[118] Summation of scores also assumes that all items are measured on the same scale. Nevertheless, the 5-point Likert scale was assumed to be continuous (having an equal interval) and thus enabled estimation of total scores, despite mixed debates about whether Likert-type scales are continuous or ordinal.[172,180]

Although CTT applications are easier to use, interpret, and are accessible in statistical software (such as SPSS), CTT has debatable assumptions. As the 'softer theory', CTT models are thought to underestimate measurement errors by assuming that '…the average error, summed over all of the items is zero',[118] implying that all sources of measurement error, combined, have minimal (or no) effect on the questionnaire scores.

IRT, the alternative measurement framework rooted in educational testing (including founder works of Georg Rasch,1960[181]), may precisely estimate measurement error and permits only the 'best' items (at least in a statistical sense) to populate an instrument.[118] However, it has not gained much recognition in the development and validation of health-related measures.[118] For instance, only 1 in 15 studies in the systematic review described in Chapter 2 employed Rasch analysis, an application of IRT, to evaluate a measure of medicine-related quality of life.[134] Despite taking into consideration participants' level of attribute per item (e.g. level of quality of life), IRT is criticised for being mostly theoretical.[118] IRT not only uses complex mathematical terminology but also has rigid assumptions. Particularly, IRT demands uni-dimensionality of the questionnaire whereby all items are expected to directly measure one construct. Streiner et al (2015) clearly stipulates that 'IRT cannot be used when the underlying construct [such as medicine burden] is itself multifaceted and complex.'[118] As previously described in Chapters 1 and 2, medicine burden is a multidimensional construct covering a range of experiences. Therefore, it was deemed inappropriate to adopt the IRT approach. It also demands extensive specialist knowledge, skills and software to perform analyses, unlike CTT models that were easy to compute. The next subsection explores factor analysis, in depth, as the predominant technique, and application of CTT, used in Chapters 4 and 6.

3.3.8 Factor analysis

3.3.8.1 Underlying principles

Factor analysis, a multivariate statistical technique, was used as the predominant technique to validate the LMQ, examining the extent to which it measured medicine burden as the hypothesised construct (i.e. construct validation). It elucidated the LMQ's dimensional structure and its constituent domains.

Principles underlying factor analysis involve correlations - there must be adequate relationships among items for it to work.[127] Extensively reported in psychometrics literature, conventional Pearson's correlations were used in all factor analyses to derive factors. Pearson's correlations assume linearity among items rated on an interval (or continuous) scale; LMQ items were rated on a 5-point Likert-type scale assumed to be continuous.

Mathematically, factors are weighted combinations (or clusters) of inter-related items.[127] For instance, the first factor (denoted as F_{1}) in the 60-item LMQ-1 is represented as: $F_1 = w_{1,1}X_1 + w_{1,2}X_2 + \ldots w_{60,60}X_{60}$. Weights for all items are denoted by $w_{1,1}$, $w_{1,2}$ to $w_{60,60}$ with subscripts referring to factor- and item- numbers respectively. Thus, $w_{1,2}$ depicts the weight for the second item contributing to the first factor. Items are represented as X_1 *to* X_{60}. There are as many factors as there are items, and criteria for selecting factors will be discussed in a later section (section 3.3.8.3). Generally, factor analysis aids data reduction[175,182] whereby a large number of items is refined to fewer coherent factors. In this thesis, factors are synonymously described as components, domains, dimensions, subscales, or constructs, depending on the context and psychometric literature.

3.3.8.2 Types of factor analyses

Two major approaches to factor analysis were employed: exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). As the name suggests, EFA is exploratory and assumes no prior hypotheses.[174,175] EFA was most relevant in preliminary work to investigate relationships among items and to generate hypotheses about factors[127] (domains) in different versions of the LMQ. CFA is an advanced statistical procedure, part of structural equation modelling (SEM). It is useful as a hypothesis-testing approach. Informed by EFA findings, CFA was used to confirm the interrelations among items and domains,[127,172] and to assess a shorter version of the LMQ (the LMQ-3) as a measure of an overarching construct of medicines burden. Briefly, CFA models are evaluated against statistical criteria (model fit indices), and if not meeting 'golden' rules, pre-specified models can be modified and alternative ones investigated.[172,180,183]

The next subsection provides an overview of the procedures used in EFA, with specific details about CFA described in Chapter 6.

3.3.8.3 Procedures for EFA

EFA procedures are iterative and multistep. To assess factorability or suitability of data for factor analysis, the strength of inter-item correlations and sample size were examined. Correlation coefficients above 0.3 among most items, are adequate for factor analyses.[175,182] Kaiser-Meyer-Olkin measure of sampling adequacy (KMO) and Bartlett's test of sphericity were also used to evaluate the adequacy and statistical significance of relationships among items.[175,184] A KMO value above 0.6 (range, 0 to 1) and Bartlett's p-value < 0.05 indicates data are factorable.[175] Subsequent steps, described below, involve selecting appropriate factor extraction techniques.

a) Choosing a factor extraction technique

Factor extraction techniques help to identify the smallest and most conceptually meaningful set of factors that can best explain the interrelationships among items.[175] A common aim of factor extraction is to attain simpler (or parsimonious) factor solutions. Parsimony, in the EFA sense, refers to achieving the least number of factors accounting for the maximum variability across all participants' scores (variance). If the first few interpretable factors can account for most of the variance, then the remaining factors can be ignored with minimal loss of information.[127] Popular extraction techniques include principal components analysis (PCA), common factor analysis using principal axis factoring (PAF), and maximum likelihood estimation (ML).

PCA estimates components (factors) by extracting the total variance of each item in the questionnaire.[175] To clarify, the total variance of an item has two parts: the fraction of variance that is common to all other items in a data set (common variance), and the fraction of variance that is specific to each item, including variations arising from measurement error (unique variance).[174] Due to its assumptions that embrace possible measurement error, PCA is controversially, sometimes, dismissed as a factor analytic technique. PAF uses common variance among items to derive factors while eliminating error variability from items.[182] Nonetheless, some authors acknowledge that PCA and common factor analysis [with PAF] '…are not competing techniques, as both methods facilitate a different purpose...'.[185] PCA is most applicable in data reduction, and was used in Chapter 4 to reduce the 60-item questionnaire to a shorter interim version (the LMQ-2).

PAF was used in Chapter 6 to explore common factors (domains) underlying the LMQ-3.

The type of data and its distribution patterns also influences the choice of a factor analytic technique. PAF makes no assumptions about the distribution of responses, unlike ML that is more suitable for analysing symmetric data with four or more response categories.[172,180] ML was used in Chapter 6 for CFA.

b) Factor retention - determining the optimal number of factors

Three criteria for factor retention are: a) Kaiser's eigenvalue (> 1) rule - the eigenvalue of a factor shows the proportion of variance explained by that factor. b) Cattell's Scree plots of eigenvalues against their corresponding factors; only factors above and to the left of inflexion points or sudden breaks in the plot are retained, as these account for most of the variance in the dataset.[175] Interpretation of scree plots, and Kaiser's criteria, is relatively subjective and both are criticised for retaining too many factors.[175] c) Parallel analysis is a more objective and accurate test,[127,171] whereby observed eigenvalues are systematically compared with average randomly-generated eigenvalues (from a computer programme). Factors are only retained if observed eigenvalues exceed the latter values,[175] indicating that they are not merely occurring by chance. A potential limitation of parallel analysis techniques lies in probable 'variation in the results [that] becomes increasingly small and essentially disappears' with bigger data sets.[186]

Irrespective, all three criteria for factor retention were triangulated to confirm the number of domains in the LMQ.

c) Factor rotation

Factor rotation helps display the pattern of factor loadings, as correlations between items and factors, in simpler and interpretable ways.[175] Two main rotation techniques either allow uncorrelated/independent factors (orthogonal rotation e.g. varimax) or correlated factors (oblique rotation e.g. promax).[175,182] In this research programme, oblique rotation techniques were used during EFA due to hypothesised inter-correlations among LMQ domains. Oblique rotations are commonly recommended in psychology-related studies where constructs (such as those underlying medicine burden) are believed to be inter-related.

d) Criteria for item retention/reduction

Decisions on item retention of deletion were made by both qualitatively reviewing each statement in the LMQ, and employing statistical criteria. Items were retained if their factor loadings were adequate (at least ≥ 0.3).[182] Factor loadings represent the relative importance of each item to its corresponding domain (factor). Factor loadings <0.3, 0.3-0.5, and ≥ 0.5 indicate weak, moderate and stronger associations among items and their corresponding domains respectively.[187] Although, higher item loadings are desirable for reliable subscales (or purer measures), there is a need to minimise substantial item loss from a questionnaire.[188] In addition, items with high communalities (>0.4) were preferable as they represented a higher proportion of shared(common) variance.[187] Items cross loading on two or more factors (≥ 0.4) were candidates for deletion, since they could be measuring a different concept/multiple concepts;[175] qualitatively reviewing the meanings and relevance of such items, and discussions with supervisors, guided item deletions.

e) Naming of factors

Naming of factors (domains) was based on statistical findings, and the qualitative meaning of items common to a domain. Items loading most strongly on the same factor (known as marker items) were examined to understand the concepts they reflected. Discussions were also held with the supervision team to agree on nomenclature of the domains in an interim version (LMQ-2) and in the final version of the questionnaire (the LMQ-3).

3.3.8.4 Reliability analysis – internal consistency and test-retest reliability

Internal consistency is a common measure of reliability. This test is relatively easy to perform, compared to test-retest reliability, which was examined in Chapter 8, as it uses data from a single survey completion.[118] Cronbach's alpha coefficient (α) is a popular index of internal consistency. It depicts relationships among a set of items in a subscale (factor). Cronbach's α values ≥ 0.7 are acceptable, but when measuring psychological constructs α < 0.7 are realistic. Cronbach's α, which is directly proportional to the number of items in a subscale, has attracted differing criticisms with respect to its usefulness as a measure of scale reliability or uni-dimensionality of subscales (the 'extent to which items in a scale measure the same thing').[189] This controversial evidence against Cronbach´s alpha is relatively surpassed by the overwhelming psychological literature reporting it as the sole measure of reliability. Moreover, not much is known about alternative, albeit complex, indices of internal consistency reliability.[190] Therefore, Cronbach's alpha is reported in Chapter 6 to reflect internal consistency of LMQ-3 subscales.

Test-retest reliability of the LMQ-3 was assessed by multiple methods (Spearman's correlations and agreement between scores using intraclass correlation coefficients-ICCs). Inter-rater reliability (involving multiple raters) was not necessary since the LMQ is a self-reported measure designed for use by only one person.

3.3.8.5 Other statistical analyses

This subsection provides an overview of other statistical analyses used in different studies constituting this thesis. Descriptive statistics were reported as frequencies and percentages for categorical variables, and means (standard deviation) or medians (range) for continuous variables. Chi-square tests were used to compare proportions for categorical variables. When comparing normally-distributed mean scores across 2 or ≥ 3 groups, independent samples t-tests or one-way ANOVA were used respectively.[174] The equivalent non-parametric tests, Mann-Whitney test or Kruskal-Wallis test, were used to compare asymmetric mean scores across 2 or ≥ 3 groups.[174]

To understand predictors of medicine burden in Chapter 9, simple and multiple linear regressions were used. Spearman's correlations were also used in Chapter 7 to investigate relationships between LMQ-3 scores and those obtained for measures of treatment satisfaction and HRQoL. Throughout this thesis, a probability value (p-value) below 0.05 represents statistical significance.

3.3.9 Sample size across studies

There is an absence of clear guidance and lack of consensus regarding a priori sample size estimation for studies into questionnaire development, and for newly-developed patient reported outcomes measures.[191] The common finding is that the sample size recommendations vary across different analytical procedures, but should be adequate for the intended research objective or data type.[191]

Across the research programme, the number of participants per study ranged from 11 cognitive interviewees to over 1000 survey responses. The qualitative interviews, of which there are no rules of thumb for sample size determination, depended on saturation of questionnaire-related issues under investigation, and provision of enough data to address the study objective. Sample sizes for the quantitative studies were dependent on the type of analytical procedure. For instance, in exploratory factor analysis 'it is not the overall sample size that is of concern - rather, the ratio of participants to items in the questionnaire, with a 5:1 or 10:1 ratio commonly recommended.[175,182] This implies that for a 60-item LMQ-1, at least 300 responses were adequate for EFA. A sample size of at least 150 participants is sufficient for estimating measurement models in confirmatory factor analysis.[183,191,192] In terms of reliability assessment, a test-retest sample size of at least 50 participants is recommended[122] but Chapter 2 revealed some stability studies[64] involving as few as ten participants. Assumptions for sample size adequacy were tested for different statistical analysis procedures conducted and reported in this thesis.

Acknowledgements

This phase of work was accomplished by myself, though four undergraduate students helped with data collection and part of the data entry. I managed and double checked all data entries, analysed, and interpreted all the findings presented in this chapter. The original questionnaire used in this chapter (LMQ-1) was developed by my primary supervisor (JK), and I adapted it for further development in this thesis chapter. The findings presented in this chapter were published in Patient Preference and Adherence[193] under the open access model that allows 'free use of original works of all types for personal, research and educational use.'

4.1 Introduction

In Chapter two, the systematic literature review identified the original 60-item Living with Medicines Questionnaire (labelled as the LMQ-1) as a promising measure specifically designed to measure overall medicine burden in the UK population,[119] but which required further development and psychometric testing, and item reduction into a more manageable tool. The present chapter describes a study conducted to further assess and shorten the LMQ-1 involving a larger sample of participants using long-term prescription medicines in the UK. I describe steps taken to further develop and investigate the LMQ-1.

To contextualise this study and its contribution to this thesis, brief background information about the history of LMQ-1 development is provided. Originally developed by Krska et al (2014),[119] the LMQ-1 was founded on qualitative interview data from 21 adult patients using multiple prescription medicines (≥ 4) long-term (for ≥ 1 year) in primary care settings of north-west England.[23] The first draft of the LMQ-1 was reported to undergo several stages of preliminary testing including item generation, deletions, and rewordings that led to the 60-item instrument plus a free-text open question.[119] Face and content validation of early drafts, to evaluate item meanings and relevance and ease of completion, was reported.[119] The questionnaire also had a free-text open question.

All items were rated on a 5-point Likert-type scale (as strongly agree, agree, neutral, disagree, or strongly disagree), which had also undergone a series of revisions and testing. Despite relevant pretesting, the LMQ-1 was tested on small samples of patients and further tests (using a larger sample) were necessary to check performance at population level and to examine the hypothesised qualitative domains and appropriateness of the tool. Moreover, initial factor analyses revealed inconsistent results across earlier versions of the LMQ, and constructs reported from the qualitative study[23] (relationships with health professionals, practicalities, information, efficacy, side effects, attitudes, impact and control) required further validation. This chapter uses a larger sample population to enable item reduction and further psychometric testing, including construct validation, of the LMQ-1.

Aim and objectives

The aim of the study presented within this chapter was to assess and investigate the domains underlying the LMQ-1 using a UK sample population of adults using prescription medicine(s).

Specific objectives were:

- To reduce the number of items in the LMQ-1 into a shorter instrument;
- To examine the domains underlying the LMQ-1, and identify and explore any domains that were not covered to improve the instrument.

4.2 Methods

The previous chapter outlined general methodology and methods employed throughout this doctoral thesis. This section discusses the methods specific to this study, which was conducted over the period June 2014 to December 2014. Ethics approval was granted by Medway School of Pharmacy Research Ethics Committee (Appendix 3). Consent for this anonymous survey-based study was implied by return or completion of the questionnaires.

4.2.1 Study instrument- The LMQ-1

Appendix 4 shows the LMQ-1 as the primary instrument used in this study. The LMQ-1 was a 60-item questionnaire with 34 positively phrased and 26 negatively phrased statements (items) scored on a 5-point Likert-type scale. This version of the questionnaire was produced in paper and electronic formats.

4.2.2 Study population

Members of the general public were targeted for this study, as the proportion of people using long-term medicines in England is high (over 50%)[31] and it enabled access to a diverse population. Inclusion criteria were: adults, using long-term prescription medicines, and living in the UK. All potential participants were required to answer screening questions to ensure they met inclusion criteria before completing the instrument.

4.2.3 Questionnaire distribution

A mixed-methods approach to questionnaire distribution was used to maximise both response rates and diversity of demographic characteristics. The two main methods of distribution were used: a) Paper questionnaires distributed to both the general public using street intercept and to community pharmacy users in south-east England. b) An on-line survey available to the UK general public, recruited via social media and health websites. All participants were given information about the study purpose prior to participation, either as an additional leaflet (paper version) or at the start of the questionnaire (on-line version).

4.2.3.1 Distribution of questionnaires through street-intercept methods

Street-intercept survey methods are reported to facilitate access to people in harder-to-reach areas of the target population.[194] Street surveys yield wider, representative, socio-demographic profiles, in terms of age, education or employment[194] and are also a cost-effective distribution method for paper surveys.[162] The street-intercept recruitment technique involved personal distribution of questionnaires to people in public areas of Medway towns of Rochester, Chatham, Gillingham, and Strood (See Figure 3-1). Potential participants were consecutively approached while waiting at bus and train stations, leisure centres or exiting major shopping centres, and sitting in

outdoor cafes, sitting in town squares, or walking in parks. Most survey distribution was conducted on weekdays between 9.00am to 5.00pm. Occasionally, paper surveys were distributed on Saturdays and Sundays, between 9.00am to 1.00pm, to target people doing weekend activities (e.g. shopping, going to or from congregations), and to recruit those who may have been missed during weekday working hours. Brief introduction about the study and polite gestures were employed to encourage participation in this phase of research.

Although more people could be approached using street-intercept methods, the response rates were not promising and more people were likely to reject the survey. This was possibly due to lack of time or interest in the research, or even perceived sensitivity of the research topic in the public recruitment setting. Some participants showed concerns about discussing their medicines (or health condition) on the 'street', while others felt they should be talking to health professionals about their medicines instead of researchers. All street survey participants were encouraged to take the questionnaire away for completion at their convenience (and in privacy), along with an information sheet, and a pre-paid (freepost) envelope for return. Only a few offered to complete the survey while waiting in public areas and returned it to the researcher in a sealed envelope.

4.2.3.2 Questionnaires and flyers dropped off at public places

Another method used to recruit the general public in this study involved dropping off printed questionnaires (in survey packs) and advertising flyers at designated public places in local areas of Medway. Survey packs contained the questionnaire, a participant information leaflet, and a pre-paid postage envelope. The study packs were prominently placed in selected public locations (such as libraries, community centres, or churches) to enhance visibility of the study, and encourage participation. Permission to advertise the study in this way was sought from area managers of public/private places. Eligible participants would pick up the study pack, complete the survey, and post it back at their convenience. In addition to covering inclusion criteria, the flyers also provided details of a link to the web-based survey, for those wishing to complete the electronic questionnaire.

4.2.3.3 Recruitment of community pharmacy users

Questionnaire distribution to community pharmacy users increased the likelihood of reaching people using long-term medicines. The paper survey was distributed to users of small-to-medium size community pharmacies (independently owned), located in Medway towns of Gillingham, Chatham and Rochester. Pharmacies located close to high streets and GP surgeries were selected owing to a higher probability of people entering the pharmacy itself. Multiple-chain pharmacies, such as Boots, were not involved in this study due to time-constraints associated with seeking additional research governance for recruitment. Moreover, it was assumed that there were no differences in characteristics of people visiting independent or multiple-chain community pharmacies.

An introductory (or invitation) letter (Appendix 5), pharmacist information sheet (Appendix 6), and a copy of the questionnaire (Appendix 4), were posted to each selected community pharmacy. The invitation letter, which provided a general study overview (including aims and rationale), asked permission to visit and distribute study packs to clients at pharmacy premises. After a 1-2-week interval, telephone calls were made to the pharmacist in charge asking if they had received the invitation study pack and to verbally ask permission to use the pharmacy premises. A replacement pack was provided, on request, to pharmacies that reported loss or no receipt of the first study invitation pack. Only pharmacies that granted permission to distribute surveys in their premises were visited, at different times of the day, during agreed operating hours, to recruit participants.

Potential participants were approached consecutively after completing their initial transaction (e.g. filling a prescription), and offered brief verbal study information, screened for eligibility, and asked to consider taking part. If they met all the inclusion criteria, potential participants were asked to complete the LMQ-1 questionnaire in the community pharmacy (e.g. while waiting for their medicines or products to be dispensed) or allowed to take it away to complete it at their convenience. On-site survey completion was dependent on participants' waiting time, and layout and waiting space in pharmacy premises. Completed questionnaires were returned directly by hand, to the researcher, in sealed envelope or in a pre-paid (freepost) envelope at

the Medway School of Pharmacy. Every questionnaire given to potential participants was accompanied by a participant invitation letter and patient information leaflet (Appendix 7). All information was deemed free of any unsubstantiated claims or benefits.

4.2.3.4 On-line survey distribution

An electronic version of the LMQ-1 was designed and launched using Qualtrics©. The on-line survey was open for a relatively longer period (approximately a year). The on-line survey was open to the UK general public to reach people from a wider geographical distribution, including the housebound, but was more likely to reach those with higher education and socioeconomic status.[118,162] The link to the survey was promoted via social media and health websites.

On social media (Facebook and Twitter), links to the on-line survey were posted alongside brief information about the study (and inclusion criteria); this was done via designated social-media accounts for the LMQ project. Target patient groups/fora were 'followed' and their posts 'liked/favorited', and recruitment posts 'harsh tagged' as a strategy to increase visibility and response rates to the survey on social media. Participants were also encouraged to share the survey link with people they felt would be interested to complete it (snowball technique).

Health websites were also used for on-line recruitment in this study phase. Permission to distribute a link to the survey on specific websites was granted by administrators. These were asked to post an invitation message, recruitment text (and inclusion criteria), and a survey link on their websites/fora. A list of websites or fora that took part in this study is illustrated in Figure 4-1.

Ataxia UK

Atrial Fibrillation Association

B & BF- Bladder and Bowel Foundation

Back Up Trust

Blood Pressure UK

Diabetes UK

Epilepsy Action

Lupus Patients Understanding & Support

Lymphoedema Support Network

Macmillan

National Eczema Society

National Osteoporosis Society

Oesophageal Patients Association

Pain Concern

Sarcoidosis Association

SIA- Spinal Injuries Association

The HIV Support Centre

The Hysterectomy Association

The ITP Support Association

The ME Association

The Pituitary Foundation

Thyroid UK

Vasculitis UK

Women's Health Concern

Yourable

Figure 4-1 List of patient organisations participating in the LMQ-1 on-line survey

4.2.4 Data preparation

Data were managed and analysed using IBM SPSS (version 22). On-line survey responses were downloaded from the provider website (Qualtrics©). Two databases were set up to handle paper and on-line surveys separately, then checked for errors and merged for analysis. Any significant differences in participant characteristics resulting from questionnaire distribution methods were examined using Chi-squared tests. Questionnaires with fewer than 50% of item completed were excluded from further analysis. As described in section 4.2.1, the 60-item LMQ-1 had a mixture of positively phrased and negatively phrased statements. Reverse scoring of negatively phrased items enabled uniformity in the direction of responses, such that higher scores depicted worse experiences with medicine use (higher burden).

4.2.5 Principal components analysis

The correlation matrix was examined for intercorrelations among items, and the Kaiser- Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's Test of Sphericity computed to assess factorability of data.[175] For item reduction, PCA was conducted on the combined dataset using oblique rotation techniques (promax), assuming inter-correlations among underlying components (factors).[188] In addition to scree plots and Kaiser's rule (eigenvalue > 1), parallel analysis (Monte Carlo PCA[171]) was used to confirm the number of appropriate factors. All items were then reviewed for potential floor or ceiling effects (i.e. items with more than 50% of answers concentrated in the first or last answer category), and item skewness and kurtosis explored. This process enabled decisions to be made on item reduction.

4.2.6 Reliability analysis

Internal consistency for the LMQ-1 was evaluated using Cronbach's alpha (α), and changes in alpha following deletion of individual items from subscales used to further inform decisions on item reduction/retention.

4.2.7 Analysis of responses to the open question

As previously described in the introductory sections, the LMQ-1 instrument included a free-text comments box that allowed respondents to add any other views about how medicines affected their day-to-day life. To assess whether there were any outstanding issues not covered by the instrument, responses were analysed thematically using the eight themes identified in the patient interviews from which the original item pool was derived.[23] Any other comments not fitting these themes were considered as potential gaps in the content of the LMQ-1 and used in the subsequent chapter to improve the instrument.

4.3 Results

4.3.1 Response rates

A total of 507 responses were obtained using paper questionnaires (45.6% of all those meeting inclusion criteria), with more than half the respondents having been recruited from nine purposively selected community pharmacies (60.5%, n=307). A total of 670 participants completed the on-line survey (68.4% of the 979 participants accessing the survey link), via health websites (38.2%, n=374) and social media (30.2%, n= 296). A few others accessed the survey via the survey link on flyers (1.1%, n=11) distributed in public areas of Medway towns.

4.3.2 Distribution of responses, assessing missing data, and floor and ceiling effects

Of the 1177 survey responses in the combined data set (paper and on-line), 544 (46.2%) questionnaires were fully completed on all items in the original 60-item pool. Item-level response rates revealed that most questions were completed by over 90% of participants except for five items with the lowest completion rates (49.8% -50.2%) (see the 3rd column of Table 4-1). Most items had skewness and kurtosis statistics < 1.0, suggesting a tendency to univariate normality of the dataset. Raw mean scores, before reverse coding, on all items ranged from 2.13 (SD ±0.71) to 4.60 (SD±1.02) indicating that average responses were neither at the scale's floor nor at ceiling. Only 5 of 60 items had both skewness and kurtosis statistics greater than one in absolute value, including an item with 68.5% of responses at the scale's ceiling (*'Q4-My medicines are important to me').*

Item ID	Item	Item response rate n (%)	Overall mean score (±SD)	Paper survey mean score (±SD)	On-line survey mean score (±SD)	P-value (2-tailed)	Skew-ness	Kurtosis
Q1	The instructions on my medicines are easy to follow	1224(99.2)	4.28(0.77)	4.35 (0.699)	4.24 (0.796)	0.015	-1.258	2.350
Q2	I find getting my prescriptions from the doctor difficult	1220(98.9)	3.72(1.16)	3.79 (1.097)	3.67(1.193)	0.069	-0.756	-0.328
Q3	I find getting my medicines from the pharmacist difficult.	1219(98.8)	3.93(1.07)	4.15 (0.969)	3.77(1.121)	<0.001	-0.995	0.327
Q4	My medicines are important to me^	1215(98.5)	4.60(0.71)	4.51 (0.789)	4.69 (0.603)	<0.001	-2.182	5.839
Q5	I find opening the packaging of my medicines difficult	1223(99.1)	3.73(1.16)	3.82 (1.130)	3.65(1.194)	0.018	-0.708	-0.498
Q6	I am concerned about running out of medicines.	1226(99.4)	2.62(1.24)	2.95(1.243)	2.38(1.172)	<0.001	0.407	-0.970
Q7	It is difficult to identify which medicine is which.	1222(99.0)	3.93(1.06)	4.06(1.018)	3.83(1.089)	<0.001	-1.026	0.463
Q8	It is easy to keep to my medicines routine.	1225(99.3)	3.67(1.12)	3.91(1.030)	3.51(1.142)	<0.001	-0.718	-0.328
Q9	I would be concerned if I forgot to take my medicines [#]	1223(99.1)	2.13(1.02)	2.32(1.034)	2.00(1.001)	<0.001	0.809	-0.019
Q10	I am concerned that I may forget to take my medicines	1223(99.1)	2.92(1.16)	3.22(1.172)	2.72(1.170)	<0.001	0.061	-1.038
Q11	I am concerned about experiencing side effects	1224(99.2)	2.26(1.10)	2.50(1.126)	2.08(1.033)	<0.001	0.646	-0.459
Q12	I am concerned about possible damaging long-term effects of taking medicines.	1226(99.4)	2.14(1.12)	2.39(1.144)	1.97 (1.079)	<0.001	0.821	-0.224
Q13	Taking medicines is routine for me	1224(99.2)	4.07(0.96)	3.84(1.054)	4.26(0.836)	<0.001	-1.264	1.508
Q14	I am comfortable taking the medicines I have been prescribed.	1227(99.4)	3.79(1.02)	4.05(0.846)	3.61 (1.089)	<0.001	-0.848	0.126
Q15	I am comfortable with the times I should take my medicines.	1227(99.4)	3.94(0.86)	4.05(0.770)	3.87(0.902)	<0.001	-0.944	0.964
Q16	I find the patient leaflet in my medicines containers useful.	1227(99.4)	3.70(1.00)	3.82(0.953)	3.60(1.020)	<0.001	-0.677	0.002
Q17	I find using my medicines difficult.	1223(99.1)	4.00(0.88)	4.09(0.856)	3.92(0.898)	0.001	-0.993	1.198
Q18	I am satisfied with the effectiveness of my medicines.	1219(98.8)	3.47(1.08)	3.80(0.891)	3.23(1.140)	<0.001	-0.573	-0.374
Q19	I am concerned that I am too dependent on my medicines.	1224(99.2)	3.09(1.19)	3.28(1.119)	2.98 (1.219)	<0.001	-0.100	-0.929
Q20	I am confident speaking to my doctor(s) about my medicines.	1223(99.1)	3.89(1.13)	4.00(0.953)	3.80(1.245)	0.003	-0.959	0.088
Q21	I understand what my doctor(s) tell me about my medicines.	1223(99.1)	4.02(0.92)	4.06(0.848)	3.99(0.977)	0.214	-1.076	1.254
Q22	The information my doctor(s) gives me about my medicines is useful.	1223(99.1)	3.61(1.09)	3.90(0.936)	3.41(1.154)	<0.001	-0.604	-0.248

Table 4-1 Distribution of responses to the 60-item LMQ-1 obtained using paper-based and on-line survey datasets

Item ID	Item	Item response rate n (%)	Overall mean score (±SD)	Paper survey mean score (±SD)	On-line survey mean score (±SD)	P-value (2-tailed)	Skew-ness	Kurtosis
Q23	I am confident speaking to my pharmacist about my medicines.	1226(99.4)	3.82(1.08)	4.21(0.815)	3.53(1.159)	<0.001	-0.684	-0.341
Q24	I understand what my pharmacist tells me about my medicines.	1225(99.3)	4.03(0.86)	4.27(0.710)	3.87(0.903)	<0.001	-0.788	0.603
Q25	The information my pharmacist gives me about my medicines is useful.	1225(99.3)	3.88(0.93)	4.20(0.764)	3.66(0.972)	<0.001	-0.658	0.225
Q26	I sometimes run out of medicines	1215(98.5)	3.05(1.23)	3.22(1.221)	2.96(1.235)	<0.001	0.015	-1.311
Q27	I accept that I have to take medicines long term	1217(98.6)	4.17(0.88)	3.98(0.973)	4.32(0.786)	<0.001	-1.468	2.647
Q28	My medicines allow me to live my life as I want to	1217(98.6)	3.45(1.15)	3.71(0.943)	3.26(1.239)	<0.001	-0.456	-0.686
Q29	My life revolves around using my medicines.	1219(98.8)	3.11(1.23)	3.35(1.157)	2.93(1.245)	<0.001	-0.186	-1.046
Q30	My medicines live up to my expectations.	1213(98.3)	3.25(1.04)	3.58(0.840)	3.00(1.090)	<0.001	-0.368	-0.438
Q31	My medicines prevent my condition getting worse	620(50.2)*	3.89(0.95)	3.92(0.904)	3.73(1.134)	0.117	-0.898	0.690
Q32	Taking medicines interferes with my social life	619(50.2)*	3.77(1.05)	3.82(1.011)	3.47(1.206)	0.006	-0.904	0.250
Q33	I trust the judgement of my doctor(s) in choosing medicines for me.	615(49.8)*	3.70(0.99)	3.79(0.952)	3.24(1.110)	<0.001	-0.807	0.330
Q34	I have to put a lot of planning and thought into taking my medicines.	617(50.0)*	3.35(1.17)	3.47(1.131)	2.79(1.112)	<0.001	-0.359	-0.798
Q35	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies).	616(49.9)*	3.84(1.09)	3.91(1.052)	3.46(1.211)	<0.001	-0.931	0.215
Q36	I am unhappy with the extent to which my medicines interact with alcohol.	1218(98.7)	3.56(1.60)	3.65(1.094)	3.49(1.029)	0.011	-0.334	-0.435
Q37	Taking medicines affects my driving ability.	1212(98.2)	3.82(1.04)	3.89(0.989)	3.77(1.064)	0.050	-0.659	-0.131
Q38	I worry that I have to take several medicines at the same time.	1220(98.9)	3.46(1.17)	3.62(1.131)	3.35(1.179)	<0.001	-0.312	-0.926
Q39	The side effects I get are worse than the problem for which I take medicines.	1220(98.9)	3.76(1.09)	3.98(0.958)	3.61(1.156)	<0.001	-0.722	-0.141
Q40	I worry that my medicines may interact with each other.	1218(98.7)	3.23(1.22)	3.47(1.164)	3.07(1.220)	<0.001	-0.105	-1.044
Q41	I can choose whether or not to take my medicines.	1195(96.8)	2.42(1.30)	2.56(1.275)	2.31(1.312)	0.001	0.518	-1.021
Q42	My doctor(s) spend enough time discussing my medicines with me.	1198(97.1)	3.12(1.20)	3.33(1.132)	2.96(1.229)	<0.001	-0.239	-1.010
Q43	I know enough about my medicines	1198(97.1)	3.75(0.99)	3.75(0.917)	3.76(1.044)	0.949	-0.775	0.115

Table 4-1 Distribution of responses to the 60-item LMQ-1 obtained using paper-based and on-line survey datasets

Item ID	Item	Item response rate n (%)	Overall mean score (±SD)	Paper survey mean score (±SD)	On-line survey mean score (±SD)	P-value (2-tailed)	Skew-ness	Kurtosis
Q44	I am able to balance my day-to-day life with taking medicines.	1196(96.9)	3.87(0.93)	3.96(0.856)	3.80(0.989)	0.004	-0.993	0.914
Q45	There is enough sharing of information about my medicines between the different health professionals providing my care.	1194(96.8)	3.03(1.17)	3.41(1.044)	2.74(1.187)	<0.001	-0.168	-0.827
Q46	I have a say in the brands of medicines I use.	1196(96.9)	2.17(1.11)	2.36(1.061)	2.03(1.120)	<0.001	0.835	-0.100
Q47	I always follow my doctor(s) advice about my medicines.	1201(97.3)	3.78(0.97)	3.98(0.784)	3.63(1.065)	<0.001	-0.876	0.395
Q48	I sometime feel I need to get information from other sources (such as books, friends, internet).	1198(97.1)	2.28(1.19)	2.80(1.235)	1.89(1.008)	<0.001	0.794	-0.402
Q49	I can change times I take my medicines if I want to	1199(97.2)	3.06(1.19)	2.93(1.160)	3.16(1.214)	0.001	-0.204	-1.105
Q50	The health professionals providing my care know enough about me and my medicines.	1196(96.9)	3.18(1.21)	3.56(1.079)	2.90(1.224)	<0.001	-0.306	-0.911
Q51	My medicines are working	1198(97.1)	3.75(0.96)	4.01(0.750)	3.55(1.053)	<0.001	-0.834	0.482
Q52	I can adapt my medicine-taking to my lifestyle	1192(96.6)	3.46(1.05)	3.60(0.973)	3.34(1.097)	<0.001	-0.565	-0.362
Q53	My doctor(s) listen to my opinions and concerns about my medicines.	1197(97.0)	3.42(1.09)	3.68(0.954)	3.22(1.152)	<0.001	-0.603	-0.329
Q54	I can vary the dose of the medicines I take.	1195(96.8)	2.44(1.21)	2.39(1.148)	2.48(1.247)	0.178	0.551	-0.813
Q55	I get too much information about my medicines	1192(96.6)	3.97(0.89)	3.79(0.931)	4.12(0.820)	<0.001	-0.939	1.174
Q56	Changes in daily routine cause problems with my medicines.	1189(96.4)	3.10(1.18)	3.43(1.131)	2.85(1.167)	<0.001	-0.135	-1.113
Q57	My doctor(s) takes my concerns about side effects seriously.	1187(96.2)	3.19(1.04)	3.42(0.959)	3.02(1.080)	<0.001	-0.281	-0.459
Q58	My medicines have an adverse effect on my sexual life.	1184(95.9)	3.30(1.11)	3.50(1.037)	3.15(1.149)	<0.001	-0.260	-0.514
Q59	The side effects are worth it for the benefits I get from my medicines.	1191(96.5)	3.27(0.97)	3.27(0.951)	3.25(0.976)	0.790	-0.286	-0.021
Q60	The medicines I use have an adverse effect on the holidays I can take.	1188(96.3)	3.59(1.124)	3.77(1.047)	3.45(1.163)	<0.001	-0.574	-0.382

Table 4-1 Distribution of responses to the 60-item LMQ-1 obtained using paper-based and on-line survey datasets

*Items with the lowest response rates due to an error of omission in the first available on-line survey, which was later realised and corrected. ^ item with highest overall mean score; # item with lowest mean score

4.3.3 Participant characteristics

More females completed both paper (62.1%, n=306) and on-line (81.6%, n=542) surveys than males ($p<0.001$), with overall age of participants ranging from 18 to 90 years. Younger respondents (< 65 years), and those with college/further education mostly completed the on-line survey, whereas more people aged 65 or over returned a paper survey ($p<0.001$). Overall, most participants (85.6%, n=992) used up to and including eight prescription medicines, 9.7% (n=113) needed assistance with using their medicines, and 27.9% (n=326) paid for their NHS prescription medicines. Table 4-2 below shows the characteristics of participants completing the LMQ-1 survey.

Characteristic		**Paper survey** n (%)	**On-line survey** n (%)	**Total sample** n (%)
Gender	Female	306(62.1)	542(81.6)	848 (73.3)
	Male	187(37.9)*(n=493)*	122(18.4) *(n=664)*	309 (26.7*) (n=1157)*
Age (years)	18-29	48(9.7)	93(13.9)	141(12.1)
	30-49	98(19.7)	258(38.7)	356(30.6)
	50-64	143(28.8)	254(38.1)	397(34.1)
	65 or over	208(41.8)*(n=497)*	62(9.3) *(n=667)*	270(23.2)*(n=1164)*
Education level	Bachelor degree or higher	148 (30.5)	301(45.2)	449(39.0)
	College level	140(28.8)	258(38.7)	398(34.5)
	Secondary level	145(29.8)	93(14.0)	238(20.6)
	Up to primary	53 (10.9) *(n=486)*	14 (2.1)*(n=666)*	67(5.8) *(n=1152)*
Employment	Employed	176(35.8)	324(49.0)	500(43.4)
	Unemployed	74(15.1)	182(27.5)	256(22.2)
	Retired	241(49.1)*(n=491)*	155(23.4)*(n=661)*	396(34.4)*(n=1152)*
Ethnicity	White	408(83.8)	613(93.4)	1021(89.3)
	Asian/Chinese	27(5.5)	28(4.3)	55(4.8)
	African/Caribbean	44(9.0)	6(0.9)	50(4.4)
	Mixed	8(1.6)*(n= 487)*	9(1.4) *(n=656)*	17(1.5) *(n=1143)*
Number of medicines				
	1-4	261(53.2)	302(45.2)	563(48.6)
	5- 8	176(35.8)	253(37.9)	429(37.0)
	≥ 9	54(11.0) *(n= 491)*	113(16.9)*(n= 668)*	167(14.4)*(n= 1159)*
Requires assistance with using medicines				
	No	453(91.5)	596 (89.4)	1049 (90.3)
	Yes*	42(8.5) *(n= 495)*	71(10.6) *(n= 667)*	113 (9.7) *(n=1162)*
Pay for prescriptions				
	No	349(71.7)	494(72.0)	843(72.1)
	Yes	138(28.3)*(n=487)*	188(27.4)*(n=682)*	326(27.9)*(n=1169)*

Table 4-2 Characteristics of participants completing theLMQ-1 survey

Notes; *Carers included spouse/partner, relative, friends, nurse, support workers, and support group
Due to variations in the completion of questions for participant characteristics, and resulting missing data, percentages are calculated separately for those answering each question; this explains the different samples sizes reported.

4.3.4 Results of the principal components analysis

A total of 544 fully completed responses (listwise deletion of missing data) were subjected to PCA. The KMO statistic (0.888) was greater than the recommended value of ≥ 0.6 and Bartlett's Test of Sphericity was significant (approx. chi-square =9788.903, df= 861, p<0.001), implying data were factorable.[187,188] Moreover, inter-item correlation coefficients were adequate and did not reveal multi-collinearity (r < 0.8),[174] which also encouraged PCA.

Multiple criteria were used to aid decisions on the number of factors to retain: Kaiser's criterion (eigenvalue > 1), scree plots, and parallel analysis.[187] The initial solution resolved into 14 components with eigenvalues > 1, and explained 61.1% of the total variation. Inspection of the scree plot revealed two sudden breaks at the 5th and 9th component (See Figure 4-2), suggesting between five and nine underlying domains.

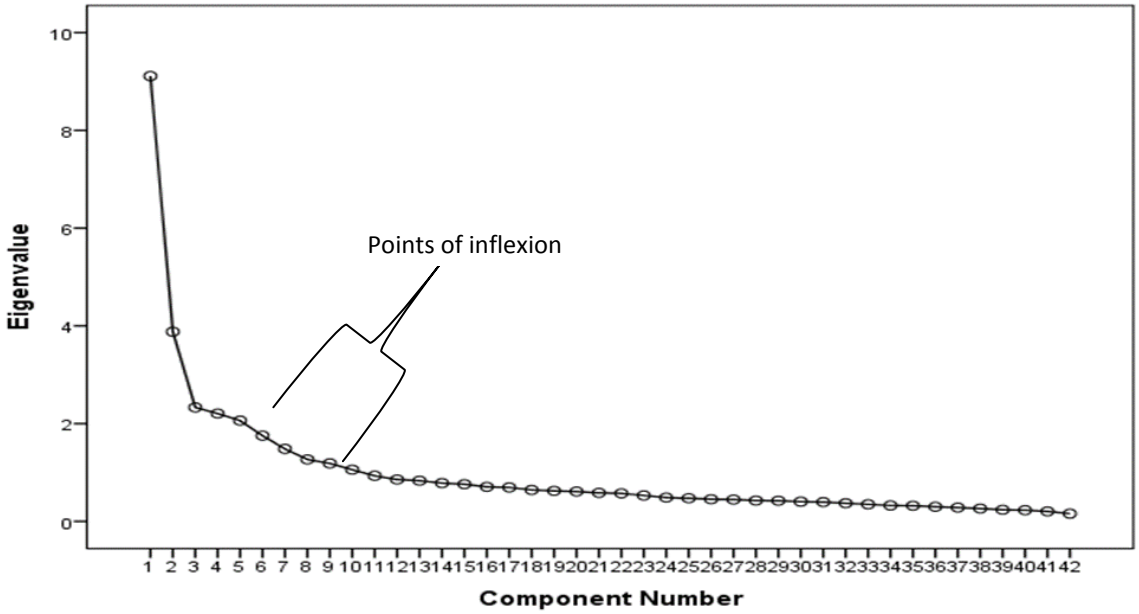


Figure 4-2 Scree plot illustrating the number of components (domains) in the LMQ-1

Note; The plot shows two possible points of inflexion (breaks in the curve) at components 5 and 9, suggesting a multidimensional factor solution and further investigations.

To verify the findings from the scree plot, parallel analysis (by Monte Carlo PCA[171]) was used and it confirmed eight components with observed eigenvalues exceeding criterion values (See Table 4-3). PCA was re-run and the number of components fixed to eight. The resulting 8-factor solution (Table 4-5) explained 57.4% of the total variation, and was conceptually interpretable.

Component	Actual/Observed eigenvalues	Criterion/Simulated eigenvalues*	Decision
1	9.962	1.4519	Accept
2	4.036	1.4163	Accept
3	2.367	1.3878	Accept
4	2.076	1.3637	Accept
5	1.976	1.3412	Accept
6	1.724	1.3242	Accept
7	1.515	1.3055	Accept
8	1.389	1.2868	Accept
9	**1.152**	**1.2686**	**Reject**
10[a]	**1.110**	**1.2526**	**Reject**

Table 4-3 Comparing eigenvalues using parallel analysis (LMQ-1)

Notes; * Generated randomly for 60 variables, in 100 replications using Monte Carlo PCA.[171]
[a]Only 10 of 60 components are shown in the table; the remaining components also had observed eigenvalues less than criterion eigenvalues and were rejected on this basis.

4.3.5 Item reduction

Items with poor factor loadings < 0.3 and/or cross loadings of ≥ 0.4 on two or more factors were deleted upon judgement that they did not fit well in underlying domains.[174,182,187] Five items with ceiling effects (showed in Table 4-1) were retained as their factor loadings exceeded the minimum threshold for item retention (≥0.3), and were also judged as conceptually relevant.

This resulted in removal of eighteen items (n=18) from the original item pool (See Table 4-4), leaving 42 items.

Item/Statement
Q6- I am concerned about running out of medicines
Q9-I would be concerned if I forgot to take my medicines
Q10-I am concerned that I may forget to take my medicines
Q14-I am comfortable taking the medicines I have been prescribed
Q15 -I am comfortable with the times I should take my medicines
Q16 -I find the patient leaflet in my medicines containers useful
Q19-I am concerned that I am too dependent on my medicines
Q26-I sometimes run out of medicines
Q36-I am unhappy with the extent to which my medicines interact with alcohol
Q39-The side effects I get are worse than the problem for which I take the medicines
Q43-I know enough about my medicines
Q44-I am able to balance my day to day life with taking medicines
Q46-I have a say in the brands of medicines I use)
Q47-I always follow my doctor's advice about medicines
Q48-I sometime feel I need to get information from other sources (such as books, friends, internet)
Q55-I get too much information about my medicines
Q58-My medicines have an adverse effect on my sexual life
Q59-The side effects are worth it for the benefits I get from my medicines

Table 4-4 Items deleted from the LMQ-1

Note; Q1-Q60 represent item codes for the 60-item LMQ-1

4.3.6 The resultant LMQ-2 factor solution

The 42-item factor solution, which was labelled as the LMQ-2, is shown in Table 4-5. Emerging factors were interpreted as: patient-doctor relationships and communication about medicines (9 items); interferences to daily life (8 items); practicalities (7 items); effectiveness (4 items); patient-pharmacist communication about medicines (3 items); acceptance of medicine use (4 items); autonomy/control over medicine use (4 items) and concerns about potential harm (3 items). Subscales have internal consistency (Cronbach's alpha) in the range of 0.592-0.887.

LMQ-2 subscale/Items	Components							
	1	2	3	4	5	6	7	8
1.Patient-doctor relationships and communication about medicines (9 items, α =0.887)								
Q53. My doctor(s) listen to my opinions and concerns about my medicines.	**.887**	.012	-.123	.062	-.080	-.030	.094	-.044
Q22.The information my doctor(s) gives me about my medicines is useful.	**.846**	-.099	.029	-.043	.116	-.074	.017	-.003
Q42. My doctor(s) spend enough time discussing my medicines with me.	**.805**	.057	.034	-.159	-.075	.087	-.010	.030
Q20. I am confident speaking to my doctor(s) about my medicines.	**.791**	.012	.062	-.049	.022	.015	.020	-.176
Q57. My doctor(s) takes my concerns about side effects seriously	**.728**	.054	-.155	.183	-.142	-.037	-.053	-.091
Q21. I understand what my doctor(s) tell me about my medicines.	**.658**	.037	.044	-.171	.197	.119	.087	-.082
Q50. The health professionals providing my care know enough about me and my medicines.	**.592**	-.100	.025	.180	.062	-.059	-.028	.137
Q33. I trust the judgement of my doctor(s) in choosing medicines for me.	**.542**	-.001	.031	.314	.015	-.159	-.129	.001
Q45. There is enough sharing of information about my medicines between the different health professionals providing my care.	**.542**	-.028	.004	.058	.062	-.003	.004	.209
2.Interferences to daily life (8 items, α = 0.838)								
Q32. Taking medicines interferes with my social life.	-.009	**.849**	-.039	.064	.015	.067	.008	-.092
Q35. Taking medicines causes me problems with daily tasks (such as work, housework)	-.048	**.820**	-.089	.091	.046	-.037	.035	-.047
Q60. The medicines I use have an adverse effect on the holidays I can take.	-.052	**.730**	-.012	.177	-.005	.006	-.019	-.150
Q29. My life revolves around using my medicines.	-.120	**.698**	-.052	.181	-.022	-.317	.100	-.143
Q37. Taking medicines affects my driving ability	.002	**.686**	-.110	.029	.040	.026	-.122	-.077
Q34. I have to put a lot of planning and thought into taking my medicines	.068	**.618**	.041	-.192	-.044	-.180	-.171	.121
Q38. I worry that I have to take several medicines at the same time	.140	**.592**	.087	-.059	-.073	.046	.047	.135
Q56. Changes in daily routine cause problems with my medicines.	.024	**.558**	.105	-.214	.070	-.009	-.136	.188
3.Practicalities (7 items, α=0.708)								
Q7. It is difficult to identify which medicine is which.	-.133	-.037	**.773**	-.034	.046	.030	.073	.019
Q1. The instructions on my medicines are easy to follow.	.059	-.163	**.683**	.139	-.045	.051	.006	-.066
Q5. I find opening the packaging of my medicines difficult	-.048	.002	**.640**	.017	-.062	-.052	.109	-.002
Q2. I find getting my prescriptions from the doctor difficult.	.244	-.064	**.635**	.087	-.163	-.043	-.192	-.121
Q3. I find getting my medicines from the pharmacist difficult	-.099	.041	**.628**	.259	.089	-.165	-.175	-.146
Q17 I find using my medicines difficult.	-.027	.295	**.465**	-.087	.040	.208	.134	-.019
Q8. It is easy to keep to my medicines routine.	.027	.083	**.400**	-.049	.009	.221	.011	.116

Table 4-5 The 42-item 8-factor solution of the Living with Medicines Questionnaire version 2 (LMQ-2)

Notes; Extraction method - Principal Component Analysis; Rotation Method: Promax with Kaiser Normalization; α= Cronbach's alpha
N= 544 fully completed responses were used. The numbers in bold represent substantive factor loadings (≥ 0.4) showing items that are adequately associated with a specific domain/subscale of the LMQ-2.

LMQ-2 subscale/Items	Components							
	1	2	3	4	5	6	7	8
4.Effectiveness (4 items , α =0.796)								
Q18. I am satisfied with the effectiveness of my medicines	-.066	037	.161	**.698**	.102	-.051	.041	.129
Q30. My medicines live up to my expectations	.073	.088	-.014	**.694**	-.008	.084	.054	.092
Q51. My medicines are working.	.090	-.007	.060	**.685**	.019	.008	.181	.137
Q31. My medicines prevent my condition getting worse.	.040	.033	.041	**.650**	-.070	.168	-.137	-.049
5.Patient-pharmacist communication about medicines (3 items, α= 0.877)								
Q25. The information my pharmacist gives me about my medicines is useful.	.030	.000	-.039	.049	**.911**	-.026	-.045	-.036
Q23. I am confident speaking to my pharmacist about my medicines	.034	.030	-.055	.037	**.879**	.002	-.041	.027
Q24. I understand what my pharmacist tells me about my medicines.	-.012	.014	.008	-.042	**.936**	.013	.006	-.035
6.Acceptance of medicine use (4 items, α = 0.592)								
Q13.Taking medicines is routine for me	-.019	.010	.060	-.114	-.030	**.824**	.001	.008
Q27. I accept that I have to take medicines long term	-.011	-.088	-.107	.254	-.049	**.739**	-.130	-.006
Q4. My medicines are important to me.	-.084	-.232	.097	.083	.053	**.494**	-.068	-.093
Q28. My medicines allow me to live my life as I want to.	.050	.185	-.045	.278	.098	**.483**	.102	.037
7.Autonomy/control over medicine use (4 items, α = 0.625)								
Q54. I can vary the dose of the medicines I take	-.002	-.245	-.010	.064	.028	-.092	**.763**	-.049
Q49. I can change the times I take my medicines if I want to.	.002	.077	-.061	-.021	-.128	.086	**.752**	-.111
Q41. I can choose whether or not to take my medicines.	.034	-.103	.115	-.106	.035	-.301	**.592**	.043
Q52. I can adapt my medicine-taking to my lifestyle.	.038	.106	.037	.194	-.004	.050	**.592**	.029
8.Concerns about potential harm (3 items, α = 0.751)								
Q11. I am concerned about experiencing side effects.	-.053	-.041	-.051	.040	-.003	-.013	-.021	**.925**
Q12. I am concerned about possible damaging long term effects of taking medicines	-.055	-.120	-.099	.205	-.029	-.019	-.080	**.902**
Q40. I worry that my medicines may interact with each other	.053	.329	.163	.011	-.068	-.061	.048	**.421**

Table 4-5 The 42-item 8-factor solution of the Living with Medicines Questionnaire version 2 (LMQ-2)

Notes; Extraction method - Principal Component Analysis; Rotation Method: Promax with Kaiser Normalization; α= Cronbach's alpha
N= 544 fully completed responses were used. The numbers in bold represent substantive factor loadings (≥ 0.4) showing items that are adequately associated with a specific domain/subscale of the LMQ-2.

4.3.7 Free-text comments – content coverage

Nearly a third of respondents (30.6%, n=360) provided free-text comments in the paper and on-line questionnaires, a total of 421 different comments, most of which supported the original content domains (97.2%).

In particular, there were 76 comments describing the impact of using medicines, many (n=71) of which were negative, revealing medicine-related disruption to daily activities, such as work. The need to plan/adjust personal schedules to cope with medicine-related demands, such as dose timing, food-requirements, storage-requirements, and need for blood tests, was perceived to be time- and energy-consuming. For instance, a participant commented that '*My worries are primarily around making sure I have my insulin with me, that I don't leave it at home/work, that I have spare pens & testing equipment available and that when going [somewhere] there's the facility to store insulin (i.e. fridge)'.*

Sixty five comments described the impact of side effects on daily activities (such as work, driving), personal life (including personal-identity, self-image, sexuality) and socialisation, with some side effects described as disabling and reducing quality of life. As an example, one participant commented that '*…the side effects of my SSRI [antidepressants], complete asexuality, …are still life altering in a very negative and permanent way.'*

In relation to efficacy (or perceived lack of efficacy), 61 comments described dependence on medicines for symptom relief, performance of daily activities, and prolonging life, while others desired alternative treatment options. For instance, one participant indicated that *'without all my pain and nerve medication I would be unable to get out of bed, move around and live and sleep so they are integral to keeping me mobile as the pain is overpowering ..so I have no choice if I want to live my life at all but to take high doses of pain meds to get through each day'* and yet another participant acknowledged that *'I need more pain relief but unable to find anything that works..'.*

Comments about practicalities (n=60) included concerns about running out of medicines, the need for more suitable packaging and labelling of medicines, as well as tools to support medicines use, such as compliance aids. Example comments were: *'life would be so much easier if I could write on the packet e.g. M T W T F S S etc. but they seem to delight in packaging them in stuff you can't write on'* and '*the constantly changing shape, colour and packaging of tablets with each re-issue is confusing - I understand the NHS has to get best value for medicines and this means changes to supply but it is very confusing for patients'.*

Relationships with healthcare providers were mentioned in 58 comments, many suggesting that discussions of medicines were inadequate, and failed to consider participants' concerns. For instance, one participant indicated that *'At no time ever has a doctor discussed side effects or interactions between my medicines. I cannot imagine ever meeting a doctor who cares enough about to be remotely interested. Do they exist?'* Some participants lacked trust and confidence in providers, and desired comprehensive, updated and meaningful information about the risks and/or benefits of their medicines; however, only 19 comments described searching for additional information mostly on-line. An example comment regarding patient-doctor communication was *'I would like doctors to give more information on the effects of taking medicine for life and risks of higher doses-they only ever give one type [of information]..'..*

Fifty-nine comments articulated participants' general attitudes towards medicines use, including worries about adherence, dependence, interactions, and concerns about branded/generic medicines. Example comments were:

> *'Sometimes forget to take my teatime tablets…can be a worry';*
>
> '*I take more than one medicine, some I am addicted to so cannot stop even if I wanted to';*
>
> *'I now take up to 27 tablets and 7 injections a day. I am very concerned about the interaction of some of these medicines';* and
>
> *'I find different brands of medication and their efficacy can vary a lot-I take thyroxine and find a great difference between the generics'.*

Of the comments falling outside the eight themes initially defined by Krska et al,[119] a few comments (n=8) described concerns about the costs associated with using long-term prescription medicines, an issue not included in the LMQ-1, illustrated by one participant: *'the cost of my medicines is my biggest concern. I have a prepayment card that helps … without being able to afford that I would find the cost very difficult. I don't think some people could manage.'* The rest of the comments described participants' health-related problems and other non-medicine-related issues.

4.4 Discussion

This chapter reported a study designed to investigate the domains underlying the 60-item LMQ-1, which was shortened to a 42- item version (the LMQ-2) using a combined dataset obtained from the UK general public and users of community pharmacies in south-east England. The findings revealed eight domains within the LMQ-2: patient-doctor relationships and communication about medicines; patient-pharmacist communication about medicines; interferences to daily life; practicalities; effectiveness; autonomy/control over medicine use; concerns about potential harm; and acceptance of medicine use. These domains closely match those identified from qualitative research (in-depth interviews with 21 patients) on which the original instrument was based. Additional comments added by questionnaire respondents within this study also supported these domains, which are thought to relate to an over-arching construct of medicines burden for which no measure currently exists.

Qualitative findings also identified themes relating to relationships and communication with health professionals, except that statistical analyses in this chapter identified domains specific to doctor- and pharmacist-related relationships or communication in the LMQ-2. Unlike the qualitative themes in the originator study,[23] the present study did not reveal 'information about medicines' as a separate domain in the LMQ-2. Issues around medicine-related information merged in the respective domains covering doctor or pharmacist communication. Patient-provider communication about medicines has been documented as a factor affecting patient's experiences of medicine use in other qualitative and quantitative studies.[23,87,136,137] Relationships with health professionals supplying prescriptions/medicines and information sharing may influence both commitment to taking medicines and perceptions of effectiveness,[195]

with poor relationships and communication becoming burdensome to some individuals due to consultation styles, the amount of information provided, conflicting information and lack of continuity of care.[196,197] Observational research shows that overall treatment burden may be compounded by patients' experiences of medicine use being neglected during consultations.[101]

In terms of medicine effectiveness, the LMQ-2 was found to have a domain corresponding with *'efficacy'* in the original qualitative themes from which the questionnaire was derived. Perceptions of efficacy and concerns about negative effects of medicines are widely reported in the literature. '*Concerns about potential harm'* and medicine-related risks emerged as a unique domain in the LMQ-2, covering issues around long-term effects, and drug-drug interactions. However, the *'side effects'* theme revealed in the qualitative interviews did not emerge as a separate domain in the LMQ-2, but generated a significant number of free-text comments. In fact, three side-effect-related items *('The side effects I get are worse than the problem for which I take the medicines'; 'My medicines have an adverse effect on my sexual life'; 'The side effects are worth it for the benefits I get from my medicines'),* and two items relating to other concerns about medicines *('I am concerned that I am too dependent on my medicines'; 'I am unhappy with the extent to which my medicines interact with alcohol')*, though conceptually relevant and described in medicine-related narratives of the lay public,[21,81] did not meet the statistical/psychometric criteria to be included in the LMQ-2. Perceptions of efficacy and concerns about negative effects of medicines are widely reported in the literature, with most patients weighing benefits from medicines against any associated harms or burden.[108,109]

Practicalities involved in using medicines (e.g. accessing prescriptions, identifying and opening packaging) were revealed in both the present study and the originators' qualitative study.[23] The '*impact of medicines on daily life'* theme, from the originator in-depth interviews, was also identified in the present study but relabelled to reflect medicine-related *'interferences'* in the LMQ-2. For instance, two marker items, as items loading most strongly on the '*interference'* factor, related to medicine-related disruptions to social life and to daily tasks (including work), and the change in domain nomenclature was thought to specify the negative impact of medicines.

Many people on long-term medicines endure inconveniences associated with their use while reluctantly accepting the need for treatment.[88,195,198] The '*attitudes towards medicines'* theme, identified in the originator interviews, seemed to relate to *'acceptance of medicine use'* in the LMQ-2 domains covering items (e.g. *'I accept that I have to take medicines long term').*

The domain *'autonomy/control over medicine use'* in the LMQ-2 was as hypothesised in the originator qualitative interviews, and covered items around autonomy to varying regimen dosing or timing. Regimens that are inconvenient (or inflexible) may lead to perceived lack of control or autonomy.[95] Perceived inability to modify regimens as well as experiences of adverse effects may add to the overall burden through interfering with daily activities.[88]

In addition, free-text comments indicated that further development work might need to incorporate cost-related items in a revised LMQ instrument. Chapter 1 revealed that prescription medicine costs may impose financial burden, and the literature indicates consequences that negatively impacts on individual wellbeing, family and social life and exacerbate treatment burden.[44,46,48,88] Further studies may generate and test cost-related items to fill the gap in the LMQ-2.

Despite missing dimensions, the LMQ-2 appears to be more comprehensive than existing instruments (reported in Chapter 2) purporting to evaluate patient experiences of medicines use. The generic nature of this questionnaire contributes to its potential usefulness in identifying a wide range of issues arising from medicines use either in single conditions or in patients with multi-morbidity; most of the domains elicited have been cited[88] as particularly burdensome to users of long-term medicines. However, future studies are desirable to not only incorporate deficient domains but also to revise/refine the questionnaire even further and confirm its suitability as a measure of prescription burden for people using long-term medicines.

Study strengths and limitations

Although item-level response rates were generally high, potentially indicating interest in the medicine-related issues covered in the questionnaire, missing data led to variations in sample sizes across different statistical procedures reported in this chapter. Nevertheless, assumptions for sample size adequacy were met for the analytical procedures, and initial pilot data were obtained from demographically diverse settings in the UK.

Elimination of poorly performing items was conducted using psychometrically sound criteria and discussions between the researcher and the supervision team. However, the item reduction process may have led to loss of potentially relevant items that require further consideration in subsequent studies. One item *('My medicines are important to me')*, with significant ceiling effects, was retained in the LMQ-2 despite possible acquiescence bias (tendencies to agree with a statement even when in doubt). Nonetheless, other items in the LMQ-2 did not reveal excess skewness in score distribution, commonly found with measures of treatment satisfaction.[109]

Potential obsequiousness bias (the tendency to alter responses in the way perceived as socially desirable), a common methodological problem with self-report measures, was minimised by the use of different self-report methods (paper and on-line), encouraging completion outside of standard health-facilities, in diverse public settings.

4.5 Chapter summary

This thesis chapter provides an initial understanding and clarification of the domains underlying the Living with Medicines Questionnaire, and proposes a shorter 42-item instrument (the LMQ-2). The chapter provides an initial test of the instrument's construct validity, but highlights the need for further research work on the instrument, particularly incorporating missing content about cost-related burden, and item generation in deficient domains (especially the impact of side effects). Inevitably, revisions to the instrument will demand further retesting. Nonetheless, the findings reported in this chapter are promising and suggest that most of the domains underlying LMQ instrument closely resemble the themes derived from the originator qualitative study (on which the questionnaire was based) that explored medicine-related issues in long-term users of medicines.

5.1 Introduction

Streiner and colleagues (2015) specify that 'most of the scales [or questionnaires] that have stood the test of time have been revised, re-tested, and tested again'.[118] Moreover, 'as our understanding of the construct we are measuring evolves, we often need to revise the scales accordingly'.[118] The original Living with Medicines Questionnaire (LMQ-1) was developed as a multidimensional generic measure of the experience of using prescription medicines for people with long- term illnesses.[119] The previous chapter (Chapter 4) described development of a shorter, 42-item version (LMQ-2), but also revealed a few gaps in the LMQ-2.

Particularly, the LMQ-2 lacked items about prescription costs and their impact on those using medicines long-term. It is estimated that 80% of the English population aged 19-59 pays for their prescriptions, and up to 73% of people living with long-term conditions pay for their prescriptions.[47,102] Many of these individuals may experience cost-related pressures and concerns, which may lead to non-adherence.[52] A cost-related component was worth incorporating into the LMQ-2.

In addition, the impact of side effects was not clearly assessed by the LMQ-2, with the 'side effects element' not emerging during the factor analyses described in Chapter 4. Regardless, side effects are noteworthy in patient's experience of medicine use owing to their impact on health and wellbeing, quality of life, and intrusions to lifestyle.[48,81,92] The impact of medicines on social life (leisure activities and social relationships) was also not explored in the LMQ-2. Some medicines may impact on ability to sustain ordinary conversations with friends or family, and thus could affect social interactions, while others fear possible interactions between medicines and social drinks (such as alcohol).[81] Disease-specific measures of social support/conflict in chronic illness refer to understanding (or misunderstandings) by family members, and the challenges of planning activities that align with medicine regimes.[199,200] To consolidate the LMQ-2, there was a need to incorporate relevant items to fill the gaps in the LMQ-2, as well as to review existing items.

There are multiple sources of items, and during questionnaire development patient-generated data, the literature (or theory), and existing scales can be used (See Table 2-3). Existing scales (such as the LMQ-2) are a particularly useful source of items; they save time and resources involved in *de novo* item generation, and items in such scales have been pretested.[118,127] Following item generation and selection for missing dimensions (cost, side effects, and social impact), and rewording existing LMQ-2 items, the revised questionnaire (LMQ-2.1) was subjected to cognitive testing.

Responding to survey questions is a complex cognitive task.[163] It involves processes such as comprehension of meanings of specific words and phrases in a questionnaire item; recalling relevant information necessary to answer a specific question; decision and judgement; and actual response formulation.[163,164] Flaws and errors may arise, at any of these processes, while responding to questionnaire items [165–168] Standard guidance on the development of patient-reported instruments stipulates that all questionnaire-items are assessed for patient understanding, including adequate readability of items for the intended population.[124] To minimise measurement errors, it is pertinent that participants understand instructions, items, and response options (answers) in the way that is intended and any potential problems are documented.[164,167]

Qualitatitve interview techniques, particularly cognitive interviewing, allow direct patient input into questionnaire understandability, layout, and format.[124] Cognitive interviews are commonly used for pretesting and optimising questionnaires in development, to ensure that questions are interpreted as intended, and ultimately to improve data quality.[166] Cognitive interviewing facilitates early identification of questionnaire problems, which may affect response rates, data quality, and questionnaire reliability and validity.[165,166] It also provides a basis for revising problematic items during questionnaire development. Cognitive interview data also contributes to content validation of existing instruments, by ensuring that they cover 'the most important …concepts and items, and that items are complete, relevant (appropriate), and understandable to the patient.'[124] Thus to study these issues, the revised LMQ (LMQ-2.1) was tested to gather data about potential questionnaire problems, all of which can supplement psychometric data on properties of questionnaires undergoing development.

Aim and objectives

This aspect of the thesis aimed to generate new questionnaire content for missing domains, revise existing items in the LMQ-2, and cognitively test questionnaire content (and relevance) in a suitable target population so as to attain a more comprehensive questionnaire.

Objectives were:

- To revise the LMQ-2 by generating new items for deficient domains and reviewing existing ones.
- To assess face and content validity of the resulting interim version (LMQ-2.1), by gaining feedback on questionnaire content.

5.2 Methods

This study was reviewed by the Medway School of Pharmacy School Research Ethics Committee (SREC), and ethics approval was granted in May 2015 (see Appendix 8).

5.2.1 New item generation

During questionnaire development, a relatively large item pool is advisable. A multi-source and stepwise item generation process was conducted. Firstly, I reviewed qualitative literature (i.e. verbatim quotes) exploring patient perceptions and experiences of prescription costs, side effects, and social impact of medicine use. In addition, medicine-related questionnaires were assessed to check for potentially relevant items with respect to the three deficient domains. Secondary data based on the 21 patient interviews that informed LMQ-1 development,[23] were re-analysed by recoding medicine use issues into the original eight domains (similar to framework analysis), and examining the 'impact' and 'side effects' domains to generate new statements from these areas. In addition, medicine use issues that fell outside of this framework, particularly cost-related difficulties, were reviewed to aid new item generation. In addition, free-text survey responses gathered using the LMQ-1 (Chapter 4), were also reviewed to identify relevant issues relating to prescription costs, side effects, and social impact of medicine use.

After discussion of potential new items, the proposed item pool was further screened and irrelevant, vague or redundant statements eliminated by collaborative efforts. A total of 12 statements were newly generated: cost (n=4), side effects (n=3), and social impact of medicines (n=2).

In addition, three global items, rated on visual analogue scales (VAS) to ascertain concepts measured by the LMQ – global satisfaction, global burden and global optimisation – were developed and tested. New items proposed during the item generation phase are shown in Table 5-1.

Items		**Source**
Cost-related statements		
1	I worry about paying for my medicines.	1,2
2	I have to pay more than I can afford for my medicines.	1,2
3	I sometimes have to choose between buying basic essentials or medicines.	1,2
4	I don't mind paying for my medicines because I need them.	1
Statements about side effects		
1	The side effects I get from my medicines are bothersome.	1
2	The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	1
3	The side effects I get from my medicines adversely affect my well-being.	1
Statements about impact on social life		
1	My medicines can interfere with my social relationships. *Reworded after cognitive interviews:* My medicines interfere with my social relationships.	1
2	My medicines affect what I can eat or drink. *Reworded after cognitive interviews:* I am concerned that my medicine(s) affect what i can eat or drink.	1
Global items to assess concepts measured by the LMQ-2		
VAS 1	Taking everything into account, how satisfied are you with your medicines?	3
VAS 2	How optimal do you feel your medicines are for you?	4
	Reworded after cognitive interviews: On balance, do you feel your medicines are right for you?	
VAS 3	Overall, how much of a burden do you feel your medicines are to you?	5

Table 5-1 New items generated about cost, side effects, and social impact.

Notes; Source of new statements or words used in the revised questionnaire:

1. Patient interviews and free-text survey data
2. Prescription Charges Coalition, England (2013/2014)[47,102]
3. Atkinson et al (2005)[74]
4. Royal Pharmaceutical Society (2013)[1]
5. Team discussions (The author and supervision team)

5.2.2 Revision of existing items

Following new item generation, existing items in the LMQ-2 and some socio-demographic variables were reviewed. I also suggested items which required rewording or adaptation from the original questionnaire (LMQ-1), based on the findings of factor analyses described in Chapter 4. Discussions were held with my supervisors to agree proposed revisions to original items, and to resolve any wording issues. Subsequently, a 58-item interim version of the questionnaire (LMQ-2.1) was created as a product of item addition, rewording, and deletions (See Appendix 14).

5.2.3 Cognitive interviews- Assessing item comprehension in the LMQ-2.1

Qualitative cognitive interviewing methodology was used. Following new item generation and revisions, I tested the resultant instrument, the LMQ-2.1, using cognitive interviews. This interim version was a six-page instrument including 58-Likert-type statements, the three VAS (global satisfaction, global burden and global optimisation), and a free-text question. Likert-type items have 5-point response options rated from strongly agree to strongly disagree, with a neutral mid-point. On the VAS, which are 10-cm lines with diametrically opposing words at the anchors, respondents were asked to mark the point that corresponds to their perceived state of satisfaction, burden, or optimisation of the medicine use experience. The last page covered participant demographics.

Two paper-based formats were created based on the order and grouping of items: an intermixed version (LMQ-2.1-I) with a relatively random order of items throughout the questionnaire, and a grouped/labelled version (LMQ-2.1-GL). In the latter version, Likert-type items were subdivided and ordered into thematic groups (domains) relating to prescription medicine use experiences: access, practical issues, cost, effectiveness, concerns, side effects, routine of medicine use, perceived interference to day-to-day life, impact on social life, communication with pharmacist(s), communication with doctor(s), and perceived control or autonomy over medicine use. This was intended to simplify and test usability of the different questionnaire formats.

5.2.4 Study population and recruitment

Members of a general public engagement group at the Medway School of Pharmacy (known as the PIPS group), which meets regularly to discuss on ongoing medicine-related research, were involved in development of the instrument. At two different face-to-face meetings, the researcher (BK) presented verbal information about the study and sought general opinions on the instrument. They were also invited to consider taking part in the study as participants (if they met the inclusion criteria: 18 years or older, using long-term prescription medicines, able to read and communicate in English, and were living in England at the time of the study), and/or to recruit others known to them (snowball technique).

Approximately 2-3 weeks after the meetings, written invitations (Appendix 9) and study packs were posted to each PIPS member who provided their full postal address. Each study pack contained: a general cover letter, a participant invitation letter, information sheet, consent form, participant details form (See Appendices 10-12 respectively), and prepaid-post envelope for returning the latter two documents. Participants willing to participate in the snowball recruitment were given additional study packs for distribution during the subsequent month, and a preprinted form with a short, introductory message to use during recruitment (See Appendix 13).

All consenting participants were contacted by telephone and/or email to schedule an interview at a time and place of their choosing. A follow-up telephone call was made a few days before the appointment to confirm interest and voluntary participation in the study. Respondents were sampled to represent diverse age ranges, gender, and number of long-term medicines used. All interviews took place between June and July 2015.

5.2.5 Interview procedures

Interviews were conducted in suitable rooms at the School, or at particpant's homes according to interviewee preferences to ensure their comfort and ease. Interviews, which lasted about an hour (range 40 minutes to 1.5 hours), were conducted to elicit thoughts or ideas about the questionnaire wording, layout, and concepts covered in the LMQ instrument. The intermixed version (LMQ-2.1-I in Appendix 14) was presented to and completed by all participants during the interviews, while the grouped version (LMQ-2.1-GL in Appendix 15) was viewed at the end of each interview to compare its format to the LMQ-2.1-I. Participants were reminded that the overall purpose of the interview was to evaluate the questionnaire, rather than share their personal experiences about living with medicines.

Before and during the interview, participants were asked to think aloud (or talk out their thoughts) while completing each item, saying whatever came up in their mind. General instructions for the interview included: reading each survey item out aloud, responding to the item, thinking out loud, and/or answering the probe question(s). As previously discussed in Chapter 3 (section 3.3.2.3), follow-up questions were employed to supplement the think-aloud process, particularly when unobvious answers and potential questionnaire problems were encountered.

The interviewer used both pre-scripted probes (in the interview guide – See Appendix 2), and spontaneous probes that were spurred by a participant's response to an item. Pre-scripted probes were omitted when the interviewer felt that they were already answered through the think-aloud process. Other probes were usually 'thought up' during any given interview, and tailored to interviewee's responses. This probe mixture was thought to achieve a balance between consistency across interviews and having a 'natural', conversational-type, interview.[167,168] Facial expressions, and non-verbal cues (including hesitation, pausing, mumbling, sighing, or intentional skipping of items) were observed, and also used to detect potentially problematic questions, and to assess difficulties experienced while completing the questionnaire. Participants were not 'helped' with answering the questionnaire to simulate completion of self-reported instruments in practice.[94]

All interviews were audio-recorded, and relevant information used to supplement shorthand field-notes (and annotations on questionnaires). Respondents' questionnaires were stored, and used in data analysis.

5.2.6 Data analysis

Although there are no 'gold' standard guidelines for analysing cognitive interview data during questionnaire development, a common aim is to identify problematic areas in a questionnaire,[167] and potential threats to instrument validity.[163,165,166]

A number of coding systems for categorising questionnaire problems exist, and these broadly cover the same domains of questionnaire problems. In a recent study, Buers et al[166] recommend the Willis coding system for analysing questionnaire problems with suggestions that 'it provides more detailed codes that indicate specific directions for revisions'.[166] However,there is inconclusive evidence that fails to confirm whether using such coding systems 'actually' make a difference during identification of questionnaire problems.[166] Moreover, these somewhat 'standardised' analyses of interview data are not only extremely time-consuming, but also dependent on the technique(s) used during cognitive testing.[168]

There are suggestions that for relatively quicker revisions, and in instances of limited resources to allow in-depth analysis, 'reliance on written outcome notes alone may be sufficient'.[168] For instance, in the development of an instrument to assess health-related quality of life among children and adolescents, Irwin and colleagues[201] compiled and analysed interview comments for all items to assess questionnaire problems, and no 'fancy'coding systems were utilised. Research specific to medicine-related questionnaires[94] employs traditional qualitative techniques, akin to constant comparison[178] to group similar comments together and to identify questionnaire problems. In the present study, recruitment was terminated after the 11th interview, as it became clear that 'sampling redundancy', which tends to occur after 8-15 interviews,[127] had been attained and no 'new' questionnaire problems emerged from the interviews.

In this study, interview comments were compiled for each item in specially designed Excel spreadsheets (Appendix 16), and analysed both on an item-by-item basis, and comparatively to assess potential questionnaire problems, including comprehension difficulties. This made it easier to compare comments about each item across all participant responses, and to explore the proportion of participants perceiving an item to be problematic. Questionnaire problems that emerged repeatedly were documented. Unique interpretations of items, different from those intended by developers, were also examined. Such problems, if left unaddressed, may emerge more frequently in an actual survey, and impact on data quality.[168] Participants' recommendations for item retention, rewording, rephrasing, or deletion of individual words, phrases or sentences, were also examined. A summary analysis report was compiled, and discussions held with supervisors on how to address items agreed as problematic, and to make further revisions to the LMQ instrument.

5.3 Results

5.3.1 Participant characteristics

Eleven adults (55% males), aged 42-75 years, participated in the cognitive interviews. Most participants used four or fewer prescription medicines (range, 1-12), once or twice daily, in tablet/capsule formulations. The study population was generally balanced with respect to educational level, but the majority were retirees, most of whom were exempt from prescription charges. All participants resided in areas of Medway in south-east England (See Table 5-2).

Characteristic		n (%)
Gender	Female	5 (45)
	Male	6 (55)
Age (years)	30-49	1(9)
	50-64	5(46)
	65-74	3(27)
	≥75	2(18)
Educational level	University	4(36)
	Technical College/Apprenticeship	3(27)
	School	4(36)
Employment	Retired	8(73)
	Employed	1(9)
	Unemployed	1(9)
	Other¥	1(9)
Ethnicity	White	9(82)
	Asian	1(9)
	Black	1(9)
Number of medicines	≤ 4	5(46)
	5-9	4(36)
	≥ 10	2(18)
Frequency of medicine use	Once per day	4(36)
	Twice per day	3(27)
	Three times per day	1(9)
	More than three times per day	1(9)
	Other^	2(9)
Formulation	Tablets/capsules	10(91)
	Any other form(s)	4(36)
Pay for medicines	Yes	1(9)
	No	10(91)
Help with medicine use	Yes*	1(9)
	No	10(91)

Table 5-2 Characteristics of participants completing the cognitive interviews

Notes; ^ when necessary; *Spouse/ partner helps with medicine use; ¥ Self-reported disabled

5.3.2 Interview findings

According to standard guidance on reporting patient understanding of self-completion instruments,[124] documentation of questionnaire issues, such as item comprehension and modifications (deletions or revisions), use of response options and perceptions of underlying concepts is beneficial to contributing to instrument validity. This section describes the findings of interview analyses.

5.3.3 Questionnaire instructions and use of visual analogue scales

All participants reported clarity of general instructions, provided on the coverpage, for questionnaire completion. Responses to probes around general instructions elicited comments such as *'..fine, very clear'P4* and '*very clear'P2.* Nevertheless, observation of participants revealed some of them skipping the instructions only to return, and check them upon encountering problematic items. Of the question-specific instructions, particularly those refering to visual analogue scales (VAS), a sample shown in Figure 5-1, findings suggest that most participants understood the instructions and had a clear understanding of where to '*mark on the line with an 'X' at the position that best reflects…'* their perceived state of satisfaction, burden, or optimisation of medicines use, stressing that *'instructions are clear…'*P7. A few complemented the VAS-type of questions saying *'..its a great way to measure, the scale is a great way to measure….'P4.* Some participants implied that prior exposure to answering VAS-type questions helped them respond: *'I have seen these before, [will respond] roughly in the middle'P3.* Only one participant was not condfident about where to mark on the line, while another recommended the use of boxes with numbers (to replace the line) and implied that he was not sure of the difference between a '5' and '6' on the line (See Figure 5-1).

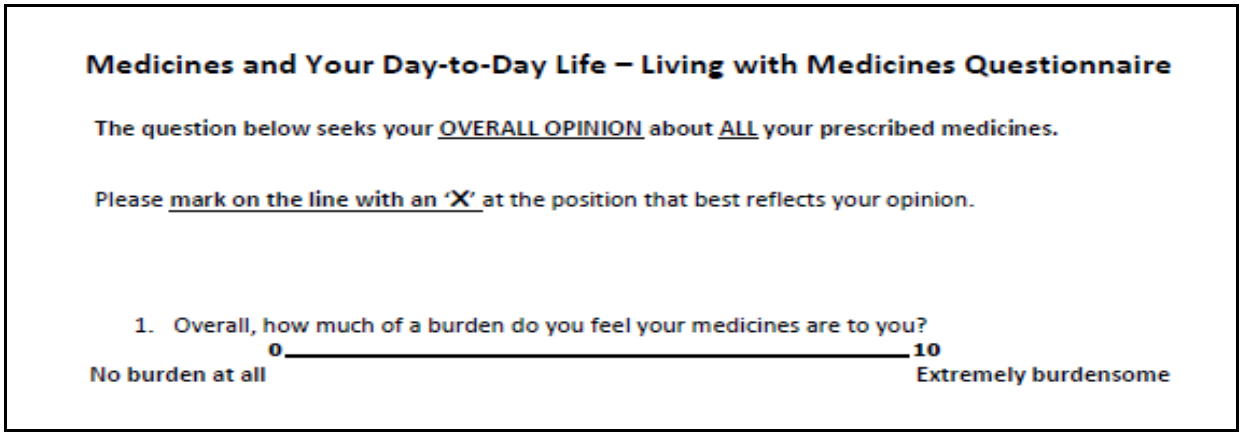


Figure 5-1 Sample visual analogue scale and completion instructions

5.3.4 Item comprehension and modifications

Table 5-3 provides a summary item-by-item analysis, and shows no major comprehension problems among most items. In this study, a major comprehension problem was defined as 'a failure of comprehension of a key term [in an item]', which may not clearly demonstrate 'alternate, but reasonable, interpretations of the question intent.'[168]

Item No	Original Statement	Comprehension
1	I find getting my prescriptions from the doctor difficult	No major comprehension problem identified *1 (9%) preferred reference to a specific type of prescription (e.g. repeat prescription)*
2	I find getting my medicines from the pharmacist difficult	No major comprehension problem identified *1 (9%) preference for positive wording* *2 (18%) Spoke of chemist rather than pharmacist*
3	I find the written instructions on how to use my medicines easy to understand.	No major comprehension problem identified *4 (36%) spoke of 'instructions on the label/packet/packaging/box/patient information leaflet'*
4	Taking medicines is routine for me	No major comprehension problem identified
5	I am satisfied with effectiveness of my medicines	No major comprehension problem identified
6	I would be worried if I forgot to take my medicines	No comprehension problem identified *3(27%) perceived a subtle/no difference between this item 6 and item 16*
7	I am comfortable with the times I should take my medicines	No major comprehension problem identified
8	I worry about paying for my medicines	No major comprehension problem identified *Some confusion of response options* *3(27%) chose 'strongly disagree' (instead of neutral opinion), even when exempt from prescription charges*
9	I worry that I have to take several medicines at same time	No major comprehension problem identified
10	I would like more say in the brands of medicines I use	No major comprehension problem identified *1 (9%) proposed addition of ' when switching from the original drug'*
11	I trust the judgement of my doctor(s)in choosing medicines for me	No major comprehension problem identified
12	It is difficult to identify which medicine is which	No major comprehension problem identified *1 (9%) preferred positive wording (i.e. use of easy rather than difficult)*
13	My pharmacist tells me enough about my medicines	No major comprehension problem identified *3(27%) spoke of '…, if I ask/talk to them'* *1(9%) preferred 'what's available or what I need to know at that stage' rather than 'enough'.*
14	I am concerned about possible damaging long term effects of taking medicines	No major comprehension problem identified
15	I feel I need more information about my medicines	No major comprehension problem identified *1(9%) preferred 'information sufficient for me…'*
16	I am concerned that I may forget to take my medicines	No major comprehension problem identified *3(27%) perceived a subtle/no difference between this item 16 and item 6*

Table 5-3 Item-by-item analysis of potential comprehension problems in the interim instrument (LMQ-2.1)

Item No	Original Statement	Comprehension
17	I can vary the dose of the medicines I take	No major comprehension problem identified
18	I find opening the packaging of my medicines difficult	No major comprehension problem identified
19	I can choose whether or not to take my medicines	No major comprehension problem identified
20	My doctor listens to my opinions about my medicines	No major comprehension problem identified *4 (36%) spoke of '…if I ask hum/if I talk to him/when consulted...'*
21	My medicines prevent my condition getting worse	No major comprehension problem identified *2 (18%) proposed addition (...may prevent...' or alternative wording '...put my condition under control...'*
22	**I am concerned that I am too dependent on my medicines**	**Comprehension problem identified** 3(27%) misinterpreted the word 'dependent' as 'addicted'. *Most interpreted statement as 'being reliant on medicines'*
23	I am unhappy with the extent to which my medicines interact with alcohol	No major comprehension problem identified *6(55%) suggested replacing the word 'unhappy' with words such as 'concerned/ worried/anxious'* *Most participants were observed to pay most attention to the last five words '…my medicines interact with alcohol.'*
24	I worry that my medicines may interact with each other	No major comprehension problem identified *1 (9%) perceived repetition between item 24 & item 9*
25	My medicines interfere with my social activities	No major comprehension problem identified *Most participants referred to individual leisure activities, as well as social activities.* *1 (9%) proposed replacing the word 'interfere' with 'impact'.*
26	I am concerned about experiencing side effects	No major comprehension problem identified
27	My doctor takes my concerns about side effects seriously	No major comprehension problem identified *4 (36%) spoke of '…if I speak/talk to him/her...'*
28	The side effects I get are worse than the problem for which I take medicines	No major comprehension problem identified *2 (18%) proposed addition of '…the side effects can be worse or can get worse';* *Statement revised to include 'The side effects I get are sometimes worse…'*
29	The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep)	No major comprehension problem identified *2 (18%) perceived repetition between this item 29¥ & item28¥*
30	**I can adapt my medicine-taking to my lifestyle**	**Comprehension problem identified:** *2 (18%) participants had problems understanding part or the entire statement '... I really don't understand that one, I will put neutral on that one...' P7*
31	I have to put a lot of planning and thought into taking my medicines	No major comprehension problem identified *1 (9%) participant preferred inclusion of the word 'sometimes' in the statement.*
32	I don't mind paying for my medicines because I need them.	No major comprehension problem identified *1 (9%) preferred the use of 'do not', another one preferred negative wording 'I mind paying...'*

Table 5-3 Item-by-item analysis of potential comprehension problems in the interim instrument (LMQ-2.1)

Item No	Original Statement	Comprehension
33	My doctor tells me enough about my medicines	No major comprehension problem identified *2 (18%) perceived repetition/confusion between this item 33 & item 13 about pharmacist*
34	My medicines live up to my expectations	No major comprehension problem identified *1(9%) acknowledged the word 'expectations' as very broad.*
35	I am confident speaking to my doctor (s) about my medicines	No major comprehension problem identified *1(9%) proposed negative wording to include 'I am not confident…..'*
36	I am confident speaking to my pharmacist about my medicine	No major comprehension problem identified *1(9%) proposed negative wording to include 'I am not confident…..'*
37	My medicines affect what I can eat or drink	No major comprehension problem identified *1(9%) proposed inclusion of examples of drinks (e.g. tea, coffee, juice)*
38	The medicines I use have an adverse effect on the holidays I can take	No major comprehension problems: 5(45%) interpreted the statement as 'medicines stopping/preventing holidays', while a few had concerns about the words 'adverse effect'
39	I can change the times I take my medicines if I want to	No major comprehension problem identified *3(27%) perceived a similarity between item 39, item 17, and item 19*
40	It is easy to keep my medicines routine	No major comprehension problem identified *4(36%) perceived repetition or subtle differences between item 40 & item 4*
41	Changes in daily routine cause problems with my medicines	No major comprehension problem identified *2(18%) proposed addition of 'can' or 'could' cause problems….* *Revised to 'Changes in daily routine causes problems with my medicines.'*
42	Taking medicines affects my driving	No major comprehension problem identified
43	I find using my medicines difficult	No major comprehension problem identified *2(18%) felt the word using is very broad including opening packaging, dispensing and self-administering of medicines*
44	I accept that I have to take medicines long term.	No major comprehension problem identified
45	I understand what my doctor(s) tell me about my medicines	No major comprehension problem identified *3(27%) perceived repetition item 45 & item 33*
46	I understand what my pharmacist tells me about my medicines.	No major comprehension problem identified *2(18%) perceived a similarity between item 46 & item 13 & item 36*
47	The side effects I get from my medicines are bothersome.	No major comprehension problem identified *6(55%) proposed alternative words to bothersome, including inconvenient/distracting, troublesome, worrying or worry me, or causing a nuisance.*

Table 5-3 Item-by-item analysis of potential comprehension problems in the interim instrument (LMQ-2.1)

Item No	Original Statement	Comprehension
48	I sometimes have to choose between buying basic essentials or medicines	No major comprehension problem identified *1(9%) perceived statement to be sensitive/embarrassing to answer* *1(9%) proposed ending the statement with 'if you have to buy'.*
49	My medicines allow me to live my life as I want to.	No major comprehension problem identified
50	I have to pay more than I can afford for my medicines	No major comprehension problem identified *1(9%) perceived statement to be sensitive/embarrassing to answer*
51	The health professionals providing my care know enough about me and my medicines	No major comprehension problem identified *2(18%) participants wanted specification of the type of health professional, while 1(9%) insisted that it should remain general to include others besides doctors and pharmacists*
52	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies)	No major comprehension problem identified 2(18%) perceived redundancy of items about the impact of medicines of everyday activities
53	My medicines interfere with my social relationships	1(9%) indicated comprehension problems *2(18%) proposed inclusion of 'interaction with friends and family'*
54	My medicines interfere with my sexual life	No major comprehension problem identified *1(9%) perceived this statement as sensitive*
55	The side effects I get from my medicines adversely affect my well-being.	No major comprehension problems: diverse interpretations of the word 'wellbeing'
56	My medicines are working	No major comprehension problem identified
57	The side effects are worth it for the benefits I get from my medicines	No major comprehension problem identified *1(9%) perceived it to be irrelevant*
58	My life revolves around using my medicines	No major comprehension problem identified
VAS 1	Taking everything into account, how satisfied are you with your medicines?	No major comprehension problem identified
VAS **2**	**How optimal do you feel your medicines are for you?**	**Major comprehension problem identified** 11(100%) revealed significant comprehension problems owing to the word 'optimal'. Arose from technical nature of the word 'optimal'
VAS 3	Overall, how much of a burden do you feel your medicines are to you?	No major comprehension problem identified *1(9%) perceived it as irrelevant ' I don't think medicines are a burden, they are there for a reason' P10*

Table 5-3 Item-by-item analysis of potential comprehension problems in the interim instrument (LMQ-2.1)

5.3.4.1 Potentially problematic items, and revisions

Potentially problematic items, items with major comprehension problems, and their revisions, are discussed sequentially in the section below.

Item 22

Although most participants correctly interpreted item 22, *'I am concerned that I am too dependent on my medicines',* as being reliant on medicines, a few others (n=3, 27%) misinterpreted the word 'dependent' to synonymously mean 'addicted'. In the context of medicine use, lay concerns about prescription medicine dependency or tolerance are not uncommon.[21,81] Even so, observation of interviewees' non-verbal expressions suggested that the words 'too dependent' had a negative connotation to them. In fact, 82% (n=9) responded with a neutral, disagree, or strongly disagree on item 22. Thus, the word 'dependent' was replaced with 'reliant' in the revised questionnaire.

Item 23

Despite no comprehension difficulties, item 23, *'I am unhappy with the extent to which my medicines interact with alcohol',* attracted diverging comments. At least half (55%, n=6) of all participants were concerned about the word 'unhappy', and suggested replacing it with words such as 'concerned, worried, or anxious'. For instance, a participant stressed that:

> *'…it's not so much 'unhappy'...coz this would mean I am an alcoholic...I am concerned or I am anxious or I am worried. 'Unhappy' denotes that I have alcoholic habits, and people may not like that question because it is making you think about alcoholic habits, and this is not what it's about? This is not an alcoholics' questionnaire, it's about medicines and their relationship with alcohol...'P3*.

Even so, observation of the reading patterns of most participants indicated that many participants paid little attention to the middle text of item 23, *'...with the extent to which...',* and subsequently the statement was rephrased to '*I am concerned that my medicines interact with alcohol.'*

Item 25

Although most participants had a clear understanding of item 25, *'My medicines interfere with my social activities'*, they mostly referred to individual leisure activities such as running, walking, gardening, as well as social activities like going to the pub with some friends. Consequently, the statement was reworded to *'My medicines interfere with my social or leisure activities'*.

Item 30

A few (18%, n=2) participants perceived comprehension problems with item 30, '*I can adapt my medicine-taking to my lifestyle'*. One participant felt the word 'adapt' was difficult in spite of having a general understanding of the entire statement: *'adapt, that's a difficult word, change perhaps…'P5.* Another participant failed to make sense of the entire statement: *'... I really don't understand that one, I will put neutral on that one...'P7.* As a result, the statement was reworded slightly to '*I can adapt using my medicines to fit my lifestyle.'*

Items 13 and 33

The two statements about doctor and pharmacist communication about medicines, with similar endings in item phrasing, *('…tells me enough'),* were perceived as repetitious and elaborated upon by some participants. While referring to item 13, '*My pharmacist tells me enough about my medicines'*, a participant exclaims:

> *'My pharmacist tells me enough, If I ask...I understand the question, I don't think pharmacist often tell, they just dispense unless you ask…but it's clear. If you ask, they will tell you, but if you don't ask, they will just give you the drug, and often it is the assistant'P4*.

As a result, items 13 and 33 were rephrased to reflect patient autonomy over acquiring medicine information: '*I get enough information about my medicines from my pharmacist'* and *'I get enough information about my medicines from my doctor*' respectively.

Item 38 – my holidays and my medicines

Responses to item 38, '*The medicines I use have an adverse effect on the holidays I can take'*, suggested potential interpretation problems. Nearly half (45%, n= 5) interpreted the statement to mean medicines prevent taking holidays:

> *'…I don't know what you have to be taking for you to say I can't go on holiday, because of what I am taking' P8.*

Other participants commonly talked of '*planning holidays'* while responding to this statement. To demonstrate this, a few participants articulated that:

> *'…it doesn't stop my holidays, it affects it, like planning how to go through customs with medicines' P10*

> *' …you can always get about things, can't you? Unless you have to take oxygen cylinders with you…. [which] make it difficult to plan holidays, perhaps.' P5*

Other participants worried about getting enough supplies before going on holidays, and suggested rephrasing the statement to '*…my medicine may interfere with my holiday plan...the question needs to be changed.' P4.* Still within item 38, the phrase 'adverse effect' also attracted a few concerns:

> *'I think people would take it [adverse effect] as they can't go, possibly you would want to know whether it means you can go on holiday or not?' P6*

> '...*adverse effect could mean side effect…' P4.*

Subsequently, item 38 was rephrased to *'The medicines I use make it difficult to plan holidays'.*

Item 39

Although no comprehension problems were detected while responding to item 39*, 'I can change the times I take my medicines if I want to'*, a few (n=3, 27%) participants acknowledged similarities with item 17 ('*I can vary the dose of the medicines I take')* and item 19 *('I can choose whether or not to take my medicines')*, which all relate to perceived autonomy/control over medicines:

> *' …number 39, isn't that somewhere else or very similar to [flips back to items 17 and 19] , we have been talking about it, very similar'P6*.

Indeed, a participant proposed merging these statements:

> *' ..., but it is linked to item 17, you could put that as 'I can vary the dose and times I take the medicines...'P3.*

Subsequently, minor changes were made to item 39 *('I can change the times I take my medicines if I want to')*, with deletion of the ending '*…if I want to'.*

Item 40

Although item 40 *('It is easy to keep my medicines routine')* was understood by all participants, nearly half (n=4, 36%) perceived repetition or subtle differences with item 4 *('Taking medicines is routine for me')*. While trying to differentiate the two items, a participant articulates that:

> '*I think they are almost similar, aren't they? Number 40 is asking if we find it easy, and number 4 is asking whether it's just routine, not whether it is easy. With the routine it gets easy, don't you think?'P6*.

Similarly, another participant mentioned that '*It is [referring to item 40] roughly the same kind of question [as item 4] I think…'P4* and when probed about possible item deletion stresses that '*…but I would keep it there'P4.* Consequently, both statements were retained in the questionnaire, to be explored in future statistical testing.

Item 45

While responding to item 45 *('I understand what my doctor(s) tell me about my medicines')*, a few participants (n=3, 27%) perceived repetitiveness with the aforementioned item 33 *('My doctor tells me enough about my medicines'):*

> *' wow, that one again, that's popped up before, that one is doctor… we had a doctor one…yeah 33 [flips back to previous page] you are being asked the same question with a different angle to see if you are being consistent with your answers...they [items 45 and 33] are saying the same thing' P3*

> *'…it is similar to one question before, I think, there was one question about my doctor tells me enough about my medicines [item 33], I saw there was a question like this, any way I don't think doctors tell people enough…' P4*

Item 46

Similarly, two (18%) participants perceived repetitiveness among items in the pharmacist-communication domain *[items 13, 36, and 46]*. For instance, while reading item 46, a participant exclaimed *'…same thing, but different angle!'P3*

Item 47

Although generally comprehensible, a few participants perceived side-effect-related statements 47 *('The side effects I get from my medicines are bothersome'),* 28 *('The side effects I get are worse than the problem for which I take medicines)*, and 29 *('The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep'),* to be repetitious or redundant. For instance, one participant was hesitant to respond to statement 47 as he felt that it was related to items 28 and 29 citing that '*….both statements are talking about the same thing, the side effects…'P1.*

Similarly, while responding to item 29, some participants mentioned that *'… a lot of people would say what's the difference between [this one] and the one before [item 28] coz if they [side effects] are really bad of course they are going to interfere with your day to day life.'P6.* The three side-effect-related items were retained for further statistical testing.

Item 51

Although no comprehension problems were detected from item 51 *('The health professionals providing my care know enough about me and my medicines'),* two participants perceived the term 'health professionals' as too general, and thus proposed specification to doctors/pharmacist:

> *'…the main health professionals that are more concerned about medicines, its only doctors and pharmacists that are more concerned about my medicines not any other...'P1*
> *'…i think it should be the doctor or the pharmacist e.g. My pharmacist/doctor providing my care know enough about me and my medicines.'P4.*

On the contrary, one participant asserted that the statement, with 'health professional' wording, encompasses all others personnel involved in patient care:

> *'that's clear, but when you say healthcare professionals, who do you mean by that? I think what comes to my mind is that a nurse comes to my home and gives me my medicines, like if I was too ill, nurse advising me, like in hospital.' P11.*

With these views in mind, the original statement was retained.

Item 55

Although generally understood, item 55 *('The side effects I get from my medicines adversely affect my well-being')* attracted diverse interpretations, with some participants expressing difficulties understanding the term 'wellbeing'.

> *'.. I think wellbeing, how do you describe wellbeing, [hesitates], for me, it's more about my physical wellbeing, basically how i feel, coz I don't understand it, I am having difficulty understanding it.. May be quality of life, i am not sure quality of life is understood by everybody'P4*

Regardless, other participants spoke of physical, mental, and emotional wellbeing, suggesting comprehension.

> *'…wellbeing, what about ability to do certain tasks, rather than wellbeing, [hesitates] it could be concentration that sort of thing, it's more overall, more generalised' P5*
> *'… affecting your wellbeing is basically how you are coping day to day'P6*
>
> *'..just basically feeling below per, feeling flat, out of sorts' P10*

Visual Analogue Scale 2 – the word 'optimal'

Perhaps, the most problematic question encountered by all participants was the second visual analogue scale *('How optimal do you feel your medicines are for you?')*, which proved difficult to understand. The technical word 'optimal', originating from the recent medicines optimisation agenda by the Royal Pharmaceutical Society,[1] was mostly unfamiliar and its intended meaning was not at all clear to most participants.

Diverse interpretations of 'optimal' included terms such as optional, optimum target, satisfaction, or effective.

> *'…that optimal, I was a bit spoofed on that, does it mean how 'optional' I can take it, what does it mean in your eyes, I mean optimal, …I didn't quite know what you mean by that, to be honest. Do you mean how good do you feel your medicines are for you...?'P2*
>
> *'How optimal, that's a good one. What do you mean by optimal? I don't know….it's not clear, I am gonna put a question mark on this one, coz I don't know what it means' P4*

The statement was subsequently revised to *'On balance, do you feel your medicines are right for you?'*, thus excluding the more technical word.

5.3.4.2 Response options

Standard guidance[124] recommends that item response options should: have adequate instructions for use; be clear and ordered appropriately; reflect distinction among response choices; and minimise floor or ceiling effects. In this study, most participants did not have problems using the five-Likert type, ordinal, scale ranging from strongly agree to strongly disagree. Some participants desired more spread out distribution of response options. For instance, one participant felt that:

> *'..there should be an extra box saying 'sometimes' [between neutral and agree]…it's not an everyday problem, but having a sometimes option could do.' P9*.

Although the questionnaire asks for personal views, opinions or experiences, some participants referred to general opinions while responding to certain statements. For instance, while responding to item *8 ('I worry about paying for my medicines),* a participant who did not pay for his prescription medicines, erroneously selected an 'agree' response upon referring to general opinion.

> *'…I worry about paying for my medicines, yes very clear, but personally, it doesn't bother me in one way or the other. But for some people, if they are paying for more than one medication…'P4*

However, the use of 'neutral opinion', as the mid-point response option, was variable. While some participants selected 'neutral opinion' when a statement was not applicable to them (as stipulated in the general instructions), others selected 'neutral' mistakenly, and when they did not fully understand the statement: *'… I really don't understand that one, I will put neutral on that one.' P7*

5.3.4.3 Perceptions of concepts (constructs) measured the by LMQ

General probing was used to elicit perceptions of the concepts evaluated by the LMQ. Most participants had a correct understanding of the instrument's concepts/purpose. One participant felt that the questionnaire was looking at the impact of medicines on day-to-day life: *'… it's just you want to know whether medicines are having an impact on your daily life...' P3.* A few others perceived the questionnaire as a measure of positive experiences of medicine use, and patient satisfaction.

> *'I think it [the LMQ] is trying to get experience of medication and satisfaction with medication, it is teasing out how people feel about medication, are they happy with it, are they satisfied with healthcare professions… I don't think this questionnaire creates a bias, say it's not negative...' P4*

Respondents were asked to give their opinions and understanding of 'medicine burden' and whether the LMQ specifically assessed this concept. Although most understood the word 'burden', as demonstrated by a participant:

> *'…I think burden, people may understand it. If you look at the word burden, it's a weight, it's a load, it wasn't there before…'P3*

Others seemed to disagree with the rationale of the concept of medicine burden:

'*I don't think medicines are a burden, they are there for a reason…' P10*

Perceptions that the benefits of using medicines tend to outweigh negative experiences have been cited in other questionnaire-evaluation studies.[94]

Another participant seemed to imply that the concept of medicine burden was a term more applicable to pharmacy professionals.

'I don't have [medicine burden] gone up to 0 coz it's no burden at all to me. I don't know if the medical profession will see any of this [concept], or whether it's just pharmacy who will get this information…' P8

5.3.4.4 General layout and format, length, and item-ordering.

Layout and format

Generally, most participants did not report problems with the layout or format of the questionnaire. For instance, while referring to the general layout a participant said, *'...that's okay, that's how you would fill a questionnaire, that's fine. It's all self-explanatory, it's easy to understand, you got it all there, haven't you?' P2*

Another participant commented that *'on the whole, I think it's quite good' P6*

Questionnaire length

Concerning the length of the questionnaire, a fair proportion of participants perceived the questionnaire as lengthy.

> *'…it's long, if you send it to people they will go, oh gosh…' P4*
>
> *'It's clear to me, but might be a bit long. I think it might be a bit long for some people, possibly…'P5*
> *'…number of questions, that's a difficult one, I presume 10 basic ones that would cover everything. May be just 10 things, [items], you don't want to get people fed up of reading all this, do you? You want them to respond to it, don't you?' P2*

However, a few others had mixed feelings about the appropriate number of questions; some acknowledged the need to balance questionnaire length with the content coverage.

> *'…actually I didn't think it was too bad [in terms of length], you need it to be that long so it gives you the picture that you want' P9*

> *'I think the questions are enough. But you might get some comments like they are a pain...but apart from that I think it's okay' P6*

Questionnaire length was directly linked to item redundancy or repetitiveness, as a commonly described problem. One participant stressed that *'In there, there is a bit that says almost the same thing' P2,* while another felt that *'sometimes it feels like you are going over the same thing' P9.*

Item-ordering

A participant responding to item 32 *('I don't mind paying for my medicines because I need them')* in the intermixed version (LMQ-2.1-I) expressed a typical concern about item ordering and grouping.

> *'…isn't that [item 32] really out of place, shouldn't they be together with item 8 [I worry about paying for my medicines] they are exactly the same but worded differently...'* P10

Similarly, while responding to item 33 *('My doctor tells me enough about my medicines'),* the same participant stressed that *'…shouldn't they be together [with related items]? Those about doctor and those about pharmacist?' P10*

Not surprisingly, further probing about questionnaire formats indicated that most participants preferred the grouped/labelled version (LMQ-2.1-GL) when compared to the intermixed version (LMQ-2.1-I).

> *'I would go with that one [the grouped and labelled] because it is guiding people to what is coming next. If you are doing it on your own, something like that [grouping and labelling] could be helpful. The heading tells me what to expect, it's about creating expectations…I think it's like doing a presentation, you set the agenda…its giving people an idea about where you are going with the next question…'P4*

> *'that's good, it keeps your mind on that particular subject better. Grouping it all together, holds it all together' P5*

'I think it's better, coz it makes it clear, as to what's expected, and to what the questions actually mean ...if it was more spacious, I like the lay out of this[grouped/labelled] better' P6

'…I think that's easier to understand [referring to grouped and labelled]' P8
'…it's almost the same ones, yeah, I noticed they are grouped, this is probably better. I would recommend this one [the grouped/labelled], it's all quite clear' P2

Some participants, on the other hand, could not immediately identify the differences between the two questionnaire versions. For instance, one participant felt that *'most of the questions are the same, at the end of the day, it's all the same' P7,* while another admits that *'I didn't see the heading, I was looking at the questions' P5*

Confidence in self-reporting

Although most participants showed confidence in using the self-reported questionnaire, assessed by direct observation, a few others expressed concerns about their competency in assessing certain aspects of their medicine use experience. As an example, a participant responding to item 5 *('I am satisfied with effectiveness of my medicines)* articulated:

'*neutral, because sometimes you don't know whether they are effective, until you go for a review, and they check your blood pressure, so you don't necessarily know.'P9*

Similarly, while responding to item13 *('my pharmacist tells me enough about my medicines')* a participant wondered *'…how do you know what is enough about medicine?' P3*

5.4 Discussion

In this chapter, I found that the vast majority of items in the LMQ instrument were interpreted as intended, and the questionnaire was generally easy to use. Efforts were made to detect and eliminate potential flaws in the LMQ. Common questionnaire problems identified were: perceived repetitiveness/redundancy among items (especially those within an individual or in similar domains), lengthy nature of the questionnaire, variability in use of response options, misinterpretation of items (and specific words), and different perceptions of the overall concept measured by the LMQ. Such issues, if left unattended, may affect responses to a questionnaire and its validity.

Direct patient input in instrument development, and testing patient understanding, is an essential process, which in addition contributes to evidence for content validity.[124] Cognitive interviewing is a widely used qualitative technique for evaluating and improving new instruments, including patient-reported questionnaires, to ensure appropriate content and comprehension by the target population.[94,165,166,201] Preliminary questionnaire validation, using a small number of participants, is a key aspect and step towards comprehensive psychometric validation.[202]
Some of the questionnaire problems identified in this study, particularly 'variation in the interpretation of items', have also been documented in other studies validating medicine-related questionnaires.[94] As discussed previously, some participants may not always read instructions, and the presence of a researcher may also create an artificial situation and affect how respondents answer questions.[94]

Perceived repetitiveness/redundancy among items was a commonly documented issue. Previous criticisms of LMQ versions indicated a lack of items covering side effects, cost, and social impact of medicines. To mitigate this, item generation included more items, intentionally, to fill these domains; thus, cognitive interview would serve as a means to sieve out irrelevant or unclear statements, in addition to future quantitative testing.

Despite diverse contributions from interviewees, it was reassuring that, except for a few revisions to wording, not many substantial modifications to the LMQ were made, and all items were retained. Nevertheless, the length of the LMQ instrument warrants further item reduction and refinement, possibly in a further statistical factor analysis, which could also help assess item redundancy.

Perhaps, another pertinent issue emerging from cognitive interview data relates to different perceptions of constructs measured by the LMQ instrument. As described in the results section, a few participants challenged the LMQ as a measure of 'medicine burden', with one participant noting that *'it's not negative'* and a few others feeling it considered positive experiences (or satisfaction) with medicine use. Similar conceptual problems have been reported while evaluating a measure of 'inherent burden of drug treatment,'[94] where not all items were 'actually perceived as burdensome by the patients,' and 'respondents were unwilling to admit medication problems when they perceived no treatment alternatives.'[94] Perceptions that the benefits of using medicines outweigh negative medicine-related experiences are commonly documented.[21,108,109] Before conclusive decisions can be made, there is a need to explore, in further studies, the validity of the 'medicine burden' construct as a key concept hypothesised to underlie the Living with Medicines Questionnaire. Additional research may also check possible correlations with existing generic measures, particularly those considering satisfaction with prescription medicines.[109]

Due to variability in the use of response options, particularly the 'neutral opinion' of the 5-point Likert-type scale, there is need to explore opportunities for improvement in this area. A possible solution could be to eliminate the specific instruction for using this response option. The cover page of the questionnaire employed in the cognitive interviews, suggested that 'if a statement does not apply to you, please tick the box for neutral opinion'. There are arguments against the use of neutral responses as midpoints,[203] and an earlier researcher stipulates that 'there is no assurance whatsoever that a subject [or participant] choosing the middle scale position harbours a neutral opinion. A subject's choice of the scale midpoint may result from: ignorance, uncooperativeness, reading difficulty, reluctance to answer, or inapplicability.'[203]

Earlier versions of the LMQ , in which statements were rated as *strongly agree, agree, mostly agree, do not agree, and strongly disagree*, also included a *'does not apply'* option for selected statements, which was later removed in subsequent revisions owing to challenges with data handling, factorability, and other analyses, a problem reported in similar studies.[94] Moreover, further revisions to the instrument introduced the 'neutral opinion' response, as a replacement to 'mostly agree' that served as midpoint option in earlier drafts of the instrument. Thus, with these considerations in mind, the instructions to using a neutral opinion were deleted from the cover page, to minimise confusion about the use of this response option. The visual analogue scales, which also lacked clearly marked midpoints and subdivisions, need further attention to minimise measurement problems for both end-users and researchers.

The order in which questions are asked may affect survey data, and the selection/testing of appropriate item ordering during scale development is relevant.[127] Item ordering was an issue arising from the cognitive interviews. In this study, intermixed- and grouped/labelled- versions were tested qualitatively. The former covered a sequence of items, which were arranged such that consecutive items related to different domains, while the latter version included items clustered in meaningful domains.

Choosing item ordering should consider the overall aim and purpose of the questionnaire. Intermixing items, haphazardly, may be more favourable when a questionnaire is intended to measure a psychological construct (such as medicine burden), and is recommended for newly developed measures.[204] Nevertheless, intermixing questions may cause confusion to respondents, affect motivation, and cause response fatigue. Perceived repetitiveness of items, a problem encountered during cognitive interviews, may also be explained by intermixed ordering of items as participants perceived duplication among items belonging to the same domain. On the other hand, thematic item grouping minimises confusion (and response burden), encourages coherence in the flow of items, and eases cognitive demands related to completing questionnaires since the contextual meaning of individual items is considered.[205] Krosnick and Presser (2010) suggest that item grouping reflects a more 'realistic world settings' where choices are usually made within context.[206]

Nonetheless, there is mixed guidance with respect to item-ordering and its impact on questionnaire properties.[207,208] Recent empirical evidence is in favour of the intermixing of survey items to create measures that reflect true reliability values, as item grouping tends to artificially inflate a measure's internal reliability and is thus regarded as unsuitable for new instruments.[204] Thus, all subsequent studies employed an intermixed version of the Living with Medicines Questionnaire.

Strengths and limitations

This study involved a substantial assessment of the face and content validity of a revised version of the LMQ, with no further psychometric testing. Content validation allows evaluation of concepts covered by the instrument from users' perspectives, and participants are able to assess the relevance of items to their treatment or condition.[209] A combination of techniques, comprising think-aloud and verbal probing, were employed to elicit questionnaire-related issues, and to examine potential flaws with questionnaire items. Nevertheless, there are methodological challenges with respect to probing techniques (for instance choosing what to say/or not) during cognitive interviews.[165,210] Although not documented, it was generally observed that participants frequently forgot to 'think-aloud', and were either reminded or probed to get them to say something. As such, the verbal probing tended to dominate the cognitive interviewing process, potentially biasing the findings.

Although the sample population involved in questionnaire evaluation was generally balanced with respect to educational level and the number of medicines used, the majority of participants were retirees, most of whom did not pay for their medicines. However this reflects the reality of the English population, the majority of whom do not pay prescription charges.[32] Although it is possible that, given this, the large majority of the sample population may have been unable to assess issues around cost-related burden. Nonetheless, items in the cost domain were understandable and perceived relevant to those not exempt from prescription charges. Similarly, this group of participants mostly managed their own medicines independently- as is the case for the large majority of patients. Again, it is likely that patients who may need support with medicines use (e.g. those requiring carers) may assess the 'practicalities' issues in the questionnaire differently.

The version of the LMQ produced following these cognitive interviews provides a baseline for further quantitative testing in a large sample of people using regular prescription medicines, for any disease/condition. The cognitive interviewing process requires varying levels of expertise and experience for interviewers. The primary interviewer (BK) was a novice, however used pre-developed probes to guide the interview. She also had prior knowledge about the concepts covered in the instrument, and practiced interviewing skills beforehand, all of which may have smoothened the cognitive interview process,[165] and enhanced validity of the findings. The potentially problematic items, which were elicited from the interviews, were resolved through discussions with my supervisors, and revisions made to item wording.

5.5 Chapter summary

The LMQ-2 was revised to incorporate new dimensions, and minor changes to the wording of individual statements were founded on patient-generated interview data, the literature, and discussions with my supervisors. Cognitive interviewing techniques contributed valuable information about face and content validity of the revised LMQ. It enabled questionnaire problems to be identified and addressed, as a step towards further instrument validation. Questionnaire properties, including acceptability, ease of use and face validity were evaluated.

Chapter 6 Formulating the LMQ-3 and assessing its construct validity

6.1 Introduction

As described in previous chapters, the original 60-item Living with Medicines Questionnaire (LMQ-1) was designed to measure medicine burden. Following preliminary item reduction, Chapter 4 presented a 42-item version questionnaire (LMQ-2) with eight domains. However, this version lacked items about cost-related burden of prescription medicines, impact of side effects, and the social impact of using medicines, which are vital aspects of the patient's medicine use experience. The LMQ-2 was therefore further developed to include these relevant factors. Chapter 5 described the generation of a 58-item interim version of the questionnaire (LMQ-2.1), and face/content validation of the LMQ-2.1 with people on long-term medicines.

Although an instrument may appear to measure what the developers intend it to measure at face value, it is worth ascertaining its underlying constructs using appropriate statistical methodology. Since the LMQ-2.1 was a product of several revisions (content addition, rewording, or deletions), as described in Chapter 5, it was deemed necessary to reinvestigate the dimensional structure of this interim version (LMQ- 2.1), so as to formulate and confirm a final questionnaire (LMQ-3).

Construct validation of 'relationships among items, domains, or concepts'[124] is indispensable for instruments undergoing development, as described in earlier chapters. In Chapter 4, factor analysis was employed for item reduction and to explore item groupings in earlier phases of LMQ development (LMQ-2). As described in the methodology section (Chapter 3), factor analysis is widely used in instrument validation and there are two common approaches: exploratory (EFA) or confirmatory factor analysis (CFA).[188] In this chapter, EFA was initially used to explore the underlying questionnaire structure of LMQ-2.1, which generated hypotheses about item groupings. EFA also facilitated item reduction to formulate the LMQ-3. As described earlier, CFA explicitly tests and confirms a priori hypothesised associations among questionnaire items and latent constructs (factors), and was used to evaluate the LMQ-3.

For this study, CFA was used to cross-validate the EFA-derived factor structure. As a more advanced statistical technique, part of structural equation modelling (SEM), CFA techniques are advantageous owing to their confirmatory approach to data analysis rather than the exploratory and descriptive approaches employed in conventional EFA.[180,183] It was also necessary to confirm the most appropriate representation of the questionnaire's (LMQ-3) dimensional structure. CFA can ascertain the 'goodness of fit' of a hypothesised model to sample data, and allows comparison of alternative measurement models (factor-structures) to understand the 'simplest' explanation of questionnaire dimensions.[188] Revisions to the LMQ, described in Chapter 5, superficially tested a visual analogue scale, a global item, designed to assess perceived medicine burden. Although global items are thought to be 'superordinate conceptually and psychologically..',[109] they may not accurately assess specific dimensions of medicine burden. Thus, a hierarchical CFA approach was also used to test the hypothesis of whether (and to what extent) collectively all LMQ-3 domains relate to medicine burden as an overarching construct. Medicine burden is hypothesised to be a general factor underlying the LMQ-3.

Aims and objectives

This psychometric validation study aimed to ascertain construct validity by:

a) Condensing the 58-item questionnaire (LMQ-2.1) into a shorter instrument (LMQ-3), and exploring its dimensionality using EFA.
b) Confirming the LMQ-3 dimensional structure by testing the EFA-derived model and testing alternative measurement models using CFA.

The next subsections describe the methodological steps undertaken to fulfil the above objectives.

6.2 Methods

Ethics approval was granted by the Medway School of Pharmacy Ethics Committee (See Appendix 8).

6.2.1 Study participants

Similar to previous studies, study participants were members of the general public living in the UK, aged 18 years or over, and using at least one regular prescription medicine for any disease/condition. Participants completed screening questions to check their eligibility to participate in the study.

6.2.2 Instruments

Participants completed the LMQ-2.1, a 58-item variant of the Living with Medicines Questionnaire. It also had a free-text open question and a section for participant demographics. The LMQ-2.1 had three visual analogue scales (VAS), as described in Chapter 5, one of which asked respondents to self-report their overall medicine burden on a 10-cm scale; the anchors were 0 'for no burden at all' and 10 for 'extremely burdensome'. An electronic version of this questionnaire was designed using Qualtrics©.

6.2.3 Study recruitment procedures

Data were gathered using an on-line survey accessible to UK residents. In this web-based survey, recruitment of participants was conducted via: a) social media including Twitter and Facebook posts through patient organisations, and b) via health websites. With respect to social media, brief information about the study (and inclusion criteria) was posted to promote the survey. Using specially-designed social-media webpages for the LMQ project, the researcher (BK) posted a survey link on different social media platforms between August and October 2015. Twitter was mostly used owing to the large number of health- and patient- organisations already known to the LMQ project (purposive sampling); many of these had participated in an earlier study described in Chapter 4. To improve response rates, tweets were posted at different times of the day, target patient groups were followed on their social media sites, and their posts were liked to increase on-line visibility of the survey. Figure 6-1 shows a sample recruitment text on Twitter.

With respect to recruitment via health websites, permission to distribute the survey link was initially sought from personnel in-charge, via email (Appendix 17), upon provision of study information. Managers of health websites were asked to post an invitation message and screening inclusion criteria on their websites or other media (e.g. social media, electronic newsletters, or via email to their panellists), alongside an anonymous survey link.

Out of 51 patient organisations contacted, 13(25.5%) agreed to take part in the study, and directly promoted the survey to potential participants. Table 6-1 below shows patient organisations that took part in this study.

	Patient organisation
1	Backup Trust
2	Epilepsy Action
3	Epilepsy UK
4	UK Health forum
5	Lupus Patients Understanding & Support
6	ME Association UK
7	MS Trust
8	Patient Information Forum
9	National Osteoporosis Centre
10	Stroke Association
11	Thyroid UK
12	The Hysterectomy Association
13	The ITP Support Association

Table 6-1 Patient organisations that participated in the LMQ-2.1 on-line survey

Notes; ME, Myalgic Encephalomyelitis (also known as chronic fatigue syndrome);
MS, Multiple Sclerosis; ITP, Immune thrombocytopenic purpura, a bleeding disorder.

Figure 6-1 Social media page (Twitter) for survey recruitment

6.2.4 Data preparation

All data were assessed for the extent of missing responses. Participants with any incomplete Liker-type item (of the 58-item LMQ-2.1) were deleted from the entire dataset (listwise deletion of missing data), to maintain consistency of sample sizes for factor analyses. The remaining sample was then split into two analytical subsamples, by simple random sampling, to ensure unbiased distribution of participants and to use the data resourcefully.[52] The first subset was used in EFA, while the other subset was used in CFA. As described in Chapter 3, items were scored on a 5-point scale (strongly agree to strongly disagree), and reverse scoring of negatively-phrased items ensured that higher scores reflected worse experiences of medicine use (higher medicine burden).

Assessment of normal distribution of responses was aided by descriptive statistics (means, skewness, and kurtosis). Multivariate normality in the CFA subset of data were assessed by Mardia's coefficient, which needs to be less than p (p+2) where p is the number of items in the data set.[211] Floor and ceiling effects (FCEs) were evaluated by checking the percentage of respondents endorsing the first and last answer category (strongly agree and strongly disagree) respectively.

6.2.5 Data analysis

6.2.5.1 EFA procedures

The rationale for using different EFA techniques was described in Chapter 3, alongside general procedures for testing suitability of data for EFA. Restated here, EFA was used in preliminary analyses to explore relationships among items and domains underlying the LMQ-2.1. All 58 Likert-type items in the LMQ-2.1 were subjected to principal axis factoring (PAF) in SPSS version 22. Oblique factor rotation (promax) was used since Chapter 4 revealed inter-correlations among domains underlying the LMQ-2; similarly, items in the LMQ-2.1 were also assumed to be inter-related. As noted earlier, the LMQ-2.1 included a global scale on medicine burden. This was not used in the factor analyses. Atkinson et al reports that global items, when combined with specific items during EFA, may confound interrelationships among subordinate constructs, leading to 'cross-loading of [the] global item across the more specific factors'.[108] Thus, only Likert-type items were used in EFA and CFA procedures.

Sample size adequacy for EFA was examined via Kaiser-Meyer-Olkin Measure (KMO). The adequacy of intervariable relationships (factorability), and absence of multicollinearity were examined by Bartlett's Test of Sphericity and Pearson's correlation matrix respectively.

To determine the appropriate number of factors underlying the EFA data, Kaiser's criterion (eigenvalues > 1), scree plots, and parallel analysis were employed. Kaiser's criterion demands that factors are retained only if their eigenvalues are ≥ 1, an eigenvalue being a number associated with each factor indicating the proportion of variance in the items that can be accounted for by that factor.[187,211] Interpretation of the scree plot is subjective,[182] thus parallel analysis was also used to confirm the optimal number of factors (domains).

Statistical criteria for item reduction during EFA were: low communalities (<0.3), poor loadings on the primary factor (< 0.3) and/or cross loading (>0.4) on two or more factors. In addition, items loading on unstable (weak) factors, having fewer than 3 items per factor, were deleted.[187]

In addition to statistical rules of thumb, qualitative scrutiny, and theoretical understanding was used to check the relevance of items and factors in the resultant factor solutions (or structures). Discussions were held with the supervision team to agree on a final factor solution. To name the factors, marker items indicating the strongest factor loadings were examined, and similarities with other items loading on the same factor were examined to derive factor nomenclature. The internal consistency (Cronbach's α) of the LMQ-3 subscales was also examined.

6.2.5.2 CFA procedures

Following item reduction to a final shorter instrument, the LMQ-3 was subjected to CFA to confirm EFA-derived hypotheses regarding the questionnaire's dimensional structure. Particularly, CFA examined the extent to which the domains elucidated by EFA techniques measured medicines burden as an overarching construct hypothesised to underlie the LMQ-3. CFA was based on maximum likelihood estimation (ML) in AMOS 22. The next subsections explore CFA methodological steps.

Model specifications

a) Path diagram and symbols used in CFA models

As a preliminary step in performing CFA, a path diagram, which visually displays a priori specified relationships among variables, can be used to illustrate a questionnaire's dimensional structure.[172,180]

Various conventional symbols can be used in CFA path diagrams:[183]

[1] Circles or ellipses denote unobserved or latent variables (e.g. factors). In CFA, measurement error is taken into consideration. Measurement error is associated with items (also known as error terms), and with factors (referred to as residual terms). Both error terms and residual terms are also unobserved variables, and thus represented as circles or ellipses.[183]

[2] Squares or rectangles denote observed variables (i.e. items or questions that were coded Q1 to Q58).

[3] Single-headed arrows denote the effect of one variable on another. They can be used to represent factor loadings between items and factors; the effect of error terms on specific items, or the effects of residual terms on factors.

[4] Double-headed arrows represent correlations (or covariance) between two variables. See Figure 6-2 for an example of a path diagram.

b) Model parameters, parsimony principle & model identification

Parameters are categorised as free or fixed. A free parameter is estimated (calculated) by the computer programme (AMOS). In CFA measurement models, parameters to estimate include factor loadings, factor variances and covariances (correlations), and error variances.[183] A fixed parameter is set equal to a constant number. For example, the first factor loading for each factor can arbitrarily be set to 1 as a prerequisite to estimating free parameters. This is known as scaling the factors, and is a precondition

in CFA model estimation. It enables the computer programme to calculate factor variances and factor correlations.[183]

When a previously 'fixed parameter' becomes a 'free parameter', then the model becomes more complex as there are more parameters to estimate. The opposite is also true. A model becomes simpler (or more parsimonious) when a free parameter becomes a fixed parameter, as fewer relationships among variables need to be explained. According to Kline (2011), 'given two models with similar fit to the same data, the simpler model is preferred, assuming the model is theoretically plausible',[183] and this is known as the principle of parsimony. Models with fewer parameters to estimate are more parsimonious than those with more parameters to estimate.[183,188]

Kline (2011) describes model complexity, which also relates to the total number of parameters to be estimated.[183] The latter are limited by the how many 'observations' are present for analysis. Different from sample size, the term 'observations', used in the context of CFA, represents known pieces of information (e.g. total number of correlations in the data matrix), also called sample moments.[183] Observations/sample moments can be calculated as a function of the number of items in a data set: $n\,(n+1)/2$. For instance, the total observations in a 41-item questionnaire is, $41(42)/2 = 861$. For a model to be identified, or amenable to CFA, there should be more observations than free parameters, and model degrees of freedom (df) should be above zero;[183] such models are said to be 'identified'. Degrees of freedom are equivalent to the differences between sample moments and the number of free parameters, and reflect the extent of model fit.[183] A model with $df < 0$ cannot be estimated (unidentified), while one with no degrees of freedom ($df = 0$) is just-identified, and does not 'test any particular hypothesis'[183] and is thus not of interest.

Types of CFA models hypothesised and tested

Different types of CFA models were hypothesised and tested.

a) First-order model

A first-order model (factor structure) of the LMQ-3 was hypothesised and tested. First-order factors are assumed to be at a single level, and there is one unidirectional path from each factor to its corresponding items.[188] This model (hereafter known as Model 1) was derived from the EFA structure. In preliminary CFA models, each item is hypothesised to load on only one factor, and zero loadings on all other factors are assumed (i.e. no cross loadings). The first factor loadings were arbitrarily set to 1 to assign a metric scale to each factor. Unlike items (observed variables) that have a scale (of 1 to 5 for strongly agree to strongly disagree), factors are unobserved (latent) variables and lack a natural scale. Similarly, measurement error terms associated with each item, represented by small circles e1 to e41 (See Figure 6-2), had their path coefficients set to 1 to estimate error variance, which is the variation in item scores not explained by the factor.[183]

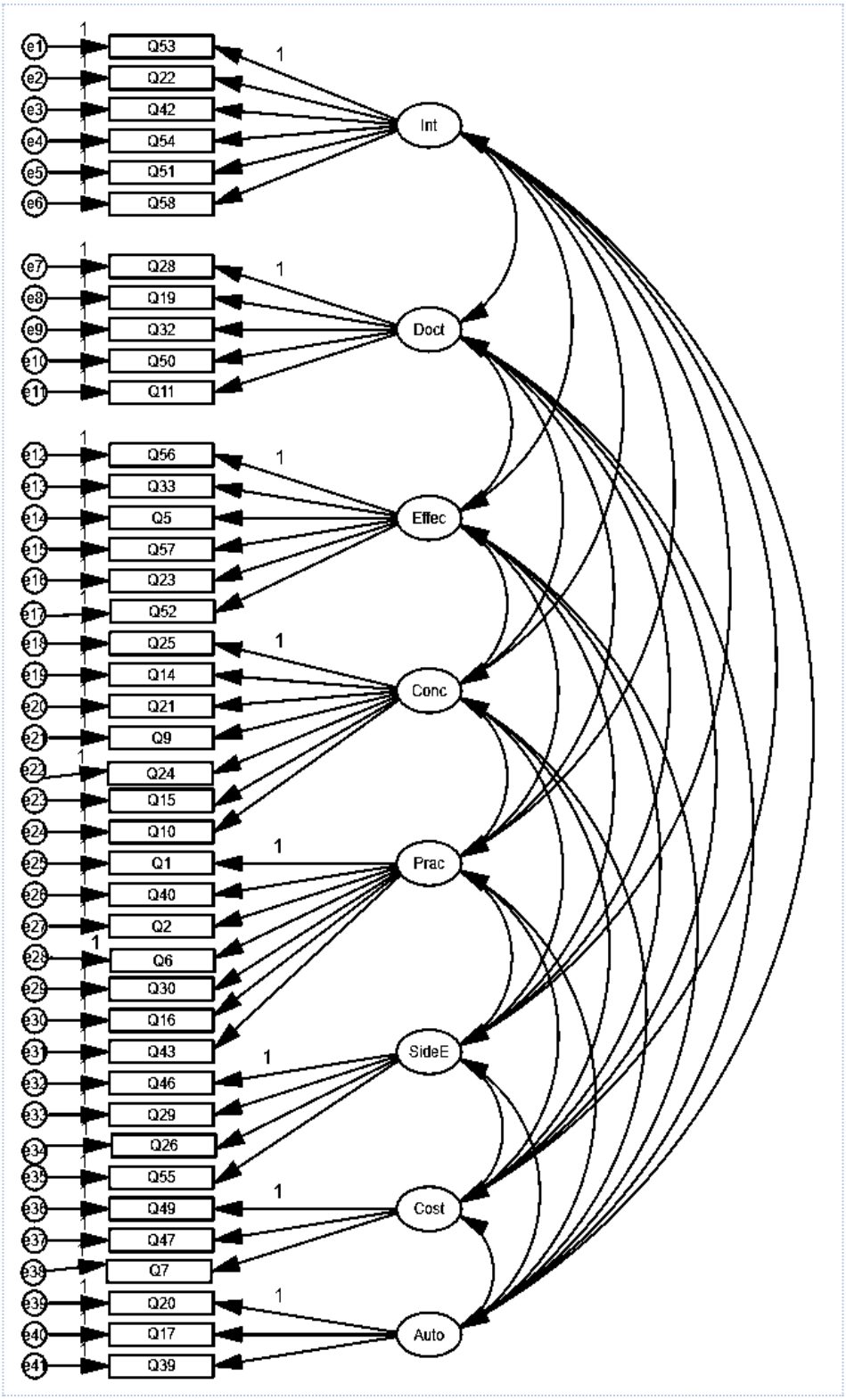


Figure 6-2 Hypothesised first order model for the LMQ-3 (Model 1)

Notes; Int = interferences with day-to-day life; Doct = patient-doctor relationships and communication about medicines; Effec =lack of effectiveness; Conc = general concerns about medicines. Prac= Practical difficulties; SideE = Side Effects; Cost =Cost-related burden; Auto = Lack of autonomy/control over medicine

b) Second-order factor model

The presence of at least three first-order factors with moderate intercorrelations (> 0.5) provides the basis for testing a higher order (or hierarchical) factor model.[188] A second-order factor model was tested (hereafter known as Model 2). Unlike Model 1, it has two unidirectional paths away from the items. A second-order factor is measured indirectly through the first-order factors and their corresponding items.[183] In Model 2, the second-order factor was hypothesised to be one general, overarching, factor (medicine burden), measured through the factors and items highlighted in Model 1. Medicine burden was hypothesised to explain the variation among the LMQ-3 domains. Standard criteria for testing hierarchical models were followed, including having at least three first-order factors with at least three items per factor.[180,183,188] See Figure 6-5 for an example of a second-order model.

Model evaluation

In addition to examining parameter estimates, particularly the sign and sizes of factor loadings, overall fit of hypothesised models and the extent to which they fit the sample data were evaluated using multiple goodness-of-fit indices.[180,183]

a) Chi-square statistic χ^2

Chi-square statistic is an index of exact or absolute model fit that depicts similarity between observed covariance matrix and reproduced (predicted) covariance matrix. The latter matrix is predicted by the model, while the former matrix is derived from sample data.[183] Unlike most traditional statistical tests, a non-significant chi-square probability ($p \geq 0.05$) is desirable as an indicator of good-fit, and implies that the reproduced covariance matrix is *not* significantly different from the observed covariance matrix.[180] The chi-square statistic tests the exact-fit hypothesis that 'there are no discrepancies between the population covariances and those predicted by the model',[183] and researchers are advised not to reject this hypothesis for p-values > 0.05. Increasing chi-square values suggest 'greater departure of the [reproduced] covariance matrix from the observed covariance matrix'.[212] Regardless, the χ^2 index is largely criticised for being sensitive and/or dependent on sample size; χ^2 p-values are often significant with big sample sizes (≥ 100)[163]. Subsequently, χ^2 statistic tends to over reject appropriately specified models and is, thus, seldom used as a sole index for examining model fit.[173,176,180]

b) Relative chi-square

Relative chi-square (χ^2/df), defined as a ratio of the chi-square value to degrees of freedom, is also an indicator of model fit.[183] Similar to the previously described chi-square statistic χ^2, relative chi-square index is also sensitive to sample size. Values less than 2-3 indicate good model fit.[213–215]

c) RMSEA

Standard guidelines support the use of other fit indices that are less sensitive to sample size.[176,216,217] One such a statistic is the Root Mean Square Error of Approximation (RMSEA) and its corresponding 90% confidence interval (CI 90%). The RMSEA statistic is 'a measure of fit between the [observed covariance matrix and predicted covariance matrix] adjusting for model complexity'.[188] RMSEA measures unexplained variance (residual), which constitutes the differences between the observed- and predicted covariance matrices.[180] RMSEA values closer to 0 suggest perfect fit, and cut-off values ≤ 0.06 depict good fit.[180,188] RMSEA values above 0.10 indicate poor or mediocre fit.[180]

d) CFI and TLI

The Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI), which are incremental fit indices, are also less sensitive to sample size and account for model complexity, and thus are more reliable.[176,188] CFI and TLI are conceptually similar and reflect the extent to which a model fits over an alternative model in which all variable are uncorrelated (known as the as the 'null' model).[188] CFI and TLI values range from 0 to 1, depicting no fit to perfect fit respectively. Increasing CFI and/or TLI values indicate greater improvement in model fit over alternative models.[176,183] Minimum values indicative of good or acceptable fit are ≥ 0.90-0.95.[216,218,219]

Exploring sources of model misfit during CFA

During CFA, it is appropriate to test respecified or modified models, especially if a priori hypothesised models are rejected.[183] To locate and correct potential causes of misfit in Model 2 (Figure 6-5), and to identify parameter estimates contributing greatly to model misfit, modification indices were examined. Modification indices (MIs) are generated by the computer programme (AMOS) and show potential areas of misspecification in models. According to Kline (2011), a modification index reflects 'the

amount by which the overall model chi-square statistic χ^2 would decrease if a particular fixed-to-zero parameter were freely estimated'.[183]

Misspecification of measurement errors may also impact on model fit. Usually CFA models are hypothesised to have uncorrelated error terms and residual terms, which were defined previously; i.e. their correlations are preliminarily fixed to zero. Modification indices were used to reveal which correlations among error-terms needed to be free or estimated to improve model fit. Similarly, model misfit can occur due to misspecification of factor loadings. In CFA, items are preliminarily fixed to load on only one factor (i.e. cross loadings on all other factors are fixed to zero). Modification indices were also used to locate potential cross-loadings. When interpreting modification indices, values reflect the amount by which a chi-square value of the model would improve. The expected parameter change (epc) is an approximation of the magnitude or difference in the estimate [from zero] for freely estimated parameters.[183]

6.3 Results

6.3.1 Survey response rates and sample size

A total of 1223 participants accessed the on-line survey over a 3-month period, and most indicated they lived in the UK (73.5%, n= 900), were 18 years or older (73.2%, n=895), and used regular prescription medicines (72.6%, n= 888). After listwise deletion of missing data, a total of 729 participants had fully completed Likert-type items (approximately 59.6% response rate). However, some participants had missing data on different demographic questions (See Table 6-2). Most participants accessed the survey directly via social media, and health websites. Other participants accessed the survey link indirectly via emails, health magazines, or newsletters promoted by participating patient organisations. The dataset was divided into two subsets: EFA subset (n=366) and the CFA subset (n=363).

6.3.2 Participant characteristics

Within the total remaining sample, participants were of age range 18 to 82 years (mean (SD), 48.7 (11.6)). The majority were female (85.8%, n= 612). Most participants (46.4%, n=329) had attained University level of education. Participants used four medicines on average (median = 4, range 1-20). Characteristics of participants across the EFA and CFA subsamples were broadly similar (See Table 6-2).

Characteristics		Total Sample n (%)	EFA subset n (%)	CFA subset n (%)
Gender	Female	612(85.8)	312 (86.7)	300(85.0)
	Male	101(14.2)*(n=713)*	48 (13.3) *(n=360)*	53(15.0) *(n=353)*
Age bracket	18-29	51(7.2)	25(7.0)	26(7.3)
	30-49	314(44.0)	155(43.2)	159(45.0)
	50-64	290(40.7)	153(42.6)	137(38.7)
	≥65	58(8.1) *(n=713)*	26(7.2) *(n=359)*	32(9.0) *(n=354)*
Education level	School	139(19.6)	73(20.5)	66(18.7)
	Technical colleg/Appren®	179(25.2)	86(24.2)	93(26.3)
	University	329(46.4)	161(45.2)	168(47.6)
	Other ∞	62(8.8) *(n=709)*	36(10.1) *(n=356)*	26(7.4)*(n=353)*
Employment status	Employed	331(46.6)	163(45.8)	168(47.5)
	Unemployed	84(11.8)	36(10.1)	48(13.5)
	Retired	126(17.8)	67(18.8)	59(16.7)
	Full-time student	20(2.8)	10(2.8)	10(2.8)
	Other	149(21.0)*(n=710)*	80(22.5)*(n=356)*	69(19.5) *(n=354)*
Ethnicity	White	684(95.9)	345(96.1)	339(95.8)
	Asian/Asian British	6(0.8)	3(0.8)	3(0.8)
	Mixed	7(1.0)	1(0.3)	6(1.7)
	Black/African/Caribbean	4(0.6)	2(0.6)	2(0.6)
	Other	12(1.7) *(n=713)*	8(2.2) *(n=359)*	4(1.1) *(n=354)*
Number of medicines	1-4	432(60.5)	220(61.1)	212(59.9)
	5-9	219(30.7)	107 (29.7)	112(31.6)
	≥10	63(8.8)*(n=714)*	33(9.2)*(n=360)*	30(8.5) *(n=354)*
Formulation used‡	Tablets/Capsules	692(94.9)	349(95.3)	343(94.5)
	Any other formulation	317(43.5) *(n=729)*	151(41.2) *(n=366)*	166(45.7) *(n=363)*
Frequency of medicine use‡	Once per day	329(45.1)	160 (43.7)	169 (46.5)
	Twice per day	285(39.1)	151(41.2)	134(36.9)
	Three times per day	149(20.4)	76(20.8)	73 (20.1)
	> 3 times per day	120(16.5)	55(15.0)	65 (17.9)
	Other times*	104(14.3) *(n=729)*	50(13.7) *(n=366)*	54(14.9) *(n=363)*
Assisted in using medicines	No- Independent	615(86.3)	306(85.2)	309(87.3)
	Yes- Has a carer:	98(13.7) *(n=713)*	53(14.8) *(n=359)*	45(12.7)*(n=354)*
	Spouse/Partner	67(68.4)	34(64.2)	33(73.3)
	Relative	10(10.2)	9(17.0)	1(2.2)
	Support worker	7(7.1)	4(7.5)	3(6..7)
	Friend	2 (2.0)	1(1.9)	1(2.2)
	Other$^{\mu}$	12(12.3) *(n=98)*	5(9.4) *(n=53)*	7(15.6*) (n=45)*
Pays for prescriptions	No	493(69.0)	245 (68.1)	248(70.1)
	Yes	221(31.0) *(n=714)*	115 (31.9)) *(n=360)*	106(29.9)*(n=354*)

Table 6-2 Characteristics of participants in the EFA and CFA subsamples

Notes; Technical colleg/Appren®, Technical college or apprenticeship;
∞ includes diploma, certificates, college, and postgraduate qualifications
* includes medicines taken when necessary (PRN), different times of the week (e.g. 1-3 times a week), fortnightly, monthly, every three months, every 5 years.
$^{\mu}$ included nurse, or multiple support from relatives, friends and carers
‡Participants could choose more than one response option, thus proportions are estimated for each of the answer categories.

6.3.3 Distribution of responses

Most responses to LMQ items were normally distributed (skewness values < 1); skew values tending to zero indicate symmetric distribution. As shown in Table 6-3, only five items had skewness and kurtosis values above one in absolute value. This may indicate potential floor/ceiling effects for these variables, which were considered for item reduction. One item, '*Q4 -Taking medicines is routine for me',* had the highest ceiling effect with 59.1% of all respondents endorsing 'strongly agree' as the top answer category. Regardless, all items had skewness < 2 and kurtosis values < 7; values below these cut-offs are not indicative of 'substantial non-normality' of data.[177]

Item	Mean	Skewness	Kurtosis	FCEs
Q1-I find getting my prescriptions from the doctor difficult	3.743	-0.718	-0.494	4.5-31.3
Q2 - I find getting my medicines from the pharmacist difficult.	3.716	-0.662	-0.475	3.5-28.5
Q3-I find the written instructions on how to use my medicines easy to understand*	4.033	-1.230	1.277	3.0-34.5
Q4 -Taking medicines is routine for me.*	4.492	-1.825	4.475	0.7-59.1 ǂ
Q5 - I am satisfied with the effectiveness of my medicines	3.448	-0.391	-0.683	4.0-15.6
Q6- I am comfortable with the times I should take my medicines.*	4.175	-1.122	1.859	0.2-33.3
Q7-I worry about paying for my medicines	3.500	-0.410	-0.857	9.2-28.5
Q8- If I forgot to take my medicines, it would worry me.	2.560	0.380	-0.903	18.6-4.5
Q9-I worry that I have to take several medicines at the same time.	3.197	-0.080	-0.885	6.9-13.9
Q10-I would like more say in the brands of medicines I use	2.626	0.319	-0.762	20.8-7.7
Q11-I trust the judgement of my doctor(s) in choosing medicines for me.	3.470	-0.493	-0.511	5.2-15.6
Q12- It is difficult to identify which medicine is which	3.874	-0.825	0.132	1.7-26.8
Q13-I get enough information about my medicines from my pharmacist.	3.352	-0.374	-0.455	6.0-12.7
Q14-I am concerned about possible damaging long term effects of taking medicines.	2.153	0.907	0.045	32.3-4.0
Q15-I feel I need more information about my medicines.	2.902	-0.037	-0.989	13.4-6.9
Q16- I am concerned that I may forget to take my medicines	3.003	-0.086	-1.133	10.2-7.7
Q17-I can vary the dose of the medicines I take.	2.538	0.326	-1.181	23.6-4.2
Q18-I find opening the packaging of my medicines difficult.	3.598	-0.689	-0.666	7.4-26.1
Q19- My doctor(s) listen to my opinions about my medicines.	3.445	-0.606	-0.348	6.5-13.9
Q20-I can choose whether or not to take my medicines.	2.355	0.516	-1.094	35.5-5.2
Q21-I am concerned that I am too reliant on my medicines.	2.951	0.140	-0.915	9.2-9.4
Q22-My medicines interfere with my social or leisure activities.	3.290	0.281	-1.066	8.2-16.9
Q23-My medicines prevent my condition getting worse.	3.653	-0.698	-0.225	4.7-21.6
Q24-I am concerned that my medicines interact with alcohol.	3.325	-0.304	-0.654	6.7-14.9
Q25-I worry that my medicines may interact with each other	2.844	0.154	-0.788	10.9-7.7
Q26-The side effects I get are sometimes worse than the problem for which I take medicines.	3.052	-0.081	-1.071	13.0-12.0
Q 27-I am concerned about experiencing side effects.	2.197	0.844	0.134	25.7-2.7
Q28-My doctor(s) take my concerns about side effects seriously.	3.249	-0.381	-0.446	6.2-9.2
Q29-The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework).	2.861	0.206	-1.053	14-11
Q 30-I have to put a lot of planning and thought into taking my medicines.	3.235	-0.216	-1.012	6.8-12.9
Q31-I don't mind paying for my medicines because I need them.	2.735	-0.310	-0.459	17.5-2.0

Table 6-3 Distribution of responses to the 58-item interim tool (LMQ-2.1)

Item	Mean	Skewness	Kurtosis	FCEs
Q32-I get enough information about my medicines from my doctor(s).	3.180	-0.287	-0.814	6.8-7.8
Q33 -My medicines live up to my expectations.	3.175	-0.311	-0.546	7.1-7.1
Q34-I can adapt using my medicines to fit my lifestyle.	3.033	-0.195	-0.774	9.1-6.1
Q35-I am not confident speaking to my doctor(s) about my medicines.	3.686	-0.779	-0.355	6.1-25.3
Q36- I am not confident speaking to my pharmacist(s) about my medicines	3.844	-0.888	0.139	2.6-27.6
Q37-I am concerned that my medicines affect what I can eat or drink.	3.342	-0.297	-0.882	6.6-17.1
Q38-The medicines I use make it difficult to plan holidays.	3.691	-0.841	0.18	5.4-22.2
Q39-I can vary the times I take my medicines.	2.680	0.191	-1.067	14.3-3.6
Q40-It is easy to keep to my medicines routine.	3.792	-0.773	0.092	0.5-18.4
Q41-Changes in daily routine causes problems with my medicines.	2.921	0.145	-1.052	7.0-7.0
Q42-Taking medicines affects my driving.	3.500	-0.516	-0.478	7.8-21.3
Q43-I find using my medicines difficult.	3.948	-0.747	0.587	0.5-23.9
Q 44-I accept that I have to take medicines long term*	4.169	-1.495	2.549	2.6-39.7
Q45-I understand what my doctor(s) tell me about my medicines.*	4.003	-1.205	2.406	1.6-23.7
Q46-The side effects I get from my medicines are bothersome.	2.713	0.232	-0.932	17.4-7.4
Q47-I sometimes have to choose between buying basic essentials or medicines.	4.027	-0.745	-0.285	1.3-43.0
Q48-I understand what my pharmacist(s) tell me about my medicines.	3.964	-0.861	1.259	1.1-24.0
Q49--I have to pay more than I can afford for my medicines.	3.628	-0.364	-0.495	4.3-28.7
Q50-The health professionals providing my care know enough about me and my medicines.	3.123	-0.191	-1.024	10.7-11.8
Q51-Taking medicines causes me problems with daily tasks (such as work, housework).	3.298	- 0.291	-0.991	7.8-16.3
Q52-My medicines allow me to live my life as I want to.	3.175	-0.118	-0.981	7.5-13.1
Q53-My medicines interfere with my social relationships.	3.489	-0.543	-0.686	6.2-19.0
Q54-My medicines interfere with my sexual life.	3.232	-0.251	-0.943	9.5-15.7
Q 55 -The side effects I get from my medicines adversely affect my well-being.	3.063	0.002	-1.018	9.5-13.0
Q 56-My medicines are working.	3.650	-0.765	0.278	4.1-17.6
Q57-The side effects are worth it for the benefits I get from my medicines.	3.344	-0.374	0.246	4.6-9.8
Q 58-My life revolves around using my medicines.	3.380	-0.370	-0.874	6.8-17.3

Table 6-3 Distribution of responses to the 58-item interim tool (LMQ-2.1)

Notes; FCEs, Floor and Ceiling Effects; *Items represent those with skewness and kurtosis values above one. ǂ Item with highest ceiling effect.

6.3.4 EFA findings

The EFA sample size (n=366), of approximately six participants per item, met the minimum recommendations[174,182] for analysing the 58-item preliminary pool. With a KMO value of 0.902 (acceptable values ≥ 0.5), the sample size was 'marvellous'[211] for EFA analyses. Bartlett's Test of Sphericity was significant (Chi-Square = 10585.7, df=1653; p< 0.001), suggesting that data were factorable with adequate inter-variable correlations.[211] Examining the Pearson's correlation matrix revealed correlations in the range of 0.001 to 0.776, with only few correlations below 0.3. Inter-item correlations above 0.3 indicate 'enough commonality to justify the presence of underlying factors'.[211] On the other hand, there was no evidence of multi-collinearity (or redundancy) among items since all inter-variable correlations were below 0.8; very highly correlated items can pose difficulties in ascertaining each item's unique contribution to its corresponding factor.

The initial EFA solution resulted into 13 factors with eigenvalues > 1, which explained 63.4% of the total variance among all items. Inspection of the scree plot revealed a sudden break in the curve (inflexion point) between factors 7 and 9 suggesting retention of 8 factors (see Figure 6-3).

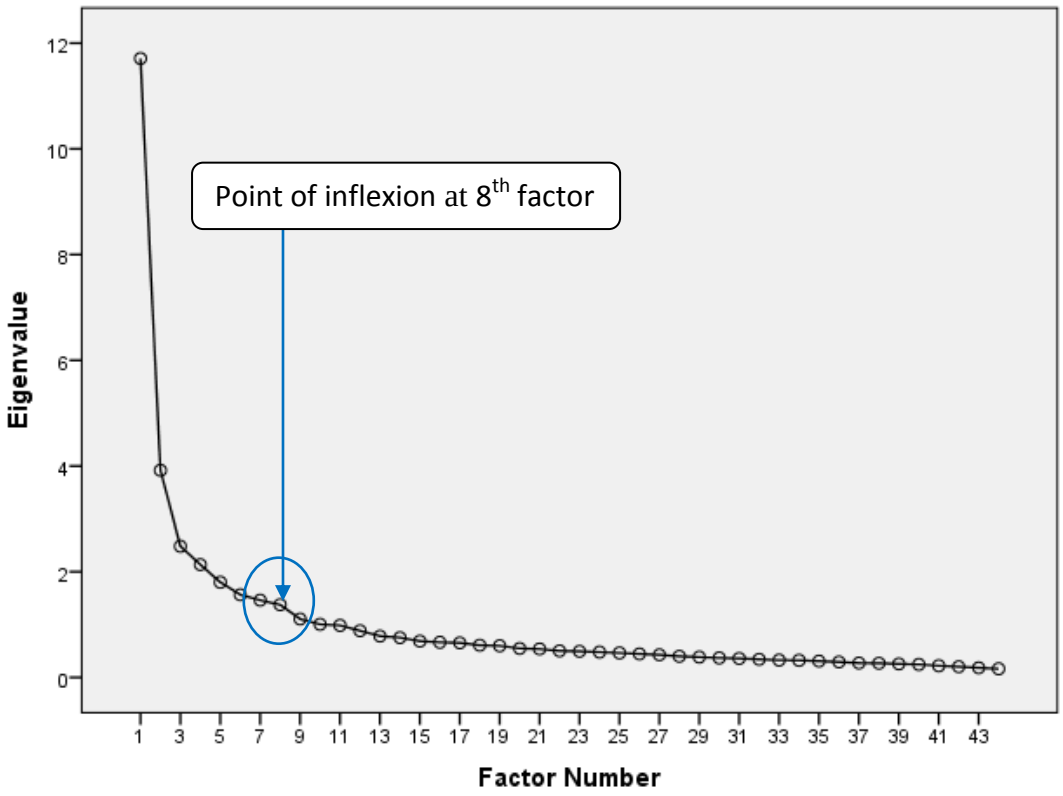


Figure 6-3 Scree plot estimating the number of factors to retain in the LMQ-2.1

To further ascertain the optimal number of factors, parallel analysis revealed seven factors meeting statistical inclusion criteria (See Table 6-4). With more iterations in EFA, factor solutions with 7 to 13 factors were further investigated. The eight-factor solution was most stable and interpretable (See Table 6-6).

Factor	Observed eigenvalues	Criterion eigenvalues*	Decision
1	13.838	1.8815	Accept
2	4.731	1.7979	Accept
3	2.834	1.7380	Accept
4	2.494	1.6846	Accept
5	1.997	1.6382	Accept
6	1.800	1.5950	Accept
7	1.739	1.5553	Accept
8	1.370	1.5172	Investigate
9	1.317	1.4819	Investigate
10	1.298	1.4478	Investigate
11	1.218	1.4161	Investigate
12	1.115	1.3842	Investigate
13	1.048	1.3541	Investigate

Table 6-4 Comparison of eigenvalues using parallel analysis (LMQ-2.1)

Notes; * Predicted eigenvalues generated, randomly, in 1000 replications/ simulations for a dataset with 58 variables, and sample size of 366 using Monte Carlo PCA for Parallel Analysis[171]

[a] Only 13 of 58 possible factors are shown in the table.

Item reduction

Seventeen (n=17) items were deleted from the preliminary 58-item pool (See Table 6-5), leaving a 41-item questionnaire. All item reduction was informed by the statistical inclusion criteria, and qualitative meanings of individual items discussed through professional judgement with the help of the supervision team, as described in the methods section. This meant that items were retained if they had adequate factor loadings (≥ 0.3), and did not cross load highly on other factors (>0.4). In addition, every stable factor required at least 3 items.

	Item	Reason for deletion
1.	I find the written instructions on how to use my medicines easy to understand	LC,PL
2.	Taking medicines is routine for me	LC, PL,HCE
3.	If I forgot to take my medicines, it would worry me	PL
4.	It is difficult to identify which medicine is which	LC, PL
5.	I get enough information about my medicines from my pharmacist	LC, PL
6.	I find opening the packaging of my medicines difficult	LC, PL
7.	I am concerned about experiencing side effects	CL*
8.	I don't mind paying for my medicines because I need them	LC, PL
9.	I can adapt using my medicines to fit my lifestyle	PL
10.	I am not confident speaking to my doctor about my medicines	UF
11.	I am not confident speaking to my pharmacist about my medicines	UF
12.	I am concerned that my medicines affect what I can eat or drink	PL
13.	The medicines I use make it difficult to plan holidays	PL, CL**
14.	Changes in daily routine causes problems with my medicines	PL
15.	I accept that I have to take medicines long term	LC
16.	I understand what my doctors tell me about my medicines	UF
17.	I understand what my pharmacists tell me about my medicines	UF

Table 6-5 Items deleted from the 58-item interim tool (LMQ-2.1)

Notes; LC=Low communality; PL=Poor loadings; HCE=highest ceiling effect; CL=cross loading; UF= loaded on an unstable factor with only two items. *This item cross-loaded significantly on two factors: 'side effects' and 'concerns'. **This item cross-loaded significantly on two factors: 'interferences with day-to-day life' and 'practical difficulties'

EFA-derived factor solution

The resultant 41-item eight-factor solution was conceptually interpretable. Factors 1 to 8 were taken to mean: interferences with day-to-day life (6 items), patient-doctor relationships and communication about medicines (5 items); lack of effectiveness (6 items); general concerns about medicines (7 items); side effects (4 items); practical difficulties (7 items); cost-related burden (3 items); and lack of autonomy/control of medicine use (3 items) (See Table 6-6).

Items	Factor							
	Int	Doct	Effec	Conc	SideE	Prac	Cost	Auto
My medicines interfere with my social relationships.	**.892**	.060	.009	-.121	-.002	-.001	.062	.018
My medicines interfere with my social or leisure activities.	**.779**	.078	-.022	.139	-.015	-.052	-.079	.000
Taking medicines affects my driving.	**.690**	-.045	-.064	.030	-.034	-.039	-.002	-.023
Taking medicines causes me problems with daily tasks (such as work, housework, hobbies).	**.644**	.025	.052	-.112	.319	-.105	.066	.014
My medicines interfere with my sexual life.	**.643**	.036	.006	-.036	.056	.011	.088	-.023
My life revolves around using my medicines.	**.480**	.034	-.078	.089	.102	.066	.052	.023
My doctor(s) listen to my opinions about my medicines.	.032	**.810**	-.051	-.018	-.028	.048	-.042	.047
My doctor(s) take my concerns about side effects seriously.	.059	**.794**	.015	-.061	-.009	-.066	.042	-.002
I get enough information about my medicines from my doctor(s).	.049	**.761**	.000	.094	-.033	.025	-.014	.043
The health professionals providing my care know enough about me and my medicines.	-.001	**.612**	.133	.044	-.051	.085	-.048	-.033
I trust the judgement of my doctor(s) in choosing medicines for me.	.001	**.556**	.152	.027	.007	.137	-.031	-.085
My medicines are working.	-.142	-.026	**.882**	-.004	.072	-.007	.067	.083
My medicines live up to my expectations.	-.043	.062	**.711**	.084	.066	.057	.040	.064
I am satisfied with the effectiveness of my medicines.	-.026	.061	**.719**	.054	.078	.032	-.071	-.018
The side effects are worth it for the benefits I get from my medicines.	-.151	.173	**.601**	.046	-.077	-.225	.062	.040
My medicines prevent my condition getting worse.	.247	-.044	**.523**	-.144	-.142	.160	-.046	-.134
My medicines allow me to live my life as I want to.	.345	.106	**.525**	.017	-.084	.023	-.087	-.007
I am concerned about possible damaging long term effects of taking medicines.	-.086	.008	.020	**.648**	.270	-.035	-.067	-.076
I worry that my medicines may interact with each other.	-.004	-.073	.128	**.639**	.165	-.061	-.018	.003
I am concerned that I am too reliant on my medicines.	.167	.043	-.028	**.635**	-.173	-.099	.037	-.096
I worry that I have to take several medicines at the same time.	-.056	-.091	.061	**.550**	-.003	.135	.126	-.091

Table 6-6 The final 41-item, EFA-derived, 8-factor solution of the Living with Medicines Questionnaire version 3 (LMQ-3)

(Table 6-6 continued on next page)

Items	Factor Int	Doct	Effec	Conc	SideE	Prac	Cost	Auto
I am concerned that my medicines interact with alcohol.	.339	-.069	-.015	**.505**	-.171	-.169	.060	.158
I feel I need more information about my medicines.	-.014	.252	.036	**.544**	.058	-.010	.022	.016
I would like more say in the brands of medicines I use.	-.196	.200	-.081	**.447**	.134	.005	.076	-.009
The side effects I get from my medicines are bothersome.	.131	-.099	-.072	.054	**.812**	.063	-.027	.024
The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	.355	-.023	-.014	-.026	**.687**	-.072	.031	.009
The side effects I get are sometimes worse than the problem for which I take medicines.	.051	.029	.078	.030	**.647**	.016	-.042	.007
The side effects I get from my medicines adversely affect my well-being.	.346	.019	.020	.016	**.612**	-.040	-.028	.013
I find getting my prescriptions from the doctor difficult.	-.093	.225	-.110	-.148	.089	**.734**	.060	.061
It is easy to keep to my medicines routine.	.044	-.079	.174	-.065	-.024	**.631**	-.009	-.018
I find getting my medicines from the pharmacist difficult.	-.017	.090	-.111	.033	-.041	**.616**	.090	.023
I am comfortable with the times I should take my medicines.	-.048	-.093	.323	.024	-.024	**.398**	.031	.010
I have to put a lot of planning and thought into taking my medicines.	.295	-.092	-.116	.169	.145	**.464**	-.036	.000
I am concerned that I may forget to take my medicines.	.170	-.139	-.056	.343	-.162	**.421**	-.139	.172
I find using my medicines difficult.	.311	-.020	.028	.102	.086	**.410**	-.021	-.102
I have to pay more than I can afford for my medicines.	.081	-.039	.029	.028	-.062	.004	**.838**	.032
I sometimes have to choose between buying basic essentials or medicines.	.130	.002	.109	-.057	.016	.013	**.704**	-.050
I worry about paying for my medicines.	-.071	-.021	-.102	.165	-.026	.132	**.679**	.004
I can choose whether or not to take my medicines.	.051	-.036	.005	.000	-.012	-.029	-.020	**.732**
I can vary the dose of the medicines I take.	-.102	.008	.086	-.179	.089	.035	.033	**.668**
I can vary the times I take my medicines.	.050	.058	.000	.051	-.021	.085	-.018	**.628**

Table 6-6 The final 41-item, EFA-derived, 8-factor solution of the Living with Medicines Questionnaire version 3 (LMQ-3)

Notes; Int = interferences with day-to-day life; Doct = patient-doctor relationships and communication about medicines; Effec = lack of effectiveness; Conc = general concerns about medicines.Prac= practical difficulties; SideE = Side Effects; Cost =Cost-related burden; Auto = Lack of autonomy/control over medicine use.

6.3.5 CFA findings

The CFA subset of data (n=363) was also adequate in size, and multivariate normality was judged acceptable by Mardia's coefficient (171.618, critical ratio= 27.532).

6.3.5.1 Estimates for the first-order model

The first-order model had 110 free parameters to be estimated: 33 factor loadings, 8 factor variances, 28 factor correlations, 41 error variances. This model has 751 degrees of freedom, and was plausible or agreeable to estimation.

Examination of standardised factor solutions revealed all factor loadings and correlations to be of reasonable sizes. As shown in Figure 6-4, first-order factor loadings were in the range of 0.396 to 0.891 and were statistically significant ($p < 0.001$) for all items. CFA confirmed inter-correlations among factors underlying the LMQ-3, although ' lack of autonomy' was least well correlated with other factors. The strongest relationship was between the factors 'side effects' and 'interferences with day-to-day life' (r=0.81). Domains relating to patient-doctor relationships, communication about medicines, and lack of effectiveness were also strongly correlated (Figure 6-4).

Item		loadings
Q53	<---	.891
Q22	<---	.808
Q42	<---	.501
Q54	<---	.753
Q51	<---	.868
Q58	<---	.489
Q28	<---	.776
Q19	<---	.769
Q32	<---	.711
Q50	<---	.767
Q11	<---	.720
Q56	<---	.774
Q33	<---	.790
Q5	<---	.843
Q57	<---	.581
Q23	<---	.558
Q52	<---	.690
Q25	<---	.674
Q14	<---	.679
Q21	<---	.484
Q9	<---	.535
Q24	<---	.430
Q15	<---	.653
Q10	<---	.396
Q1	<---	.537
Q40	<---	.737
Q2	<---	.449
Q6	<---	.601
Q30	<---	.551
Q16	<---	.508
Q43	<---	.676
Q46	<---	.816
Q29	<---	.835
Q26	<---	.699
Q55	<---	.854
Q49	<---	.864
Q47	<---	.756
Q7	<---	.698
Q20	<---	.574
Q17	<---	.717
Q39	<---	.473

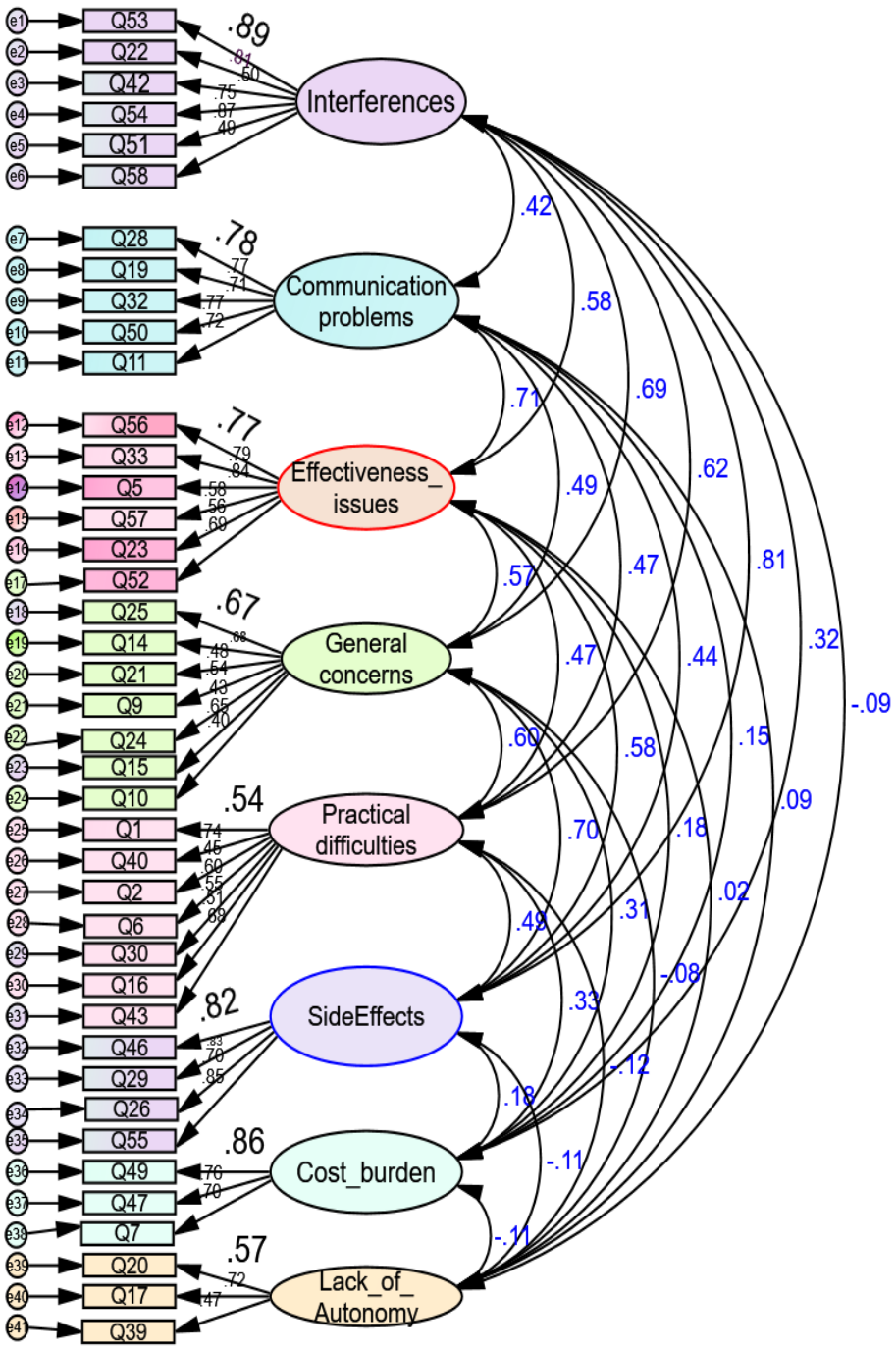


Figure 6-4 First-order model estimates (Model 1)

Notes; Standardised path estimates are shown. The numbers in blue(between curved arrows) represent correlations among the eight factors; the numbers in the left column (starting at 0.891) clarify item loadings; these are the numbers between factors and the items rounded to 2 decimal points.

6.3.5.2 Estimates for the second-order model

In the hypothesised second-order model, all factor loadings were in the range of 0.39 to 0.89 and statistically significant ($p<0.001$) except for 'autonomy', that did not load significantly on medicine burden (- 0.09, $p= 0.224$). The 'interferences' domain loaded most strongly on medicine burden (0.88), followed by 'side-effects' (0.85), and 'general concerns' (0.81) (Figure 6-5).

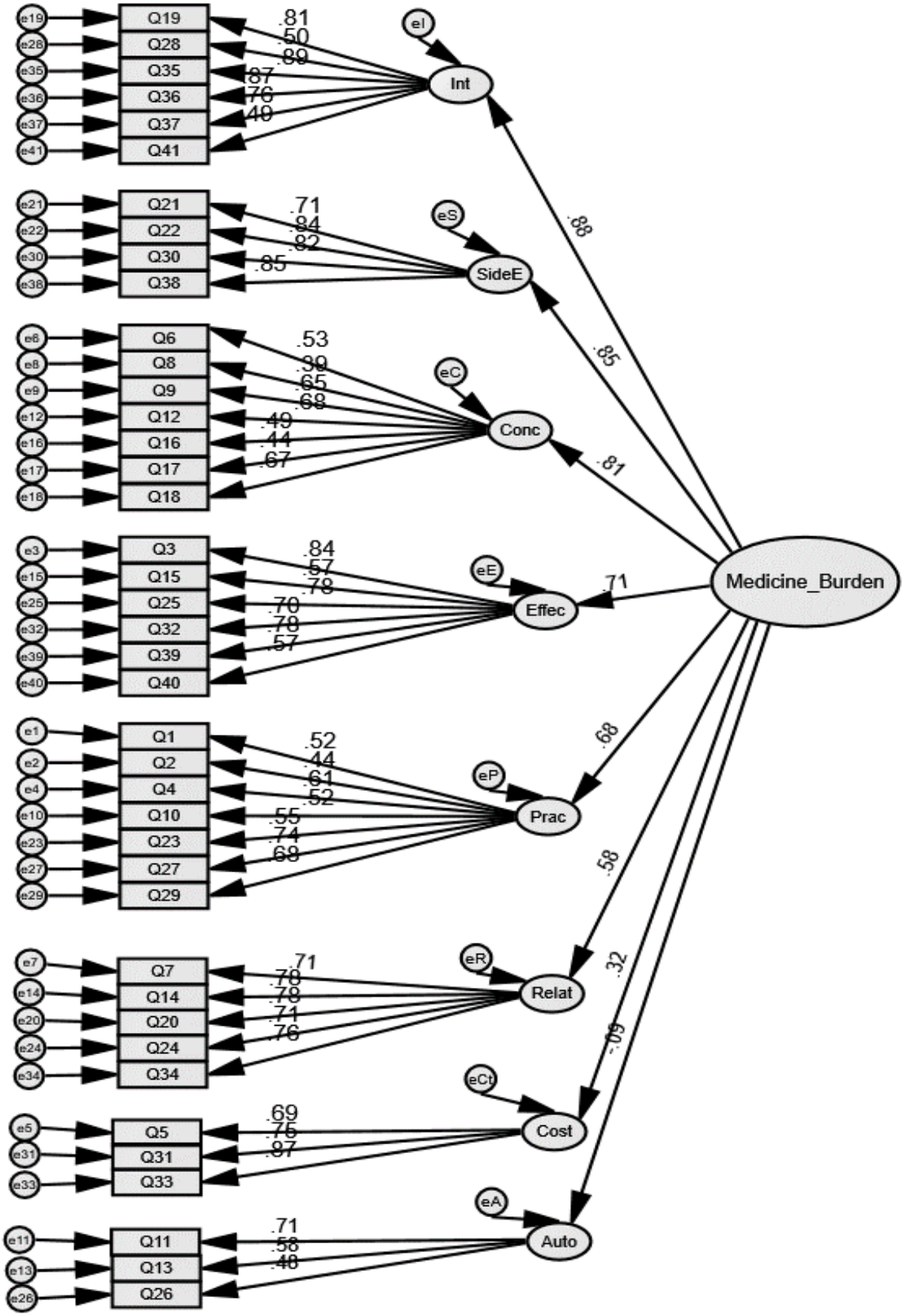


Figure 6-5 Second-order model estimates (Model 2)

Notes; Standardised path estimates are shown; Int = interferences with day-to-day life; Relat = patient-doctor relationships and communication about medicines; Effec = lack of effectiveness; Conc = general concerns about medicines; Prac= practical difficulties; SideE = Side Effects; Cost =Cost-related burden; Auto = Lack of autonomy/control over medicine use; e1 to e41 represent errors for each item; eI to eA represent residuals for each domain.

6.3.5.3 Comparison of model fit indices for the first- and second-order models

In terms of model fit, the chi-square χ^2 probability value was significant ($p < 0.001$) for both models 1 and 2, inferring that neither model fitted the data exactly. As previously described, chi-square χ^2 tests are sensitive to sample size and alternative fit indices were used to assess model fit. Although relative chi-square values (χ^2 /df <3) and RMSEA coefficients (< 0.06) depicted adequate model fit for both models, CFI/TLI values were slightly below the target of ≥ 0.90. Therefore, statistically and strictly speaking, both the first- and second-order models, hypothesised a priori, did not attain 'good' fit to the sample data. Table 6-7 compares model fit indices across all models tested.

Model	χ^2	df	p-value (target p>0.05)	χ^2 /df (target < 3)	TLI (target ≥ 0.90)	CFI (target ≥ 0.90)	RMSEA (90% CI) target (< 0.06)	AIC
Model 1 (first-order)	1471.151	751	<0.001	1.959	0.881	0.891	0.051 (0 .048 -0.055)	1691.151
Model 2 (second-order)	1606.344	771	<0.001	2.083	0.866	0.874	0.055 (0.051-0.058)	1786.344
Model 3 (revised second-order)	1288.357	765	<0.001	1.684	0.915	0.921	0.043 (0.039- 0.048)	1480.357

Table 6-7 Comparison of fit indices for all models tested in CFA (LMQ-3)

Notes; χ^2 = Chi square statistic, df= degrees of freedom, χ^2 /df= relative chi-square, TLI= Tucker Lewis Index; CFI= Comparative fit index; AIC- Akaike's Information Criteria

From Table 6-7, it is clear that Model 1 and Model 2 had close model fit to the data. However, the second-order model (Model 2) had fewer parameters (n=90) to estimate when compared to the first-order model (n=110). As previously described in the methods section, the principle of parsimony proposes that given two models with relatively similar fit, the simpler model (that is one with fewer parameters to estimate) is preferable, as long as it is conceptually plausible. Thus, the second-order factor model was adopted as the simpler model explaining inter-relationships among the 41 items and 8 domains in the LMQ-3 under an overarching general factor (medicine burden).

6.3.5.4 Testing a revised second-order model –Model 3

To improve fit of the simpler model, further modifications were made to the second-order model, deriving Model 3. Model fit indices for the latter are included in Table 6-8. This revised second-order model (Figure 6-6) revealed relatively better model fit indices with CFI and TLI values above 0.9, indicating acceptable fit for this somewhat complex model.[173,212]

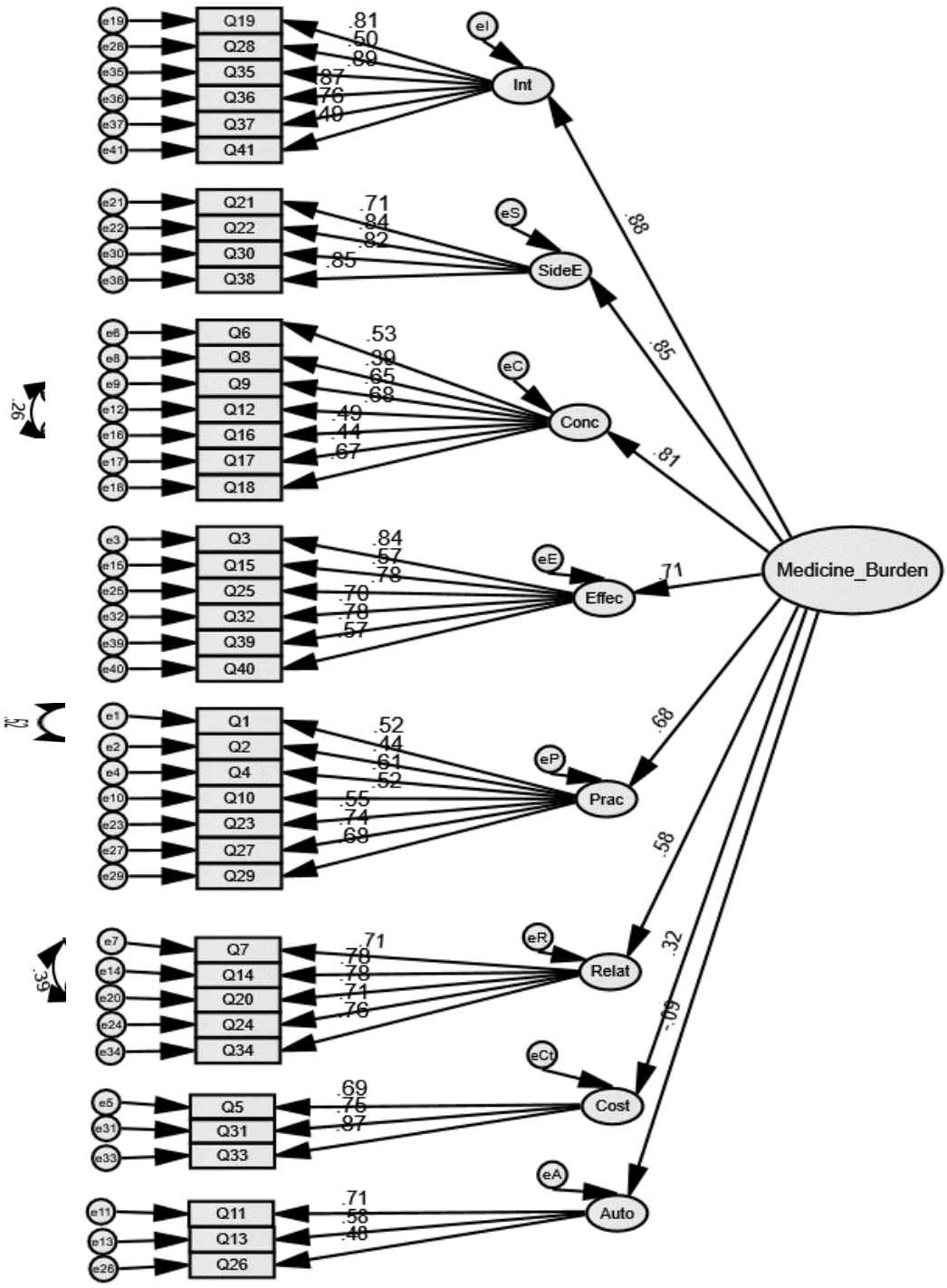


Figure 6-6 Revised second-order model estimates (Model 3)

Notes; Standardised path estimates are shown; Interferences = interferences with day-to-day life; HCPs= Healthcare professionals; Effectiveness = lack of effectiveness; Concerns = General concerns about medicines; Cost =Cost-related burden; Autonomy = Lack of autonomy/control over medicines. Curved arrows on the left = error terms allowed to correlate for the pairs of items.

6.3.5.5 Explaining modifications in Model 3

Figure 6-6 shows that there were three modifications in Model 3 .i.e. three pairs of correlated error terms for item pairs loading in 'concerns', 'practicalities' and 'communication/relationship' domains. As described in the methods section, these modifications were guided by their large modification indices (MI > 20) generated by the computer programme (see Table 6-8). Allowing correlations among error terms enabled understanding relationships among closely related items. For instance, the correlation between error terms corresponding to two items in the 'practicalities' domain (0.52), *'I find getting my prescriptions from the doctor difficult' and 'I find getting my medicines from the pharmacist difficult',* was strongest and reflects that the two items measure something in common besides that reflected by their respective domain. All model modifications were informed by empirical data, substantive reasoning, and professional judgement based on earlier qualitative work about the meaning of items (See Chapter 5). Table 6-8 details other modifications in Model 3.

All but one item in Model 3 loaded adequately on their respective domains; '*I feel I need more information about my medicines'* cross-loaded almost equally on 'patient-doctor communication/relationships' (factor loading = 0.35) and on 'general concerns about medicines' (factor loading = 0.37). This item was initially hypothesised to relate to the latter domain, following the preliminary EFA.

	Path		Description	Modification Index	Expected parameter change
Q1	<-->	Q2	Correlation between error terms associated with two items, loading on 'practical difficulties'. I find getting my prescriptions from the doctor difficult. I find getting my medicines from the pharmacist difficult.	92.890	0.502
Q14	<-->	Q20	Correlation between error terms associated with two items loading on the 'doctor/relationships' domain. My doctor(s) take my concerns about side effects seriously. My doctor(s) listen to my opinions about my medicines.	29.228	0.162
Q12	<-->	Q16	Correlation between error terms associated with two items loading on 'concerns'. I am concerned about possible damaging long-term effects of taking medicines. I am concerned that I am too reliant on my medicines.	22.042	0.204

Table 6-8 Modifications in the revised second-order model (LMQ-3)

6.3.6 Internal consistency

Except for one subscale, 'autonomy', all LMQ-3 subscales had acceptable internal consistency (Cronbach's α coefficients > 0.7) as shown in Table 6-9.

Subscale (number of items)	EFA subsample	CFA subsample
Doctor (n=5)	0.870	0.860
Interferences (n=6)	0.865	0.863
Practicalities (n=7)	0.738	0.769
Effectiveness (n=6)	0.851	0.858
Concerns (n=7)	0.796	0.757
Cost (n=3)	0.801	0.806
Side effects (n=4)	0.901	0.879
Autonomy (n=3)	0.692	0.610

Table 6-9 Internal consistency (Cronbach alpha) for LMQ-3 subscales

Notes; Doctor = patient-doctor relationships and communication about medicines; Interferences = interferences with day-to-day life; Practicalities= practical difficulties; Effectiveness = Lack of effectiveness; Auto = Lack of autonomy/control over medicine; Concerns = General concerns about medicines; Cost =Cost-related burden; Side effects = Side effect-related burden

6.4 Discussion

This study aimed to formulate the LMQ-3 and ascertain its construct validity through exploratory and confirmatory factor analyses. The LMQ-3 is a multidimensional scale, as revealed by these standard, iterative, multi-step, analyses conducted using responses from the adult general public in the UK using at least one prescription medicine.

The revised second-order model (Model 3) attained the best model fit (CFI/TLI > 0.9), when compared to all alternative models tested. Re-specified models tend to have improved model fit since they are products of modifications, such as allowing correlation of measurement error terms that reflected strong relationships among items measuring a common attribute. Revisions to models, aimed at addressing poorly fitting parameters, were data driven and conceptually justifiable. However, excessive model modification aimed at attaining near-perfect fit to sample data is not recommended to avoid model instability.[180] In addition, some researchers, like Marsh et al (2004), warn against dependence on restrictive 'golden statistical rules' for evaluating model fit.[219] For complex measurement models with multiple domains, and items per subscale, such as that underlying the LMQ-3, 'it is almost impossible to get an [excellent] fit' defined by higher cut-off values for CFI and TLI (≥ 0.95).[219] There is a need to balance demands for optimising model fit and attaining standard cut-off values and ensuring adequate questionnaire content coverage, and interpretability of the model. Therefore to minimise further model complexity and enhance parsimony and model stability, Model 2 (Figure 6-5) was selected as the 'simplest' and most interpretable representation of concepts underlying the LMQ-3.

The preferred LMQ-3 measurement model (Model 2) comprised 41 items, which were best represented as one overarching construct, medicine burden, measured indirectly by the eight inter-correlated, yet distinct, subscales: 1) interferences with day-to-day life; 2)side-effect-related burden; 3) general concerns about medicines; 4) practical difficulties; 5) lack of effectiveness; 6) patient-doctor relationships/ communication problems; 7) cost-related burden; and 8) lack of autonomy/control over medicines use. The first three subscales were the strongest measures/predictors of medicine burden, followed by subscales 4-6 in decreasing strength respectively. Cost-related burden

moderately explained medicine burden. The 'autonomy' domain was least associated with medicine burden.

As described in the introductory chapters, patients' experiences of living with medicines are wide-ranging[88] and as indicated previously, 'interferences with day-to-day life' was the prime indicator of medicine burden. It covered specific issues such as disruptions to daily tasks, social and leisure activities, social relationships, sexual life, and the need to carefully plan medicine regimens to fit lifestyle. For people with cognitive and or physical difficulties, exacerbated by aging and polypharmacy (or its side effects), planning and performing 'complex tasks dependent on cognition' can be especially difficult.[220] Medicine use routines tend to be planned alongside usual activities of daily life (e.g. having meals, sleeping), and changes in daily routine could also be disruptive to medicine use experiences. Nevertheless, an item intended to measure the latter concept, *'Changes in daily routine causes problems with my medicines',* did not meet inclusion criteria and was excluded from the final item pool.

The side-effect dimension strongly explained medicine burden, and was closely associated with the 'interferences' domain described above. The burden of side effects, and their impact on physical, social, and emotional wellbeing, is well documented.[92] Side effects were also strongly associated with concerns about medicines in this study. Medicines are often perceived by the general public to be damaging and harmful, and to have long-term effects.[21,81] Concerns about harm from side effects are also related to perceived dependency from long-term use of medicines.[81]

Practical difficulties were significantly related to the 'interference' domain. The practical difficulties subscale covered issues around access to prescriptions, obtaining regular medicine supplies, identification of different medicines, and general use of medicines. The burden of self-care, including of managing medicine routines and self-administration of medicines, has been documented as a demanding activity.[48,50,85,89] Managing medicine routines can be time- and resource-demanding, with respect to accessing medicines, learning how to use therapies, and/or monitoring regular use.[50,89] This may even be worsened by complex regimens (e.g. quantity and frequency of

use),[83,98] varied formulations or their packaging, and switching between generics and brands.[100] Regardless, some of these concepts were not adequately captured in the final LMQ-3 since three potentially relevant items were excluded due to poor performance in the psychometric analyses: *'I find the written instructions on how to use my medicines easy to understand'; 'It is difficult to identify which medicine is which'; and 'I find opening the packaging of my medicines difficult'*. Regardless, the LMQ-3 has an item hinting on patient autonomy to choose which brands of medicines to use. Such a statement, '*I would like more say in the brands of medicines I use',* although clustered in the 'general concerns' domain, may indirectly reflect issues around medicine formulations, packaging, or dosage regimen used by patients, and need for brands/generics that minimise practical difficulties while enhancing the medicine use experience.

In this study, negative experiences with effectiveness were also related to medicine burden. Medicine-related benefits are often weighed against any associated burden among patients who may deliberately ignore any inconveniences of medicine use.[195,198] Although many patients value the positive effects of medicines, including relief of symptoms, control/managing illnesses, and prevention of illness-associated morbidity or mortality as the prime rationale for using medicines, their expectations may not always be met.[115] Perceived inadequacies in desired outcomes may impact negatively on individuals' overall experiences of medicine use, and influence medicine-related behaviour including non-adherence.[23,88]

Poor doctor-patient relationships and communication about medicines were also significantly correlated with medicine burden. Interpersonal relationships and information sharing by healthcare providers influences factors such as patient-provider partnerships and increased commitment to use medicines,[195,221] which in turn affects perceived effectiveness. Some of the items in the 'doctor' domain related to trust and confidence in health professionals, as well as information sharing. Patient trust and confidence is also associated with positive attitudes and experience with medicine use, and attainment of treatment outcomes.[23] Poor patient-provider relationships may deter information sharing and could be burdensome to some individuals. Medicine-information-related burden may also be exacerbated by poor consultation styles,

conflicting information, patient understanding and the amount of information provided.[196,197]

One of the differences between the 41-item final LMQ-3 and the LMQ-2 (reported in Chapter 4) is the lack of a domain on 'patient-pharmacist communication about medicines', the items for which did not meet the inclusion criteria in the present study. This finding poses a specific challenge to pharmacists who have a professional responsibility to support patients with medicines use through existing or new pharmacy services. However as the 'pharmacist' domain did not factorise – it formed a psychometrically unstable factor with fewer than three items loading in the final measure, it was judged to be of low importance as a separate domain.

One potential reason for this is that patient-communication experiences, in terms of medicine use, are explained mostly by doctor-communication and less by pharmacist-communication. Many studies show that patients prefer to talk to doctors about medicines than to pharmacists,[222] even though pharmacists are more accessible. Patient/public perceptions of the pharmacist's role may complicate this issue, as pharmacists are often perceived as busy and pharmacies lacking in facilities for private/confidential consultations.[223] Moreover, increasingly many patients have medicines delivered to their homes directly and have no interaction with a pharmacist. None of the additional comments provided in the studies cited pharmacist interaction as contributing to burden, or indeed other health professionals who may discuss medicines with them. It is important to recognise that the LMQ was not developed as a measure of satisfaction with pharmacists or their services.

Therefore, it could be argued that the lack of a 'pharmacist communication' domain in the final LMQ-3 was not detrimental. This is especially the case if pharmacists are to take the lead in supporting patient evaluations of their own medicines. Patients are more likely to give an accurate reflection of challenges with doctor-communication, represented in the LMQ-3, than when reporting deficiencies with pharmacist-communication to pharmacists themselves. Further work may establish the latter proposition, as well as the impact of pharmacist-communication on medicine burden levels among individual patients.

A new addition to the LMQ-3 structure was the 'cost' subscale. Cost-related burden was found to be moderately correlated with medicine burden. As described previously, the financial burden associated with long-term prescription medicines can be a demanding aspect of the medicine use experience, for not only chronically-ill patients but also their family and social life.[46,51,52,102,104,224] Although only approximately a third of patients paid for their prescription medicines in this study, the cost domain was clearly associated with medicine burden. According to the Prescription Charges Coalition, a group of patient-organisations advocating to 'end unfair prescription charges for people with long-term medical conditions' in England, cost-related burden is real and impacts on non-adherence, and other aspects of day-to-day life, particularly affecting the younger population and those in lowest income brackets.[47,102]

Perceived lack of autonomy over medicine use was a relatively weak indicator of medicine burden compared to other domains in LMQ-3. Statistical analyses indicated that decreasing autonomy to vary regimen dose or timing (or even stopping medicines) was not significantly associated with medicine burden. This may suggest that negative experiences with respect to the autonomy to change dosing schedules or time are not necessarily burdensome in this sample of the public. Paradoxically, experimental analyses to delete the 'autonomy' subscale from the hierarchical model (Model 3) did not improve model fit significantly, and thus this dimension was retained. Further studies are needed to cross-validate the relative importance of perceived lack of autonomy in explaining medicine burden, and overall medicine use experiences.

Regardless, inconvenient regimes can negatively impact on the medicine use experience, and lead to perceived loss of control over medicines use.[95,225] Moreover, qualitative studies indicate that patients who experience difficulties in 'exerting control over medicine routines specified by health professionals'[23] may perceive more medicine burden as inflexible schedules may interfere with day-to-day life. Practical difficulties and autonomy subscales were also slightly correlated in this study. Some patients may manipulate their medicine regimens, especially when they experience unbearable burden,[88] while others unable to cope may feel negative emotions about

their medicines.[78] For those able to adapt medicine regimes to fit in with their lifestyle, they may perceive little or no medicine burden. Coping strategies may draw on family and social support, health provider support, and personal strategies like information seeking, record keeping, adjusting regimes, use of reminders, and pill organisers.[88,221]

Study strengths and limitations

All data were utilised resourcefully to suit the analyses performed. All factor analyses were conducted on an adequate sample of survey responses from adults, using regular medicines, recruited via the general public in the UK, although limited to web-based survey methodology. Although the survey was accessed by a wider, geographically-representative, population across the UK, it is likely that issues around prescription costs and charges, currently applicable to England only, were irrelevant to the few participants living elsewhere in the UK. The majority of respondents were females, and the results may be representative of those with higher education levels and access to the internet.

Poorly performing items were eliminated using psychometrically sound criteria, and conceptual decisions guided by discussions with the supervisory team. Nevertheless, item deletion may have led to loss of potentially relevant items. A factorially complex item, *'I feel I need more information about my medicines'*, was retained in the final LMQ-3. Streiner and Norman (2008) suggest that such an item cross loads comparably well on two or more factors, and may pose measurement problems as it appears to assess multiple constructs.[127] Future work on the LMQ-3 may consider the specificity of this item, as a possible candidate for item reduction when devising a shorter version of the instrument. Nevertheless, further studies, described in Chapter 7 and 8, were conducted to double check psychometric properties of all items.

6.5 Chapter summary

This study set out to refine the LMQ-2.1 and assess the construct validity of a newer and shorter version of the questionnaire (LMQ-3). The 41-item, 8-factor, modified second-order measurement model (LMQ-3) revealed better model fit statistics, and was most interpretable. Of the eight LMQ-3 subscales (interferences with day-to-day life; side-effect-related burden; general concerns about medicines; practical difficulties; lack of effectiveness; patient-doctor relationships/communication problems; cost-related burden; and lack of autonomy/control over medicines use), the first seven were adequately and significantly correlated with medicine burden, as the hypothesised overarching construct purported to underlie the measure. All seven subscales had acceptable internal consistency, and the 'autonomy' subscale was close to attaining the target Cronbach's alpha.

This chapter extends knowledge on the LMQ as a measure of medicine burden and adds to the understanding of the best representation of its dimensions, and their internal consistency. The findings also contribute to evidence of the questionnaire's measurement properties, particularly construct validity. Since there are no 'gold-standard' measures of prescription medicine burden, future studies could explore how the LMQ-3 and its subscales relate to other measures of medicine-related experiences. Such studies can help to further validate the LMQ-3 and double check construct validity. This is the subject of Chapter 7 of this thesis.

Chapter 7 Criterion-related validation of the LMQ-3

Acknowledgements

Data used in Chapter 7 was collected by myself (BK), with assistance from five undergraduate students conducting their final-year research projects at the Medway School of Pharmacy. BK sought ethics approval and research governance for all study sites and co-ordinated all data collection. The students conducted part of the data entry. All datasets were double-checked, cleaned and merged by BK, who conducted the analysis and interpreted the results presented in this chapter.

7.1 Introduction

In the previous chapter, construct validity of the Living with Medicines Questionnaire (LMQ-3) was assessed, confirming the internal structure of the instrument. Although its overarching construct of medicine burden and eight subordinate domains were illuminated, the preceding chapter also revealed the need for further construct validation. Particularly, there was a need to cross-validate LMQ-3 concepts and how they relate to other medicine-related attributes (such as treatment satisfaction), so as to fully understand the constructs described in Chapter 6. It was necessary to conduct further testing of the instrument's psychometric properties (i.e. construct validity) to help substantiate the nature of concepts underlying the LMQ-3.

Standard guidance defines criterion validity as 'the extent to which the scores of [an] instrument are related to a known gold standard measure of the same concept'.[124] Criterion testing is a form of external validation, in which relationships with other measures of the same construct are verified.[226] However, the same guidance acknowledges that 'for most [instruments], criterion validity cannot be measured because there is no gold standard' measure of the same concept under investigation.[124]

In the absence of a 'gold-standard' measure of medicine burden, alternative measures provide an option. Criterion-related validation can help explore the degree to which a newly developed measure (e.g. the LMQ-3) relates to previously validated measures of similar or dissimilar constructs that are presumably related.[227,228] In other words, 'measures of constructs that theoretically should not be related to each other are, in fact, observed to not be related to each other (known as divergent or discriminant validity)' or 'measures of constructs that theoretically should be related to each other are, in fact, observed to be related to each other (known as convergent validity)'.[228]

In Chapter 2, the Treatment Satisfaction Questionnaire for Medication (TSQM-II) was identified as a generic measure of satisfaction with prescription medicines for any disease/condition,[109] and it has been widely used in other questionnaire validation studies.[83,130,229] One such study involved validation of the Treatment Burden Questionnaire (TBQ), also identified in Chapter 2, where a negative relationship was established between treatment burden and treatment satisfaction.[83] Although a similar negative relationship is expected between medicine burden and satisfaction with therapy, it has not yet been established, empirically, using TSQM-II dimensions of effectiveness, side effects, convenience, and general satisfaction.

More so, health-related quality of life (HRQoL), which encompasses multiple dimensions including physical, mental and psychosocial components, is another widely researched concept[128] whose association with medicine burden is unknown. However, it is well documented that using medicines impacts on different aspects of HRQoL.[23,92,134,149] It was thus relevant to compare the LMQ-3 with a suitable measure of HRQoL. The EuroQol five-dimensional questionnaire, the EQ-5D-5L,[230] was selected as an additional comparator tool to verify the medicine burden concept, and how its various components were related (or not) to HRQoL dimensions.

Aim and objective

This chapter aimed to examine the criterion-related validity of the LMQ-3, against suitable measures administered to an adult patient population using regular prescription medicines in south-east England.

The specific objective was to examine the divergent/discriminant validity of the LMQ-3 by comparing patient scores on the LMQ-3 (and its subscales) with those obtained using the TSQM-II, and the EQ-5D-5L.

7.2 Methods

7.2.1 Study design

This was a cross-sectional validation study, conducted between October and December 2015, in which all three questionnaires (the LMQ-3, TSQM-II and EQ-5D-5L) were self-completed at the same time. The National Research Ethics Service (NRES Committee South Central -Oxford C) approved this study (See Appendix 18). Separate research governance approvals were granted by participating organisations (Appendix 19). All participants had access to study information (Appendix 20), and consent was implied by return of complete questionnaires.

7.2.2 Study participants and inclusion criteria

Similar to previous studies (described in Chapters 4-6), participants were adults (18 years or older), using at least one long-term prescription medicine for any disease/condition, and living in England.

7.2.3 Study instruments

The questionnaires employed in this validation study were the LMQ-3, the TSQM-II, and the EQ-5D-5L. All three questionnaires were combined and printed in form of a booklet to ease handling and completion. The ordering of questionnaires in the booklet prioritised the LMQ-3, then the TSQM-II as another medicine-related questionnaire, and the EQ-5D-5L came last. A brief overview of each instrument is provided, including characteristics, rationale for selection and a priori hypotheses.

7.2.3.1 The LMQ-3

As described in Chapter 6, the LMQ-3 is a self-completion questionnaire with 41 Likert-type statements rated on a 5-point rating scale (strongly agree to strongly disagree) (See Appendix 21). It also has visual analogue scales, including a global item assessing overall medicine burden (VAS-burden). The LMQ-3 also has a free-text question, and participant characteristics. In terms of scoring, Likert-item responses are coded from 1 to 5, while the VAS-burden is rated using a 0-10 scale, with anchors indicating 'no burden at all' to 'extremely burdensome'.

As described in previous chapters, negatively phrased items were reverse scored, such that higher scores reflect higher medicine burden. Subscale/domain scores were a sum of item scores per domain (relating to interferences with day-to-day life; side effects; general concerns about medicines; practical difficulties; lack of effectiveness; patient-doctor relationships/communication problems; cost-related burden; and lack of autonomy/control over medicines use). The LMQ-3 total scale score (i.e. overall composite score) is the sum of all subscale scores. Figure 7-1 summarises LMQ-3 scoring.

<u>Subscale/domain scores</u>
[1] Interferences score=Q19 + Q28 + Q35 + Q36 + Q37 + Q41
[2] Side-effect-burden score = Q21 + Q22 + Q30 + Q38
[3] General concerns score=Q6 + Q8 +Q9 + Q12 + Q16 + Q17 + Q18
[4] Practical difficulties score = Q1 + Q2 + Q4 + Q10 + Q23 + Q27 + Q29
[5] Lack of effectiveness score =Q3 + Q15 + Q25 + Q32 + Q39 + Q40
[6] Patient-doctor communication problem score=Q7 + Q14 + Q20 + Q24 + Q34
[7] Cost-burden score = Q5 + Q31 + Q33
[8] Lack of autonomy score=Q11 + Q13 + Q26
<u>Total scale score</u>
= [1] + [2] + [3] + [4] + [5] + [6] + [7] + [8]

Figure 7-1 Scoring of LMQ-3 items and subscales/domains

The LMQ-3 was the primary study instrument whose scores were hypothesised to relate to the TSQM-II and the EQ-5D-5L as described below.

7.2.3.2 The TSQM-II

Permission to use the TSQM Version II was granted by the Quintiles group Inc. (See Appendix 22). The TSQM-II is a short, 11-item, self-completion, generic questionnaire tested in patients with a range of long-term conditions, and assesses satisfaction with various prescription medicines.[109] It has four internally consistent subscales (Cronbach's alpha range, 0.85-0.87) including satisfaction with side effects, effectiveness, convenience, and global satisfaction. Items are scored on a 6 or 7-point Likert-type scale with descriptive anchors (e.g. extremely dissatisfied to extremely satisfied). The TSQM-II instrument also has a binary response option assessing whether (or not) patients experience side effects. All TSQM-II scores are transformed according to a standard scoring algorithm (See Appendix 22), and range from 0 to 100.

The TSQM-II was selected for use in this study because of its face-, content-, and construct validity, and the fact that it has been tested for comprehension in the UK population. Moreover, as a popular measure of treatment satisfaction, this questionnaire has been widely used as a criterion-referenced tool to validate other instruments, including the Treatment Burden Questionnaire (TBQ).[83] The latter questionnaire was not used as a criterion-reference in the present study since some of its items are not specific to prescription medicines.[231] For instance, they relate to treatment burden associated with laboratory tests and self-monitoring, and difficulties associated with doctor appointments.[83] Moreover, the original questionnaire was developed and tested in a French population, and the more recently validated English translation[232] was not easily accessible at the time of the study.

Hypotheses

A negative relationship between medicine burden and treatment satisfaction was hypothesised i.e. higher perceived medicine burden corresponding to lower satisfaction with medicines use. Composite scores on the LMQ-3, and its subscales, were predicted to show negative correlations with scores on the TSQM-II global satisfaction, side effects, effectiveness, and convenience subscales. Correlations between the latter three TSQM-II subscales and three LMQ-3 subscales (also relating to side effects, effectiveness (or lack of it) and practical difficulties) were expected to be stronger since these subscales appear to overlap, at least at face value.

7.2.3.3 The EQ-5D-5L

Permission to use the EQ-5D-5L (UK English version) was granted by the EuroQol Research Foundation (See Appendix 23). The EQ-5D-5L is the EuroQol's five-dimensional, self-administered, questionnaire. It is a standardised, commonly used generic measure of HRQoL that has demonstrated validity and reliability in diverse settings. [230,233] It was selected for use in this study as a widely acceptable tool recently recommended for use within the English NHS.[234] Unlike the relatively longer health status questionnaires (such as the 36-Item Short- Form Health Survey (SF-36),[235,236] the EQ-5D-5L is short and consists of 5 questions assessing mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Its length was exploited to minimise response burden, an important factor to consider for participants having to complete three questionnaires overall.

Designed to improve its sensitivity and discriminatory properties, the EQ-5D-5L has five answer options reflecting no problem, slight problems, moderate problems, severe problems and extreme problems, which are scored from 1 to 5 respectively.[230,233] The EQ-5D-5L also has a 20- cm visual analogue scale, the EQ-VAS, rated from 'the worst health you can imagine' (scored as 0) to 'the best health you can imagine' (scored as 100).[233]

Hypotheses

It was hypothesised, a priori, that medicine burden would be negatively related to overall health status[88,92] i.e. higher perceived medicine burden would be associated with the lower self-reported general health scores. It was also anticipated that negative correlations between LMQ-3 medicine burden and HRQoL domains of the EQ-5D-5L would be of small to moderate magnitude, since the two instruments were hypothesised to measure distinct constructs. Generally, low correlations between LMQ-3 and EQ-5D-5L subscales were expected.

7.2.4 Study settings and procedures

Three recruitment settings were used in this study: community pharmacies, GP practices, and outpatient waiting areas of the Medway Maritime Hospital. Research governance to access the outpatient areas was granted by the Research and Development department at the Hospital (See Appendix 19), which also provided a letter of access for individual researchers. Permission to recruit via local community pharmacies and GP practices (in areas of Kent and Medway) was obtained for each study site.

a) Community pharmacy recruitment

Recruitment via community pharmacies, conducted over a 6-week period, was intended to capture medicine use experiences of users of pharmacy services. The justification for distributing surveys via pharmacies was described under general methodology in Chapter 3, and in Chapter 4 where similar methods were applied. A purposive sample of small-medium sized pharmacies (independents) was selected from the NHS choices website (http://www.nhs.uk/pages/home.aspx), and used to recruit potential participants. Multiple-chain community pharmacies (e.g. Boots) were excluded from survey distributions owing to time-demanding procedures for obtaining in-house governance. More so, it was assumed that there was no difference in patient characteristics across different pharmacy service providers. All pharmacies were located in Medway towns and areas of Kent, within close proximity to the Medway School of Pharmacy for easier access.

Letters of invitation, study information, and copies of the questionnaires were sent to pharmacists in charge at selected community pharmacies, followed by a phone call after a week to verbally ask for permission and to arrange questionnaire distributions. Potential participants were people waiting in the pharmacy (e.g. those refill their prescriptions). Across all three recruitment settings, screening for pre-defined inclusion criteria was done verbally by asking patients if they used long-term medicines, checking they were 18 years or older and resident in England. Screened participants were provided with survey packs containing questionnaires, participant information, and freepost envelopes for returning completing questionnaires.

b) Recruitment via General Practices

Similar to procedures used in pharmacy recruitment, GP practices were purposively selected from the NHS choices websites for their location in areas of Medway and Kent, near to the School of Pharmacy. Practices with more registered patients were selected to access a higher footfall of patients. Similar to pharmacy recruitment, letters of invitation (and study information) were sent to GP practice managers followed by a phone call, to recruit practices to the study.

Once permission to distribute study packs to people waiting for appointments was obtained, practices were visited by researchers. Potential participants were those waiting for GP appointments; they were approached directly or with help from practice administrators to invite them to the study. Brief verbal information about the study was provided, and potential participants were verbally screened for eligibility to participate. If meeting all criteria, a study pack containing the questionnaire booklet was provided. Participants could choose to complete the questionnaires while waiting for their appointment with the GP or could take them away and return them using the prepaid envelope provided. Recruitment in practices was conducted over a three-week period.

c) Recruitment via outpatient clinics

A three-week questionnaire distribution exercise was conducted in outpatient clinics of the Medway Maritime hospital. As stated previously within the methodology section (Chapter 3), recruitment of participants via the local hospital was intended to capture medicine use experiences of patients in secondary care. The hospital has a diverse and high footfall of patients. Similar to other recruitment settings, a letter of invitation was sent to the outpatients' area manager followed by a phone call, to recruit outpatient clinics to the study.

Once permission was obtained, seven different outpatient areas were visited by researchers to distribute study packs to people waiting for appointments. These areas provide care under specialities, including dermatology, gynaecology, general surgery, rheumatology, urology, general medicine, neurology. Potential participants were approached directly and screened for eligibility, similar to other recruitment settings.

Participants completed questionnaires while waiting for appointments or off-site; the former returned completed questionnaires in sealed envelopes to either researchers or dropped them in designated boxes in the outpatient areas (e.g. at the reception) where they were collected on the same day. Again, questionnaires completed outside the premises were returned by post using prepaid envelopes.

7.2.5 Data analysis

7.2.5.1 Data preparation

All data were entered in SPSS (version 22). All data were double-checked, cleaned, and pooled from all sources. Quality checks were made to correct potential errors, visually and by descriptive statistics, to enhance accuracy of data. The extent of missing data was assessed for all items, and demographic questions. Subscale (domain) and total scale (composite) scores on all LMQ-3 were computed as per Figure 7-1. Computation of TSQM-II subscale and global scale scores was done in accordance with the developer's algorithm (See Appendix 22).[109] Raw item scores on the EQ-5D-5L, and its general health scale (the EQ-VAS) scores were used. The distribution of scores on all three instruments was assessed using descriptive statistics including medians, mean, and range of scores.

7.2.5.2 Correlation analyses

To address the primary study objective, correlations between scores on the LMQ-3, the TSQM-II, and the EQ-5D-5L were examined. Spearman's' rank correlation coefficient (r_s), a non-parametric test, was reported for the asymmetrical scores. The magnitude and direction (as positive or negative) of correlations were assessed. Correlations below 0.34, 0.35-0.50, and > 0.5 were interpreted as weak/small, moderate, and high (or strong) respectively, and p-values <0.05 were deemed statistically significant.[83] Positive correlations denote that an increase in one variable corresponds to an increase in another, while negative correlations suggest an inverse relationship.

7.3 Results

7.3.1 Response rates

Out of a purposive sample of 20 community pharmacies, and 20 GP practices contacted initially, six pharmacies (30%) and five GP practices (25%) granted permission to recruit participants from their premises. Seven of eight (87.5%) outpatient clinics were accessible for hospital recruitment. A total of 1306 questionnaires were distributed across all study sites: 220 questionnaires in GP practices; 150 questionnaires in community pharmacies; and 936 questionnaires in outpatient clinics. Overall, 422 questionnaires were returned representing 32.3% response rate. Site-specific response rates were 44.7% (n=67), 36.4% (n=80), and 29.4 % (n=275) for community pharmacies, GP practices and outpatient clinics respectively.

Item-level response rates were excellent (95% to 100%) for all but two LMQ-3 Likert-type items *('Q33-I have to pay more than I can afford for my medicines'* and *'Q5-I worry about paying for my medicines')* that had responses missing for 6.8% and 9.3% of all participants respectively. Pairwise deletion of missing data was used to include participants that provided responses necessary for each analysis.

7.3.2 Patient population

Half of all participants were female (52.8%, n= 208). The mean age was 56.1 (± 18.17), including those between 18-92 years, and the vast majority of participants were 65 years or over (40.5%, n=170). Nearly half of the respondents were retirees (45.6%, n=187). The mean number of medicines used was 4.6 (±3.67), with some participants self-reporting to use up to 26 medicines (median= 4, range 1-26). Hyperpolypharmacy (10 or more medicines) was experienced by 13% (n=54) of all participants. All participants' characteristics are presented in Table 7-1.

Characteristic		Frequency (%)
Gender	Female	208(52.8)
(n= 394)	Male	186(47.2)
Age	18-29	51(12.1)
(n = 420)	30-49	81(19.3)
	50-64	118(28.1)
	65 or over	170(40.5)
Education level	School	158(40.3)
(n=392)	Technical college/Apprenticeship	117(29.9)
	University	89(22.7)
	Other	28(7.1)
Employment status	Employed	159(38.8)
(n=410)	Unemployed	44(10.7)
	Retired	187(45.6)
	Full-time student	20(4.9)
Ethnicity	White	353(86.5)
(n= 408)	Asian/Asian British	15(3.7)
	Mixed	10(2.4)
	Black/African/Caribbean	26(6.4)
	Other	4(1.0)
No. of medicines	1-4	236(56.7)
(n=416)	5-9	126(30.3)
	10 or more	54(13.0)
Formulation used	Tablets/capsules	284(70.3)
(n = 404)	Parenteral formulations	30 (7.4)
	Mixed formulations	90 (22.3)
Frequency of use	Once per day	146(35.9)
(n = 406)	Twice per day	136(33.5)
	Three times per day	49(12.1)
	More than 3 times per day	47(11.6)
	Other times**	28(6.9)
Managing medicines	No (Autonomous)	349(85.7)
(n=407)	Yes (Requires assistance)	58(14.3)
Medicines carer	Spouse/ Partner	33(58.9)
(n=56)	Relative	10(17.9)
	Support worker	7(12.5)
	Friend	4(7.1)
	Other$^{\mu}$	2(3.6)
Paying for prescriptions *(n= 408)*	No	267(66.6)
	Yes	141(33.4)

Table 7-1 Characteristics of participants in the criterion-related validation study

Notes; $^{\mu}$includes GP practice nurse; ** Different times of the day, week, or month

7.3.3 Distribution of scores on all instruments

Compared to the LMQ-3 domain scores, TSQM-II scores were skewed towards the scale's ceiling (indicating higher self-reported satisfaction with medicines). For instance, the satisfaction with side effects subscale had a median score of 100 (observed and possible range of scores, 0-100), suggesting that the average participant was fully satisfied with their experience of side effects. Median scores on the EQ-5D-5L indicated no or slight problems with the five aspects of health for this sample population. Overall health status was good as indicated by a median score of 75 on the EQ-VAS, where 100 represents the best imaginable health. Table 7-2 illustrates score distribution across all questionnaires used in this study.

Domains per instrument	No. of items per domain/scale (possible range)	Median score (Observed range)	Mean score observed (SD)
LMQ-3			
Patient-doctor communication	5 (5-25)	12.0(5-25)	12.5(3.9)
Practical difficulties	7(7-35)	15.0 (7 -28)	15.4 (4.1)
Cost- burden	3(3-15)	6.0 (3-15)	6.6 (3.0)
Side-effect-burden	4(4-20)	9.0 (4-20)	9.8(3.6)
Lack of effectiveness	6(6-30)	14.0 (6-29)	13.9 (3.7)
General concerns	7(7-35)	20.0(7-35)	20.2 (5.1)
Interferences with daily life	6(6-30)	13.0 (6-29)	13.8(4.8)
Lack of autonomy/control	3(3-15)	10.0 (3-15)	10.2(2.6)
LMQ-3 total /composite score	41(41-205)	101.0 (50-172)	102.7(20.0)
VAS-burden scale score	1(1-10)	1.5(0-10)	2.8(3.0)
TSQM-II			
Satisfaction with effectiveness	2 (0-100)	66.7(0-100)	68.2(18.4)
Satisfaction with side-effects	3 (0-100)	100 (0-100)	83.5(22.7)
Satisfaction with convenience	3 (0-100)	72.2(16.7-100)	72.6(17.0)
Global satisfaction	2(0-100)	66.7(0-100)	70.9(18.8)
EQ-5D-5L			
Mobility	1(1-5)	1.0 (1-5)	1.7(1.0)
Self-care	1(1-5)	1.0(1-5)	1.3(0.7)
Usual activities	1(1-5)	1.0(1-5)	1.7(1.0)
Pain/discomfort	1(1-5)	2.0(1-5)	2.1(1.1)
Anxiety / depression	1(1-5)	1.0(1-5)	1.7(0.9)
EQ-VAS for general health state	1 (0-100)	75.0 (1-100)	69.4(20.5)

Table 7-2 Distribution of scores obtained using the LMQ-3, TSQM-II and EQ-5D

Notes; the EQ-5D-5L is scored such that higher scores depict severe problems with a specific aspect of HRQoL (1 indicates no problem, 5 indicates extreme problems).
All scores on the TSQM-II are measured so that higher scores depict greater satisfaction
All scores on the LMQ-3 are measured such that higher scores depict greater medicine burden

7.3.4 Criterion-related validity of the LMQ-3

The magnitude of correlations between LMQ-3 scores and those on the TSQM-II were in the range of 0.010-0.628, suggesting weak to strong correlations among subscales (See Table 7-3). As predicted, correlations were strongest between thematically comparable subscales of the two instruments: LMQ-3 lack of effectiveness with TSQM-II satisfaction with effectiveness (r_s = - 0.628); LMQ-3 side-effect-burden with TSQM-II satisfaction with side effects (r_s = -0.597); and LMQ-3 practical difficulties with TSQM-II satisfaction with convenience of medicine use (r_s = -0.529). The correlations between treatment satisfaction and autonomy- and cost-related burden were generally weak (r_s < 0.232) (See Table 7-3).

LMQ-3	TSQM-II Satisfaction with Effectiveness	TSQM-II Satisfaction with Side-Effects	TSQM-II Satisfaction with Convenience	TSQM-II Global satisfaction
Patient-doctor communication	-0.476	-0.278	-0.360	-0.394
Practical difficulties	-0.367	-0.405	-0.529	-0.426
Cost-related burden	-0.141	-0.193	-0.157	-0.232
Side-effect-burden	-0.414	-0.597	-0.449	-0.516
Lack of effectiveness	-0.628	-0.376	-0.424	-0.571
General concerns	-0.406	-0.469	-0.401	-0.410
Interferences with day-to-day life	-0.360	-0.560	-0.451	-0.430
Lack of autonomy/control	0.139	0.010[¥]	0.057[¥]	0.121
LMQ-3 total scale score	-0.554	-0.623	-0.564	-0.616

Table 7-3 Correlations between LMQ-3 scores and TSQM-II scores

Notes; All cell entries are Spearman's correlations.
All correlations are significant at the p< 0.05 level (2-tailed), except those denoted by[¥] for non-significant.
All scores on the TSQM-II (and its subscales) are measured so that higher scores depict higher satisfaction
All scores on the LMQ-3 are measured such that higher scores depict higher medicine burden

Overall, the correlation between scores on the LMQ-3 total scale and the global satisfaction scale was strong and negative (r_s = -0.616) as hypothesised (see Figure 7-2). This confirms the negative relationship between medicine burden and treatment satisfaction i.e. higher medicine burden was associated with lower satisfaction with using medicines.

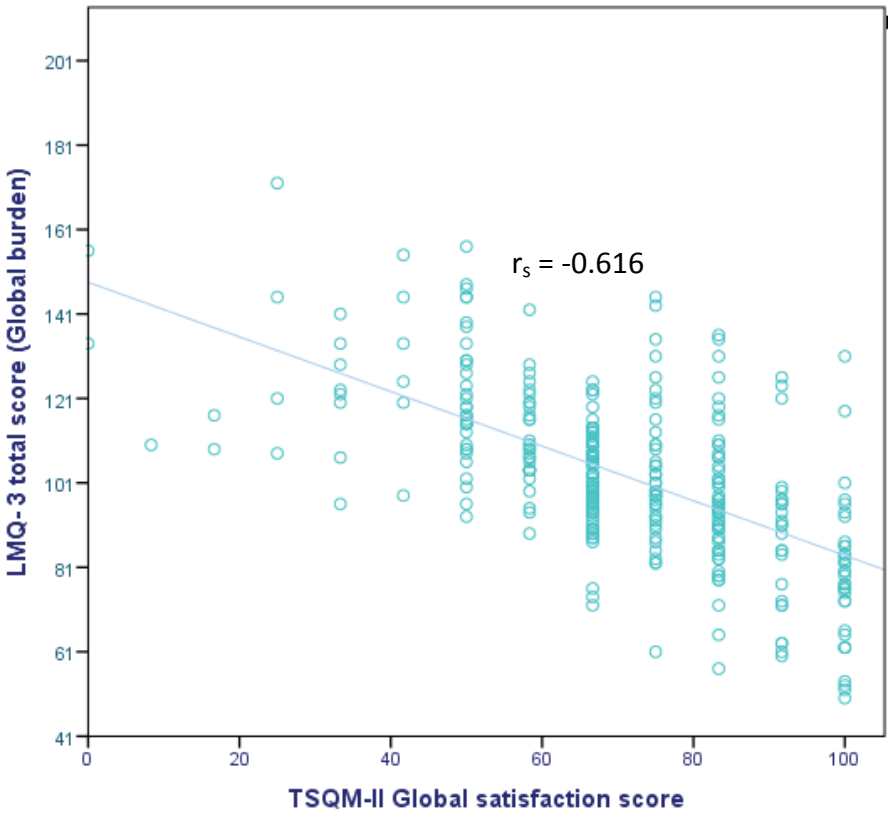


Figure 7-2 Scatter plot showing a negative relationship between medicine burden and treatment satisfaction

Correlations between LMQ-3 and EQ-5D-5L scores were in the range of 0.041-0.436, depicting weak to moderate relationships between dimensions of medicine burden and health-related quality of life (See Table 7-4). In terms of specific aspects of HRQoL, self-reported anxiety/depression was moderately and positively associated (r_s = 0.436) with overall medicine burden assessed by the LMQ-3 total scale score. This finding demonstrates the psychological features of medicine burden. The pain/discomfort subscale was positively correlated with side-effect-burden (r_s =0.304). Higher side-effect-burden scores were weakly associated with lower general health scores (r_s = -0.317). Perceptions of therapeutic ineffectiveness were weakly associated with increasing pain/discomfort (r_s = 0.305) and anxiety/depression (r_s =0.300), but lower general health (r_s = -0.307). Lack of autonomy to vary regimes (r_s = -0.081) and cost-related burden (r_s =0.022) did not show any significant correlations ($p > 0.05$) with general health status as measured by the EQ-VAS (See the last column of Table 7-4).

LMQ-3	EQ-5D-5L Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	General health†
Patient-doctor communication	0.111*	0.104*	0.141**	0.169**	0.234**	-0.192**
Practical difficulties	0.177**	0.217**	0.215**	0.172**	0.237**	-0.231**
Cost-related burden	- 0.043	0.033	-0.066	-0.041	0.025	0.022
Side-effect-burden	0.208**	0.265**	0.248**	0.304**	0.323**	-0.317**
Lack of effectiveness	0.237**	0.232**	0.248**	0.305**	0.300**	-0.307**
General concerns	0.149**	0.145**	0.156**	0.259**	0.324**	-0.237**
Interference with day-to-day life	0.264**	0.290**	0.312**	0.315**	0.352**	-0.360**
Lack of autonomy/control	0.150**	0.056	0.115*	0.083	0.022	-0.081
LMQ-3 total scale/composite score	0.306**	0.284**	0.318**	0.382**	0.436**	-0.383**

Table 7-4 Correlations between LMQ-3 scores and EQ-5D-5L scores

Notes; All cell entries are Spearman's correlations.
**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).
Each dimension of the EQ-5D-5L is scored such that higher scores depict severe problems with a specific aspect of HRQoL.
†General health, as measured by the EQ-VAS, is scored in such a way that higher scores depict best imaginable health

Overall, higher medicine burden, as measured by the LMQ-3 total scale score, was associated with lower general health status reported on the EQ-VAS (r_s = - 0.383), and this relationship was of moderate size and statistically significant (p<0.001 (See Figure 7-3).

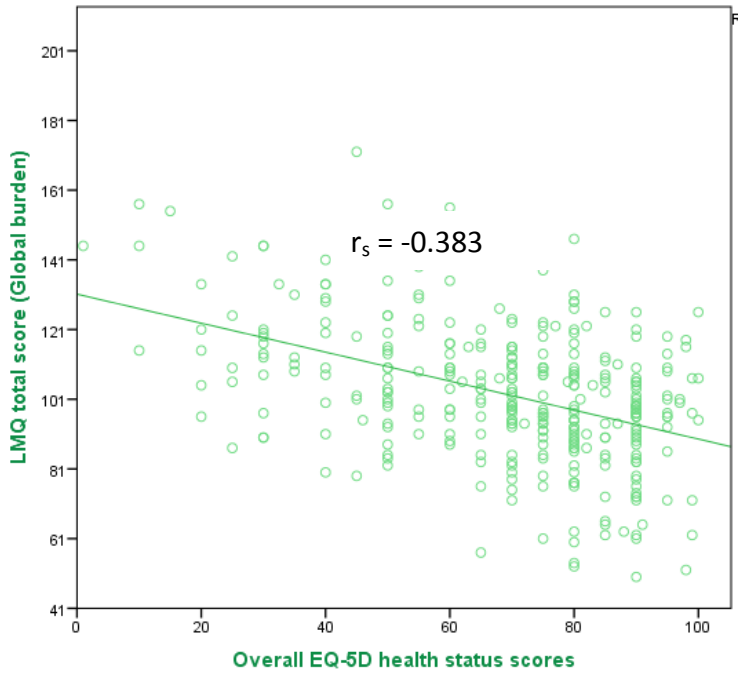


Figure 7-3 Scatter plot showing a negative relationship between medicine burden and general health status

7.4 Discussion

This chapter aimed to test criterion-related validity of the LMQ-3 by comparing the instrument to generic measures of treatment satisfaction and health-related quality of life (HRQoL). Since medicine use experiences are often evaluated in terms of satisfaction,[109,130,231,237] this study was designed to double check construct validity of the LMQ-3 by testing its correlation with a measure of treatment satisfaction. The burden construct was found to be related to treatment satisfaction and HRQoL, and all observed correlations were in the anticipated direction.

A negative relationship between medicine burden and satisfaction with various aspects of medicine use was revealed. This finding is similar to that established by Tran et al (2012) who also revealed a negative relationship between treatment satisfaction and treatment burden, a broader concept relating to patient workload associated with all healthcare activities.[83] In terms of specific aspects of medicine use, the LMQ-3 and TSQM-II have three subscales that correspond directly, relating to effectiveness, side-effects and practicalities or ease of use of medicines, and their inter-correlation was strong (range, -0.529 to -0.628). This finding affirms criterion-related (and construct validity) of the LMQ-3. Although less strong, similar correlations were observed between treatment burden scores and those on the TSQM-II (range, -0.26 to -0.53), which also depicted negative relationships.[83]

Other LMQ-3 subscales, particularly medicine-related interferences with day-to-day living were also negatively associated with all aspects of treatment satisfaction. Peyrot and colleagues (2012), in their validation study of a disease-specific measure of satisfaction with medicines among diabetic patients (known as the DSMRQ), found negative relationships between 'interference' and satisfaction with efficacy (-0.262), side effects (-0.273), ease of medicine use (-0.366) and global satisfaction (-0.292).[229] These correlations are generally lower than those reported between the LMQ-3 interference domain and all TSQM-II domains in the present chapter (-0.360 to -0.560), suggesting that interferences are moderately-to-strongly associated with dissatisfaction with regimens.

The DSMRQ also covers medicine-related social burden, negative events, and negative mood that were associated with dissatisfaction with medicine use.[229] The former three concepts are akin to those assessed by LMQ-3 items related disruptions to social activities and/relationships, side-effect burden, and general concerns respectively, which were all negatively associated with treatment satisfaction.

Patient-doctor communication problems about medicines were also related to dissatisfaction with effectiveness. This finding is similar to that reported in Chapter 6 where moderately strong correlations between communication- and effectiveness-related domains of the LMQ-3 were elucidated. Cost-related burden was also moderately associated with dissatisfaction with medicine use in the present study, a finding that is not surprising.

In terms of HRQoL, a trend of weak to moderate correlations was observed between all LMQ-3 domains and health dimensions of mobility, self-care, and performance of usual activities, pain/discomfort, and anxiety/depression. This finding infers discriminant validity of the LMQ-3 and depicts conceptual differences between constructs underlying the LMQ-3 and the EQ-5D-5L. Although there is limited guidance on the standard cut-off values for correlations indicative of discriminant (or divergent) validity, all inter-correlations were below 0.8 suggesting that the three instruments used in this study assess different constructs.[218] Overall, it is empirically reasonable to confirm discriminant validity of the LMQ-3 and its subscales.

Irrespective of the tool's validity, research has shown that different treatments, including medicines, impact on HRQoL both positively and negatively.[238] In the present study, medicine burden was negatively associated with general health status; higher burden scores corresponded to lower general health status. In other studies, the level of discomfort associated with life-long therapies affects patients' perceptions of their own HRQoL,[239] and is significantly associated with symptoms such as depression and fatigue, while some therapies may restrict usual activities.[240] The impact of side effects on patient's symptoms, functional status, and general HRQoL has been widely documented.[48,89,92] In this chapter, side-effect-burden was negatively related to general health status ratings, in line with previous research.

Psychosocial aspects of medicine use may have an impact on patients' HRQoL by influencing symptom status, physical and mental status, and general health perceptions.[92] General concerns, including worries about drug-drug or drug-alcohol interactions and fears related to long-term effects, were moderately associated with anxiety/depression, and with general health. According to Murawski and Bentley (2001), 'a patient may experience…subconscious anxiety in response to concerns about his/her medications... Alternatively, the same patient's functional status might be impaired as a result of their conscious anxiety concerning their medicine use and its effects… [moreover] patient anxiety...may be induced in response to [biological] changes …occurring as a consequence of pharmaceutical therapy…'.[92] Regardless, autonomy to vary regimes and cost-related burden were not significantly associated with general health status, implying that these aspects of medicine burden may not have affected HRQoL for this sample of participants.

A standard generic measure of HRQoL, the EQ-5D-5L, was used in this study. This and related health status measures have been recently criticised for having 'minimal to moderate sensitivity to pharmaceutical care interventions' and unlikely to detect changes due to 'the burden of medicines on quality of life'.[241] A similar finding was reported by Krska and Rowe in 2010.[242] Although this study did not primarily set out to investigate the impact of medicine burden on quality of life, it is apparent that there was a dearth of suitable comparator instruments for validating a new measure of medicine burden. The SF-36,[235,236] although recently cited as more sensitive in detecting changes in HRQoL due to pharmaceutical care interventions life',[241] is relatively lengthy, thus was not employed as a criterion-reference questionnaire in this study. More recently, the Medication-Related Quality of Life Scale (MRQoLS-v1.0) specifically considers 'the overall effect of polypharmacy on quality of life.[149] However, the MRQOLS-v1.0 was only tested in the Chinese population and a suitable adaptation for the English population was not available at the time of conducting this study, and was thus not used as a criterion-reference instrument. Moreover, the MRQOLS-v1.0 is largely focussed on subjective wellbeing, assessing the impact of medicines on role limitations (including interferences with work, social- or leisure activities), self-control, and vitality (relating to feelings of fatigue/being worn out),[149] and no other aspects of HRQoL and was considered to be limited conceptually.[231]

Study strengths and limitations

Multiple recruitment sites, across primary and secondary care, enabled a diverse patient population and adequate sample size for the study. Despite this, the vast majority of participants were outpatients, possibly due to the high footfall of patients at the local hospital clinics that had relatively longer waiting times, which enabled more on-site survey completion, compared to community pharmacies and GP practices. Self-reports indicated that the sample population, encountered during routine outpatient care, had relatively good health status scores. It is uncertain whether similar findings would be obtained with the frail, housebound, or inpatients that were excluded from this study, by virtue of the method employed.

Standard criterion-reference tools were used in this validation study. The lack of a gold-standard measure of prescription medicine burden implies that concepts underlying the LMQ-3 may not be fully cross-validated. As previously discussed, the TBQ,[83,232] a broader generic measure of treatment burden, was not used as a possible comparator tool despite having a few items on medicine-related burden. Future cross-validation studies would benefit from checking associations between LMQ-3 items and those of the recent English adaptation of the TBQ. Irrespective, validated criterion-related measures of treatment satisfaction and HRQoL were exploited to test hypothesised relations with medicine burden. Though not an objective of this study, causal associations among medicine burden, treatment satisfaction, and/or HRQoL were not established and further analyses may attempt to model their interrelations.

All new questionnaires should not only be valid but also demonstrate adequate reliability to enable future use in research and/or clinical settings. Up to this phase of research, all studies on the LMQ-3, and its interim versions, have focussed on validation of the tool to understand whether it measures what it purports to measure. All studies have confirmed that, on the whole, the LMQ-3 measures medicine burden and the concept has been rigorously tested in various settings and patient populations.

Additional studies should examine test-retest reliability of the LMQ-3, to check the stability of scores, as another key psychometric property. This is relevant if the instrument is to be adapted in future clinical research or practice, including pharmaceutical interventions which may result in changes in medicines over time. This is the subject of Chapter 8. In addition, predictive validity of the LMQ-3, as well as gaining a further understanding of risk factors associated with medicine burden is necessary to target interventions to those most affected by medicine burden; this will be explored in Chapter 9.

7.5 Chapter summary

This chapter provides evidence for criterion-related validity of the LMQ-3. It confirms that the Living with Medicines Questionnaire (LMQ-3) assesses a distinct concept, medicine burden, which is negatively related to treatment satisfaction and HRQoL as measured by the TSQM-II and EuroQol five-dimensional questionnaire respectively. This finding sheds more light on understanding the concept of medicine burden, and strengthens construct validity of the LMQ-3.

Chapter 8 Test-retest reliability of the LMQ-3

8.1 Introduction

In the previous chapters, extensive work demonstrated validation of the Living with Medicines Questionnaire (LMQ-3) as an instrument designed to assess medicine burden among patients using regular medicines in England. All studies leading up to this chapter have focussed mainly on questionnaire validity, especially to understand which concepts underlie the LMQ-3, and to confirm if it measures what it was intended to measure (construct validity). However, standard guidance on development and validation of new patient-reported measures demands testing both validity and reliability.[124]

Among investigations on questionnaire reliability, both internal consistency and test-retest reliability are widely recommended.[118,127] Chapter 6 reported acceptable internal consistency (Cronbach's $\alpha \geq 0.7$) for all but one subscale of the LMQ-3, and further tests were necessary. Test-retest reliability of the revised instrument (LMQ-3), and how it performs when administered at different time points, had not been fully established.

Test-retest reliability reflects stability of the measure and its ability to obtain consistent scores in a stable group of patients.[243] According to Rust and Golombok (2015), a questionnaire is deemed reliable if 'a respondent obtains similar scores on different occasions, providing the respondent has not changed in a way which affects his or her response to the questionnaire'.[244] A test-retest study involves administering the same questionnaire twice to the same group of respondents, usually two weeks apart. The test-retest interval is selected to ensure that a participant's status has not changed (or is unlikely to change) and to minimise recall of the first set of responses.[244,245] Assessing test-retest reliability is relevant if the instrument is to be used in longitudinal research or practice involving follow-up interventions planned over different times.

Aim

The aim of this study was to examine the test-retest reliability of the LMQ-3 in a sample of eligible members of the public in England.

8.2 Methods

8.2.1 Study design

A repeated cross-sectional survey, in which the same questionnaire was completed on two separate occasions by the same participants, was conducted between June and August 2016.

8.2.2 Study setting & participant inclusion criteria

Ethics approval was granted by the Medway School of Pharmacy (See Appendix 24). The Kent Adult Research Unit (KARU), a public engagement group managed by the School of Psychology at the University of Kent, was used to recruit potential participants. About 300 members of the general public living in England, mostly resident in Kent or neighbouring counties, are signed up with the KARU database. The database holds participants' details including email addresses. In this study, permission to recruit via the KARU database was granted by the database co-ordinator. Participants were included in the study if 18 years or older, using at least one regular prescription medicine, and willing to complete the same questionnaire twice. Screening questions were administered at the start of every survey to ensure that only participants who fulfilled the aforementioned inclusion criteria had access to the study.

8.2.3 Study instrument

The LMQ-3 the final instrument derived from Chapter 6 and tested in Chapter 7, which comprises 41 Likert-type statements clustered in eight domains, was used in this study. Statements are rated on a 5-point scale (i.e. strongly agree to strongly disagree). The LMQ-3 also has a global item, a 10-cm visual analogue scale to self-report medicine burden. In addition, the LMQ-3 has a free-text question and a section on participant characteristics. Similar to other study tools used in this doctoral programme, the LMQ-3 was designed and administered in English. The questionnaire was formatted for on-line use in Qualtrics© software. The study invitation and participant information (including a statement of implied consent) were embedded alongside the electronic questionnaire, and a unique url link (https://msp.eu.qualtrics.com/SE/?SID=SV_ekEVUe3u9O4LpKB) generated. All survey completion was anonymous.

8.2.4 Recruitment procedures

All KARU members were invited to the study, via email, by the database co-ordinator. The first link to the questionnaire was promoted in the invitation email and on the University of Kent website (See Figure 8-1). Email recruitment was used to access and follow-up a 'closed pool' of the same participants, which was relevant to matching test-retest responses.

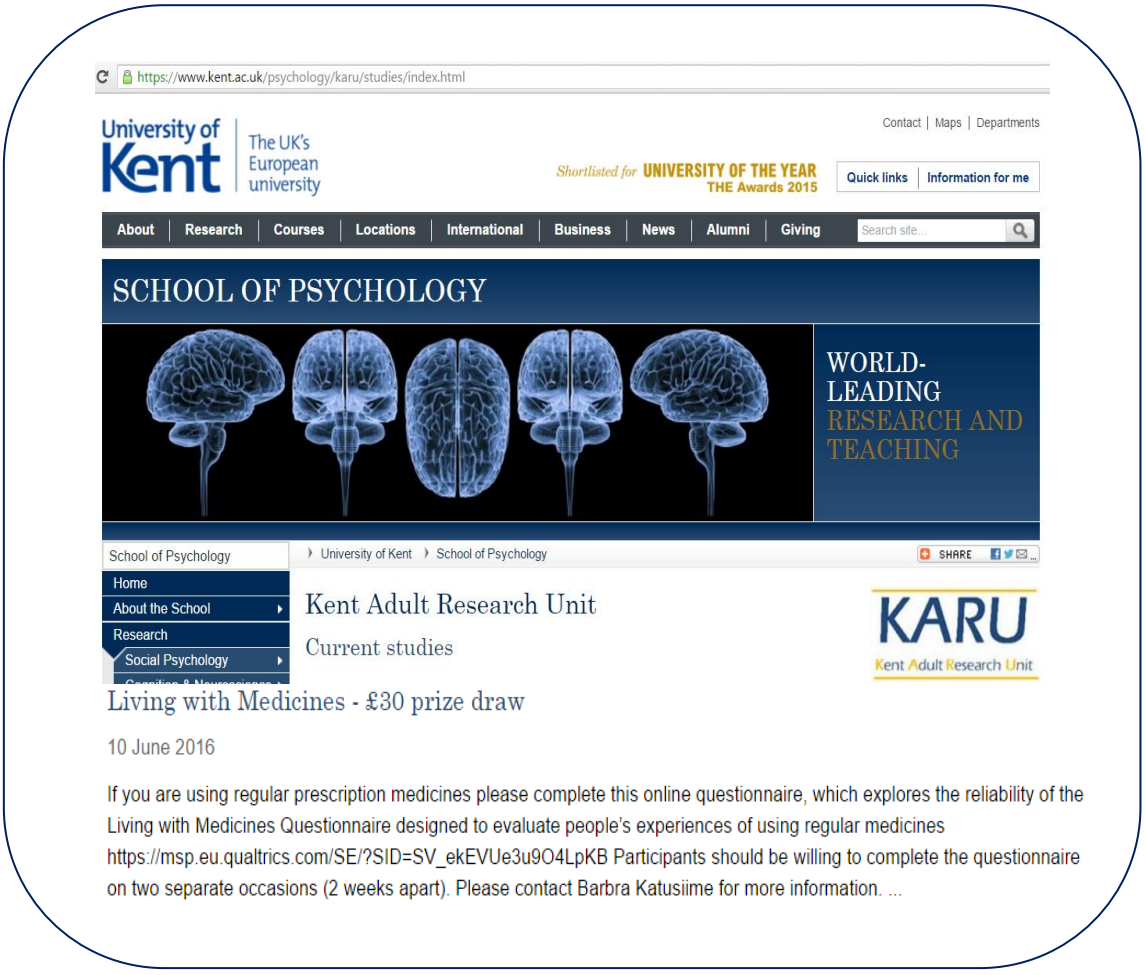


Figure 8-1 Advert for test-retest study on the University website

Participants who accessed the first questionnaire were invited to take the second survey (retest). Consenting participants provided their email addresses, which were used to send the link to the retest questionnaire. About two weeks after the date the baseline survey link was sent to potential participants, the researcher sent them another survey link via Qualtrics Mailer©. As noted previously, the test-retest interval was selected to minimise recall of answers from the first questionnaire.[244]

Two reminder e-mails, including a notification prior to closing the surveys, were sent to follow-up participants who had not completed the retest questionnaire to maximise response rates. A small incentive, entry in a prize draw to win an Amazon shopping voucher (worth £30) for a randomly selected participant, was used to encourage completion of the repeat survey. During the retest surveys, the instructions cautioned participants against trying to deliberately remember answers from the first survey.

8.2.5 Data cleaning and matching of test-retest responses

All data were downloaded from Qualtrics©, directly into SPSS version 23, and screened for errors, outliers, and missing data. All test responses were matched to retest responses so that each eligible participant had two scores: a test score and the corresponding retest score on every item. The two sets of responses were matched using participant characteristics and demographic data. Postcodes were particularly useful in matching test-retest responses, since they served as a unique identification code for each participant. Where participants shared the same postcode, other characteristics such as gender, age, level of education, and number of medicines, were used to match responses. Participants missing retest scores were excluded, and only those with both test and retest scores were retained in the final dataset.

8.2.6 Statistical analysis

Stability of scores was assessed for individual items, subscales (domains), and the LMQ-3 total/composite scale.

For item-by-item analysis, agreement, which 'quantifies how close two measurements made on the same subject are', between test and retest scores was examined by different methods.[246] The percentage of exact score agreement, where test-retest score differences equalled zero, was calculated to reflect the fraction of participants who selected exactly the same answer on test and retest questionnaires. For each item, the test-retest score differences were calculated as test score – retest score. The percentage of participants with test-retest score differences of ± 1 point or lower, which reflect 'near misses' (e.g. the difference between endorsing strongly agree on test and agree on retest), was also examined.[247]

Intraclass correlation coefficients (ICCs) and their 95% confidence intervals were also used to assess agreement between item scores.[118] ICCs were also calculated for subscale scores and the LMQ-3 composite score (total scale score). The average ICC value, estimated by the two-way mixed effects method available in the statistical package, was reported to account for multiple ratings at test and retest occasions. ICC values of ≥ 0.7 are recommended as a minimum standard for reliability.[122] Bland-Altman plots were used to present some of the data visually, by displaying the limits of agreement[122] between LMQ-3 composite scores at test-retest time points. Spearman's correlations were also examined across all subscales and for the composite score; coefficients range from 0 to 1 reflecting worst possible to perfect relationships (consistency) between test-retest assessments.[244]

8.3 Results

8.3.1 Response rate

Of the 45 participants who accessed the study invitation, 35 (77.8%) completed the baseline questionnaire. All 35 consented to answer the retest questionnaire, 30 (85.7%) of whom completed it fully.

8.3.2 Test-retest duration

The median and mode test-retest duration was 15 days (~2.1 weeks). One participant completed the questionnaires within one week while another completed them just over five weeks apart (See Figure 8-2).

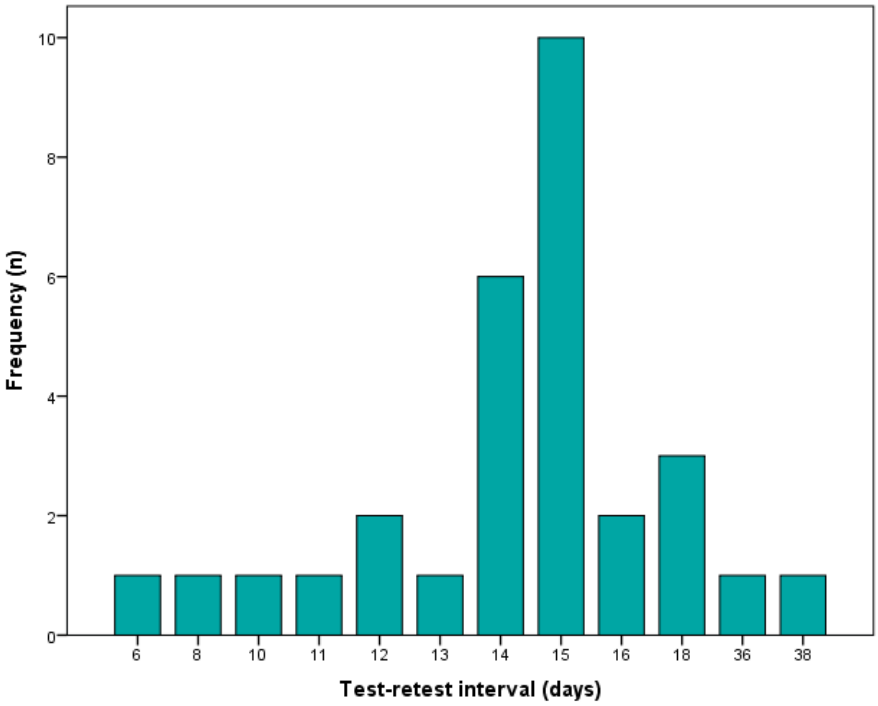


Figure 8-2 Bar chart showing the test-retest intervals for the LMQ-3

8.3.3 Participant characteristics

Across both test and retest samples, participants were of median age 68 years (range 29 to 86). The vast majority (77%, n=23) were retirees of 65 years or older. Two-thirds (67%, n=20) were female. Just over half had University level of education (57%, n=17). The median (range) of medicines used was four (1-9), in mostly tablet/capsule formulation (93%, n=28). Most participants managed medicine use independently (97%, n=29). Only 10% (n=3) of participants paid for their prescription medicines (See Table 8-1).

Characteristic		n	%
Gender	Female	20	67
	Male	10	33
Age (years)	18-29	1	3
	30-49	1	3
	50-64	5	17
	65 or over	23	77
Education level	School	5	17
	Technical college/ Apprenticeship	5	17
	University	17	57
	Other*	3	10
Employment status	Employed	5	17
	Retired	23	77
	Other^	2	7
Ethnicity	White	29	97
	Mixed	1	3
Number of medicines	1-4	16	53
	5-9	14	47
Type of medicines	Tablets/Capsules	28	93
	Parenteral formulations	16	53
Frequency of medicine use	Once per day	18	60
	Twice per day	10	33
	Three times per day	6	20
	More than 3 times per day	1	3
	Other times**	2	7
Help with using medicines	Manages independently	29	97
	Assisted by spouse/partner	1	3
Paying for prescriptions	No	27	90
	Yes	3	10

Table 8-1 Characteristics of participants in the test-retest study

Notes; *includes professional qualifications, and other courses (e.g. PGCE);
^includes full time carer, part-time self-employed;
** includes 'PRN as required' and injections once a week.

8.3.4 Item-level stability

To assess item-level stability, the percentage agreement between test-retest scores was examined as described in the methods section (8.2.6). The third column of Table 8-2, which considers the percentage of exact agreement between test-retest scores, indicates that 40% to 80% of participants obtained the same score at test-retest times across all Likert-type items; only five of the 41 items had percentage of exact agreement below 50%.

Stability of item scores was also examined by the percentage of participants with test-retest score difference of ± 1 point or lower on the rating scale (See Column 4 in Table 8-2 under % (n) with test-retest difference in scores within ±1 point). A greater percentage of participants (76.7% to 100%) scored within ± 1 point of the Likert-type rating scale between test-retest time points. The VAS-burden, 10-cm rating scale, had the least percentage (30%) of participants with the same scores at test and retest time points. However, 70% of participants scored within ± 1 point for both measurements over the study period. Figure 8-3 illustrates that two participants' VAS-burden scores changed by more than 2 points, in absolute value across test-retest assessments (i.e. test-retest difference of 3.0 and 8.7). This finding suggests that scores obtained using the global item were reasonably stable over the retest interval.

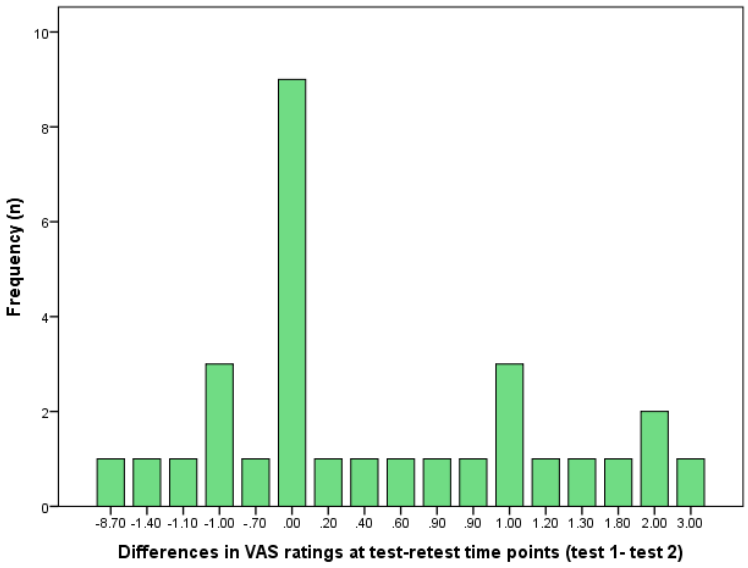


Figure 8-3 Bar chart showing relative stability of VAS ratings over the test-retest period

Note; The chart shows that most participants had scores within ± 1 point on the 10-cm visual analogue scale (VAS), showing relative stability of the global item.

Intraclass correlation coefficients (ICCs) were also assessed at item level, as shown in the last column of Table 8-2. The vast majority (37/41) of Likert-type items had ICC values above the recommended value (≥ 0.700-0.947). Only four items had ICC values below 0.7, as the target cut-off for test-retest reliability:[122] *('Q37-My medicines interfere with my sexual life'; 'Q28- Taking medicines affects my driving'; 'Q40-The side effects are worth it for the benefits I get from my medicines'; and 'Q21-My doctor takes my concerns about side effects seriously').* Overall, these findings indicate that most item scores were relatively stable over the retest period based on multiple criteria.

	Statement/Domain	% (n) of exact agreement between test-retest scores	% (n) with test-retest difference in scores within ±1 point	ICC [95% CI]
	Interference to day-to-day life			
Q19	My medicines interfere with my social or leisure activities	60.0%(18)	90.0%(27)	0.802 [0.585-0.906]
Q28	Taking medicines affects my driving	66.7%(20)	93.3%(28)	0.623[0.208-0.821]
Q36	My medicines interfere with my social relationships	56.7%(17)	86.7%(26)	0.733[0.439-0.873]
Q34	Taking medicines causes problems with daily tasks	70.0%(21)	86.7%(26)	0.768 [0.499-0.893]
Q37	My medicines interfere with my sexual life	53.3%(16)	83.3%(25)	0.674[0.307-0.847]
Q41	My life revolves around using medicines	60.0%(18)	86.7%(26)	0.772[0.521-0.891]
	Patient-doctor communication/relationships			
Q10	I trust the judgement of my doctor(s) in choosing medicines for me.	70.0% (21)	90.0%(27)	0.857[0.687-0.935]
Q14	My doctor(s) listen to my opinions about my medicines	50% (15)	90.0%(27)	0.866 [0.719-0.936]
Q21	My doctor takes my concerns about side effects seriously.	63.3%(19)	90.0%(27)	0.561 [0.065-0.794]
Q24	I get enough information about my medicines from my doctor(s)	56.7%(17)	93.3%(28)	0.761[0.491-0.888]
Q33	The health professionals providing my care know enough about me and my medicines	46.7%(14)	90.0%(27)	0.771[0.519-0.891]
	Side effects			
Q20	The side effects I get are sometimes worse than the problems for which I take my medicines	53.3%(16)	86.7%(26)	0.764[0.504-0.888]
Q22	The side effects that I get from my medicines interfere with my day to day life	73.3%(22)	93.3%(28)	0.917[0.825-0.960]
Q30	The side effects I get from my medicines are bothersome	73.3%(22)	100%(30)	0.947[0.888-0.975]
Q38	The side effects I get from my medicines adversely affect my wellbeing	53.3%(16)	86.7%(26)	0.797[0.568-0.905]
	General concerns			
Q8	I worry that I have to take several medicines at the same time	63.3% (19)	90.0%(27)	0.845[0.674-0.926]
Q9	I would like more say in the brands of medicines I use	50.0%(15)	93.3(28)	0.786[0.550-0.898]
Q7	I feel I need more information about my medicines	56.7%(17)	90.0%(27)	0.707 [0.384-0.860]
Q13	I am concerned about possible damaging long-term effects of taking medicines	60%(18)	96.7%(29)	0.895[0.780-0.950]
Q16	I am concerned that I am too reliant on my medicines	50% (15)	90.0%(27)	0.720[0.411-0.867]
Q18	I am concerned that my medicines interact with alcohol	46.7%(14)	86.7%(26)	0.830[0.643-0.919]
Q17	I worry that my medicines may interact with each other	53.3%(16)	90.0%(27)	0.835[0.653-0.921]

Table 8-2 Test and retest stability of the LMQ-3 at item level

	Statement/Domain	% (n) of exact agreement between test-retest scores	% (n) with test-retest difference score within ±1 point	ICC [95% CI]
	Practical difficulties			
Q1	I find getting my prescriptions from the doctor difficult.	63.0% (19)	100%(30)	0.908 [0.808-0.956]
Q2	I find getting my medicines from the pharmacist difficult	66.7% (20)	93.3%(28)	0.869[0.724-0.937]
Q4	I am comfortable with the times i should take my medicines	60% (18)	86.7%(26)	0.840[0.644-0.928]
Q6	I am concerned that I may forget to take my medicines	40% (12)	83.3%(25)	0.788[0.554-0.899]
Q23	I have to put a lot of planning and thought into taking my medicines.	46.7%(14)	86.7%(26)	0.823[0.628-0.916]
Q26	It is easy to keep my medicines routine	46.7%(14)	86.7%(26)	0.743[0.460-0.878]
Q29	I find using my medicines difficult	70%(21)		0.884[0.749-0.946]
	Perceived effectiveness			
Q3	I am satisfied with the effectiveness of my medicines	56.7%(17)	86.7%(26)	0.787 [0.525-0.905]
Q15	My medicines prevent my condition getting worse	76.7% (23)	100%(30)	0.866[0.719-0.936]
Q25	My medicines live up to my expectations	73.3% (22)	100%(30)	0.866[0.719-936]
Q35	My medicines allow me to live my life as I want to	66.7%(20)	90.0%(27)	0.730[0.432-0.871]
Q39	My medicines are working	66.7%(20)	96.7%(29)	0.824[0.631-0.916]
Q40	The side effects are worth it for the benefits I get from my medicines	53.3%(16)	86.7%(26)	0.569[0.055-0.804]
	Patient-doctor communication/relationships			
Q10	I trust the judgement of my doctor(s) in choosing medicines for me.	70.0% (21)	90.0%(27)	0.857[0.687-0.935]
Q14	My doctor(s) listen to my opinions about my medicines	50% (15)	90.0%(27)	0.866 [0.719-0.936]
Q21	My doctor takes my concerns about side effects seriously.	63.3%(19)	90.0%(27)	0.561 [0.065-0.794]
Q24	I get enough information about my medicines from my doctor(s)	56.7%(17)	93.3%(28)	0.761[0.491-0.888]
Q33	The health professionals providing my care know enough about me and my medicines	46.7%(14)	90.0%(27)	0.771[0.519-0.891]
	Cost-related burden			
Q5	I worry about paying for my medicines	66.7%(20)	80.0%(24)	0.848[0.671-0.930]
Q31	I sometimes have to choose between buying basic essentials or medicines	80.0%(24)	90.0%(27)	0.892[0.763-0.951]
Q32	I have to pay more than I can afford for my medicines.	76.7%(23)	93.3%(28)	0.850[0.685-0.929]
	Lack of autonomy			
Q11	I can vary the dose of the medicines I take	56.7% (17)	86.7%(26)	0.862[0.710-0.934]
Q12	I can choose whether or not to take my medicines	43.3%(13)	76.7%(23)	0.712[0.391-0.865]
Q27	I can vary the times I take my medicines	60.0% (18)	90.0%(27)	0.825[0.633-0.917]
	VAS-burden score	30.0%(9)	70.0%(21)	0.789[0.556-0.899]

Table 8-2 Test and retest stability of the LMQ-3 at item level

Note; ICC intraclass correlation coefficients; CI- confidence intervals (CI); VAS, visual analogue scale; N=30

8.3.5 Stability of subscales and composite score

Stability of all eight subscales of the LMQ-3, and its total scale (composite score), was also assessed by similar methods (See Table 8-3). All subscales had satisfactory ICC values ranging from 0.733-0.929 between test-retest measurements. The ICC values for the LMQ-3 composite score was excellent (0.954) between test-retest administrations. Spearman's correlations, presented in Table 8-3, revealed mixed findings across subscale scores between test-retest assessments, four of which were below the target correlations of 0.7.

Subscales	**Spearman's correlation (p-value)**	**ICC (95% CI)**
Patient-doctor communication	0.52 (p=0.003)	0.733[0.439-0.873]
Practical difficulties	0.71 (p<.001)	0.896[0.782-0.951]
Cost-burden	0.56 (p=0.001)	0.759 [0.494-0.885]
Side-effect-burden	0.84 (p<0.001)	0.929[0.849-0.967]
Lack of effectiveness	0.64 (p<0.001)	0.872[0.733-0.939]
Concerns	0.80 (p<0.001)	0.909[0.809-0.957]
Interferences	0.64 (p<0.001)	0.774 [0.525-0.893]
Lack of autonomy	0.70 (p<0.001)	0.843[0.671-0.925]
LMQ-3 total scale (composite score)	0.90 (p<0.001)	0.954 [0.902-0.978]

Table 8-3 Test-retest stability of LMQ-3 subscales and total scale

Note; ICC, intraclass correlation coefficient

A Bland-Altman plot was used to visualise agreement between LMQ-3 composite scores over the test-retest period (See Figure 8-4). The upper and lower limits of agreement, represented by the two broken lines, were 16.87 and -14.73 respectively. All except one participant scored between these limits suggesting 'reasonable' agreement of composite scores across the study duration. In Figure 8-4, the continuous horizontal line across the chart portrays the mean of the differences between test-retest composite scores, which was close to zero over the retest interval. Looking at the spread of composite scores shows a generally horizontal distribution, depicting no systematic increase or decreases of test-retest score differences. These findings complement the presented evidence for stability of the LMQ-3 total scale.

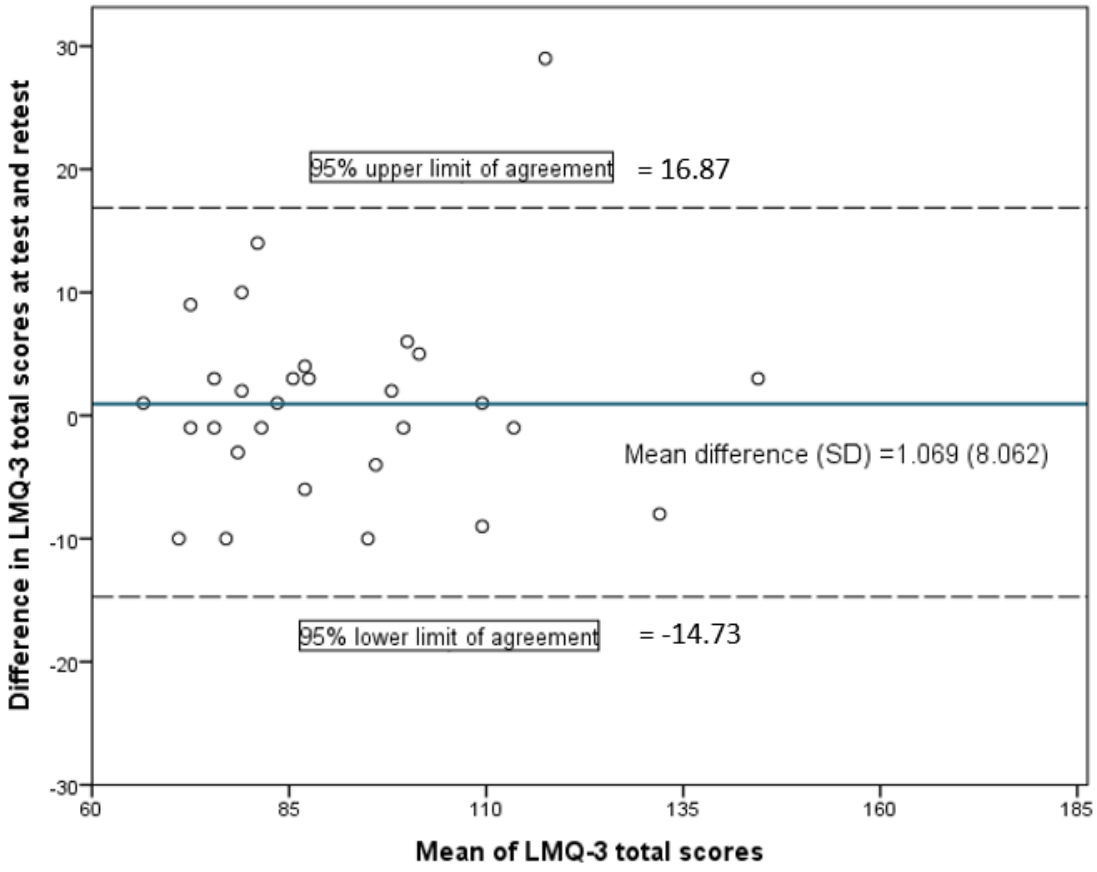


Figure 8-4 Bland-Altman plot showing agreement between LMQ-3 composite scores over the test-retest period

8.4 Discussion

This chapter presented an evaluation of the test-retest reliability of the LMQ-3. Overall, the LMQ-3 has excellent stability of scores when administered at different time points. Item-level analyses indicated that the vast majority of item scores were reasonably consistent over the test-retest interval. Overall, the data presented contributes to evidence of the reliability of the LMQ-3.

However, these findings ought to be interpreted in light of the methods used in this study. The choice of methods to estimate reliability coefficients in test-retest studies is debatable. Multiple techniques were used to assess consistency and agreement of item-, subscale- and composite- scores over the study period. A combination of methods was adopted to minimise the limitations of reporting single estimates of reliability.[248] Spearman's or Pearson's correlations between test-retest scores are commonly reported in questionnaire validation studies.

Although correlational techniques are cited to overestimate the true reliability,[118] in this chapter their estimates were generally lower than expected for certain subscales. Regardless, 'relatively small' correlations are associated with homogeneous samples,[249] such as those involved in the study. In particular, the present study was largely comprised of elderly retirees signed up to research studies at a single setting. Correlational techniques, though predominant in psychometric literature, are criticised for measuring linear relationships between scores instead of their agreement.[118,250] Correlational methods are criticised as 'an inappropriate and liberal measure of reliability'[118] citing inability to detect systematic bias associated with learning/practice effects[251] following exposure to the first survey.

Intraclass correlation coefficients (ICCs) are increasingly preferred over Pearson's/Spearman's correlations when examining agreement between test-retest scores on a continuous scale.[118,248] Therefore ICCs were also tested for items, subscales, and the LMQ-3 total scale. The desired magnitude of reliability coefficients depends on the instrument's intended purpose.[118]

ICCs values of ≥ 0.70 and ≥ 0.90 are recommended for tools used in health research- and clinical settings respectively.[118] Values above 0.9 are often ambitious, while values close to 1 suggest higher reliability.[118] In this study, the LMQ-3 composite score had an excellent ICC value (0.954) at test-retest assessment. Only four items in the LMQ-3 had ICCs below 0.7, which is the bare minimum value for reliability of research-intended tools.[127,252] However, the finding suggests adequate stability for most items.

All eight subscales of the LMQ-3 also had acceptable ICC values above 0.7. However, the 'patient-doctor communication' subscale, which also has items on patient interactions and relationships with providers, had the least reliability coefficient (an ICC value of 0.733) when compared to other subscales. On the other hand, the 'side-effect-burden' subscale showed the highest stability (an ICC value of 0.929). Relatively longstanding concepts may show higher consistency when measured over time than those that may vary with day-to-day experiences. The present study did not assess whether participants had new medicine-related appointments with their doctors or health providers over the test-retest period, which may have affected reliability values of the 'patient-doctor communication' subscale. Nevertheless, data revealed consistency in self-reports of medicine use characteristics over the study period (such as the number, frequency, and formulation of medicines) that may indirectly infer stability of medicine use experiences. It is also possible that the relatively high stability of the 'side-effect-burden' subscale is related to minimal changes in the experience or impact of side effects over the short study duration.

Although most measures of medicine-related experiences are not assessed for test-retest reliability,[231] test-retest assessments of the Treatment Burden Questionnaire (TBQ), a convenient comparison for reliability coefficients, revealed ICC values relatively lower than those of the LMQ-3 i.e. 0.77 (95% CI, 0.70-0.82) versus 0.954 (95% CI, 0.902-0.978) respectively.[83,232] Regardless, caution needs to be exercised when comparing LMQ-3 reliability coefficients with those reported for a distinct measure of overall treatment burden, as different study conditions (e.g. patient populations, sample size) involved in the two studies may have affected the reliability values differently.

The time interval to retest is a factor to consider in test-retest reliability studies. In the present study, the median test-retest interval was two weeks, but the range was one week to just after five weeks from the baseline survey. There is no consensus regarding test-retest intervals, but 1-2 weeks is usual.[122,127] Median retest intervals as short as 1-7 days have also been reported.[243] A retest period of two weeks to one month was used while validating the TBQ[83] and it is likely that the LMQ-3 retest intervals were appropriate and balanced. Regardless, selection of an optimal test-retest interval is a delicate balance between minimising recall of initial test responses and preventing change of participants' circumstances.[118,122,245] Broadly, shorter retest intervals are associated with improved reliability coefficients, but may be affected by recall bias.[251] In the present study, the instructions to the retest survey cautioned participants against trying to deliberately remember answers from the first survey.

In test-retest studies, it is worth considering the nature of the construct under investigation, and how likely it is to change over a given time. For instance, certain psychological traits (e.g. mood) are liable to rapid changes[118] similar to clinical states of patients with advanced cancer are 'prone to a faster rate of clinical deterioration'.[243] However, medicine burden is a multifaceted attribute with physical, psychosocial, and clinical aspects and, as a relatively new concept,[88] its long-term stability is not well understood. Medicine burden, and how it affects individual patients over time, is not well studied. A few researchers purport that 'in the absence of any intervention, self-management attitudes and behaviours are relatively stable concepts'.[253] Nevertheless, medicine use experiences may vary over time and are unique to individuals; some people accept and persist with regimens despite any difficulties, others are unable to cope and reject their treatment regimens.[21] For those who continue to juggle medicine use, they may manipulate dosing or timing of regimens, stop medicines completely or even switch to alternative treatment options.[88] This is especially true if the interferences, associated with day-to-day use of medicines, become unbearable.

Implications for research and practice

Whether intended for use in research or clinical practice, patient-reported measures are often selected based on their psychometric properties, including test-retest reliability. Data from this chapter contributes to evidence for the LMQ-3 measurement properties, most of which have been demonstrated in studies described in previous chapters. It is now evident that the LMQ-3 is stable and can obtain consistent scores over time. A questionnaire that demonstrates stability of responses over a short period may predict long-term stability. Moreover, the higher the reliability of a questionnaire, the better its discriminative capability;[118] this feature can be exploited to identify patients most at risk of medicine burden.

With a stable instrument, the LMQ-3 may be used in future longitudinal/prospective research and/or practice to monitor levels of medicine burden in at-risk populations, which are defined and tested in Chapter 9. Keeping track of individuals' accounts of medicine burden over time may help inform future targeted interventions. Follow-up of patients with the greatest burden could be done at appropriate time points determined by the patient (say at quarterly, bi-annually, or annually).

Upon ascertaining long-term stability of scores, the LMQ-3 could be used as a screening tool for recruiting patients in interventional studies designed to improve patients' experience of care. Further research could use the LMQ-3 as an outcome measure in trials evaluating new medicines or pharmaceutical care interventions. All the aforementioned applications of the LMQ-3 would only be plausible if its sensitivity to change and responsiveness are determined in future validation studies. Sensitivity to change is the 'ability to measure any degree of change' following an intervention,[118] and responsiveness related to the 'ability of a questionnaire to detect clinically important changes over time, even if these changes are small'.[122]

Study limitations and strengths

Stability of participants' circumstances is a prerequisite in test-retest study designs.[243] In fact, guidelines suggest that an instrument's reproducibility relates to the extent to which 'repeated measurements in stable persons provide similar answers'.[122] This study involved a stable sample population in terms of their prescription medicine use

experiences over the study period. Data revealed consistency in self-reports of prescribed regimens (number of medicines, frequency and formulations) over the study period; these may indirectly infer stability of medicine use experiences.

Paradoxically, 'reliability cannot be conceived of as a property that a particular instrument does or does not possess; rather, any measure will have a certain degree of reliability when applied to certain populations under certain conditions',[118] and reliability estimates reflect the performance of a measure in a given population. The present study was limited to a self-selected, small purposive sample of the public, living mostly in south-east England and signed up to an on-line database as volunteers for research studies. The sample participant group is, thus, not geographically representative of users of long-term medicines in England, and LMQ-3 test-retest reliability may differ with diverse patient cohorts. Although participants were mostly older people (age ≥ 65), reflecting characteristics of people likely to use long-term medicines - to whom the LMQ-3 may be applied in practice, the relatively homogenous study population may have led to miscalculates of reliability coefficients.[248]

Although the sample size in this chapter (n=30) was lower than that recommended for test-retest studies (n≥ 50),[122] the reliability coefficients were mostly adequate across items, subscales, and for the LMQ-3 composite score. It is unlikely that a bigger sample size may change the present findings, as indicated by other researchers assessing test-retest reliability of patient questionnaires.[254] Regardless, 95% confidence intervals (CI) around some reliability coefficients showed wide variations (See the last columns of Table 8-2 and Table 8-3 respectively).

For item-level stability, the percentages of absolute and relative agreement between test retest score were assessed based on Nevill's study.[247] The percentage of absolute agreement reflects the extent to which respondents provide the same answer on the two assessments, while relative agreement may accommodate 'near misses' or small differences between test-retest scores e.g. a participant who strongly agrees with an item on test- but agrees on retest assessment. Nevill and colleagues (2001) stipulated that, for relative stability, at least 90% of participants should have test-retest score differences within ± 1 point, as differences above ≥ ± 4 points on a 5-point rating scale reflect 'wide

disagreements' among test-retest scores.[247] Although, this chapter revealed that some LMQ-3 items met Nevill's criterion, these indices of item-score stability are somewhat arbitrary,[249] and restricted to 5-point scales- it is possible that it was not suitable for assessing stability of responses on the 10-cm visual analogue scale which showed wider disagreements in scores. Nonetheless, additional reliability analyses were conducted for the latter scale.

Methods based on the proportion of exact score agreement are prone to obtaining the same answer by chance and may 'overlook the nature of disagreement' between test-retest scores.[247] It is important, however, to recognise that few medicine-related questionnaires have assessed test-reliability by percentage of exact agreement between scores, for example, the patients' attitudes towards deprescribing (PATD) questionnaire,[64] which assesses constructs different from the LMQ-3's.

Finally yet importantly, this test-retest study may have imposed response burden, as participants had to retake a relatively lengthy survey in a short space of time. Thus, the present sample size represents decent efforts among participants who were offered the chance to be entered into a draw for £30 to complete both test and retest surveys. However, it is unlikely that this very small incentive may have affected the response rates.[118]

8.5 Chapter summary

This chapter set out to determine the test-retest reliability of the LMQ-3, as assessment of the extent to which the instrument obtains consistent scores over time. The findings are promising and suggest that the LMQ-3 has excellent test-retest reliability and obtains relatively consistent scores in the same group of participants over a short period of time (1-5 weeks); this was assessed through multiple methods. The findings presented in this chapter are a first step towards determining longitudinal validity (i.e. responsiveness) of the LMQ-3, which could be used in future research and/or practice to monitor those most at risk of medicine burden. The next chapter will explore patient attributes and treatment characteristics associated with medicine burden, in addition to interpreting LMQ-3 questionnaire scores further.

Chapter 9 Interpretation of scores, prevalence of medicine-related difficulties, and predictors of medicine burden

9.1 Introduction

Chapters 4 to 8 have focussed on measurement properties of the Living with Medicines Questionnaire (LMQ), particularly testing various aspects of the instrument's validity and reliability. Despite being the mainstay of this doctoral thesis, the work reported in these Chapters has paid little or no attention to the prevalence of medicine-related problems uncovered by this measure. It is, thus, important to consider what proportion of the population experience or perceive difficulties with their long-term prescription medicine(s). A recent systematic review and metasynthesis of qualitative studies indicated the need for further research and '[quantitative] sub-group analysis to determine the common types of [medicine] burden in a specific …healthcare setting'.[88] Thus, further investigations were necessary to understand aspects of medicine-related burden that are challenging to most individuals.

As a new concept, the level(s) of medicine burden have also not yet been established empirically and yet preceding chapters indicated the need to target future interventions to those with 'high' or 'excessive' medicine burden. Like many psychological and clinical screening tools, the LMQ is scored along a 'quantitative continuum'.[255] The LMQ collects self-reported scores using multiple items assessing various aspects of the medicine burden construct. Item scores are summed up to produce a total scale score (or composite score), which depicts the overall experience of prescription medicine use. Chapter 7 revealed that higher LMQ composite scores reflected worse experiences of prescription medicine use (higher medicine burden). It is relevant to classify levels of medicine burden, based on this composite score, to estimate the proportion of the general population that is most affected.

Discriminative capability, in distinguishing groups of people with certain characteristics, is also a desirable property for new measurement tools.[118] From the previous chapter, the questionnaire's reliability properties were hypothesised to confer discriminative ability to the LMQ, but further empirical work was needed to confirm this.

Ideally, an instrument should be able to show 'different levels of the construct' in cohorts that are known to be different or logically should be different (i.e. known-groups validity).[256] Earlier work using the original LMQ found that the instrument could differentiate between people using different a number of medicines,[193] but this version of the questionnaire was subsequently modified. Following questionnaire revisions reported in Chapter 5, the revised LMQ (versions 2.1 and 3) incorporated additional medicine-related questions (e.g. about frequency of administration, or formulation) and demographic-related questions, including postcodes to estimate levels of relative deprivation in the respondent's area of residence. Further analyses were needed to check if the revised questionnaires could distinguish people using different formulations (e.g. oral solid dose versus other dosage forms), or those administering medicines at different time intervals.

To confirm significant predictors of prescription medicine burden, additional work was also necessary. It was relevant to investigate whether and to what extent the aforementioned medicine-related attributes and other socio-demographic characteristics (e.g. age, employment status) were associated with medicine burden. This is especially relevant if the LMQ is to be used as a screening tool for identifying patients most at risk of medicine burden or in guiding decisions related to assigning patients to clinical and/or research interventions that are based on individual assessments.

Aim and research questions

To determine the prevalence and levels of medicine burden, and to explore factors associated with negative experiences of medicine use in the sample populations used in the development of the instrument.

Research questions posed were:

1) What proportion of people experience difficulties with medicine use? What are the cutoffs or levels of medicine burden as measured by the LMQ? What percentage of the sample population experiences high medicine burden?
2) Is the LMQ able to show different levels of medicine burden in groups of people that have different treatments characteristics?
3) What socio-demographic- and treatment-related characteristics are associated with negative experiences of medicine use, and to what extent do they predict medicine burden?

9.2 Methods

9.2.1 Datasets, recruitment, and study instruments

Two existing datasets gathered via a national and a regional survey, used in Chapter 6 and Chapter 7 respectively, were reanalysed. National-level data were gathered using an on-line survey accessible to the general public via social media, health websites, electronic health magazines and newsletters, and via direct email invitation by participating patient organisations or fora. Regional-level data were gathered through face-to-face recruitment (using paper-based questionnaires) of patients in primary and secondary care settings (GP practices, community pharmacies and outpatient clinics of Medway Maritime Hospital) in south-east England. Ethics approval and research governance were obtained for each phase of data collection from relevant committees.

With ready access to the two datasets, secondary data analysis provided an expedient and cost-effective means of answering new research questions using existing variables.[257] As described in Chapter 6, an interim version of the LMQ (the 58-item LMQ-2.1) was used to gather national-level data. Chapter 7 reported a survey dataset gathered using the LMQ-3, which comprised 41 Likert-type items (derived from the LMQ-2.1) covering different views and experiences of medicine use. Both datasets were reconciled to ensure that only common variables were retained for the secondary data analysis for this chapter. The survey dataset obtained using the original questionnaire (LMQ-1), in Chapter 4, was not used in this secondary data analysis owing to substantial differences in the items and demographic questions when compared to the other two datasets.

Total scale scores were calculated based on the 41 Likert-type items present in the final questionnaire (ie LMQ-3) that were common to the two datasets to enable comparison of findings. Total-scale scores and subscale/domain scores were calculated as described in Chapter 7 and possible composite scores ranged from 41 to 205. Both datasets had a 10-cm visual analogue scale assessing perceptions of medicine burden, based on the question, ‘overall, how much of a burden do you feel your medicines to you?’ (rated from 0 for no burden at all to 10 for extremely burdensome). This visual analogue scale was piloted and tested in a study described in previous chapters.

Both datasets included demographic information, including age, gender, education levels, employment status, ethnicity, and postcodes. Postcodes were used to calculate indices of multiple deprivation (IMD ranks) using the English indices of deprivation 2015 on-line tool[258] available at http://imd-by-postcode.opendatacommunities.org/. Additionally, datasets contained medicine-related variables including the number of medicines, formulations used, frequency of use, ability to manage medicines independently or need for social support, and paying for prescriptions. Both datasets included free-text comments, which elaborated on experiences of medicine use for some participants.

9.2.2 Participants

All participants were at least 18 years of age and used at least one long-term prescription medicine. Participants in the national survey resided anywhere in the UK, whereas participants in the regional survey were mostly residents of south-east England.

9.2.3 Data preparation

All datasets were managed using SPSS version 24.

9.2.3.1 Missing data and outliers

For this secondary data analysis, the two datasets were examined for missing data. It was observed that although most participants completed all Likert-type items, some demographic questions or those asking about treatment-related characteristics were not fully completed. Participants with incomplete answers on the 41 Likert-type items were eliminated from the analyses. For analyses involving demographic- or treatment-related characteristics, all statistical analyses were based on pairwise deletion of missing data where respondents with data on variables involved in a specific analysis were retained. Although pairwise deletion of missing data led to variations of sample sizes across this chapter, listwise deletion would have significantly reduced the sample sizes across both datasets. Scatter plots and box plots assessed outliers, visually.

9.2.3.2 Dummy coding and recoding of variables

To facilitate regression analyses, all categorical variables with more than two levels were recoded to create dummy variables- these are dichotomous variables that are recoded as 0 or 1.[174] For instance, age categories (18-29, 30-49, 50-64, and ≥65) and categories of number of medicine (to 1-4, 5-9, and ≥ 10) were recoded into three and two dummy

variables respectively, using the first group as a reference. Reference categories were coded based on logic, theory, or were based on category with the majority of participants.[250] For instance, when coding dosage forms, tablets/capsule were used as the reference variable that was assumed to be more convenient than 'any other formulation' or a 'combination of tablets/capsules and 'any other formulation'. Similarly, using medicines 'once daily' was taken as the simplest dosing frequency and used as the reference category when comparing other frequencies of administration in the regression analyses.[98] Ethnicity was recoded to a binary variable (white and other) as the other subcategories had very few participants.

9.2.3.3 Sample size requirements

Sample size requirements were variable across the different statistical analyses. For regression analyses, Tabachnick and Fidell (2013) recommend the sample size to be greater than 50 + 8m; where m represents the number of independent variables.[182] Using this criterion, the minimum sample size for regression analysis was exceeded.

9.2.4 Analyses

9.2.4.1. Descriptive statistics

To answer the first research question, descriptive statistics, including percentages and frequencies, were used to describe self-reported experiences with medicine use and the prevalence of medicine burden, which was derived from the distribution of LMQ composite scores. Five categories of medicine burden were hypothesised to exist, determined by dividing LMQ composite scores into quintiles and the proportion of respondents in each determined. The categories were: 41-73 to reflect 'no burden at all'; 74-106 to reflect 'minimal burden'; 107-139 to indicate 'moderate degree of burden'; 140-172 to reflect 'high burden', and those with scores in the range of 173-205 were categorised as 'extremely high burden'. To verify this classification of medicine burden, further analyses were conducted. Correlations between LMQ composite scores were run against scores based on the visual analogue scale 'overall, how much of a burden do you feel your medicines are to you?'. Also, cross-tabulations (contingency tables) compared proportions of participants in the five categories of burden with similar categories of self-ratings on the visual analogue scale.

Participants in the 'high' or 'extremely high' medicine burden categories based on the two assessments were deemed to 'certainly' have these levels of medicine burden.

9.2.4.2. Free-text comments

The two survey datasets also included an open-ended question, 'If you have any other views about how your medicines affect your day-to-day life, please describe them here'. This open question served as a qualitative data collection tool that enabled elaboration of lived experiences covered in the tick-box type questions in the two surveys, thus allowed participants to add a 'voice' to their views and experiences of medicine use. These were analysed thematically based on the eight domains underlying the revised questionnaires that were revealed and tested in Chapter 6; this was thought to give a holistic picture of challenging medicine-related experiences.

9.2.4.3. Between-group differences

To answer the second research question, checking if there were significant differences in medicine use experiences between groups of participants predicted to experience different degrees of burden, such as those with different treatment characteristics, composite mean scores were compared; this constituted the known-groups validation. Statistical tests used included: independent-samples t-tests for dichotomous variables, and one-way ANOVAs where variables had three or more categories. These parametric tests were used since the data were normally distributed. Post hoc comparisons were assessed using Tukey HSD test or the Gabriel test depending on whether or not assumptions for homogeneity of variance were met; the latter were assessed using Levene's test. The significance value of all tests was set at p-value less than 0.05.

9.2.4.4. Regression analysis

9.2.4.4.1. Simple and multiple linear regressions

To address the third research question, socio-demographic and treatment-related factors associated with LMQ composite scores were examined. Preliminary bivariate analyses (simple linear regressions) were used to test each candidate independent variable against the dependent variable. The variables which achieved p-values <0.05 and/or those with p-values < 0.2 in either dataset were considered for inclusion in the multivariable regression models.[250] To estimate the explanatory power of the combination of independent variables, standard multiple linear regressions (forced entry method),[175] were conducted using LMQ composite scores as the dependent variable.

A priori hypotheses

Decisions about which variables were included in the regression analyses were based on previous research or logic. Experiences of medicine use were hypothesised to relate to demographic characteristics, particularly age, and socioeconomic status.[48,88,259] The latter was thought to relate to financial-burden of paying for long-term prescriptions medicines, particularly for the unemployed. Living in areas of higher level of relative deprivation, measured using the English IMD 2015, was hypothesised to impact negatively on the medicine use experience, as was thought to relate to access to healthcare e.g. GP appointments, pharmacist consultation or even access to prescription medicines. Medicine use experiences were hypothesised to also relate to regimen complexity, particularly the number of medicines, frequency of administration and the formulation used.[98,260] The need for social support with managing medicines was also predicted to indicate higher medicine burden[88] with respect to day-to-day practicalities of using medicines.

9.2.4.4.2. Testing regression assumptions

To accurately estimate the regression models, a number of assumptions needed to be met. Firstly, the dependent variable, the LMQ composite score, needed to be continuous, which is the case.

a) Assessing normality

Normality of residuals, another prerequisite in multiple regression analyses, was assessed using histograms and the normal probability plots (P-P plots).[250]

b) Assessing multicollinearity

Other regression assumptions relate to absence of multicollinearity, ensuring that independent variables are not too strongly correlated with each other. Collinearity diagnostic tests were used to assess this assumption. One such test, known as the variance inflation factor (VIF), was used to assess if a predictor variable had a strong relationship with other hypothesised predictors. Although it is not clear-cut, as a rule of thumb, Field (2013) indicates that VIF values above 10 are undesirable.[174] Tolerance is another diagnostic for test for multicollinearity, calculated as 1/VIF; values below 0.1 suggest serious problems with multicollinearity.[174]

c) Testing for homoscedasticity and independence of errors

Homoscedasticity, also known as homogeneity of variance, and independence of errors (residuals) are also prerequisite assumptions for multiple regression. They relate to residuals in the model that should be independent of the fitted values (i.e. do not increase or decrease with fitted values)[250] and how well the model fits the data. A scatter plot of residual values against values of the dependent variable predicted by the model, the zpred vs. zresid plot (standardised predicted value against standardised residual), was used to assess these assumptions.[174] If the assumptions are met, 'there should be no systematic relationship between the errors in the model and what the model predicts', and no curvy patterns in the data points should be observed on the scatter plot.[174]

9.2.4.4.3. Regression model evaluation

Overall model fit was evaluated using R-squared (R^2) and adjusted R-squared (adj R^2) as an 'a measure of how much of the variability in the outcome is accounted for by the predictor [variables]', while its adjusted value reflects generalisability of the model to the population.[174] Regression coefficients, including B-values that are unstandardised and beta (β) values that are standardised, were used to estimate the magnitude and direction of the relationship (as positive or negative) between each predictor variable and the outcome variable. Standardised values are easier to interpret and are directly comparable. Beta values (β) are cited to provide better insight into the 'importance' of a variable in the model.[174] B-values are also indicative of the extent to which 'each predictor affects the outcome if the effects of all other predictors are held constant.'[174] The t-test associated with each B-value was used to assess whether or not the predictor variable made a significant contribution to the model ($p < 0.05$). Predictor variables with smaller p-values (<0.05) of the t-test statistic indicated greater and significant contribution to the regression model.

9.3 Results

9.3.1 Sample characteristics

The characteristics of participants in the national-level dataset (from here on, referred to as Sample 1), recruited via the LMQ-2.1 survey, were described in Chapter 6 (see Table 6-2). Repeated here for clarity purposes, 729 participants had fully completed all 41 Likert-type items of the LMQ-2.1. However, some participants did not provide responses to some of the demographic questions, or to some questions relating to their medicine regimens. Participants in Sample 1 were of mean age 48.7 (SD±11.6). Most participants in this sample were female (83.9%, n= 612) and the mean number of medicines used was 4.6 (SD±3.7).

In Sample 2, which is the region-level dataset completed using the LMQ-3, 336 completed all 41 Likert-type items. Similar to Sample 1, some participants had missing data on demographic- and treatment-related questions. Over half of participants were female (61.9%, n= 208). The mean age was slightly higher (56.1 ± 18.17) compared to Sample 1, but the mean number of medicines used was similar (4.6 ± 3.7). Participants' characteristics for Sample 2 were presented in Table 7-1.

9.3.2 Prevalence and narratives of medicine-related problems

To estimate the percentage of people experiencing different medicine-related problems assessed by the LMQ, item-level analyses were conducted for each dataset. Table 9-1 shows the percentage of participants endorsing specific Likert-type statements. Sample quotations from the free-text comments, which relate to each of the eight domains underlying the LMQ, have been included to illustrate the statistical findings.

Practical difficulties

About 1 in 6 reported difficulties getting their prescriptions across the national (17.2%, n=125) and the regional samples (16.1%, n=54). Similar findings were revealed for difficulties relating to accessing medicines from the pharmacist: 16.6% (n=121) versus 11.6% (n=39) of the national and regional sample, respectively, agreed/strongly agreed that they found getting their medicines from the pharmacist difficult. Up to a third (33.7%, n=246) of the national sample admitted to putting a lot of planning and thought into using their medicines, though a lower proportion of the regional sample (18.8%, n=63) had the same challenge. Practical difficulties relating to access to prescription medicines are illustrated in the quotes below;

> *'My GP will not allow me to get a prescription unless I have less than 2 weeks of tablets left. This makes planning for holidays difficult at times.'*
> Female, 48 years, uses one prescription medicine

> *'I run out of meds because I cannot see the doctor, I run out of meds because I cannot get to the chemist. When I change to a different doctor (i.e. I move home) it takes me a long time to get my GP prescribing medicines that my consultant wants me to take… I have to buy medicines on the internet…I can't get medicines prescribed long term for my medical conditions that last for years but come and go..'* Female, 54 years, six prescription medicines

> *'GP management insist all prescriptions are requested in person at the surgery, the opening times are incompatible with my work hours. Fortunately … pharmacist has a collection service, so is able to request, collect and dispense on my behalf.'* Female, 47 years, uses one prescription medicine

A few participants reported difficulty with using their medicines in general: 8.0% (n= 58) versus 6.3% (n=21) for the national and regional sample respectively.

Cost-related burden

About 30.3% (n=221) of the national sample paid for their prescription medicines. Although the cost of prescription medicines did not appear to be worrisome for the vast majority, about 1 in 5 participants worried about paying for their medicines across the national (22.8%, n=166) and regional samples (24.1%, n=81) respectively.

A few participants echoed their concerns about costs of long-term medicines through additional comments:

> *'Paying for them [prescription medicines] is my biggest problem/worry. I am long term sick and unable to work. Yet don't qualify for free prescriptions. Long-term illness should qualify in England.'* Female, 39 years, uses three medicines

> *'I rely on my medicines… All these prescriptions are of a high cost to my budget as i may have eight items on one prescription. I was forced to take ill health retirement and my pension of service is very low.'*
> Female, 54 years, uses five medicines

> *'…it is a nightmare having to pay out ridiculous amounts for drugs that are essential to me being able to function!'* Female, 21 years, uses seven medicines

Perceived effectiveness

Across the national and regional samples respectively, the vast majority of participants felt that their medicines were working (63.9 %(n=466) to 75% (n=252)), and prevented their condition getting worse (64.2 %(n=468) to 77.4 %(n=260)).

> *'As my AED's [medicines] help control my seizures I am very grateful they exist..'*
> Female, 37 years, uses five prescription medicines

However, a smaller proportion (12.5 %(n=42) to 25.0 %(n=182)) were dissatisfied with the effectiveness of their medicines across both datasets.

> *'Have no effect on the amount of pain i am in, which makes my life revolve around pain & depression'* Female, 63 years, uses sixteen medicines

> *'Find them ineffective, but nothing else is available for my condition.'*
> Female, 53 years, uses three prescription medicines

> *'Not very effective at helping but have been told I cannot try others as the alternatives are not on the NICE list.'*
> Female, 48 years, uses seven prescription medicines

Communication about medicines with healthcare professionals

Most participants reported good communication and relationships with health providers, in terms of their medicine use experiences. For instance, about a half (52.7% (n=177) to 55.6% (n=405)) felt that doctor(s) listened to their opinions about their medicines for regional- and national-level data respectively. However, about a third (33.8%, n=246) of participants in the national survey dataset did not feel that they got enough information about their medicines (see Table 9-1). For instance, while some participants expressed concerns about lacking information about risks of using medicines, others mistrusted health professionals.

> *'I was given no information about the long-term side effects on the other systems of my body. ..I feel more… information needs to be given into the long term side effects and patients informed'* Female, 25 years, uses two prescription medicines

> *'I feel that my doctor does not review or explain why he has prescribed the particular drugs that he has for me.'* Female, 71 years, uses two medicines

> *'I don't feel that I have a GP that I can talk to or who believes or supports me. I have no faith in them now.'* Female, 54 years, uses nine prescription medicines

Concerns about using medicines

Over half of participants were concerned about long-term effects of using medicines among regional (58.3%, n=196) and national-level samples (73.9%, n=539) respectively. Other concerns related to potential drug-drug interactions, and worries relating to switching between branded/originator medicines to generic versions.

> *'My only concern is long term effects, which no one knows*.'
> Female, 61 years, uses four medicines

> *'I take many medications for several conditions and I am not sure they always take interactions into account and have had a few reactions to medications…'*
> Female, 46 years, uses ten medicines

> *'I had been stable on a branded medication for over 10 years, but they have just discontinued it. So now I feel anxious that this latest generic will put me back to square one.'* Female, 55 years, uses five medicines

Side effects experience

About half of the national sample agreed or strongly agreed that the experience of side effects was bothersome (51.1%, n=372) and that side effects interfered with day-to-day life (45.8%, n=334). About 20.2% (n= 68) and 20.8% (n=70) of the regional sample were bothered by side effects and acknowledged their interferences/impact on life.

> *'Side effects are the problem of most concern.'*
>
> Male, 70 years, uses seven medicines

> *'Exhaustion, nausea, dizziness, cold getting better- the immunosuppressants and [ulcerative colitis] UC medications. ..really awful side effects they have on me- low white blood cell rate & low red blood cell rate & coming down consistently'*
>
> Female, 55 years, uses ten medicines

> *'My medication causes horrible side effects that affect my quality of life.'*
>
> Female, Age 27, uses three medicines

In addition to general concerns about side effects, one participant hinted at the burden resulting from prescribing cascades associated with having more medicines prescribed to counteract the side effects of existing medicines.

> *'I worry on a daily basis about the strong side-effects of Prednisolone; the personality changes also affect everyone around me. It is annoying because of one medicine I have to take several others to counteract those side-effects…'*
>
> Female, Age 54, uses five medicines

Interference to day-to-day life

About 3 in 10 participants (30.6%, n=223) in the national dataset agreed or strongly agreed that using medicines interfered with their social or leisure activities; a slightly higher prevalence when compared to that reported in the regional-survey dataset (20.2%, n=68). Medicines were perceived to affect social relationships (13.1% versus 24.5% and sexual lives (14.9% versus 29.4%) among the national- and regional- samples respectively. Interferences to daily tasks were also reported by some participants.

> *'[Medicines] they make me tired, meaning that I can't get out a lot, have a social life or do a lot of activities. They also make me dizzy, so I often find it hard to be fully focused and present during conversations, making social interaction sometimes challenging... I find it hard to remember to take them and to fit this in to whatever activity I am doing, but this isn't really something I can avoid so I just have to get used to it.'* Female, 18 years, uses one medicine

'it is hell!! I have very little social life, virtually no sex life …'
Female, 21 years, uses seven medicines

'After only taking my medication for a short time I feel the tablets have affected me socially. Mainly by giving me bloated stomach and flatulence.'
Female, 49 years, uses one medicine

'Also, sometimes it is difficult to say whether my medication is adversely affecting my daily life/hobbies/socialising, or if it's my condition (as in, I have a choice - I can be unable to go out because I'm in too much pain, or I can be unable to go out because I've taken opiates).' Female, 28 years, uses eight medicines

A few others hinted at the social stigma associated with using certain formulations.

'My medicine is prescribed as patches and I have not been offered tablets (though I know they exist) and the patches and dirty mark they leave is embarrassing.'
Female, 47 years, uses one medicine

'I have to carry a glucose test kit, insulin pen, needles and sugar for hypos. It's often hard to carry the supplies discreetly thus advertising my condition which undermines confidence at times.' Male, 34 years, uses two medicines

'Possibly the largest burden is the social effect of sometimes having to take them in public (feelings of shame/guilt/furtiveness at being obviously 'on painkillers', and having to answer questions about what I've just taken).'
Female, 28 years, uses eight medicines

Patient autonomy/control over their regimens

Most participants reported limited empowerment to alter their medicine regimes to suit their lifestyle. For instance, over a half (57.5% to 64.5%) reported that they could neither change the dose nor the times (45.8% to 53.9%) they use their medicines, if they wanted to.

'If consultant at hospital has prescribed medication, and then you are discharged, it is often very difficult to get GP to alter dose or change medication. Should be given indicator when starting new meds or different dose...'
Female, 64 years, uses five medicines

'I am not given choices on medicines and treatments available to treat my symptoms.' Female, 46 years, uses ten medicines

Statements in their respective domains	National-level dataset Sample 1 (LMQ-2.1) (N=729)[¥]			Regional-level dataset Sample 2 (LMQ-3) (N=336)[¥]		
	Agree/ Strongly Agree %(n)	Disagree/ Strongly Disagree %(n)	Neutral opinion %(n)	Agree/ Strongly Agree %(n)	Disagree/ Strongly Disagree %(n)	Neutral opinion %(n)
Practical difficulties (7 items)						
I find getting my prescriptions from the doctor difficult.	17.2(125)	70.5(514)	12.3(90)	16.1(54)	68.7(231)	15.2(51)
I find getting my medicines from the pharmacist difficult	16.6(121)	70.2(512)	13.2(96)	11.6(39)	76.5(257)	11.9(40)
I am comfortable with the times i should take my medicines	86.8(633)	5.2(38)	8.0(58)	81.8(275)	8.1(27)	10.1(34)
I am concerned that I may forget to take my medicines	41.7(304)	42.1(307)	16.2(118)	26.8(90)	54.5(183)	18.8(63)
I have to put a lot of planning and thought into taking my medicines.	33.7(246)	45.3(330)	21.0(153)	18.8(63)	59.0(198)	22.3(75)
It is easy to keep my medicines routine	75.0(547)	11.7(85)	13.3(97)	74.7(251)	8.9(30)	16.4(55)
I find using my medicines difficult	8.0(58)	77.4(564)	14.7(107)	6.3(21)	85.2(286)	8.6(29)
Perceived effectiveness (6 items)						
I am satisfied with the effectiveness of my medicines.	52.8(385)	25.0(182)	22.2(162)	70.8(238)	12.5(42)	16.7(56)
My medicines prevent my condition getting worse	64.2(468)	17.0(124)	18.8(137)	77.4(260)	8.4(28)	14.3(48)
My medicines live up to my expectations	40.9(298)	26.8(195)	32.4(236)	62.5%(210)	9.5%(32)	28.0(94)
My medicines allow me to live my life as I want to	43.3(316)	33.8(246)	22.9(167)	67.3(226)	11.9(40)	20.8(70)
My medicines are working	63.9(466)	12.6(92)	23.5(171)	75.0(252)	6.3(21)	18.8(63)
The side effects are worth it for the benefits I get from my medicines	41.3(301)	12.6(92)	41.3(301)	35.7(120)	17.6(59)	46.7(157)
Communication/relationships with HCPs (5 items)						
I trust the judgement of my doctor(s) in choosing medicines for me.	56.8(414)	20.7(151)	22.5(164)	70.2(236)	11.6(39)	18.2(61)
My doctor(s) listen to my opinions about my medicines	55.6(405)	22.1(161)	22.3(163)	52.7(177)	19.6(66)	27.7(93)
My doctor takes my concerns about side effects seriously.	45.4(331)	22.8(166)	31.8(232)	51.2(172)	14.3(48)	34.5(116)
I get enough information about my medicines from my doctor(s)	44.0(321)	33.8(246)	22.2(162)	53.6(180)	22.3(75)	24.1(81)
The health professionals providing my care know enough about me and my medicines	44.0(321)	36.5(266)	19.5(142)	59.2(199)	18.8(63)	22.0(74)
Cost-related burden (3 items)						
I worry about paying for my medicines	22.8(166)	49.2(359)	28.0(204)	24.1(81)	51.5(173)	24.4(82)
I sometimes have to choose between buying basic essentials or medicines	8.9(65)	68.9(502)	22.2(162)	9.5(32)	77.1(259)	13.4(45)
I have to pay more than I can afford for my medicines.	13.7(100)	49.1(358)	37.2(271)	15.5(52)	64(215)	20.5(69)

Table 9-1 Percentage of participants endorsing (agreeing or disagreeing) with the 41 Likert-type statements common to the two datasets

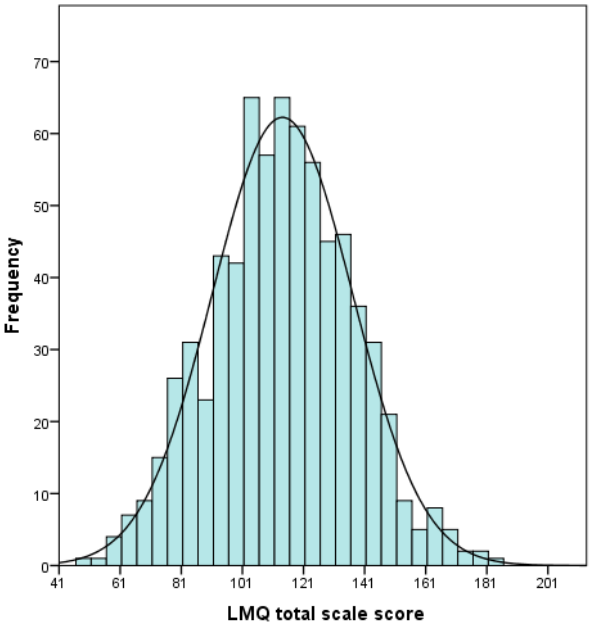
Statement Statements in their respective domains	National-level dataset Sample 1 (LMQ-2.1) (N=729)			Regional-level dataset Sample 2 (LMQ-3)(N=336)¥		
	Agree/ Strongly agree %(n)	Disagree/ Strongly Disagree %(n)	Neutral opinion %(n)	Agree/ Strongly Agree %(n)	Disagree/ Strongly Disagree %(n)	Neutral opinion %(n)
Concerns about medicine use (7 items)						
I worry that I have to take several medicines at the same time	32.1(234)	41.6(303)	26.3(192)	22.3(75)	55.4(186)	22.3(75)
I would like more say in the brands of medicines I use	49.2(359)	21.3(155)	29.5(215)	26.8(90)	35.4(119)	37.8(127)
I feel I need more information about my medicines	42.7(311)	33.6(245)	23.7(173)	33.9(114)	44.6(150)	21.4(72)
I am concerned about possible damaging long-term effects of taking medicines	73.9(539)	13.9(101)	12.2(89)	58.3(196)	26.4(89)	15.2(51)
I am concerned that I am too reliant on my medicines	41.3(301)	33.7(246)	25.0(182)	36.0(121)	39.9(134)	24.1(81)
I am concerned that my medicines interact with alcohol	23.6(172)	45.8(334)	30.6(223	19.6(66)	48.5(163)	31.8(107)
I worry that my medicines may interact with each other	44.1(322)	30.5(222)	25.4(185)	35.7(120)	35.7(120)	35.7(120)
Side-effect-burden (4 items)						
The side effects I get are sometimes worse than the problems for which I take my medicines	36.8(268)	40.5(295)	22.8(166)	21.1(71)	51.8(222)	27.1(91)
The side effects that I get from my medicines interfere with my day to day life	45.8(334)	33.1(241)	21.1(154)	20.8(70)	58.1(195)	21.1(71)
The side effects I get from my medicines are bothersome	51.1(372)	25.9(189)	23.0(168)	20.2(68)	63.7(214)	16.1(54)
The side effects I get from my medicines adversely affect my wellbeing	36.5(266)	40.5(295)	23.0(168)	14.3(48)	67.8(228)	17.9(60)
Interference to day-to-day life (6 items)						
My medicines interfere with my social or leisure activities	30.6(223)	53.1(387)	16.3(119)	20.2(68)	64.9(218)	14.9(50)
Taking medicines affects my driving	17.3(126)	54.9(400)	27.8(203)	11.3(38)	72.3(243)	16.4(55)
My medicines interfere with my social relationships	24.5(179)	59.1(431)	16.3(119)	13.1(44)	71.1(239)	15.8(53)
Taking medicines causes problems with daily tasks	28.7(209)	50.2(366)	21.1(154)	14.6(49)	74.4(250)	11.0(37)
My medicines interfere with my sexual life	29.4(214)	46.6(340)	24.0(175)	14.9(50)	65.8(221)	19.3(65)
My life revolves around using medicines	29.5(215)	51.2(373)	19.3(141)	27.1(91)	54.1(182)	18.8(63)
Autonomy/control (3 items)						
I can vary the dose of the medicines I take	32.6(238)	57.5(419)	9.9(72)	18.8(63)	64.5(217)	16.7(56)
I can choose whether or not to take my medicines	25.4(185)	64.1(467)	10.6(77)	27.4(92)	55.0(185)	17.6(59)
I can vary the times I take my medicines	30.2(220)	53.9(393)	15.9(116)	34.8(117)	45.8(154)	19.3(65)

Table 9-1 Percentage of participants endorsing (agreeing or disagreeing) with the 41 Likert-type statements common to the two datasets

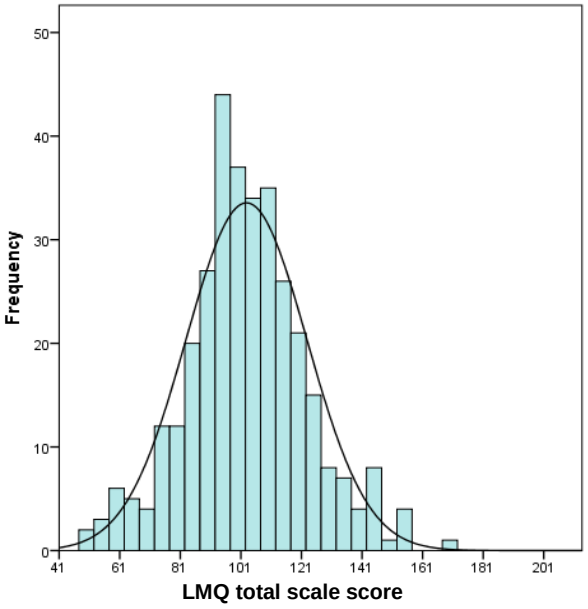
Note: ¥ sample with complete responses across all Likert-type items

9.3.3 What proportion of people experience high medicine burden?

Figure 9-1 illustrates the distribution of LMQ composite scores for the two samples, which were used to classify levels of medicine burden.



Mean (SD) =114.1(23)
Sample 1 (LMQ-2.1)



Mean (SD) =102.8(20)
Sample 2 (LMQ-3)

Figure 9-1 Histograms showing distribution of LMQ composite scores

For the national-level sample, data showed that the majority had minimal (34.3%, n= 250) or moderate (47.7%, n=348) burden. Just over 1 in 10 (13.3%, n=97) participants had scores reflecting high burden, while five participants (0.7%) had scores reflecting 'extremely high burden'. For Sample 2, analyses revealed fewer participants with high medicine burden (4.8%, n=16) and while none of them showed 'extremely high burden' (See Figure 9-2).

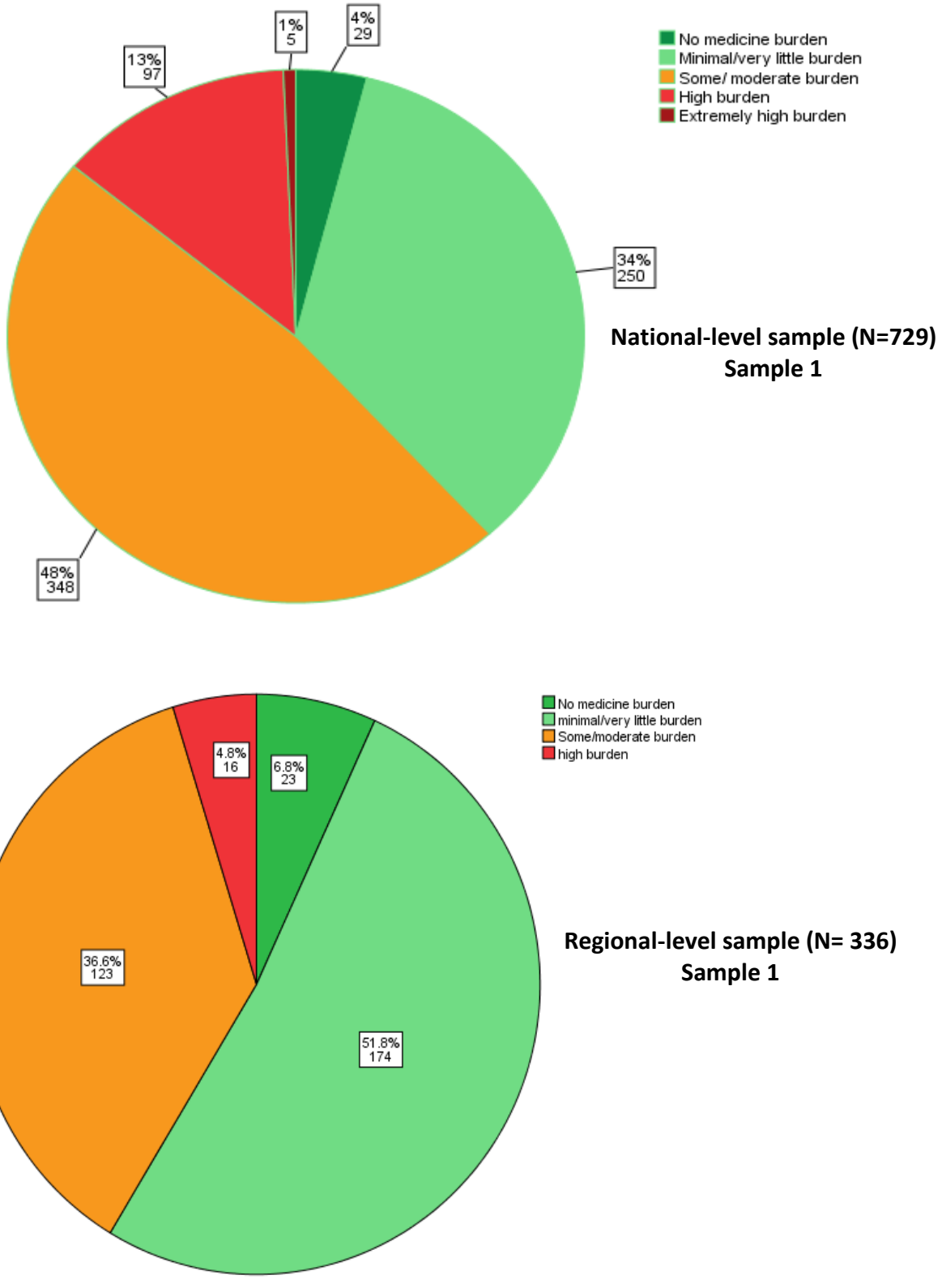


Figure 9-2 Prevalence of medicine burden in the sample populations

Verifying medicine burden categories against self-perceptions of burden

Further descriptive analyses, in the form of correlations and cross-tabulations with scores on the 10-cm visual analogue scale assessing perceptions of burden (VAS burden), were conducted to verify the five categories of medicine burden based on overall composite scores. A positive, moderately strong, correlation between VAS burden scores and composite scores was obtained for both national- ($r=0.542$, $p<0.001$) and regional samples ($r= 0.571$, $p<0.001$), suggesting that perceptions of medicine burden were related to experiences of burden in the appropriate direction.

For cross-tabulations, the VAS burden scores were divided into five groups: 0.0- 2.0; 2.1-4.0; 4.1-5.9; 6.0-7.9; 8.0- 10.0; scores range from 0 to 10 depicting 'no burden at all' to 'extremely burdensome'. Of the 29 national-survey participants assessed to have 'no burden' based on composite scores, the vast majority (79.3%, n=23) had perception ratings in the lowest category (0.0-2.0) of the VAS scale. Similar findings were found in the second sample, where all but one participant (95.7%, n=22) assessed to have 'no burden' based on composite scores had perceptions ratings in the lowest category of the VAS scale (0.0-2.0). These findings may suggest that, on the whole, LMQ composite scores in the range 41-73 closely reflect absence of medicine burden.

Of the five national-survey participants assessed as having 'extremely high burden' based on composite scores, 80% (n=4) had perception ratings in the topmost category (8.0-10.0) of the VAS scale. None of the participants in the second sample (Sample 2) had composite scores and VAS ratings reflecting 'extremely high burden' or 'extremely burdensome' respectively. In Sample 2, about 68.8% (n=11) of those with 'high burden' based on composite scores had perception ratings in the topmost category (8.0-10.0) of the VAS scale. This finding indicates that LMQ composite scores of ≥ 140 reflect, for the most part, higher levels of medicine burden.

The data showed that the middle categories of medicine burden (i.e. 'minimal burden' and 'moderate burden'), based on composite scores, were less discriminative (See Table 9-2).

		LMQ composite score				
	VAS scores	No burden (41-73)	Minimal burden (74-106)	Moderate burden (107-139)	High burden (140-172)	Extremely high burden (173-205)
National Sample 1 (N=704)*	0.0- 2.0	79.3% (23)	44.5%(106)	11.0%(37)	5.2%(5)	0.0%(0)
	2.1 -4.0	3.4%(1)	22.7%(54)	21.4%(72)	9.4%(9)	0.0%(0)
	4.1-5.9	6.9%(2)	14.3%(34)	31.0%(104)	16.7%(16)	20.0%(1)
	6.0-7.9	6.9%(2)	12.2%(29)	20.2%(68)	28.1%(27)	0.0%(0)
	8.0-10.0	3.4%(1)	6.3%(15)	16.4%(55)	40.6%(39)	80.0%(4)
Regional Sample 2 (N=334)*	0.0- 2.0	95.7% (22)	68.2%(118)	30.3%(37)	6.3%(1)	0.0%(0)
	2.1-4.0	4.3%(1)	12.1%(21)	15.6%(19)	0.0%(0)	0.0%(0)
	4.1-5.9	0.0%(0)	11.0%(19)	23.8%(29)	6.3%(1)	0.0%(0)
	6.0-7.9	0.0%(0)	1.7%(3)	18.9%(23)	18.8%(3)	0.0%(0)
	8.0-10.0	0.0%(0)	6.9%(12)	11.5%(14)	68.8%(11)	0.0%(0)

Table 9-2 Cross-validation of medicine burden categories derived using LMQ-3 composite scores

Notes; *Reflects the sample size for participants that had complete data on both the LMQ composite scores and VAS burden scores. Colour codes green = minimal/no burden; yellow = some degree of burden; orange = 'certainly' high/extremely high degree of burden

Table 9-2 shows that for national-level sample, a total of 70 participants (~ 9.6% of the original sample) 'certainly' had high/extremely high medicine burden following two assessments using composite scores (≥ 140) and VAS ratings (≥ 6.0); only 14 (~ 4.2%) of the regional sample participants 'certainly' experienced high/extremely high burden. Table 9-3 summarises the characteristics of the latter subgroups. Appendix 25 illustrates free-text comments from participants with scores reflecting 'certainly' high/extreme medicine burden.

Characteristics		Sample 1 (N=70) % (n)	Sample 2 (N=14) % (n)
Gender	Female	79(55)	64(9)
	Male	21(15)	36(5)
Age	18-29	10(7)	0(0)
	30-49	36(25)	57(8)
	50-64	47(33)	36(5)
	65 or over	7(5)	7(1)
Ethnicity	White	96(67)	79(11)
	Other	4(3)	21(3)
Employment	Employed	36(25)	43(6)
	Unemployed	40(28)	36(5)
	Retired	11(8)	21(3)
	Full time student	7(5)	0(0)
	Other	6(4)	0(0)
Paying for prescriptions	Yes	26(18)	57(8)
	No	74(52)	43%(6)
Managing medicines	Independent	66(46)	71(10)
	Needs support	33(23)	29(4)
Number of medicines	1-4	49(34)	7(1)
	5-9	34(24)	64(9)
	10 or more	17(12)	29(4)
Formulation	Tablets/capsules	59(41)	50(7)
	Mixed*	41(29)	50(7)

Table 9-3 Characteristics of participants with 'certainly' high or extremely high medicine burden based on their LMQ-3 composite scores and global VAS ratings

Note; *both parenteral and non-parenteral forms; VAS- Visual Analogue Scale

9.3.4 Subgroup differences

Differences in medicine burden (measured by LMQ composite scores) were examined with respect to participants' socio-demographic and treatment characteristics for both the national and regional samples (See Table 9-4).

Characteristics		**National-level data** Sample 1 (LMQ-2.1) (N=729**)**		**Regional-level data** Sample 2 (LMQ-3) (N=336)	
		Mean(SD)	p-value	Mean (SD)	p-value
Gender	Female	113.8(25.2)		103.6 (19.4)	
	Male	114.6(22.5)	.784	101.2 (20.5)	.289
Age (years)	18-29	119.9(20.3)		104.6(18.4)	
	30-49	114.3(22.4)		108.4(22.4)	
	50-64	113.7(24.1)		102.8(20.5)	
	≥65	107.8(23.1)	.055	98.4(17.5)	.007*
Education	School	114.5(23.3)		103.4(21.5)	
	College/App[$]	115.9(23.3)		100.5(20.1)	
	University	112.0(22.6)		103.4(20.0)	
	Other	124.8(22.3)	.073	107.7(15.2)	.439
Employment	Employed	111. 1(21.6)		103.2(20.1)	
	Unemployed	122.2(24.2)		118.0(21.5)	
	Retired	109.1(21.84)	<.00*	98.3(17.3)	<.001*
Ethnicity	White	113.6(23.2)		101.9(19.4)	
	Other	122.5(17.5)	.070	106.8(22.6)	.153
No. of medicines	1-4	111.1(23.2)		100.3(17.7)	
	5-9	117.2(21.6)		107.8(23.8)	
	≥ 10	121.4(24.2)	<.001*	104.4(20.3)	.010*
Formulation	Tablet/capsule	113.3(23.7)		102.4(18.7)	
	Any other	96.8(17.6)		103.4(17.6)	
	Combinations#	116.0(22.1)	.001*	103.1(24.8)	.954
Frequency of use	Once daily	106.3(22.5)		97.8(16.0)	
	Twice daily	117.7(24.9)		101.7(20.0)	
	Thrice daily	111.9(21.3)		111.4(23.8)	
	≥ 4 times daily	121.3(21.1)	<.001*	112.7(22.1)	<.001*
Managing medicines	Independent	112.1(22.8)		100. 8(19.5)	
	Requires help	124.6(22.1)	<.001*	116.4(17.8)	<.001*
Paying for prescriptions	No	114.0(23.8)		100.6(19.5)	
	Yes	113.6(21.5)	.844	106.2(20.3)	.014*

Table 9-4 Differences in medicine burden by demographic and treatment characteristics

Notes; *statistically significant findings; [$] App – apprenticeship; # Combinations of tables/capsules and 'any other formulation

9.3.4.1 Socio-demographic characteristics

Gender; Gender did not seem to affect medicine use experiences in the sample populations. Across both samples, there were no statistically significant differences ($p>0.05$) in mean composite scores between males and females based on findings of the independent-samples t-tests. The qualitative analyses revealed most free-text comments were from females, most of which described negative experiences.

Age*;* One-way ANOVAs indicated that medicine use experiences significantly differed with age. For instance, post-hoc Tukey HSD tests on the regional-level data revealed significantly lower mean composite scores (98.4±17.5) among those 65 years and over when compared to the 18-29-year-olds (104.6±18.4). The same finding was observed in the national dataset, except that it was marginally significant. This finding may suggest that increasing age is associated with lower self-reported medicine burden, while younger participants seem to report relatively worse experiences with medicine use.

Employment status; One-way ANOVAs revealed statistically significant differences in medicine uses experiences in terms of employment status. Across both samples, unemployed participants, including those self-reporting to be homebound, disabled, or those unable to work due to illness or other reasons, had the highest mean composite scores (reflecting relatively higher medicine burden) when compared to employed or retired participants ($p < 0.001$) (See Table 9-4).

Education and ethnicity*;* Across both samples, there were no statistically significant differences in medicine use experiences in terms of the level of education and ethnicity ($p>0.05$).

Deprivation levels and medicine burden

As shown in Table 9-5, significant differences were found between deprivation levels and medicine burden levels (LMQ composite scores); higher relative deprivation levels (lower IMD ranks) were associated with increasing medicine burden (higher LMQ-3 composites).

Deprivations levels	**Sample 1**			**Sample 2**		
	N (550)	Mean IMD rank	p-value	N (279)	Mean IMD Rank	p-value
No burden at all	21	24850		18	18459	
Minimal/very little burden	188	18725		149	17415	
Some/moderate burden	263	17152		100	15755	
High burden	74	15768		12	9841	
Extremely high burden	4	10022	< 0.001			0.025

Table 9-5 Relationship between relative deprivation in area of residence and medicine burden

9.3.4.2 Medicine-related characteristics

Number of medicines; One-way ANOVAs revealed statistically significant differences in mean composite scores across number of medicines categories. Post-hoc tests for multiple comparisons (Tukey HSD) showed significantly higher scores (higher burden) among those using 5-9 medicines when compared to those using 1-4 medicines across both subsamples ($p < 0.05$). Further subgroup analyses showed variations in levels of medicine burden with respect to the number of medicines used (See Figure 9-3).

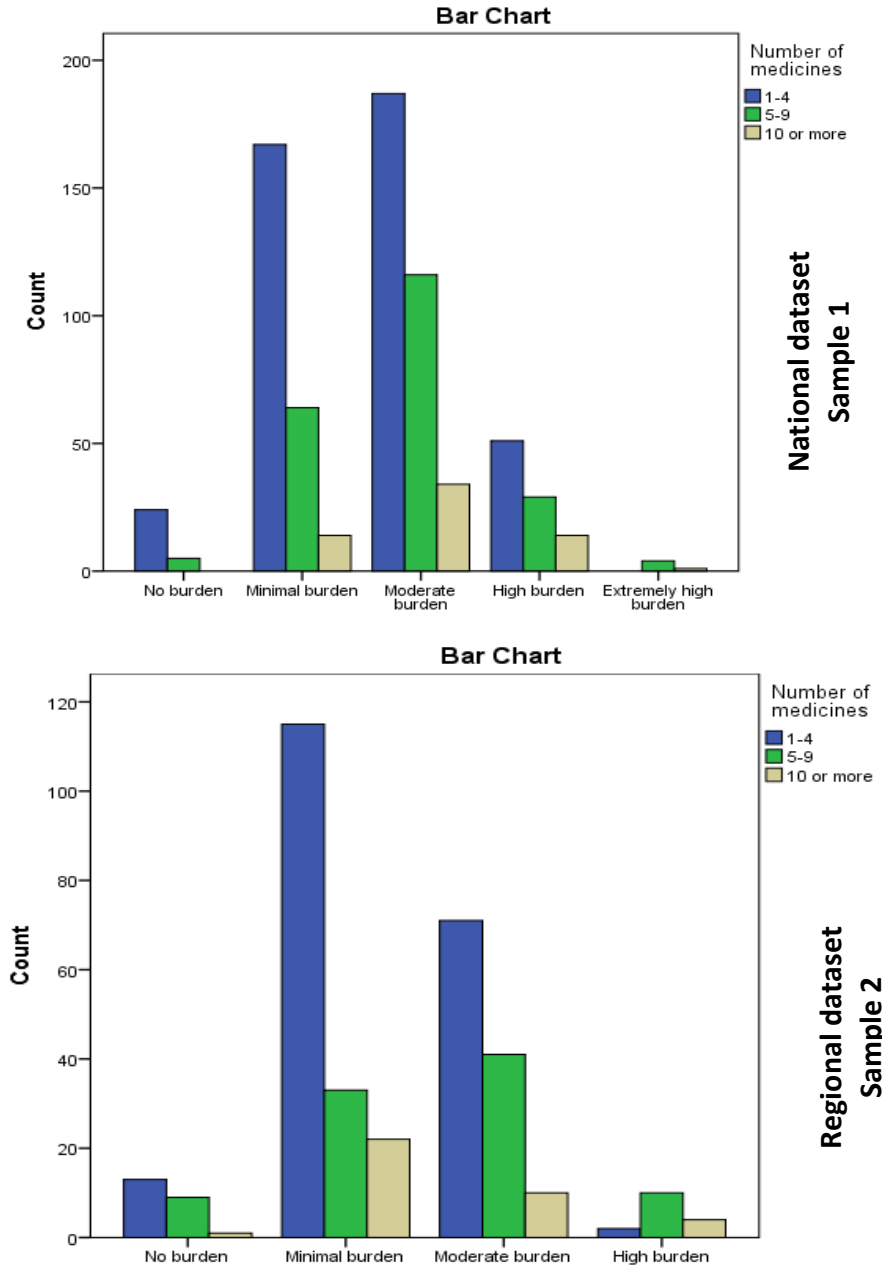


Figure 9-3 Comparison of medicine burden categories with number of medicines used across the two sample populations.

Note; The figure shows that the number of prescription medicines used varies across different levels of medicine burden. The first bar chart (for national-level data) shows that people with extremely high medicines were mostly using 5-9 medicines. The regional-level data shows that people with high medicine burden were also mostly using five or more medicines

Formulation; There were variations in medicine use experiences with regards to the formulation of medicine used. Based on national-level data, one-way ANOVAs (and post-hoc Games-Howell tests) showed significantly ($p < 0.001$) higher mean scores (higher burden) for people using a combination of tablets/capsules and 'any other' formulations (116.0±22.1) compared to those using a non-oral solid dose formulation (96.8± 17.6). Data from the second subsample revealed mixed findings, with no statistically significant differences across formulation types ($p =0.954$).

Frequency of medicine use; For both samples, one-way ANOVAs showed significant differences in medicine use experiences with respect to the frequency of medicine use. Mean composite scores generally increased with more frequent medicine use per day. Across the national sample, post hoc (Tukey) tests showed significantly higher mean composite scores among participants using medicines four or more times daily (121.3±21.1) when compared to those using medicines once daily (106.3±22.5) ($p <0.001$).

Ability to manage medicine use; Across both datasets, independent samples t-tests revealed significantly lower mean composite (less burden) scores among participants managing medicines independently when compared to those needing social support with managing their medicines use ($p<0.001$) (See Table 9-4).

Paying for prescriptions; Mixed findings were observed with regards to paying for prescriptions. In the regional sample, participants who paid for their prescriptions had relatively higher burden (composite mean scores =106.2±20.3) than those who did not pay for their prescriptions (composite mean scores =100.6±19.5) ($p=0.014$), but the national-level sample showed no statistically significant differences ($p=0.781$).

Cost-burden mean scores were significantly higher among the unemployed (7.7(±3.1) to 8.8(±3.2)) and compared to those employed (6.9 (±2.9) to 7.3(±3.2)) across Samples 1 and 2 respectively; one-way ANOVAs followed by post-hoc Tukey-HSD tests revealed significant findings (p-values, <0.001 to 0.022). Cost burden scores did not vary significantly with the number of medicines in either sample (p-values, 0.084 to 0.189).

9.3.5. Findings of regression analyses

To address the third research question, predictors of medicine burden were investigated through simple- and multiple linear regression analyses.

9.3.5.1. Assumptions for regressions

To ensure suitability of both datasets for regression analyses, specific statistical assumptions were tested, as previously described in the methods section.

Multicollinearity; All intervariable correlations between independent variables were below 0.9, and thus the multicollinearity assumption was met.[174] For both datasets, tolerance values were above 0.1 (range of 0.136 to 0.952), reflecting absence of multicollinearity.[174,175] VIF values were all below 10 (range, 1.05-7.345) confirming that there were no serious problems with multicollinearity among predictor variables.[174,175]

Normality; As shown in Figure 9-1, both datasets had relatively normal distributions of LMQ composite scores as the dependent variable. For both samples, histograms of standardised residuals also appeared 'bell-shaped' and P-P plots revealed most data points to be reasonably close to- and lying along the diagonal line (See Figure 9-4).

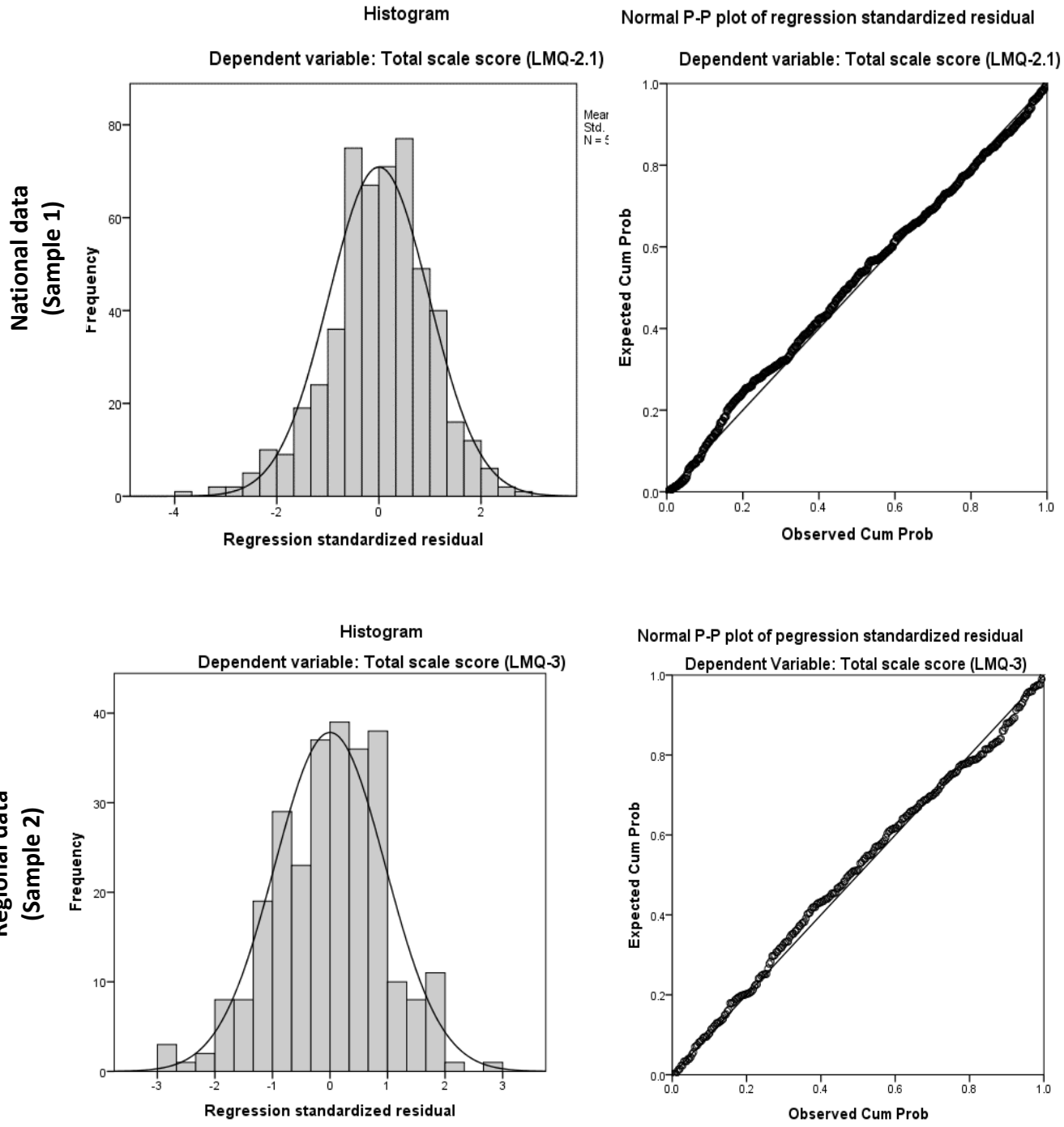


Figure 9-4 Histograms and P-P plots of normally distributed residuals

Homoscedasticity & independence of errors; For both samples, the scatterplots showed that most residuals were distributed haphazardly and no systematic pattern was immediately visible, thus the assumptions for homoscedasticity and independence of errors were not violated (Figure 9-5).

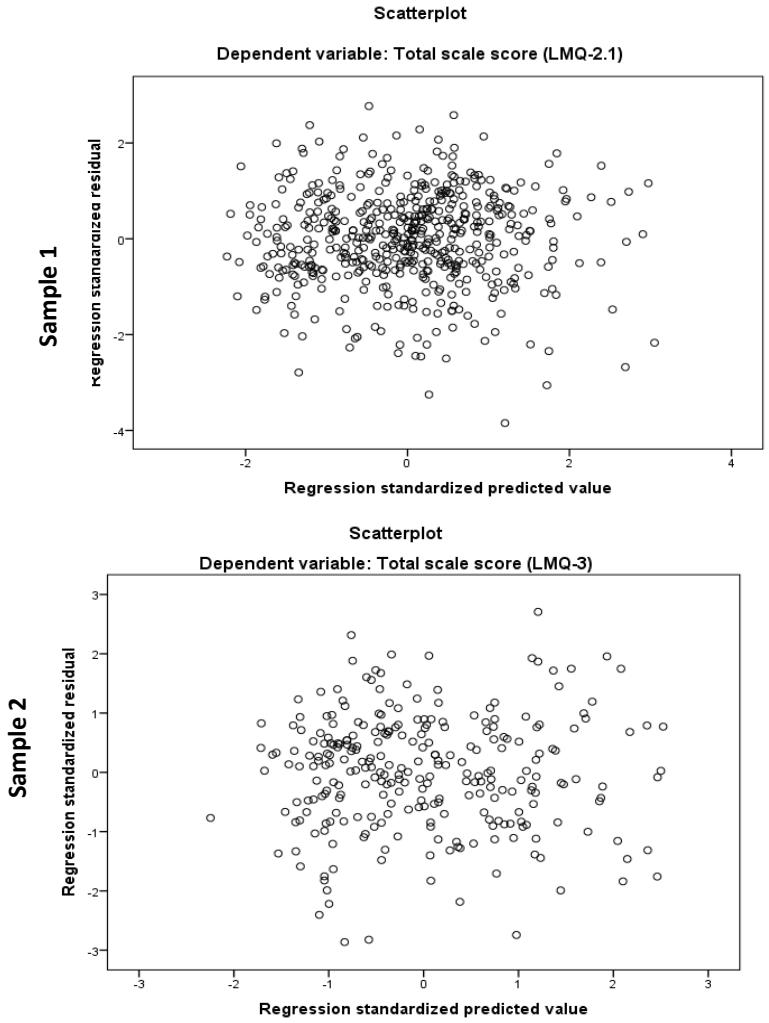


Figure 9-5 Scatter plots of standardised residuals against standardised predicted values

Note; The Graph from National-level data (Sample 1) is at the top and that for Regional-level data (Sample 2) is at the bottom

Outliers, data points whose standardised residual values are greater than 3 in absolute value,[175] were assessed using scatter plots shown in Figure 9-5. Only a few outliers were present in Sample 1, but were retained in subsequent analyses owing to the large sample size in this dataset (n=729) and possibly minimal impact on the findings.[175]

9.3.5.2. Findings from simple linear regression

Simple linear regression was used to estimate the relative contribution of each independent variable to the prediction of LMQ composite scores as the dependent variable (See Table 9-6). Independent variables tested were those identified to show significant differences in composite scores in the preceding subgroup analyses (i.e. age, employment status, number of medicines, formulation, frequency of administration, managing medicines independently or need for social support and paying for prescriptions). In addition, deprivation level and perceptions of burden were tested as independent variables.

The findings revealed that nearly a third of the total variation in LMQ composite scores was predicted by self-perceptions of medicine burden across both sample populations (R^2=29.4% to 32.6%). Other statistically significant predictors of negative experiences of medicines use, from the simple regression analysis, are presented in Table 9-6.

Independent variable	Sample 1 (LMQ-2.1)				Sample 2 (LMQ-3)				
	B	**SE**	*β*	*p*	B	SE	*β*	*p*	R^2 (%)~
Age (years)	-0.21	0.07	-0.11	.004*	-0.17	0.1	-0.16	. 005*	1.2-2.4
Employment Employed [a]									
Unemployed	10.5	2.1	0.19	.000*	14.6	3.4	0.23	.000*	4.8-9.1
Retired	-2.6	2.2	-0.04	.242	-5.14	2.3	-0.13	.026*	
Deprivation level[§]	0.00	0.00	-0.19	.000*	0.00	0.00	-0.18	.003*	3.2-3.5
Number of medicines 1-4 [a]									
5-9	5.7	1.9	0.11	.002*	7.44	2.47	.167	.003*	
≥ 10	9.9	3.1	0.12	.001*	4.02	3.53	.063	.256	2.2-2.7
Formulation Tablets/cap[a]									
Any other form	-16.8	5.1	-0.124	.001*	0.69	4.1	0.009	.868	
Combinations#	2.4	1.7	0.051	.177	0.40	2.7	0.008	.882	0.0-2.0
Frequency Once daily [a]									
Twice daily	7.3	1.76	0.16	.000*	3.2	2.6	0.074	.209	
Thrice daily	6.3	2.12	0.11	.003*	13.0	3.5	0.208	.000	
≥ 4 times daily	11.9	2.29	0.20	.000*	14.2	3.5	0.234	.000	
Other times	-4.31	2.48	-0.06	.083	2.5	4.4	0.032	.568	6.1-7.2
Managing medicines Independent [a]									
Requires help	12.52	2.48	0.188	.000*	15.56	3.2	0.259	.000*	3.5-6.7
Paying for prescriptions No[a]									
Yes	-3.73	1.89	-0.007	.844	5.57	2.26	0.135	.014*	0.0-1.8
Perceptions of burden[ǂ]	4.303	0.254	0.542	.000*	3.80	0.30	0.571	.000*	29.4-32.6

Table 9-6 Simple linear regression analyses of predictors of medicine burden

Notes; [a] reference variable; B- Unstandardised coefficients; β- Standardised beta coefficients;
[§]Area deprivation levels based on IMD ranks for England 2015;
ǂ 'Overall, how much of a burden do you feel your medicines are to you?;
¥ 'Taking everything into account, how satisfied are you with your medicines?';
[§]Index of Multiple Deprivation Rank 2015;
~ R-squared range reported for both samples;
# Combinations of tablets/capsules and 'any other formulation
*p < 0.05

9.3.5.3. Results from multiple regressions

To investigate the combined effect on LMQ composite scores and the explanatory power of all independent variables, standard multiple linear regressions (forced entry method) were conducted based on the regional-level sample (Sample 2) which used the final version of the questionnaire (LMQ-3). Analyses showed statistically (or marginally) significant predictors of negative experiences: a) being unemployed (β =0.10 , p=0.053); b) relative level of deprivation in a participant's area of residence (β =-0.11, p =.023); c) needing assistance/social support with medicine use (β =0.13, p= 0.008); d) paying for prescription medicines (β =0.09, p= .068); and e) perceptions of medicine burden (β =0.48,p <.001). This model explained 36% of the variance in LMQ composite scores (See Table 9-7).

Independent variable	B	SE B	β	p-value
Constant	94.0	2.38		.000
Unemployed	5.86	3.01	0.10	.053
Deprivation level[§]	0.00	0.00	-0.11	.023
Help/support with managing medicines	8.25	3.09	0.13	.008
Paying for prescriptions	3.63	1.98	0.09	.068
Perceptions of burden	3.10	0.33	0.48	.000

Table 9-7 Multiple regression analyses of predictors of medicine burden

Note; R-squared = .356; Adjusted R-squared =.344; §Index of Multiple Deprivation Rank 2015; n= 275

9.4 Discussion

Using secondary data obtained from earlier studies, this chapter interpreted questionnaire scores of the LMQ-3. Particularly, this chapter investigated the prevalence of medicine use issues covered in the questionnaire. The results indicated variations in medicine use experiences across the sample populations.

Although the vast majority reported positive experiences with various aspects of medicine use, a fair proportion also reported practical difficulties (including problems accessing prescriptions and medicines), ineffective therapies, and impacts of side effects. A few indicated gaps in communication and relationships with healthcare professionals, citing a genuine lack of information about their medicines. Cost-related burden appeared to affect a smaller proportion of the sample population, particularly the unemployed. General concerns about medicine use often related to possible long-term harm and risks associated with medicine use. For others, planning and using different regimens, around usual life's demands (e.g. work, meals, sleep), hindered performance of tasks, social and/or leisure activities, and restricted social life. These findings support medicine-related issues reported in the literature (as discussed in Chapter 1 and 2), and some have been discussed in Chapter 6 and 7.

The findings are supported by recent reviews of qualitative studies, exploring patient perspectives of treatment and medicine burden.[85,86,88,89] Individuals' views of their regimen, within the context of life's demands and responsibilities (e.g. family, work, school), may also affect perceived or actual treatment burden.[260] For instance, Demain et al reported biographical disruption (including restriction of activities and social stigma), relational disruptions (e.g. strain to family and social relationships), and biological disruptions associated with side effects from using different therapies.[95]

Autonomy/flexibility to vary regimens appeared to be limited in the sample population, and most participants reported minimal or no control over their regimen dosing or timing. Flexibility in regimes, where clinically beneficial, may reduce perceived medicine burden and encourage persistence with long-term medicine use.[221,241,260] On the hand, loss of independence, freedom, and/or spontaneity associated with adherence to strict regimens can be burdensome for some

individuals.[95] Moreover, demands in time and effort to organise and use certain therapies (such as nebulised medicines, or prolonged, inpatient, iron chelation therapies[238,240]) may infringe on individual freedom and arouse negative emotions and feelings 'in the sense of not being 'carefree''.[95]

This study also attempted to define and verify levels of medicine burden, as measured by the LMQ-3 instrument. It was found that about 1 in 10 of the national sample population experienced and self-reported high medicine burden. The findings suggest that, although broadly the LMQ-3 may be able to categorise the degree of medicines burden, allocating individuals to the category which they perceive themselves to be 'right' may be more problematic. One of the peculiar findings is that people's perceptions of medicine burden may not necessarily align well with their experiences of medicine burden, when different aspects of medicine use are taken into consideration using the LMQ-3 composite score. For instance, a few participants' composite scores reflected 'high' medicine burden, and yet they did not perceive their medicines as burdensome (as indicated by low VAS rating) when asked directly using one question 'overall how much of a burden do you feel your medicines are to you'. The latter finding may reflect a range of issues, including necessity beliefs about medicines.[110,112] In addition, evaluation or appraisal of medicines often involves weighing risks against benefits of using medicines,[17,108,109] and many participants may appreciate the prevention of disease, symptom control, and reduction in mortality, which they set against actual burden. Thus, medicines are not necessarily viewed as a 'burden' among some participants on long-term prescription medicines, but rather a 'necessity' to get through life.

The findings also indicate that one general question may not accurately assess the overall experience of medicine use and thus confirms the advantage of using the LMQ-3 composite score that uses multiple item scores when quantifying the level of medicine burden. However, the study also showed that perceptions of medicine burden significantly affect actual levels of burden.

To examine the questionnaire's known-groups validity, sub-group analyses were tested for different treatment-related characteristics. The LMQ-3 questionnaire was able to discriminate between participants using different formulations, number of medicines, and frequency of administrations. Particularly, higher burden scores were obtained among those using combination of formulations (both oral and non-oral types), five or more medicines, and among those using medicines more frequently (i.e. four or more times daily). These findings are related to regimen complexity, which affects adherence.[261,262]

There is limited literature investigating treatment characteristics associated with medicine burden. Sawicki et al suggests that burden relates to 'number of therapies required on a daily basis, the frequency of such therapies, the complexity of administering therapies, and the amount of time needed to complete a therapy.'[260] The latter was not investigated in this study, and future studies using the LMQ-3 may incorporate patient estimates of the time needed to use or plan medicines on a regular basis as a possible indicator of medicine burden.

In the US, Vijan et al found higher perceived burden among diabetic patients using a combination of parenteral (e.g. insulin injections) and oral medicines when compared to those using oral agents alone.[259] Similar finding were reported by Sawicki et al who also found that using more types of nebulized, inhaled, and oral medications were all associated with higher treatment burden.[260] Vijan also reported treatment burden ratings to increase in a 'fairly linear pattern based on increasing frequency of administration'.[259] The present study found that medicine burden scores generally increased with frequent use of medicines per day.

The number of medicines was associated with higher medicine burden scores, although this finding was inconclusive when examining the combined effects of multiple explanatory variables in the regression analyses; the number of medicines used was a not a statistically significant predictor of negative experiences when all other factors were included in the multiple regression model. In a recent conceptualisation of medicine-related burden, Mohammed and colleagues also establish that medicine burden is a multifactorial construct and that it goes beyond the

number of medicines used.[88] The authors suggest that people using the same number of medicines may have different levels of medicine burden, as they could struggle with different aspects of medicine burden; a finding clarified by the qualitative data. Illustratively, Zarowitz (2011) noted that 'for some patients, one medication may be too much, and for others, 15 medications may be too few',[8] while Cadogan and colleagues question 'when many is not too many' in their recent opinion paper on polypharmacy.[16]

In terms of demographic characteristics, medicine burden was not statistically related to gender, education levels, or ethnicity, although qualitative data indicated more females reporting negative experiences. One study investigating treatment burden among adult patients with cystic fibrosis in the US reported statistically significant gender differences whereby females had higher treatment burden scores than males; however, no significant differences were found in terms of age.[260] The present study, on the contrary, found that, compared to younger participants (<65 years), those aged 65 years or older tended to report lower medicine burden. This may be explained by a tendency to report positive experiences (higher satisfaction) in this age group, possibly due to lower expectations of care in this group,[106] and greater acceptance of need for and gratitude for medicines in older people.

Unemployed participants, including those self-reporting to be homebound and unable to work due to illness or other reasons, had worse medicine use experiences when compared to those employed or retired, and this may be due to cost-related burden. In addition, living in an area of higher level of relative deprivation was significantly associated with poor experiences of medicine use. People of low socioeconomic status may experience challenges with medicine use, as it affects access to healthcare, including obtaining prescription medicines.

Those in need of social support to manage their medicines were also found to report higher medicine burden compared to those managing independently. In fact, needing help/support with managing medicines was a statistically significant predictor of higher medicine burden in the regression analysis, as was paying for prescriptions.

Implications for research and practice

Now that we know the prevalence and levels of medicine burden, as well as treatment-related or demographic characteristics associated with higher medicine burden, future research or practice may target those affected. Individuals identified as 'high burden' could be targeted for medicine use reviews or other medicine-related intervention/services to plan ways of reducing the burden among of those using long-term medicines.

Prescribers and suppliers of long-term medicines should consider medicine-related burden, and further studies may engage providers to investigate their understanding and perception of medicine burden, as a step towards engaging in meaningful conversations with patients about their medicines. Providers should be made aware of the potential burden of treatments for long-term conditions, as this may be an initial step to discussing issues affecting some people.

Communication gaps between people on long-term medicines and HCPs may also be addressed. Huang (2008) suggests that ´actively acknowledging the burden of life with treatments early on in the disease; and anticipating the psychological distress that people may experience over time' could prove beneficial for patient-centred communication.[263] Again, patient education not only about the effects of disease but also about the effects and demands of treatments may be beneficial in managing expectations, reducing psychological burden,[263] and improving experiences of long-term use of medicines.

Where possible, and clinically justifiable, simplifying/modifying medicine regimens could reduce the burden.[263] Pharmaceutical companies and related research could develop and test formulations that are less burdensome e.g. those with lower frequency of administration. Evaluation of medicine burden as an outcome when developing new medicine agents may be incorporated in medicines development guidance, particularly for long-term medicines.[263]

For patient populations that are particularly at risk of adverse effects of medicines, such as the elderly, reviewing medicines that complicate the regimen or even

reviewing clinical targets to less intense treatments, may be beneficial.[263] If warranted, and if part of patient preferences, wants or wishes, medicine use review to uncover unnecessary medicines may help in discontinuing/deprescribing as this could potentially reduce medicine burden. As recommended by Vijan et al (2005), 'treatment burden [and medicine burden may] be explicitly considered when making clinical and policy decisions about the management of chronic diseases'.[259]

Where modifications to regimens or cessation is not possible, reassuring individuals that they can adapt to living with medicines and/or discouraging 'fears' of medicines may prove useful.[259] Coping strategies could include focussing on the positive effects of using medicines (e.g. having control over their disease/condition and preventing long-term complications),[263] and seeking social support.[221]

Study strengths & limitations

This study employed secondary data to address new research questions, and further studies may be needed to attempt to cross-validate the current findings using primary data.

While the two datasets used were adequate, in terms of sample size and content coverage of variables used in all analyses, it is worth noting that the two questionnaire versions employed in this study (LMQ-2.1 and LMQ-3) were administered through different methods (on-line versus face-to-face recruitment respectively). Although they shared a vast proportion of items and demographic questions, on which all analyses were based, it is uncertain that the differing number of items in the data collection instruments did not affect the results. The use of combined datasets is increasingly popular in clinical research. This is evident in studies such as meta-analyses where information from individual studies is pooled from several sources to derive findings that are more conclusive. Nevertheless, challenges such as missing data, between-practice variations, and other methodological differences in the way data are collected may affect the results. Efforts were made to examine and minimise potential heterogeneity across the two datasets, including reconciling items across the two datasets, assessing missing data and checking normality of responses.

It was difficult to assess the impact of using multiple recruitment sites (general practices, hospital outpatient areas, community pharmacies, and the general public) on the response patterns, but it is likely that using multiple sources of data enhances generalisability and reliability of findings reported in Chapter 9. Moreover, using the LMQ across various settings also serves as a preliminary test of acceptability of the instrument in these settings, and employing paper- and electronic distribution of the measure considered alternative methods by which patients may report medicine use issues. Nonetheless, the sample populations comprised mostly females partly because relatively more women than men use prescription medicines in England.[31]

Also, multiple linear regressions were conducted using one sample dataset, (the final LMQ-3 or regional sample), despite relatively larger sample for National-level data (gathered using an interim questionnaire) that covered the views of those in wider geographical area. The national survey was accessed across the UK, and it is likely that cost-related items were irrelevant to people living in Scotland owing to different schemes for paying (or not) for prescriptions.

Methods for determining optimal cut-off scores, reflecting appropriate classifications of individual levels of an attribute (e.g. level of burden), for clinical and psychological scales, are wide ranging.[118,255] Future studies may use the Receiver Operating Characteristic (ROC) analysis to confirm the sensitivity and specificity of LMQ-3 cut-off scores for the categories of medicine burden, once a 'gold standard' comparator measure of medicine burden is available.

9.5 Chapter summary

This study determined the prevalence of medicine-related difficulties, defined levels of medicine burden based on LMQ composite scores, as well as examined potential predictors of medicine burden. Using secondary survey data, the findings showed that medicine-related issues assessed using the LMQ are wide ranging, and affect users of long-term medicines differently. Although the vast majority report positive experiences with different aspects of medicine use, this study found that about 10% of the national-level sample population reported high medicine burden. Burden levels differed with multiple factors such as employment status, the relative level of deprivation in area of residence, needing support with managing medicines, and paying for prescriptions. Perceptions of burden significantly influenced the actual levels of medicine burden reported by individuals.

10.1 General introduction

In today's health systems, including the English National Health Service (NHS), it is increasingly desirable to understand and monitor patients' experiences, in order to enhance the quality of their care.[75,234] Monitoring experiences of medicines use is a priority since prescription medicines are the most common healthcare intervention.[1] Given the growing numbers of people using long-term medicines for multiple chronic conditions, thus having to deal with the additional burden of polypharmacy, the need to not only understand but also to measure this burden is urgent. This is evidenced by recent policy and research funding initiatives by the National Institute for Health Research (NIHR) to establish useful ways of measuring and addressing the problem of inappropriate polypharmacy in the UK.[4,264]

Patient reported experience measures (PREMs), and patient-reported outcome measures (PROMs), provide a means for exploring, understanding and reporting personal experiences and outcomes of healthcare interventions respectively.[234] As described in Chapters 1 and 2, the medicine use experience is multifactorial including patient-related factors (e.g. type and severity of disease condition(s)), medicine-related factors (e.g. formulation, cost, regimen complexity, effectiveness) and health-system-related factors (e.g. access to medicines and health-provider communication).

As direct assessments, PREMs and PROMs can 'help patients to judge how they feel about their own experiences and outcomes of care, including the benefits and risks of treatment',[231] when compared to clinician-driven measures that tend to focus on 'prescriber-defined outcomes'[231] (e.g. inappropriate prescribing and drug-related problems,[19] and adherence[265]). The literature review revealed the dominance of measures of satisfaction with treatments.[108,109,129,130] In addition, there are tools to assess patient satisfaction with pharmacy services,[266] including the Community Pharmacy Patient Questionnaire (CPPQ) that is mandatory across England and Wales.[267] Measures such as the CPPQ, currently used to gather patient feedback, are designed to improve organisational efficiency and enable compliance with clinical governance requirements, therefore focus on process and structural indicators (such as waiting time) and superficially assess medicine-related communication.

It is well documented that satisfaction measures are prone to acquiescence bias (tendency to give positive responses),[268] and patients are unlikely to be open about negative medicine use experiences through satisfaction tools.

Other tools to obtain information on actual use of medicines have neither been standardised nor validated.[269] Tools to assess medicines management ability,[270,271] as one aspect of the medicine use experience, are also common, but most require health professional assistance to assess issues such identification of medicines, or ability to read and follow written instructions, and thus are not direct assessments from patients. Moreover, no gold-standard measure of medicine management ability exists to date.[271] Existing tools assessing treatment burden or medicine use experiences consist of disease-specific measures, mainly in diabetes,[120] but also specific medicines, such as inhalers for asthma,[272] parenteral iron-chelation used for managing blood disorders,[240] and antipsychotics.[273] As already noted in Chapter 1, the increasing prevalence of multimorbidity and polypharmacy implies that more patients have to cope with multiple, complex treatment regimens and generic measures are potentially more relevant and applicable to assessing broader experiences.

The overall aim of this research programme was to identify, develop, and test a generic measure of negative experiences (burden) of long-term prescription medicine among the adult English population. The Living with Medicines Questionnaire (LMQ) was developed and validated as a multifaceted outcome measure for this purpose. This thesis presents the LMQ (version 3) as the only available, in-depth, generic measure of the burden associated with using medicine-only therapies long-term.

As already described in previous chapters, a mixed methods approach was used to identify, develop and test the LMQ's measurement properties (i.e. different forms of validity and reliability) and its potential applications. Face and content validity, ascertaining the meaning and relevance of questionnaire content, was tested in a qualitative, cognitive interview study. A series of iterative, cross-sectional, surveys of the target sample population (users of long-term prescription medicines for any disease/condition) enabled item reduction, from a 60-item originator tool (LMQ-1) to a more manageable, 41-item, tool (See Appendix 26 for item tracking). Survey data allowed evaluation of other questionnaire properties, particularly construct validation

that established the eight domains of medicine burden. Criterion-related validation revealed relationships among medicines burden, and other relevant concepts (i.e. treatment satisfaction and health-related quality of life measured by the TSQM-II and EQ-5D-5L respectively). Forms of reliability (internal consistency and test-retest) were also assessed for the LMQ-3, and interpretation of questionnaire scores allowed qualitative meanings that clarified levels of medicine burden (as none, minimal, moderate, high or extremely high). The next section discusses the overall key findings of this research programme.

10.2 Discussion of key findings

The key finding established from this research programme was that the Living with Medicines Questionnaire (LMQ-3) is a generic, comprehensive, valid, reliable, and interpretable measure of medicines burden suitable for use among adults using long-term medicines for any disease/condition (s) in England. As a multidimensional tool, the LMQ-3 covers different medicine use issues: interferences with day-to-day life; patient-doctor relationships and communication about medicines; lack of effectiveness; general concerns; side effects; practical difficulties; cost-related burden, and lack of autonomy/control over medicines use. All eight domains were confirmed to contribute to prescription medicine burden, an overarching construct underlying the LMQ-3. These findings addressed the primary research question of this thesis.

Having proposed a suitable measure, it was worth considering the extent of the burden problem in the sampled population and likely causal factors as a secondary, yet indispensable, research objective. The present thesis established that about 1 in 10 patients in England are at risk of high-level medicine burden, a finding that is not surprising. This finding indicates that the vast majority of patients do not perceive medicines use experiences as burdensome. Qualitative findings (in Chapters 5) indicated that some patients do not view their prescription medicines (or their effects) as a 'burden'. In addition, subgroup analyses in Chapter 9 confirmed that people's perceptions of medicine burden might not necessarily align well with their experiences of medicine burden, self-reported through the LMQ-3 composite score; this may explain the relatively low prevalence of the problem.

There is limited data on actual medicines usage in England. The 2013 Health Survey for England estimated that approximately 50% (n= 4398) of all adults used at least one prescription medicine based on a sample of 8,795, and 22%-24% had used three or more medicines in the week before the survey. Growing polypharmacy, as highlighted in Chapter 1, remains a cause for concern. Data from NHS digital, formerly the Health and Social Care Information Centre (HSCIC), shows that the average number of prescription items dispensed in the community (by community pharmacists, dispensing doctors in rural areas, and in general practices) in England per head of the population was 19.6 in 2014 compared to 13.7 in 2004.[32] Data from prescribing records of 1,777 patients in general practices in England, in 2012, suggested that 17% were prescribed 5-9 medicines, and about 10% used ten or more medicines.[274] In the present thesis, 21.6% and 24.2% of participants taking part in a nationwide survey used 5-9 and 10 or more medicines, suggesting an upward trend in polypharmacy. Extrapolating these data to predict the numbers affected by high levels of prescription medicine burden at a population level is not that straightforward. What is clear, however, is that a number of people using long-term medicine(s) are overwhelmed by a range of medicine-related challenges beyond the number of medicines used.

This thesis confirms that prescription medicine burden is multifactorial, similar to the findings of earlier researchers.[88,92] Empirical findings depicted multiple factors that significantly influence self-reported levels of medicine burden among users of long-term medicines in the study samples, including socio-demographic characteristics. Relatively higher self-reported medicine burden was found among younger adults (age < 65 years), the unemployed, and among those living in areas with a higher relative level of deprivation.

Socioeconomic factors are cited to influence medicines use experiences, [48,88,259] thus these findings are not surprising. Younger patients (< 65 years) may have higher expectations of healthcare,[106]and less acceptance of the need for medicines when compared to older patients (> 65 years), which may translate into higher perceived burden. The financial-burden of paying for long-term prescriptions medicines may affect some patients, particularly the unemployed or those with lower disposable incomes.[46,52,224] Residents of areas with a higher level of relative deprivation, measured using the English indices of multiple deprivation (IMD 2015),[258] may

experience challenges with access to healthcare (e.g. difficulties getting prescriptions, GP appointments, and/or pharmacist consultations). This in turn may affect the overall medicine use experiences.

A number of medicine-related factors were significantly associated with higher self-reported medicine burden. Managing medicines independently was associated with lower burden. On the other hand, higher medicine burden was reported among those acknowledging assistance or social support with day-to-day practicalities of using medicines. Qualitative data revealed spouses/partners or relatives, paid carers, or healthcare professionals (e.g. district nurses) as a common source of support. The literature review in Chapter 1 highlighted multiple factors that affect patient capacity (ability to handle workload demands imposed by healthcare), including social support.[84] Coping strategies for managing medicine-related demands tend to draw on family and health provider networks, and 'lack of or inadequate [social] support can limit the patients' capacity to manage, further exacerbating their burden'.[88] It is likely that excessive medicine burden on the patient, if transferred to carers (e.g. family or friends), may cause relational disruptions.[95]

Mixed findings were revealed in terms of the number of medicines used versus the level of medicine burden reported by individuals. This thesis revealed a unique, albeit unexpected, finding that higher medicine burden is not necessarily associated with a larger number of medicines used. Some studies have reported positive associations between treatment burden and the number of medicines,[83,232] and quantitative data in this thesis found a similar, but inconclusive, trend. Qualitative data showed that some patients using one prescription medicine reported higher levels of medicine burden associated with different aspects of medicine use (e.g. impact on social life or interferences with day-to-day life), while others using five or more medicines reported no or minimal burden. The present thesis confirms that medicine burden goes beyond the number of prescription medicines used. This finding is in agreement with a recent qualitative synthesis exploring medicine burden, which cited that 'patients on the same number of medicines may experience different levels and aspects of MRB [medicine-related burden];[88] this was established in the subgroup analyses illustrated in Chapter 9 (See Figure 9-3). The finding also aligns well with views that polypharmacy is not just about the 'numbers'.[4,8,16]

Higher medicine burden was also associated with more frequent medicine use (e.g. four times daily versus once daily) and using a combination of formulations (tablets/capsules and non-oral types). Complex medicine regimens can be difficult to manage alongside day-to-day life and may aggravate burden.

Although polypharmacy is mostly defined in terms of the number of medicines prescribed and/or their appropriateness, the findings indicate that evaluations of medicines use should consider other factors. This is especially important since views of appropriateness of medicines differ between patients and health professionals. Appropriateness of medicine use in practice is mostly evaluated from the biomedical perspective by health professionals who often consider medicine benefits and risks stipulated in evidence-based guidelines, and pay little or no attention to the subjective experiences discussed in this thesis. Clearly, there is a need to prioritise the patient perspective and guidelines or tools that solely rely on the number of medicines as the only indicator to screen patients in need of medicines support or review may need to be revised.

Individual beliefs and perceptions towards medicines may also influence the level of medicine burden reported, as hypothesised in the theoretical framework in Chapter 1 (See Figure 1-7). Although this thesis did not evaluate patients' beliefs (and concerns) about their specific medicines and illness perceptions, it is well documented that they influence medicine use.[110,112,114] Minimal-to-moderate medicine burden, reported by the vast majority of participants, may be associated with stronger beliefs about the necessity (and effectiveness), fewer concerns about harms of medicines, and stronger perceptions of disease/symptom severity; further work is needed to confirm this. It is likely that most patients perceived greater benefits of their regimens (such as prevention of mortality) than medicine-related issues evaluated by the LMQ (e.g. interferences to day-to-day life, practical difficulties, and communication problems with health professionals). Treatment-related decisions by individuals (e.g. adherence or persistence) are influenced by weighted evaluations of benefits versus risks, harms and/or inconvenience of medicines use.[108,109] If effectiveness is not achieved, tolerating side effects or medicine-related discomforts/inconveniences becomes more weighted,[108,109] and could translate into higher levels of perceived burden.

For those that experience significant levels of medication burden, the consequences can be wide-ranging. Medicine burden is likely to cause non-adherence, an undesirable behaviour from the provider's perspective. From the patient perspective, 'rationalised non-adherence' is an undisclosed coping strategy and may be a manifestation of workload-capacity imbalances among those with intolerable treatment burden.[95] Sub-optimal clinical outcomes (e.g. poor symptom control, disease progression or relapse, deterioration of health and quality of life), may arise from any form of non-adherence. Besides decreasing health-related quality of life, medicine-related burden may directly or indirectly affect other aspects of an individual, including decreased productivity associated with time and energy invested in performing healthcare tasks (e.g. in seeking doctor appointments, repeat prescriptions and refills).[48]

10.3 Summary of key contributions to knowledge

The findings presented in this thesis contribute to new knowledge by identifying, developing and validating a novel outcome measure of medicine-related burden, the LMQ-3. To my knowledge, this is the first research programme to develop and test an instrument for this purpose. The tool presented offers a practical and timely means of evaluating medicine use challenges, including psychosocial disruptions, which are encountered in the day-to-day lives of some users of long-term regimens and yet rarely considered in health settings. The need to evaluate medicine burden among patients, clearly identified as the rationale for this multiphase research programme, is crucial in lieu of the growing polypharmacy, multimorbidity, and subsequent patient complexity in England. Given the increasing need to assess patients' experiences and outcomes of healthcare interventions, it was considered worthwhile to develop and validate a multidimensional scale for assessing the effects of medicine-only interventions.

Through in-depth review of the literature and critical analyses of existing theories of treatment- and medicine-related burden, most of which required further development and empirical testing, a collated conceptual framework of prescription medicine burden was formulated (See Figure 1-7) and some constituent factors investigated. The framework provides insight into likely causative factors and potential consequences of medicine burden.

This research programme confirmed that healthcare system factors, particularly patient-provider communication and relationships impact significantly on the medication burden reported by an individual.

Prescription costs also affect access and use of medicines and Chapter 9 showed that 30% of the on-line national sample population who paid prescription charges had concerns about the financial burden of using medicines long-term, which most affected unemployed patients that were not exempt from prescription charges. According to the 2015 report by NHS digital (formerly HSCIC), 9.4% of prescriptions were 'charged at the point of dispensing' in 2014,[32] although this finding was based on prescription records and the proportion of people who self-report paying prescription charges may vary. In this research programme, 10% of the test-retest sample (n=30), recruited via an on-line public panel in Kent, paid the prescription charge while 33% of the criterion validation sample (n=408), recruited face-to-face in community pharmacies, GP practices and outpatient clinics in Kent, made the co-payment. The figures reported may reflect, partly, the sample demographics and methods of data collection, and further studies are needed to ascertain the actual number of people who pay to obtain their long-term prescription medicines in England as a step towards identifying those affected by medicine costs.

In terms of medicine characteristics, regimen complexity was established as a predictor of medicine burden especially among those using medicines four or more times daily. The LMQ-3 instrument can identify patients with practical difficulties, including those related to administering medicines, as well as patients concerned about formulations (and brands). Issues around lack of effectiveness are also covered in the measure as hypothesised in the conceptual framework (Figure 1-7).

Psychological concerns about long-term harm (and dependency) are covered in the final measure, and perceptions of burden were found to predict negative experiences of long-term medicines use. Satisfaction with treatments was negatively associated with medicine burden as hypothesised in the conceptual framework. Future work may test the impact of resilience or use of different coping strategies to manage burden, perceived locus of control and self-efficacy beliefs on individual levels of burden. These factors were hypothesised in the initial framework to affect medicine burden but further empirical work is needed.

Individual characteristics established to significantly predict medicine burden levels were age, employment status, and residence in areas with higher deprivation levels, suggesting that people who are under 65 years of age, unemployed or residents in more deprived areas may be at risk of higher medicine burden and could be included in future targeted interventions. Needing social support, in the form of help with managing medicine use, was established as a predictor of medicine burden as hypothesised a priori. Future work may empirically test the hypothesised consequences of medicine burden, particularly non-adherence and how burden impacts on other patient outcomes. The present research programme established a negative association between medicine burden and HRQOL and targeted interventions may minimise the impact of medicine burden on physical, emotional and social functioning.

Incorporating the first reported systematic review of generic, patient-reported, measures of different aspects of the medicine use experience (see Chapter 2), which was published in the journal of Patient Related Outcome Measures,[231] this thesis provides a starting point for researchers and/or clinicians who need to select suitable outcome measures for use in designing, planning and implementing other healthcare interventions. The systematic review also confirmed that medicine use experiences are wide-ranging and complex, and that no single instrument, to-date, covers all issues affecting users of long-term prescription medicines.[231]

Although the original 60-item Living with Medicines Questionnaire, developed by Krska and colleagues,[119] was initially reported as a suitable measure of medicine burden, further investigations and empirical tests revealed that it required extensive modifications (including additions to content coverage) and further testing. These modifications were reported in Chapter 5 and the resulting interim questionnaire, the LMQ-2, is also published in the journal of Patient Preference and Adherence.[193] As a novel contribution, the proposed final instrument, the LMQ-3, encompasses more diverse and relevant patient-generated domains presented in the form of 41 comprehensible and psychometrically sound statements/items.

The proposed tool (LMQ-3), unlike most instruments encountered in the literature, is patient-focused both in content and intended purpose. The LMQ-3 is grounded in patients' lived experiences of medicines use, with significant patient involvement in

item generation, modification, and testing. It also includes a free-text response box to enable clarifications of challenging experiences.

The burden of medicines on individual patients and at population level has not been previously quantified, and this thesis presents an initial attempt to do so. Earlier discussions of key findings (see section 10.2) revealed that about 10% of adults using long-term prescription medicines in England are prone to high-level medicine burden. This preliminary estimate of the prevalence of medicine burden, though it demands further cross-validation studies, provides new evidence that may inform planning and designing of national-level, targeted, interventions to identify and support those most affected.

The next sections discuss potential implications for future research, clinical practice, and policy before acknowledging potential strengths and limitations of the present thesis.

10.4 Implications for research

As a generic tool, the LMQ-3 was designed to evaluate user experiences for different medicine classes used in variable chronic conditions. Further comparative research may test suitability of the tool in assessing treatment-specific experiences in particular patient cohorts (e.g. those with diabetes, asthma, epilepsy). For researchers wishing to develop a disease-specific version of the LMQ-3, it would enable further understanding of unique medicine-related challenges faced by patients with similar long-term conditions. Such studies would enable an understanding of the contextual relevance and sensitivity of the LMQ-3 in assessing issues specific to certain patient groups and determine if some of the items (questions) are more relevant (or not) to those using certain classes of medicines.

The LMQ-3 was designed as a self-reported tool for completion by patients. Collecting patient-reported data from all patients may not always be feasible, as some conditions (e.g. cognitive difficulties like in Alzheimer's disease, dexterity problems in Parkinson's disease) may affect reliability and accuracy of self-reports.[275,276] Data collection by proxy (on the patient's behalf) may enhance wider application of the LMQ-3, and support evaluation of challenging medicine-related experiences of those unable to self-report. A new research area would involve testing usability of the LMQ-3 by carers

of patients who do not manage their own medicines. As healthcare proxies,[276] carers would enable identification of unique issues and patients' difficulties among, for instance the disabled or housebound, and allow them to identify areas of support. Nonetheless, the use of proxy measures may under or overestimate the experienced burden, as only the patient knows how he or she actually feels;[276,277] assistance in completion of the questionnaire could offer an alternative means to proxy administration.[277]

The LMQ-3 could be tested for completion via different modes (e.g. telephone) beyond the existing written (text) format. Such an application would support capturing of medicine use experiences for people with reading/writing difficulties.

Increasingly, more people have access to the Internet and portable devices (e.g. tablets, iPads, and smart phones). Technological adaptations of the LMQ-3, for instance through user-friendly 'apps' to house and access the tool may offer an additional means of reporting to those who prefer electronic/digital media over paper-based administration. Such electronic data may not only enhance self-monitoring of challenging experiences in everyday settings but could also be easily shared with authorised health professionals to offer targeted support.

The predominant cross-sectional study designs (surveys) may not have allowed for accurate modelling of causative relationships among concepts of medicine burden explored in this thesis. Future research may investigate longitudinal validity of the LMQ-3 to confirm sensitivity to change and/or responsiveness (i.e. ability to detect any amount of change after an intervention[118]), as a relevant measurement property. A recent systematic review and meta-analysis established that 'existing measures [of health-related quality of life] may have minimal to moderate sensitivity to pharmaceutical care interventions', and 'may not be sensitive enough to evaluate the burden of medicines'.[241] Ascertaining sensitivity properties of the LMQ-3 would enable assessments of reductions (or increments) in medicine burden following targeted pharmaceutical care interventions. With such data, the LMQ-3 may be used in monitoring patients affected by high medicine burden over time or support its use as an outcome measure in clinical trials evaluating the impacts of new medicines or formulations. The LMQ-3 could also be trialled to assess the effects of medicine burden on different clinical outcomes and adherence.

Cross-cultural adaptations of the LMQ-3, for instance the recent translation for Arabic-speaking countries,[278] may support the tool's usability in different research or clinical practice settings. At the time of writing this thesis, the LMQ-3 was being used in different medicine-related interventions internationally (in Belgium, Slovenia and Qatar) and such data may aid further improvements in the tool. Further validation work on the LMQ-3 may also obtain views, particularly from healthcare professionals, on how best to use it in practice.

As a relatively comprehensive tool encompassing a wide-range of relevant issues, shortening the LMQ-3 instrument, without greatly losing its content, presents another challenge. Classical test theory (CTT) was adopted in this research programme as a predominant measurement framework recommended in health services research,[179] and alternative analytical frameworks, particularly item response theory or

Rasch analysis could be employed in future studies to formulate a shorter, more precise instrument. This analytical approach alongside new qualitative data from different users of long-term medicines may help in selecting the 'best' and 'most relevant' items. However, future item-reduction may attempt to balance adequate content coverage with practical usability/feasibility in clinical practice, while minimising respondent burden.

10.5 Implications for clinical practice

Evaluation of patients' experiences of care is increasingly promoted within the NHS in England,[234,275] and suitable tools are desirable. With an estimated 10% prevalence pf high-level medicine burden in the English population, and more people likely to be at risk owing to a growing population, health systems need to be aware that medicine use can present challenging experiences for many individuals. As already reported, insufficient up-to-date data on actual medicine usage in England may not allow accurate projections of the magnitude of the burden problem. However, it is clear that a substantial proportion of patients have real, day-to-day, medicine-related challenges.

With demographic variations in patient reporting (e.g. with age), and likely fears of reporting negative experiences to prevent any consequences (such as changes to medications, including cessation), health professionals need to take a proactive approach in identifying those at risk of high-level, intolerable, burden. Patients may

need to be encouraged to share their day-to-day experiences of medicine-use during consultations with health professionals, but this may be constrained in busy practice settings. This will be discussed further in Section 10.6 under policy implications.

A key implication for clinical practice relates to health professional awareness of the challenges of long-term prescription medicine use for individuals beyond side effects and efficacy-related problems. Not all health professionals may appreciate that prescription medicines use can be burdensome to some individuals with long-term conditions. It is well-known that patients' evaluations of prescription medicines use experiences differ from those of health professionals.[17,18] Several studies show that patients are more concerned about their experiences of medicines, long-term impact, and juggling medicine use with day-to-day life than health professionals.[18,23,81]

The latter are reported as more concerned about 'prescribing problems, evidence-based guidelines, and …challenge[s] of complex decision-making', including deprescribing.[18,279] Moreover the literature shows that health professionals tend to focus on biomedical problems and strict adherence to therapies, while giving less consideration to psychosocial and everyday issues that may affect patients.[37,78,101] This implies that evaluations of patients' experiences (and medicine burden) in clinical practice presents a new challenge; what may be viewed as a problem for the patient may not be perceived as a problem to the health professional. Subsequently, it is extremely important that health professionals are made aware of the potential burden of long-term medicines on patients' lives beyond what they hear in brief patient-consultations. Increased awareness may be an initial step to having meaningful discussions with affected patients or those at risk of high medicine burden.

For prescribers and/or pharmacists, knowledge of correlates and consequences of medicine burden may also enable selection of medicine regimes (and convenient formulations) that are least burdensome to patients, for instance by prescribing regimes with manageable dosing frequencies and dosage units per day. Such changes in prescribing patterns may not only minimise patient workload of using complex medicine regimes, but may also, in the long-term, trigger pharmaceutical companies to test and formulate products that impose minimal medicine burden.

Where changes in formulations are not possible, providing information (and reassurance) about how patients can adapt medicine regimes to their day-to-day schedules could empower them to cope with potential disruptions associated with regular medicine use, for instance by building confidence, resilience, and/or acquiring practical skills and resources to minimise medicine-related challenges.

The LMQ-3 could be adapted for use before or during medicine use reviews in community pharmacies in England or other medicine-related support services. Patients could, for instance, complete the questionnaire prior to appointments for reviews with pharmacists, and self-reports used to kick-start conversations and/or aid in-depth discussions about different challenges with medicine use and means to alleviate these. Pharmacists could keep track of burden levels reported by individuals, and monitor any fluctuations as a result of changes to prescriptions or to individual circumstances including physical/mental health, social/family life and social economic status. Such data may not only support person-centred pharmacy practice, but also could help in the development of health interventions to support long-term medicine use. A shorter form of the LMQ-3 may support such evaluations of the medicine use experiences in busy pharmacy settings. Further work involving pharmacists may be required to inform/support the uptake of the LMQ-3 in community pharmacy practice.

For patients, most importantly, the LMQ-3 tool could help them in pinpointing potentially problematic areas, and in seeking individualised support to address specific medicine-related challenges. For instance, those experiencing problems with access to prescriptions or medicines could ask for repeat dispensing via electronic prescriptions sent directly to community pharmacies and/or home delivery of their medicines. Patients with practical difficulties could ask for pre-packaged pill organisers, and those with psychosocial concerns may seek reassurance from skilled health providers or other social support (from family, friends, or peer support groups).

The LMQ-3 could be used, in practice, to keep track of individuals' accounts of medicine burden as this may help inform future targeted interventions. Follow-up of patients at risk or those experiencing high medicine burden could be done at appropriate time points (e.g. quarterly, bi-annually, or annually), according to patient's preferences and needs to plan suitable interventions. Individuals identified as 'high

burden' could be targeted for additional medicine-related support in suitable interventions/services designed to reduce medication burden.

10.6 Implications for policy

Although health policies and NHS England are increasingly emphasising patient-centred care and improving outcomes and quality of life for people with long-term conditions,[57,74,75,79] they offer limited guidance on appropriate tools to evaluate service user experiences of healthcare interventions. The routine use of patient-reported measures has been recommended since 2009, but only to assess outcomes of elective surgical procedures.[234] Recent evidence suggests challenges of using PROMS to monitor outcomes of managing long-term conditions in primary care practices in England, owing to complexity and diversity of interventions, and limited patient engagement manifesting in low response rates.[275]

The medicines optimisation agenda in England, which is also supported by NHS England, emphasises an understanding of the patient's experiences, as the primary tenet, but does not clarify how to measure or monitor these in practice. NICE policy guidelines, on the other hand, encourage discussions with patients and consideration of their values and preferences in health professional decision-making, but a biomedical evidence-based approach to prescribing is still dominant in practice with little or no consideration of psychosocial or day-to-day aspects of medicine use in prescribing decisions.

National inclusion criteria for patients targeted for medicine use reviews and support are mostly disease-oriented, for instance cover respiratory conditions and patients with or at risk of cardiovascular disease.[280] Other criteria consider quantitative cut-offs (e.g. prescription of at least four medicines),[280] and yet acknowledging that '..the number of medicines…may not be the only factor to consider when reviewing [the impact of] polypharmacy'.[57] The latter is emphasised and supported by the findings of this thesis, and points to the need for a holistic approach in evaluating and monitoring patients' experiences of medicine therapies. Nonetheless, the lack of suitable patient-centred tools to support these evaluations is also a challenge. Again, the NICE guidelines[57] recommend tools such as the START/ STOPP, but these are mostly prescriber-led and serve as screening tools for drug-related problems (e.g. potentially

inappropriate medicines, drug interactions, ADRs) and offer guidance on deprescribing. There is a need to consider patients' subjective experiences in screening algorithms for medicine-related support services (such as the targeted MURs), and to trial patient-reported tools (such as the LMQ-3) in this process. This may support the person-centred agendas set out in the aforementioned policy documents, and contribute to improvements in patients' overall experiences of care.

Patient-provider communication about medicines emerged as a significant factor associated with medicine burden. With an increasing drive to provide more self-management services (e.g. smoking cessation, diet and exercise) to a growing population, time constraints, more so to discuss medicine-only issues, are a real challenge in today's clinical settings. Policy makers and/or practice managers may review consultation times and allocate resources to enable in-depth patient-provider discussions of medicine use experiences to minimise medicine burden. There is some evidence that lengthening patient consultation time may indirectly contribute to better clinical outcomes and cost-savings for the health system.[281,282] Potential long-term benefits of curbing medicine burden (e.g. better adherence, fewer drug-related problems and hospitalisation) could counteract the costs associated with longer consultations; further empirical work, however, needs to confirm these potential benefits.

The burden associated with accessing regular prescriptions from the doctor, organising refills from community pharmacies, amidst usual day-to-day responsibilities (such as work, school), usually every 28 days, can affect some individuals. For patients on stable, life-time, medicines, this burden may be lessened through longer prescribing intervals and repeat dispensing in community pharmacies, which allows patients to obtain regular prescription medicines 'without a face-to-face consultation with the prescriber at each issue'.[283] Although this may be convenient, minimising time and travel demands and financial burden for patients who pay for their prescriptions, repeat dispensing could lead to '.. a missed opportunity for identifying medicines-related issues before they become problems.'[283] Regular medicine reviews or communication may help to follow up patients with repeat prescriptions, particularly those with longer intervals, to explore potential challenges.

Reviewing of policies for prescription charges in England, for instance to include exemptions for people with all life-threatening, long-term, conditions (such as asthma) and those living in areas with high deprivation levels, may enhance access to medicines and prevent cost-related burden on individual patients.

10.7 Overall strengths and limitations

The standard methodological approach used in this complex, iterative, multi-phase research programme of instrument development and validation, discussed in-depth in Chapter 3, is a key strength. The literature review (in Chapter 2) highlighted inconsistencies in methods of development (and minimal or no patient involvement) among some tools purporting to measure medicine-related experiences of patients.

This thesis adhered to standard guidance on the development of patient-reported outcome measures[122,124,154] It achieved this, firstly, by involving the target population using long-term prescription medicines (for any disease/condition) at all stages of instrument development and validation of the LMQ-3. The concepts underlying medicine burden were generated and tested by patients, thus supporting the LMQ-3 as a patient-centred tool.

Secondly, the LMQ-3 underwent rigorous validation processes using a mixture of qualitative and quantitative methodology. Different recruitment techniques (face-to-face and on-line) were used to reach out to varying cohorts of patients in different settings and the general public in England, generating adequate responses to investigate psychometric properties of the LMQ-3 (i.e. face/content validity, construct validity, criterion-related validity, and reliability). The use of multiple data collection methods was underpinned by the pragmatic mixed-methodological approach chosen for this research programme. By triangulating multiple research techniques (including a systematic review, cross-sectional surveys, and qualitative interviews), the resulting data enabled comprehensive revisions, validation and interpretation of the LMQ measure and its underlying concepts. Nonetheless, multiple statistical testing employed in the various studies has its limitations - it is possible that some of the results reported as statistically significant occurred by chance (giving a false positive), particularly the simple linear regression results reported in Chapter 9. A combined analysis of predictors of medicine burden, through multiple regression, was used to

overcome this possible effect. Future work may address challenges of multiple statistical testing a priori, for instance by setting more stringent probability values (e.g. using Bonferroni correction).

Nevertheless, the sample populations enrolled in this research programme may not be representative of the entire English population using long-term medicines, and further studies are necessary to cross-validate the reported findings. The questionnaire distribution methods used may not have adequately captured experiences of housebound patients, especially those with no internet access. Regardless, nearly half of all qualitative cognitive interviews, though primarily aimed to evaluate the LMQ, were conducted in participants' homes.

Across most studies reported in this thesis, participants had relatively higher education levels, with up to 48% and 57% reporting University-level education among participants in the construct validation (chapter 6) and test-retest (chapter 8) samples respectively. However, 23% of the criterion-validation sample (Chapter 7) reported the same level of education. This may reflect the methods used for participant recruitment in the respective studies; on-line recruitment, used in Chapter 6 and 8 tends to include those with higher level of education compared to face-to-face distribution that was used in the study reported in Chapter 7. Chapter 9, however, established no significant association between education status and medicine burden.

As a self-completed questionnaire, which allows direct assessment of individual experiences, the LMQ-3 is, also, prone to different forms of response bias. The mixture of positively- and negatively-phrased items in the LMQ-3 and the intermixed order of items across different content domains in the questionnaire, may have minimised 'automatic responses' and increased the reliability of the tool in supporting subjective patient evaluations of medicine use experiences.

Across all studies, survey response rates were reasonable (32% to 60%). Caution needs to be exercised when comparing these response rates with those reported in other studies, due to different study conditions (e.g. varying patient populations, settings, study duration, or instruments used and their mode of distribution). However, the response rates obtained across this research programme were slightly higher than those reported during the validation of a generic measure of treatment burden (TBQ)

in an English-speaking sample.[232] In a multinational study, including the UK, 20% of all patients invited to complete the TBQ measure on-line, via a patient website, responded over a 2-month period, 9% of whom were from the UK.[232] As discussed in Chapter 3, questionnaire response rates are affected by multiple factors including the modes of questionnaire distribution. Electronic formatting of on-line surveys, although minimising missing data at item-level, means that overall response rates are hard to compute.[118] On-line surveys, which attracted a higher number of responses in this research programme, tend to reach out to a geographically wider sample and are less laborious or time demanding to distribute or promote. Self-completed paper surveys achieved the lowest response rates possibly due to issues such as willingness to complete and return questionnaires (by post or by hand).[161] Across all studies, it was difficult to interview non-respondents and reasons for non-completion may not be fully understood, but lack of time or interest in the study was observed in some potential participants during paper distribution.

As already noted, the length of the LMQ-3 is a potential limitation that may have affected response rates. CTT methodology, as a more liberal approach[118] to item reduction, may have led to retention of more items (n=41) and domains (n=8) in the final tool presented, thus leading to a relatively lengthy questionnaire. Nevertheless, the number of items in the LMQ-3 is comparable to other broad measures of medicine-related experiences, particularly the PROMPT-QoL that has 43 items in ten domains.[134] As already proposed, further item reduction may facilitate uptake of the LMQ-3 in practice settings.

The scoring system and levels/cut-off scores for overall medicine burden (e.g. none, minimal, moderate, high) were based on grouping composite scores. Although it is common practice to stratify patients' scores into distinct groups to aid clinical decision making (for example, in determining eligibility for interventions and/or treatment allocation),[255,284] LMQ-3 cut-off values and burden categories, obtained by inspecting the distribution of scores for one sample population, require further investigation. Assumptions of linearity of the 5-point Likert-type scale used for LMQ-3 items, similar to most CTT-derived measures, may have underestimated measurement error[118] and potentially affected the precision of medicine-burden levels, at least in statistical

sense. Nevertheless, professional judgement of the researcher and supervision team were used to double-check data used to defined levels of burden.

The language used in describing the hypothesised concepts underlying the LMQ-3 (i.e. medicine burden) is a particular challenge and potential limitation to the findings reported here-in. Although empirical qualitative work, described in Chapter 5, revealed minimal language problems, as most patients understood the meanings of different items in the LMQ-3 instrument, a few indicated potential problems with the word 'burden'. The word was used in the global item, '*overall, how much of a burden do you feel your medicines are to you?*' The findings and literature show that medicines use may not be perceived as a 'burden' among some patients using long-term medicines, but rather as a 'necessity'; different interpretations of 'burden' are likely to affect accurate assessments based on this item. Additional qualitative research may be needed to explore, in-depth, the connotations of 'burden' in terms of prescription medicine use.

10.8 Thesis summary

Long-term use of prescription medicines (and polypharmacy) can be a double-edged sword; with clinical benefits (such as prevention of disease and/or mortality) in contexts of chronic illness and multimorbidity, but also wide-ranging challenges for individuals who have to cope with different practical, psychosocial and sometimes financial issues surrounding the use of medicines. The findings presented in this thesis indicate that although most people using prescription medicines report positive experiences (low medicine burden), a significant proportion report problems and negative impacts and thus may need more support.

Prescription medicine burden is a relatively new concept, but increasingly recognised as a challenging and multifactorial problem. Nevertheless, there is no clear evidence on the most appropriate way to address or evaluate medicine burden and its impact on individuals. A systematic review of measures of medicine-related experiences identified a potential measure of burden (the 60-item LMQ-1), but which required extensive development and validation. This research programme further developed and validated the Living with Medicines Questionnaire, and a final version (the LMQ-3) was derived as a multi-dimensional, generic, patient-generated, measure of medicine

burden, applicable to any long-term condition (or disease), suitable for use in the adult English population.

The tool was founded on patients' experiences of medicine use for any long-term condition. Questionnaire content and measurement properties were tested iteratively through a series of qualitative and quantitative studies involving users of long-term prescription medicines in England. A wide range of domains are covered in the LMQ-3: interferences with day-to-day life, patient-provider relationships and communication about medicines, practical difficulties, lack of effectiveness, side effects, general concerns, cost-related burden, and lack of autonomy/control over medicines.

The LMQ-3 is a 41-item novel measure of medicine-related burden with adequate construct validity and reliability. The LMQ-3 is recommended for use in future research studies and/or clinical settings to not only quantify medicine burden but also as an outcome measure in pharmaceutical or clinical interventions that attempt to alleviate burden. Ultimately, the identification, prevention, and/or reduction of medicine burden, through patient-led interventions may improve patient outcomes, particularly health-related quality of life, and overall experiences of care.

References

1. Royal Pharmaceutical Society. Medicines optimisation: Helping patients to make the most of medicines. Good practice guidance for healthcare professionals in England [Internet]. 2013. Available from: http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf [Accessed 06/05/2016].

2. Qato D., G.C. Alexander, R.M. Conti, M. Johnson, P. Schumm, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. Journal of the American Medical Association. 2008;300(24):2867–78.

3. World Health Organization. Adherence to long-term therapies: evidence for action. [Internet]. 2003 p. 1–211. Available from: http://apps.who.int/medicinedocs/en/d/Js4883e/ [Accessed 04/01/2014].

4. Duerden M, Avery T, Payne R. Polypharmacy and medicines optimisation-Making it safe and sound. London: The King's Fund; 2013.

5. The Pharmaceutical Society of Northern Ireland. Medicines for human use: POM, P, GSL & General pharmacy regulations. General legal requirements. A guide for pharmacists in Northern Ireland [Internet]. 2010. Available from: http://www.psni.org.uk/documents/599/GuideLegalRequirements+MedsHumanUsePPOMGSL.pdf [Accessed 09/02/2017].

6. World Health Organization. A glossary of terms for community health care and services for older persons [Internet]. 2004. Available from: http://www.who.int/kobe_centre/ageing/ahp_vol5_glossary.pdf?ua=1 [Accessed 10/02/2017].

7. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. Journal of Clinical Epidemiology. 2012;65(9):989–95.

8. Zarowitz BJ. Polypharmacy: When Is Enough, Enough? Geriatr Nurs. 2011;32(6):447–9.

9. Best O, Gnjidic D, Hilmer SN, Naganathan V, McLachlan AJ. Investigating polypharmacy and drug burden index in hospitalised older people. Internal Medicine Journal. 2013;43(8):912–8.

10. Bjerrum L, Rosholm J, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. European Journal of Clinical Pharmacology. 1997;53(1):7–11.

11. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open. 2015;5(12):e009235.

12. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: Misleading, but manageable. Clinical Interventions in Aging. 2008;3(2):383–9.

13. Steinman M, SethLandefeld C, Rosenthal G, Berthenthal D, Sen S, Kaboli P. Polypharmacy and prescribing quality in older people. Journal of the American Geriatrics Society. 2006;54(10):1516–23.

14. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Medicine. 2015;13(1):1–10.

15. Gnjidic D, Le Couteur DG, Pearson S-A, McLachlan AJ, Viney R, Hilmer SN, et al. High risk prescribing in older adults: prevalence, clinical and economic implications and potential for intervention at the population level. BMC Public Health. 2013;13(1):115.

16. Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: When many is not too many. Drug Safety. 2016;39(2):109–16.

17. Morecroft C, Cantrill J, Tully MP. Patients' evaluation of the appropriateness of their hypertension management—A qualitative study. Research in Social and Administrative Pharmacy. 2006;2(2):186–211.

18. Bokhof B, Junius-Walker U. Reducing polypharmacy from the perspectives of general practitioners and older patients: A synthesis of qualitative Studies. Drugs Aging. 2016;33(4):249–66.

19. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. European Journal of Clinical Pharmacology. 2013;70(1):1–11.

20. Britten N. Patients' ideas about medicines: a qualitative study in a general practice population. Br J Gen Pract. 1994;44(387):465–8.

21. Pound P, Britten N, Morgan M, Yardley L, Pope C, Daker-White G, et al. Resisting medicines: a synthesis of qualitative studies of medicine taking. Social Science & Medicine. 2005;61(1):133–55.

22. Carter SR, Moles R, White L, Chen TF. Medication information seeking behavior of patients who use multiple medicines: how does it affect adherence? Patient Education and Counseling. 2013;92(1):74–80.

23. Krska J, Morecroft CW, Poole H, Rowe PH. Issues potentially affecting quality of life arising from long-term medicines use: a qualitative study. Int J Clin Pharm. 2013;35(6):1161–9.

24. Heaton J, Brittena N, Krska J, Reeve J. Person-centred medicines optimisation policy in England: an agenda for research on polypharmacy. Primary Health Care Research and Development. 2016;1–11.

25. Haider SI, Johnell K, Thorslund M, Fastbom J. Analysis of the association between polypharmacy and socioeconomic position among elderly aged > or =77 years in Sweden. Clinical Therapeutics. 2008;30(2):419–27.

26. Hajjar ER, Hanlon JT, Sloane RJ, Lindblad CI, Pieper CF, Ruby CM, et al. Unnecessary drug use in frail older people at hospital discharge. Journal of the American Geriatrics Society. 2005;53(9):1518–23.

27. Barrett K, Lucas E, Alexander GC. How polypharmacy has become a medical burden worldwide. Clinical Pharmacist [Internet]. 2016 [cited 2017 Apr 8]; Available from: http://www.pharmaceutical-journal.com/opinion/insight/how-polypharmacy-has-become-a-medical-burden-worldwide/20201251.article [Acessed 08/04/2017]

28. Richards M. Extent and causes of international variations in drug usage: a report for the Secretary of State for Health. London; 2010.

29. Office of Health Economics. International comparison of medicines usage: quantitative analysis. Available from: http://www.abpi.org.uk/our-work/library/industry/documents/meds_usage.pdf [Accessed 08/04/2017].

30. The Daily Mail UK. We're a nation of pill-poppers: Prescriptions up 50% in the past decade as one billion handed out a year and experts warn of harmful side-effects. Available from: http://www.dailymail.co.uk/news/article-3152878/We-nation-pill-poppers-Prescriptions-50-past-decade-one-billion-handed-year-experts-warn-harmful-effects.html [Accessed 10/02/2017].

31. The Health and Social Care Information Centre. Use of prescribed medicines [Internet]. 2014. Available from: http://content.digital.nhs.uk/catalogue/PUB16076/HSE2013-Ch5-pres-meds.pdf [Accessed 10/02/2017]

32. Health and Social Care Information Centre. Prescriptions dispensed in the community. England 2004-14 [Internet]. 2015. Available from: http://content.digital.nhs.uk/catalogue/PUB17644/pres-disp-com-eng-2004-14-rep.pdf [Accessed 10/02/2017].

33. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records

from primary and secondary care. British Journal of Clinical Pharmacology. 2014;77(6):1073–82.

34. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. The Lancet. 2012;380(9836):37–43.

35. Guthrie B, Payne K, Alderson P, McMurdo ME, Mercer SW. Adapting clinical guidelines to take account of multimorbidity. British Medical Journal. 2012;345:e6341.

36. Hughes LD, McMurdo MET, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age and Ageing. 2012;42(1):62–9.

37. Reeve J, Bancroft R. Generalist solutions to overprescribing: a joint challenge for clinical and academic primary care. Primary Health Care Research & Development. 2014;15(01):72–9.

38. Gillam SJ, Siriwardena AN, Steel N. Pay-for-Performance in the United Kingdom: Impact of the Quality and Outcomes Framework—A Systematic Review. Annals of Family Medicine. 2012;10(5):461–8.

39. Health and Social Care Information Centre. QOF - Prescribable statins [Internet]. 2016. Available from: https://dd4c.hscic.gov.uk/dd4c/publishedmetadatas/intid/679 [Accessed 01/01/2017].

40. Petty DR, Zermansky AG, Alldred DP. The scale of repeat prescribing-time for an update. BMC Health Services Research. 2014;14(1):76.

41. Wilson PM, Kataria N, McNeilly E. Patient and carer experience of obtaining regular prescribed medication for chronic disease in the English National Health Service: a qualitative study. BMC Health Services Research. 2013;13(192):1–11.

42. Zermansky AG. Who controls repeats? British Journal of General Practice. 1996;46(412):643–7.

43. NHS Digital. Electronic Prescription Service [Internet]. 2017. Available from: https://digital.nhs.uk/Electronic-Prescription-Service [Accessed 01/03/2017].

44. Noyce PR, Huttin C, Atella V, Brenner G, Haaijer-Ruskamp FM, Hedvall M-B, et al. The cost of prescription medicines to patients. Health Policy. 2000;52(2):129–45.

45. Department of Health, The Rt Hon Alistair Burt. NHS charges from April 2016. Written statement to Parliament. [Internet]. 2016. Available from:

https://www.gov.uk/government/speeches/nhs-charges-from-april-2016 [Accessed 10/02/2017].

46. Schafheutle EI, Hassell K, Noyce PR. Access to medicines: cost as an influence on the views and behaviour of patients. Health & Social Care in the Community. 2002;10(3):187–95.

47. The Prescription Charges Coalition. Paying the Price. Prescription Charges and Employment [Internet]. 2014. Available from: http://www.prescriptionchargescoalition.org.uk/uploads/1/2/7/5/12754304/prescription_charges_and_employment_report_feb_2014.pdf [Accessed 21/09/2015].

48. Sav A, King MA, Whitty JA, Kendall E, McMillan SS, Kelly F, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. Health Expectations. 2013;1–13.

49. Sav A, Kendall E, McMillan SS, Kelly F, Whitty JA, King MA, et al. 'You say treatment, I say hard work': treatment burden among people with chronic illness and their carers in Australia. Health and Social Care in the Community. 2013;21(6):665–74.

50. Eton DT, Ramalho de Oliveira D, Egginton JS, Ridgeway JL, Odell L, May CR, et al. Building a measurement framework of burden of treatment in complex patients with chronic conditions: a qualitative study. Patient Related Outcome Measures. 2012;3:39–49.

51. Piette JD, Heisler M, Horne R, Alexander GC. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. Social Science & Medicine. 2006;62(4):846–57.

52. Burcu M, Alexander GC, Ng X, Harrington D. Construct validity and factor structure of survey-based assessment of cost-related medication burden. Medical Care. 2015;53(2):199–206.

53. Department of Health. Pharmacy in the future: implementing the NHS Plan [Internet]. 2000 p. 1–26. Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005917 [Accessed 31/08/2016].

54. The Audit Commission for Local Authorities and the National Health Service in England and Wales. A spoonful of sugar-medicines management in NHS hospitals. London; 2001.

55. All Wales Medicines Strategy Group. Polypharmacy: Guidance for prescribing [Internet]. 2014. Available from:

http://www.awmsg.org/docs/awmsg/medman/Polypharmacy%20-%20Guidance%20for%20Prescribing.pdf [Accessed 10/02/2017].

56. Scottish Government Model of Care Polypharmacy Working Group. Polypharmacy Guidance [Internet]. 2015. Available from: http://www.sign.ac.uk/pdf/polypharmacy_guidance.pdf [Accessed 28/03/2016].

57. National Institute for Health and Care Excellence. Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NG5 [Internet]. 2015. Available from: https://www.nice.org.uk/guidance/ng5 [Accessed 10/02/2017].

58. Campanelli CM. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2012;60(4):616–31.

59. Hanlon JT, Schmader KE. The Medication Appropriateness Index at 20: Where it started, where it has been and where it may be going. Drugs & Aging. 2013;30(11):doi:10.1007/s40266-013-0118-4.

60. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and Ageing. 2015;44(2):213–8.

61. Avery AJ, Rodgers S, Cantrill JA, Armstrong S, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. The Lancet. 2012;379(9823):1310–9.

62. Spencer R, Bell B, Avery AJ, Gookey G, Campbell SM. Identification of an updated set of prescribing-safety indicators for GPs. British Journal of General Practice. 2014;64(621):e181–90.

63. Oborne CA, Batty GM, Maskrey V, Swift CG, Jackson SHD. Development of prescribing indicators for elderly medical inpatients. British Journal of Clinical Pharmacology. 1997;43(1):91–7.

64. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Development and validation of the patients' attitudes towards deprescribing (PATD) questionnaire. International Journal of Clinical Pharmacy. 2013;35(1):51–6.

65. Thompson W, Farrell B. Deprescribing: what is it and what does the evidence tell us? The Canadian Journal of Hospital Pharmacy. 2013;66(3):201.

66. Hardy JE, Hilmer SN. Deprescribing in the last year of life. Journal of Pharmacy Practice and Research. 2011;41(2):146.

67. Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA. Deciding when to stop: towards evidence-based deprescribing of drugs in older populations. Evidence-based Medicine. 2013;18(4):121–4.

68. Patterson S, Hughes C, Kerse N, Cardwell C, Bradley M. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database of Systematic Reviews. 2012;(5):CD008165.

69. Health and Social Care Board. Community pharmacy medicines use review (MUR) service guidance for conducting MURs [Internet]. 2014. Available from: http://www.hscbusiness.hscni.net/pdf/Guidance_for_conducting_MURs.pdf [Accessed 08/04/2017].

70. Pharmaceutical Services Negotiating Committee. New Medicine Service (NMS) [Internet]. 2017. Available from: http://psnc.org.uk/services-commissioning/advanced-services/nms/ [Accessed 08/04/2017].

71. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. British Journal of Clinical Pharmacology. 2012;74(4):573–80.

72. Latif A, Boardman HF, Pollock K. Understanding the patient perspective of the English community pharmacy Medicines Use Review (MUR). Research in Social and Administrative Pharmacy. 2013;9(6):949–57.

73. Latif A, Pollock K, Boardman HF. The contribution of the Medicines Use Review (MUR) consultation to counseling practice in community pharmacies. Patient Education and Counseling. 2011;83(3):336–44.

74. NHS England. Everyone counts: planning for patients 2014/2015 to 2018/19 [Internet]. 2013. Available from: http://www.england.nhs.uk/wp-content/uploads/2013/12/5yr-strat-plann-guid-wa.pdf [Accessed 27/11/2014].

75. NHS England. Health and high quality care for all, now and for future generations. NHS England welcomes publishing of medicines optimisation [Internet]. 2013. Available from: http://www.england.nhs.uk/2013/05/02/med-opt/ [Accessed 27/11/2014].

76. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database of Systematic Reviews. 2016;(3):CD006560.

77. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 2014;(4):CD007768.

78. Reeve J, Dickenson M, Harris J, Ranson E, Dohnhammer U, Cooper L, et al. Solutions to problematic polypharmacy: learning from the expertise of patients. British Journal of General Practice. 2015;65(635):319–20.

79. NICE. Patient experience in adult NHS services: improving the experience of care for people using adult NHS services. Clinical guideline [CG138] [Internet]. 2012. Available from: https://www.nice.org.uk/guidance/cg138 [10/02/2017].

80. Haslbeck JW, Schaeffer D. Routines in medication management: the perspective of people with chronic conditions. Chronic Illness. 2009;5(3):184–96.

81. Britten N. Medicines and Society: Patients, Professionals and the Dominance of Pharmaceuticals. Hampshire & New York: Palgrave Macmillan; 2008. 205 p.

82. Oxford University Press. Definition of burden in English [Internet]. 2014. Available from: http://www.oxforddictionaries.com/definition/english/burden [Accessed 24/04/2014].

83. Tran V-T, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. BMC Med. 2012;10:68.

84. Shippee ND, Shah ND, May CR, Mair FS, Montori VM. Cumulative complexity: a functional, patient-centered model of patient complexity can improve research and practice. Journal of Clinical Epidemiology. 2012;65(10):1041–51.

85. Gallacher K, Morrison D, Jani B, Macdonald S, May CR, Montori VM, et al. Uncovering treatment burden as a key concept for stroke care: A systematic review of qualitative research. PLoS Medicine. 2013;10(6):e1001473.

86. Gallacher K, May CR, Montori VM, Mair FS. Understanding patients' experiences of treatment burden in chronic heart failure using Normalization Process Theory. Annals of Family Medicine. 2011;9(3):235–43.

87. Moen J, Bohm A, Tillenius T, Antonov K, Nilsson JL, Ring L. 'I don't know how many of these [medicines] are necessary..' - a focus group study among elderly users of multiple medicines. Patient Education and Counseling. 2009;74(2):135–41.

88. Mohammed MA, Moles RJ, Chen TF. Medication-related burden and patients' lived experience with medicine: a systematic review and metasynthesis of qualitative studies. BMJ Open. 2016;6(2):1–16.

89. Eton D, Ridgeway J, Egginton J, Tiedje K, Linzer M, Boehm D, et al. Finalizing a measurement framework for the burden of treatment in complex patients with chronic conditions. Patient Related Outcome Measures. 2015;6:117–26.

90. May CR, Eton DT, Boehmer K, Gallacher K, Hunt K, MacDonald S, et al. Rethinking the patient: using Burden of Treatment Theory to understand the changing dynamics of illness. BMC Health Services Research. 2014;14:281.

91. Leppin AL, Montori VM, Gionfriddo MR. Minimally Disruptive Medicine: A pragmatically comprehensive model for delivering care to patients with multiple chronic conditions. Healthcare. 2015;3:50–63.

92. Murawski MM, Bentley JP. Pharmaceutical therapy-related quality of life: conceptual development. Journal of Social and Administrative Pharmacy. 2001;18(1):2–14.

93. Renberg T. Patient perspectives on community pharmacy services [Internet]. Acta Universitatis Upsaliensis; 2009. Available from: https://www.diva-portal.org/smash/get/diva2:236069/FULLTEXT01.pdf [Accessed 21/11/2016].

94. Renberg T, Kettis Lindblad Å, Tully MP. Testing the validity of a translated pharmaceutical therapy-related quality of life instrument, using qualitative 'think aloud'methodology. Journal of Clinical Pharmacy and Therapeutics. 2008;33(3):279–87.

95. Demain S, Gonçalves A-C, Areia C, Oliveira R, Marcos AJ, Marques A, et al. Living with, managing and minimising treatment burden in long term conditions: A systematic review of qualitative research. PLoS One. 2015;10(5):e0125457.

96. Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S. People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. Journal of the American Geriatrics Society. 2013;61(9):1508–14.

97. Rofail D, Abetz L, Viala M, Gait C, Baladi J, Payne K. Satisfaction and adherence in patients with iron overload receiving iron chelation therapy as assessed by a newly developed patient instrument. Value in Health. 2009;12(1):109–17.

98. George J, Phun Y-T, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. Annals of Pharmacotherapy. 2004;38(9):1369–1376.

99. Williams B, Shaw A, Durrant R, Crinson I, Pagliari C, de Lusignan S. Patient perspectives on multiple medications versus combined pills: a qualitative study. The Quarterly Journal of Medicine. 2005;98(12):885–93.

100. Desmarais JE, Beauclair L, Margolese HC. Switching from brand-name to generic psychotropic medications: A literature review. CNS Neuroscience & Therapeutics. 2011;17(6):750–60.

101. Bohlen K, Scoville E, Shippee ND, May CR, Montori VM. Overwhelmed patients: a videographic analysis of how patients with type 2 diabetes and clinicians

articulate and address treatment burden during clinical encounters. Diabetes Care. 2012;35(1):47–9.

102. Prescription Charges Coalition. Paying the Price: Prescription charges and people with long-term conditions [Internet]. 2013. Available from: http://www.prescriptionchargescoalition.org.uk/uploads/1/2/7/5/12754304/paying_the_price_report.pdf [Accessed 02/03/2017].

103. Elliott RA, Shinogle JA, Peele P, Bhosle M, Hughes DA. Understanding medication compliance and persistence from an economics perspective. Value in Health. 2008;11(4):600–10.

104. Piette JD, Beard A, Rosland AM, McHorney CA. Beliefs that influence cost-related medication non-adherence among the 'haves' and 'have nots' with chronic diseases. Patient Preference and Adherence. 2011;5:389.

105. Aziz H, Hatah E, Makmor Bakry M, Islahudin F. How payment scheme affects patients' adherence to medications? A systematic review. Patient Preference and Adherence. 2016;10:837–50.

106. Bowling A, Rowe G, Lanmbert N, Waddington M, Mahtani K, Kenten C. The measurement of patients' expectations for health care: a review and psychometric testing of a measure of patient's expectations. Health Technology Assessment. 2012;16(30).

107. Bandura A. Self-efficacy: The exercise of control. Vol. 4th. New York: W.H Freeman and Company; 1997. 604 p.

108. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004;2:12–12.

109. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical Construct Validity of the Treatment Satisfaction Questionnaire for Medication (TSQM Version II) among Outpatient Pharmacy Consumers. Value Health. 2005;8:S9–24.

110. Horne R, Weinman J, Hankins M. The Beliefs about Medicines Questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health. 1999;14(1):1–24.

111. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Advances in Therapy. 2005;22(4):313–56.

112. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. Journal of Psychosomatic Research. 1999;47(6):555–67.

113. Gatti ME, Jacobson KL, Gazmararian JA, Schmotzer B, Kripalani S. Relationships between beliefs about medications and adherence. American Journal of Health-System Pharmacy. 2009;66(7):657–64.

114. Andersson Sundell K, Jönsson AK. Beliefs about medicines are strongly associated with medicine-use patterns among the general population. International Journal of Clinical Practice. 2016;70(3):277–85.

115. Dohnhammar U, Reeve J, Walley T. Patients' expectations of medicines--a review and qualitative synthesis. Health Expectations. 2016;19(2):179–93.

116. Lefcourt HM. Locus of control. 1991; Available from: http://psycnet.apa.org/psycinfo/1991-97206-008 [Accessed 02/11/2017].

117. Williams A, Manias E. Exploring motivation and confidence in taking prescribed medicines in coexisting diseases: a qualitative study. Journal of Clinical Nursing. 2013;23(3–4):471–81.

118. Streiner DL, Norman GR, Cairney J. Health Measurement Scales: A practical guide to their development and use. 5th ed. New York: Oxford University Press; 2015. 432 p.

119. Krska J, Morecroft C, Rowe P, Poole H. Measuring the impact of long-term medicines use from the patient perspective. International Journal of Clinical Pharmacy. 2014;36(4):675–8.

120. Eton DT, Elraiyah TA, Yost KJ, Ridgeway JL, Johnson A, Egginton JS, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. Patient Relat Outcome Meas. 2013;4:7–20.

121. Worth A, Hammersley V, Knibb R, Flokstra-de-Blok B, DunnGalvin A, Walker S, et al. Patient-reported outcome measures for asthma: a systematic review. NPJ Primary Care Respiratory Medicine. 2014;24.

122. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34–42.

123. Speight J, Barendse SM. FDA guidance on patient reported outcomes. British Medical Journal. 2010;340.

124. US Department of Health and Human Services Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims [Internet]. 2009. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf [Accessed 30/10/2015].

125. Trujols J, Portella MJ. Not all PROMs reflect patients' perspectives. British Medical Journal. 2013;346.

126. Trujols J, Portella MJ, Iraurgi I, Campins MJ, Siñol N, Cobos JP de L. Patient-reported outcome measures: Are they patient-generated, patient-centred or patient-valued? Journal of Mental Health. 2013;22(6):555–62.

127. Streiner DL, Norman GR. Health Measurement Scales: A practical guide to their devlopment and use. 4th ed. New York: Oxford University Press; 2008. 428 p.

128. Bowling A. Measuring health: A review of quality of life measurement scales. 3rd ed. Maidenhead: Open University Press; 2005. 211 p.

129. Bharmal M, Payne K, Atkinson M, Desrosiers M, Morisky D, E. G. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health and Quality of Life Outcomes. 2009;7(36).

130. Ruiz MA, Antonio P, Javier R, Javier S, Fernando V, José LA. Development and validation of the 'Treatment Satisfaction with Medicines Questionnaire' (SATMED-Q)©. Value in Health. 2008;11(5):913–26.

131. Quinlan P, Magid SK, O'Flaherty D, Peirce A, Stone PW. Patient satisfaction with medication management. Journal of Nursing Care Quality. 2007;22(1):34–9.

132. Blalock SJ, Patel RA. Drug therapy concerns questionnaire: initial development and refinement. Journal of the American Pharmacists Association. 2004;45(2):160–9.

133. Okere AN, Renier CM, Morse J. Development and validation of a survey to assess patient-perceived medication knowledge and confidence in medication use. Journal of Nursing Measurement. 2014;22(1):120–34.

134. Sakthong P, Suksanga P, Sakulbumrungsil R, Winit-Watjana W. Development of Patient-reported Outcomes Measure of Pharmaceutical Therapy for Quality of Life (PROMPT-QoL): A novel instrument for medication management. Research in Social and Administrative Pharmacy. 2015;11(3):315–38.

135. Horne R, Faasse K, Cooper V, Diefenbach MA, Leventhal H, Leventhal E, et al. The Perceived Sensitivity to Medicines (PSM) scale: an evaluation of validity and reliability. British Journal of Health Psychology. 2013;18(1):18–30.

136. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Quality in Health Care. 2001;10(3):135–40.

137. Jenkins L, Britten N, Stevenson F, Barber N, Bradley C. Developing and using quantitative instruments for measuring doctor-patient communication about drugs. Patient Education and Counseling. 2003;50(3):273–8.

138. Linacre, JM. Reliability and separation of measures [Internet]. Available from: http://www.winsteps.com/winman/reliability.htm [Accessed 25/10/2015].

139. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. Journal of Clinical Hypertension. 2008;10(5):348–54.

140. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical Care. 1986;24(1):67–74.

141. Carter SR, Bulanadi MG, Katusiime B, Chen TF, Corlett S, Krska J. Comprehensibly measuring patients' subjective thoughts, feelings and experiences of living with medicines – the Living with Medicines Questionnaire (LMQ). International Journal of Clinical Pharmacy. 2015;37:424–5.

142. Horne R, Chapman SCE, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: A meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12):e80633.

143. Dias-Barbosa C, Balp, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. Patient Preference and Adherence. 2012;39.

144. May C, Montori VM, Mair FS. We need minimally disruptive medicine. British Medical Journal. 2009;339:b2803.

145. Baker R. Development of a questionnaire to assess patients' satisfaction with consultations in general practice. British Journal of General Practice. 1990;40(341):487–90.

146. Kinnersley P, Stott N, Peters T, Harvey I, Hackett P. A comparison of methods for measuring patient satisfaction with consultations in primary care. Family Practice. 1996;13(1):41–51.

147. Ridd MJ, Lewis G, Peters TJ, Salisbury C. Patient-Doctor Depth-of-Relationship Scale: Development and Validation. Annals of Family Medicine. 2011;9(6):538–45.

148. Byer B, Myers L. Psychological correlates of adherence to medication in asthma. Psychology, Health & Medicine. 2000;5(4):389–93.

149. Tseng HM, Lee CH, Chen YJ, Hsu HH, Huang LY, Huang JL. Developing a measure of medication-related quality of life for people with polypharmacy. Quality of Life Research. 2015;

150. Krska J, Morecroft C, Poole H, Rowe P. A novel instrument to measure medicines-related quality of life. International Journal of Clinical Pharmacy. 2013;35:488.

151. Mokkink LB, Terwee CB, Knol DL, Stratford PW, Alonso J, Patrick DL, et al. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: a clarification of its content. BMC medical research methodology. 2010;10(1):22.

152. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of Life Research. 2010;19(4):539–49.

153. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. Quality of Life Research. 2012;21(4):651–7.

154. European Medicines Agency. Reflection paper on the regulatory guidance for the use of health-related quality of life(HRQL)measures in the evaluation of medicinal products [Internet]. 2005. Available from: https://www.ispor.org/workpaper/emea-hrql-guidance.pdf [Accessed 12/02/2017].

155. Smith F. Conducting your pharmacy practice research project. 2nd ed. London: Pharmaceutical Press; 2010. 227 p.

156. Donyai P. Research methodologies related to pharmacy practice: An Overview. In: Babar Z-U-D, editor. Pharmacy practice research methods. Springer International Publishing; 2015. p. 25–30.

157. Babar Z-U-D. Pharmacy practice research methods. Springer; 2015. 251 p.

158. Winit-Watjana W. Research philosophy in pharmacy practice: necessity and relevance. Internaional Journal of Pharmacy Practice. 2016;

159. Cohen L, Manion L, Morrison K. Research methods in education. 7th ed. New York: Routledge; 2011. 784 p.

160. International Conference on Harmonisation Working Group. ICH harmonised tripartite guideline: guideline for good clinical practice E6(R1). International

Conference on Harmaonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Current Step 4 version. Washington DC; 1996.

161. Bowling A. Mode of questionnaire administration can have serious effects on data quality. Journal of Public Health. 2005;27(3):281–91.

162. Saramunee K, Mackridge A, Phillips-Howard P, Richards J, Suttajit S, Krska J. Methodological and economic evaluations of seven survey modes applied to health service research. Journal of Pharmaceutical Health Services Research. 2015;7:43–52.

163. Tourangeau R, Rips LJ, Rasinski K. The psychology of survey response. 1st ed. Cambridge: Cambridge University Press; 2000. 401 p.

164. Sudman S, Bradburn NM, Schwarz N. Thinking about answers: The application of cognitive processes to survey methodology. San Francisco: Wiley; 2010. 304 p.

165. Beatty PC, Willis GB. Research synthesis: The practice of cognitive interviewing. Public Opinion Quarterly. 2007;71(2):287–311.

166. Buers C, Triemstra M, Bloemendal E, Zwijnenberg NC, Hendriks M, Delnoij DM. The value of cognitive interviewing for optimizing a patient experience survey. International Journal of Social Research Methodology. 2014;17(4):325–340.

167. Willis GB. Cognitive interviewing: A tool for improving questionnaire design. 1st ed. Thousand Oaks, London & New Delhi: Sage Publications; 2005. 348 p.

168. Willis GB. Reducing survey error through research on the cognitive and decision processes in surveys. In: Meeting of the American Statistical Association Raleigh-Durham, North Carolina. 1999.

169. Tierney E, McEvoy R, O'Reilly-de Brún M, de Brún T, Okonkwo E, Rooney M, et al. A critical analysis of the implementation of service user involvement in primary care research and health service development using Normalization Process Theory. Health Expectations. 2016;19(3):501–15.

170. Medway NHS Foundation Trust. Annual Report and Accounts 2012-13 [Internet]. 2013. Available from: file:///C:/Users/User/Downloads/Annual%20Report%20and%20Accounts%20FINAL%20PRINT%20VERSION%20(1).pdf [Accessed 13/02/2017].

171. Watkins MW. Monte Carlo PCA for parallel analysis. A standalone Windows program that computes Parallel Analysis criteria (eigenvalues) by performing a Monte Carlo simulation. [Internet]. State College, PA: Ed & Psych Associates. 2000. Available from: http://edpsychassociates.com/Watkins3.html [Accessed 01/06/2014].

172. Byrne BM. Structural equation modeling with AMOS. Basic concepts, applications, and programming. 2nd ed. New York: Taylor and Francis Group LLC; 2010. 385 p.

173. Blunch NJ. Introduction to structural equation modeling using IBM SPSS statistics and AMOS. 2nd ed. London: Sage Publications; 2013. 312 p.

174. Field A. Discovering statistics using IBM SPSS statistics. and sex abd drugs and rock 'n' roll. 4th ed. London: Sage; 2013. 915 p.

175. Pallant J. SPSS survival manual: a step by step guide to data analysis using IBM SPSS (5. uppl.). 4th ed. Crows Nest, NSW: Allen & Unwin; 2013. 368 p.

176. Jackson DL, Gillaspy Jr JA, Purc-Stephenson R. Reporting practices in confirmatory factor analysis: an overview and some recommendations. Psychological Methods. 2009;14(1):6.

177. Kim H-Y. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. Restorative Dentistry & Endodontics. 2013;38(1):52–4.

178. Ridolfo H, Schoua-Glusberg A, Willis GB, Miller K. Analyzing cognitive interview data using the constant comparative method of analysis to understand cross-cultural patterns in survey data. Field Methods. 2011;23(4):420–38.

179. Hankins M. The application of Classical Test Theory (CTT) to the development of Patient-Reported Outcome Measures (PROMs) in health services research. [Internet] [doctoral]. University of Brighton; 2009. Available from: http://eprints.brighton.ac.uk/12293/ [Accessed 13/02/2017].

180. Byrne BM. Structural equation modeling with Mplus: Basic concepts, Applications, and Programming. 2nd ed. New York & London: Routledge; 2013. 432 p.

181. Rasch G. Rasch measurement: Research papers, explorations and explanations [Internet]. 1960. Available from: www.rasch.org/rasch.htm [Accessed 13/02/2017].

182. Tabachnick BG, Fidell LS. Using multivariate statistics. 6th ed. Boston: Pearson Education; 2013. 983 p.

183. Kline RB. Principles and Practice of Structural Equation Modeling. 3rd ed. New York: The Guilford Press; 2011. 427 p.

184. Dziuban CD, Shirkey EC. When is a correlation matrix appropriate for factor analysis? Some decision rules. Psychological Bulletin. 1974;81(6):358.

185. Winter JCF de, Dodou D. Common factor analysis versus principal component analysis: a comparison of loadings by means of simulations. Communications in Statistics - Simulation and Computation. 2016;45(1):299–321.

186. O'connor BP. SPSS and SAS programs for determining the number of components using parallel analysis and Velicer's MAP test. Behavior Research Methods, Instruments, & Computers. 2000;32(3):396–402.

187. Costello A, Osborne J. Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. Practical Assessment Research & Evaluation. 2005;10(7).

188. Kahn JH. Factor analysis in counseling psychology research, training, and practice principles, advances, and applications. Couns Psychol. 2006;34(5):684–718.

189. Sijtsma K. On the use, the misuse, and the very limited usefulness of Cronbach's alpha. Psychometrika. 2009;74(1):107–20.

190. Dunn TJ, Baguley T, Brunsden V. From alpha to omega: A practical solution to the pervasive problem of internal consistency estimation. British Journal of Psychology. 2014;105(3):399–412.

191. Anthoine E, Moret L, Regnault A, Sébille V, Hardouin J-B. Sample size used to validate a scale: a review of publications on newly-developed patient reported outcomes measures. Health and Quality of Life Outcomes. 2014;12:2.

192. Myers ND, Ahn S, Jin Y. Sample size and power estimates for a confirmatory factor analytic model in exercise and sport: a Monte Carlo approach. Research Quarterly for Exercise and Sport. 2011;82(3):412–23.

193. Krska J, Katusiime B, Corlett SA. Validation of an instrument to measure patients' experiences of medicine use: the Living with Medicines Questionnaire. Patient Prefer Adherence. 2017;11:671–9.

194. Miller KW, Wilder LB, Stillman FA, Becker DM. The feasibility of a street-intercept survey method in an African-American community. American Journal of Public Health. 1997;87(4):655–8.

195. Chen C-H, Wu J-R, Yen M, Chen Z-C. A model of medication-taking behavior in elderly individuals with chronic disease. Journal of Cardiovascular Nursing. 2007;22(5):359–65.

196. Carpenter DM, DeVellis RF, Fisher EB, DeVellis BM, Hogan SL, Jordan JM. The effect of conflicting medication information and physician support on medication adherence for chronically ill patients. Patient Education and Counseling. 2010;81(2):169–76.

197. Miller SM. Monitoring and blunting: validation of a questionnaire to assess styles of information seeking under threat. Journal of Personality and Social Psychology. 1987;52(2):345.

198. Bajcar J. Task analysis of patients' medication-taking practice and the role of making sense: a grounded theory study. Research in Social and Administrative Pharmacy. 2006;2(1):59–82.

199. Paddison C. Family support and conflict among adults with type 2 diabetes. European Diabetes Nursing. 2010;7:29–33.

200. Talbot F, Nouwen A, Gingras J, Gosselin M, Audet J. The assessment of diabetes-related cognitive and social factors: the Multidimensional Diabetes Questionnaire. Journal of Behavioral Medicine. 1997;20(3):291–312.

201. Irwin DE, Varni JW, Yeatts K, DeWalt DA. Cognitive interviewing methodology in the development of a pediatric item bank: a patient reported outcomes measurement information system (PROMIS) study. Health and Quality of Life Outcomes. 2009;7:3.

202. Collins D. Pretesting survey instruments: an overview of cognitive methods. Quality of Life Research. 2003;12(3):229–38.

203. Frary RB. Hints for designing effective questionnaires [Internet]. ERIC Clearinghouse on Assessment & Evaluation, the Catholic University of America; 1996. Available from: http://staff.unak.is/not/andy/NursResearchMethods0506/Questionnairing/HintsForDesigningEffectiveQuestionnaires.pdf [Accessed 15/02/2017].

204. Goodhue DL, Loiacono ET. Randomizing survey question order vs. grouping questions by construct: An empirical test of the impact on apparent reliabilities and links to related constructs. In: System Sciences, 2002 HICSS Proceedings of the 35th Annual Hawaii International Conference on [Internet]. IEEE; 2002. p. 3456–3465. Available from: http://ieeexplore.ieee.org/abstract/document/994385/ [Accessed 16/07/2014].

205. Brancato et al G. Recommended practices for questionnaire development and testing in the European statistical system. In: Proceedings of Q2006–European Conference on Quality in Survey Statistics. 2006.

206. Krosnick JA, Presser S. Question and questionnaire design. Handbook of survey research. 2010;2(3):263–314.

207. Schell KL, Oswald FL. Item grouping and item randomization in personality measurement. Personality and Individual Differences. 2013;55(3):317–21.

208. Schurr KT, Henriksen LW. Effects of item sequencing and grouping in low-inference type questionnaires. Journal of Educational Measurement. 1983;20(4):379–91.

209. Dietrich H, Ehrlenspiel F. Cognitive interviewing: A qualitative tool for improving questionnaires in sport science. Measurement in Physical Education and Exercise Science. 2010;14(1):51–60.

210. Blair J, Brick P. Current practices in cognitive interviewing. 2009;5691–700.

211. Beavers AS, Lounsbury JW, Richards JK, Huck SW, Skolits GJ, Esquivel SL. Practical considerations for using exploratory factor analysis in educational research. Practical Assessment Research & Evaluation. 2013;18(6):1–13.

212. Bollen KA. A new incremental fit index for general structural equation models. Sociological Methods & Research. 1989;17(3):303–16.

213. Ullman JB. Structural equation modeling: Reviewing the basics and moving forward. Journal of Personality Assessment. 2006;87(1):35–50.

214. Carmines EG, McIver JP. Analyzing models with unobserved variables: Analysis of covariance structures. Social measurement: Current issues. 1981;65–115.

215. Schumacker RE, Lomax RG. A beginner's guide to structural equation modeling. Psychology Press; 2004.

216. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Structural equation modeling: a multidisciplinary journal. 1999;6(1):1–55.

217. Brown TA. Confirmatory factor analysis for applied research. 2nd ed. New York & London: The Guilford Press; 2015. 462 p.

218. Cabrera-Nguyen P. Author guidelines for reporting scale development and validation results in the Journal of the Society for Social Work and Research. Journal of the Society for Social Work and Research. 2010;1(2):99–103.

219. Marsh HW, Hau K-T, Wen Z. In search of golden rules: Comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. Structural Equation Modeling: A Multidisciplinary Journal. 2004;11(3):320–41.

220. Cao YJ, Mager DE, Simonsick EM, Hilmer SN, Ling SM, Windham BG, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. Clinical Pharmacology and Therapeutics. 2008;83(3):422–9.

221. Ridgeway JL, Egginton JS, Tiedje K, Linzer M, Boehm D, Poplau S, et al. Factors that lessen the burden of treatment in complex patients with chronic conditions: a qualitative study. Patient Preference and Adherence. 2014;8:339.

222. Stevenson FA, Cox K, Britten N, Dundar Y. A systematic review of the research on communication between patients and health care professionals about medicines: the consequences for concordance. Health Expectations. 2004;7(3):235–45.

223. Krska J, Morecroft CW. Views of the general public on the role of pharmacy in public health. Journal of Pharmaceutical Health Services Research. 2010;1(1):33–8.

224. Schafheutle EI. Patients' views on the UK policy of prescription charges—Insights from qualitative interviews. Res Social Adm Pharm. 2008;4(4):343–54.

225. Russell C, Kilburn E, Conn V, Libbus M, Ashbaugh C. Medication-taking beliefs of adult renal transplant recipients. Clinical Nurse Specialist. 2003;17(4):200–8.

226. Babbie ER. The Basics of Social Research. 5th ed. Wadsworth: Cengage Learning; 2009. 576 p.

227. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychological Bulletin. 1959;56(2):81–105.

228. Trochim WMK. Convergent & Discriminant Validity [Internet]. Research methods knowledge base. 2006. Available from: http://www.socialresearchmethods.net/kb/convdisc.php [Accessed 31/08/2016]

229. Peyrot M, Harshaw Q, Shillington A, Xu Y, Rubin R. Validation of a tool to assess medication treatment satisfaction in patients with Type 2 diabetes: the Diabetes Medication System Rating Questionnaire (DMSRQ). Diabetic Medicine. 2012;29:1060–6.

230. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.

231. Katusiime B, Corlett S, Reeve JL, Krska J. Measuring medicines related experiences from the patient perspective : a systematic review. Patient Relat Outcome Meas. 2016;7:157–71.

232. Tran V-T, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. BMC Medicine. 2014;12(1):109.

233. Rabin R, Oemar M, Oppe M, Janssen B, Herdman M. EQ-5D-5L user guide. Basic information on how to use the EQ-5D-5L instrument Rotterdam: EuroQol Group. 2011;22.

234. Devlin N, Appleby J. Getting the most out of PROMs: putting health outcomes at the heart of NHS decision-making. 1st ed. London: The King's Fund; 2010. 84 p.

235. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Annals of medicine. 2001;33(5):350–357.

236. McHorney CA, Ware JE, Lu JF, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Medical Care. 1994;32(1):40–66.

237. Delestras S, Roustit M, Bedouch P, Minoves M, Dobremez V, Mazet R, et al. Comparison between two generic questionnaires to assess satisfaction with medication in chronic diseases. PloS one. 2013;8(2):e56247.

238. Abetz L, Baladi J-F, Jones P, Rofail D. The impact of iron overload and its treatment on quality of life: results from a literature review. Health and Quality of Life Outcomes. 2006;4:73.

239. Arboretti R, Tognoni G, Alberti D. Pharmacosurveillance and quality of care of thalassaemic patients. European Journal of Clinical Pharmacology. 2001;56(12):915–922.

240. Rofail D, Viala M, Gater A, Abetz-Webb L, Baladi J-F, Cappellini MD. An instrument assessing satisfaction with iron chelation therapy: Psychometric testing from an open-label clinical trial. Advances in Therapy. 2010;27(8):533–46.

241. Mohammed MA, Moles RJ, Chen TF. The impact of pharmaceutical care interventions on health-related quality-of-life outcomes: A systematic review and meta-analysis. Annals of Pharmacotherapy [Internet]. 2016 [cited 2016 Sep 8]; Available from: http://aop.sagepub.com/content/early/2016/06/29/1060028016656016

242. Krska J, Rowe PH. Outcome measures: a sensitive approach. International Journal of Pharmacy Practice. 2010;18(2):125–7.

243. Paiva CE, Barroso EM, Carneseca EC, de Pádua Souza C, dos Santos FT, Mendoza López RV, et al. A critical analysis of test-retest reliability in instrument validation studies of cancer patients under palliative care: a systematic review. BMC Medical Research Methodology. 2014;14:8.

244. Rust J, Golombok S. Modern Psychometrics. 2nd ed. London: Routledge; 2015. 366 p.

245. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD, the Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? Value in Health. 2007;10:S94–105.

246. Bartlett JW, Frost C. Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. Ultrasound in Obstetrics & Gynecology. 2008;31(4):466–75.

247. Nevill AM, Lane AM, Kilgour LJ, Bowes N, Whyte GP. Stability of psychometric questionnaires. Journal of Sports Sciences. 2001;19(4):273–8.

248. Werner MU, Petersen MA, Bischoff JM. Test-retest studies in quantitative sensory testing: a critical review. Acta Anaesthesiologica Scandinavica. 2013;57(8):957–63.

249. Vencato MM. Development and validation of the Brunel Lifestyle Physical Activity Questionnaire [Internet] [Thesis]. Brunel University School of Sport and Education PhD Theses; 2009. Available from: http://bura.brunel.ac.uk/handle/2438/4446 [Accessed 18/02/2017].

250. Bowers D, Bowers. Medical statistics from scratch: An introduction for health professionals. 2nd ed. Chichester and Hoboken: John Wiley & Sons; 2008. 302 p.

251. Broglio SP, Ferrara MS, Macciocchi SN, Baumgartner TA, Elliott R. Test-retest reliability of computerized concussion assessment programs. Journal of Athletic Training. 2007;42(4):509–14.

252. Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. Psychological Bulletin. 1979;86(2):420–8.

253. Boger E. Self-management following stroke. Concepts and measurement [Internet]. University of Southampton; 2014. Available from: http://eprints.soton.ac.uk/362824/ [Accessed 31/08/2016].

254. Velde JL van der, Blok BMJF, Vlieg-Boerstra BJ, Elberink JNGO, Schouten JP, DunnGalvin A, et al. Test–retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Quality of Life Research. 2009;18(2):245–51.

255. Maruish ME. The use of psychological testing for treatment planning and outcomes assessment: General considerations. 3rd ed. Vol. 1. London, Mahwah, New Jersey: Routledge; 2004.

256. Davidson M. Known-groups validity. In: Encyclopedia of quality of life and well-being research. Springer; 2014. p. 3481–3482.

257. Boo S, Froelicher ES. Secondary analysis of national survey datasets. Japan Journal of Nursing Science. 2013;10(1):130–5.

258. Department for Communities and Local Government. English indices of deprivation [Internet]. 2015. Available from: http://imd-by-postcode.opendatacommunities.org/ [Accessed 22/03/2017]

259. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy. Journal of General Internal Medicine. 2005;20(5):479–482.

260. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. Journal of Cystic Fibrosis. 2009;8(2):91–96.

261. Witticke D, Seidling HM, Lohmann K, Send AF, Haefeli WE. Opportunities to reduce medication regimen complexity: a retrospective analysis of patients discharged from a university hospital in Germany. Drug Safety. 2013;36(1):31–41.

262. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. The American Journal of Geriatric Pharmacotherapy. 2011 Feb;9(1):11–23.

263. Huang Elbert S. The key to preventing burnout: understanding the burden of diabetes treatment. Diabetes Voice. 2008;53(3):33–5.

264. Payne RA. Developing and evaluating a measure of inappropriate polypharmacy in primary care — SPCR [Internet]. 2016. Available from: https://www.spcr.nihr.ac.uk/projects/developing-and-evaluating-a-measure-of-inappropriate-polypharmacy-in-primary-care-rand-appropriateness-and-cprd-epidemiological-study [Accessed 23/02/2017].

265. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. BMC Medical Research Methodology. 2011;11(1):149.

266. Panvelkar PN, Saini B, Armour C. Measurement of patient satisfaction with community pharmacy services: a review. Pharmacy World & Science. 2009;31(5):525–37.

267. Pharmaceutical Services Negotiating Committee. Community Pharmacy Patient Questionnaire (CPPQ) [Internet]. Community Pharmacy Patient Questionnaire (CPPQ). Available from: http://psnc.org.uk/contract-it/essential-service-clinical-governance/cppq/ [Accessed 23/02/2017].

268. Kane RL, Radosevich DM. Conducting health outcomes research. Sudbury: Jones & Bartlett Learning; 2011. 369 p.

269. Paterson C, Britten N. A narrative review shows the unvalidated use of self-report questionnaires for individual medication as outcome measures. Journal of Clinical Epidemiology. 2005;58(10):967–73.

270. Farris KB, Phillips BB. Instruments assessing capacity to manage medications. Annals of Pharmacotherapy. 2008;42(7):1026–36.

271. Elliott RA, Marriott JL. Standardised assessment of patients' capacity to manage medications: a systematic review of published instruments. BMC Geriatrics. 2009;9(1):27.

272. Campbell JL, Kiebert GM, Partridge MR. Development of the Satisfaction with Inhaled Asthma Treatment Questionnaire. European Respiratory Journal. 2003;22(1):127–34.

273. Rofail D, Gray R, Gournay K. The development and internal consistency of the Satisfaction with Antipsychotic Medication scale. Psychological Medicine. 2005;35(7):1063–72.

274. General Medical Council. Investigating the prevalence and causes of prescribing errors in general practice: The PRACtICe study [Internet]. 2012. Available from: http://www.gmc-uk.org/Investigating_the_prevalence_and_causes_of_prescribing_errors_in_general_practice___The_PRACtICe_study_Reoprt_May_2012_48605085.pdf [Accessed 03/03/2017]

275. Peters M, Crocker H, Jenkinson C, Doll H, Fitzpatrick R. The routine collection of patient-reported outcome measures (PROMs) for long-term conditions in primary care: a cohort survey. BMJ Open. 2014;4(2):e003968.

276. Howland M, Allan KC, Carlton CE, Tatsuoka C, Smyth KA, Sajatovic M. Patient-rated versus proxy-rated cognitive and functional measures in older adults. Patient Related Outcome Measures. 2017;8:33–42.

277. Healthcare Improvement Scotland. Guide to using patient reported outcome measures (PROMs) more inclusively [Internet]. 2012. Available from: file:///C:/Users/User/Downloads/User%20Guide%20Final.pdf [Accessed 27/03/2017]

278. Zidan A, Awaisu A, Hasan S, Kheir N. The Living with Medicines Questionnaire: Translation and cultural adaptation into the Arabic context. Value Health Reg Issues. 2016;10:36–40.

279. Ailabouni NJ, Nishtala PS, Mangin D, Tordoff JM. Challenges and enablers of deprescribing: A general practitioner perspective. PLoS One [Internet]. 2016 Apr 19 [cited 2017 Mar 27];11(4). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4836702/

280. Pharmaceutical Services Negotiating Committee. National target groups for MURs [Internet]. 2017. Available from: http://psnc.org.uk/services-commissioning/advanced-services/murs/national-target-groups-for-murs/ [Accessed 27/03/2017]

281. Haas D, Krosner Y, Mukerji N, Kaplan R. Delivering higher value care means spending more time with patients. Harvard Business Review [Internet]. 2014; Available from: https://hbr.org/2014/12/delivering-higher-value-care-means-spending-more-time-with-patients [Accessed 28/02/2017].

282. Kaplan RS, Haas DA, Warsh J. Adding value by talking more. New England Journal of Medicine. 2016;375(20):1918–20.

283. PrescQIPP Community Interest Company. Repeat prescribing in primary care. Bulletin 124 [Internet]. 2016. Available from: https://www.prescqipp.info/repeat-prescriptions/send/258-repeat-prescriptions/2535-bulletin-124-repeat-prescribing [Accessed 02/04/2017]

284. Mazumdar M, Glassman JR. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. Statistics in Medicine. 2000;19(1):113–32.

Appendix 1 Full search strategy for systematic review

Search title: Instruments measuring medicine-related experiences

Ovid Embase (1995 t0 2015 week 16)

1. medicine.mp. or exp medicine/
2. medication.mp. or exp drug therapy/
3. medication.mp. or exp drug therapy/
4. exp patient/ or exp inappropriate prescribing/ or exp prescription/ or prescri$.mp. or exp treatment planning/
5. drug.mp. or exp drug administration/ or exp drug/ or exp drug self administration/ or 'drug toxicity and intoxication'/ or adverse drug reaction/ or drug interaction/ or exp repeated drug dose/ or exp 'drug use'/ or new drug/ or drug administration route/ or drug underdose/ or topical drug administration/ or generic drug/ or exp drug dosage form/ or exp drug effect/ or multiple drug dose/ or 'food and drug administration'/ or food drug interaction/ or exp drug labeling/ or auricular drug administration/ or herb drug interaction/ or low drug dose/ or exp prescription drug/ or long acting drug/ or acute drug administration/ or exp drug efficacy/ or exp drug dose/ or drug choice/ or exp chronic drug administration/ or exp 'drug cost'/ or drug quality/ or exp recommended drug dose/ or drug potency/
6. therapy/ or drugs/ or polypharmacy/ or treatment/ or prescription drugs/
7. (therapy adj3 (drug$ or medic$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. pharmaceutical therapy.mp.
9. (pharmaceutical adj3 therapy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. polypharmacy/ or exp drug therapy/
11. *treatment outcome/ or treatment duration/ or *treatment failure/ or exp time to treatment/ or *treatment planning/ or *treatment indication/ or *treatment refusal/ or treatment.mp. or exp treatment contraindication/ or topical treatment/
12. (prescription adj3 medicine$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. drug seeking behavior/ or exp drug self administration/
14. exp patient/ or *attitude/ or *attitude to health/ or Drug Us$ Attitude$.mp. or exp prescription/
15. ((Drug or medicine) adj3 dos$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
16. side effect/ or side effect assessment/
17. exp Choice Behavior/ or exp Drug Therapy/ or exp Health Care Costs/ or prescription drug*.mp. or exp Consumer Attitudes/ or exp Consumer Behavior/ or exp Prescription Drugs/ or Physicians/ or Health Promotion/ or exp Drug Usage/
18. exp 'Medical Treatment (General)'/ or exp Drug Therapy/ or regular medicine*.mp.
19. exp Treatment Compliance/ or exp Drug Therapy/ or regimen.mp. or exp Drug Dosages/
20. exp Polypharmacy/ or exp Prescription Drugs/ or exp Drug Therapy/ or exp Coping Behavior/ or exp Treatment Compliance/ or multiple medicine$.mp.
21. (excessive adj3 medicine$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
22. exp Drug Therapy/ or unnecessary medicine$.mp.
23. (tak$ adj3 medicine$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. (Medicine adj3 us$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

25. (taking adj3 medicine$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
26. (administ$ adj3 medicine$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
27. (self adj3 medic$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
28. (medicine$ adj manag$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
29. or/1-28
30. (instrument$ or tool$ or scale* or indicator$ or technique or method$ or form$ or survey* or questionnaire$ or self report or measure or (patient adj3 report$) or outcome measure or PROM or PRO or quantif$ or rate or rating or assess$ or evaluat$ or estimat$ or develop$ or valid$ or reliab$ or psychometr$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
31. (patient experience$ or experienc$ or view$ or perception$ or attitude$ or belief$ or concern$ or worr$ or burden$ or (medic$ adj5 burden$) or pill burden or problem or distress or (medicin$ adj3 problem) or (drug adj3 problem) or financial burden or (cost adj3 burden) or psycholog$ or social activit$ or family or friend$ or time or travel or emotion$ or satisf$ or dissatisf$ or happ$ or unhapp$ or (cop$ adj5 medic$) or (cop$ adj3 drug$) or behav$ or lifestyle or routine or life or activities of daily living).mp. or (*day/ adj3 lif$.mp.) or life.mp. or live$.mp. or health$.mp. or fitness.mp. or wellbeing.mp. or quality of life.mp. or self care.mp. or impact.mp.
32. *doctor patient relation/ or *patient care/ or exp patient attitude/ or *health care quality/ or exp questionnaire/ or patient/ or exp *patient satisfaction/ or patient experience$.mp. or *psychological aspect/
33. (patient adj3 view$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
34. (patient adj3 perception$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
35. (patient adj3 attitude$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
36. (patient adj3 belief$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
37. (patient adj3 concern$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
38. (patient adj3 worr$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
39. (patient adj3 burden$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
40. (patient adj5 satisf$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
41. (patients$ adj3 dissatisf$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
42. ((patient$ adj3 happ$) or (patient$ adj3 unhapp$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
43. ((cop$ adj5 medic$) or (cop$ adj5 drug$) or (medic$ adj5 behav$) or (medic$ adj5 lifestyle) or (medic$ adj5 routin$) or (medicine adj5 lif$) or (medicine$ adj10 activities of daily living)).mp. or (medicine.mp. adj5 *day/) or (drug adj5 health$).mp. or (drug therapy adj10 fitness).mp. or (pharmaceutical therapy adj5 quality of life).mp. or (drug adj5 self care).mp. or (drug$ adj5 impact).mp.

44. ((cop$ adj5 medic$) or (cop$ adj5 drug$) or (medic$ adj5 behav$) or (medic$ adj5 lifestyle) or (medic$ adj5 routin$) or (medicine adj5 lif$) or (medicine$ adj10 activities of daily living)).mp. or (medicine.mp. adj5 *day/) or (drug adj5 health$).mp. or (drug therapy adj10 fitness).mp. or (pharmaceutical therapy adj5 quality of life).mp. or (drug adj5 self care).mp. or (drug$ adj5 impact).mp.
45. ((cop$ adj5 medic$) or (cop$ adj5 drug$) or (medic$ adj5 behav$) or (medic$ adj5 lifestyle) or (medic$ adj5 routin$) or (medicine adj5 lif$) or (medicine$ adj5 activities of daily living) or (drug adj5 health$) or (drug therapy adj5 fit$) or (pharmaceutical therapy adj3 quality of life) or (drug adj5 self care) or (drug$ adj5 impact)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
46. or/31-45
47. 29 and 46
48. 30 and 47
49. develop$.mp.
50. 48 and 49
51. psychometr$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
52. 50 and 51
53. limit 52 to (human and english language and embase and (adult <18 to 64 years> or aged <65+ years>))
54. limit 53 to yr='1995 -Current'

PsycINFO and PSych articles

1. medicine.af.
2. medication.mp. or exp Drug Therapy/
3. 'prescribing (drugs)'/ or drug therapy/ or drugs/ or polypharmacy/ or treatment/ or prescription drugs/
4. exp Drug Usage Screening/ or exp Drug Therapy/ or exp Drug Seeking/ or exp Drug Usage Attitudes/ or drug*.mp. or exp Drug Usage/ or exp Drug Self Administration/ or exp Drug Dosages/ or exp 'Side Effects (Drug)'/
5. exp Prescription Privileges/ or exp Prescription Drugs/ or prescription*.mp.
6. exp Choice Behavior/ or exp Drug Therapy/ or exp Health Care Costs/ or prescription drug*.mp. or exp Consumer Attitudes/ or exp Consumer Behavior/ or exp Prescription Drugs/ or Physicians/ or Health Promotion/ or exp Drug Usage/
7. (prescription adj3 medicine).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
8. exp 'Medical Treatment (General)'/ or exp Drug Therapy/ or regular medicine*.mp.
9. exp Treatment Compliance/ or exp Drug Therapy/ or regimen.mp. or exp Drug Dosages/
10. polypharmacy.mp. or exp Polypharmacy/
11. exp Polypharmacy/ or exp Prescription Drugs/ or exp Drug Therapy/ or exp Coping Behavior/ or exp Treatment Compliance/ or multiple medicine$.mp.
12. (excessive adj3 medicine$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13. exp Drug Therapy/ or unnecessary medicine$.mp.
14. drug therapy.mp. or exp Drug Therapy/
15. therapy.mp. or exp Treatment/
16. overprescrib$.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

17. (tak$ adj3 medicine$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
18. (tak$ adj3 medicine$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
19. Medicine us$.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
20. taking medicine.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
21. (administ$ adj3 medicine$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
22. (self adj3 medic*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
23. (medicine$ adj manag$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
24. or/1-23
25. (instrument$ or tool$ or scale* or indicator$ or technique or method$ or form$ or survey* or questionnaire$ or self report or measure or (patient adj3 report$) or outcome measure or PROM or PRO or quantif$ or rate or rating or assess$ or evaluat$ or estimat$ or develop$ or valid$ or reliab$ or psychometr$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
26. (patient experience$ or experienc$ or view$ or perception$ or attitude$ or belief$ or concern$ or worr$ or burden$ or (medic$ adj5 burden$) or pill burden or problem or distress or (medicin$ adj3 problem) or (drug adj3 problem) or financial burden or (cost adj3 burden) or psycholog$ or social activit$ or family or friend$ or time or travel or emotion$ or satisf$ or dissatisf$ or happ$ or unhapp$ or (cop$ adj5 medic$) or (cop$ adj3 drug$) or behav$ or lifestyle or routine or life or activities of daily living).mp. or (*day/ adj3 lif$.mp.) or life.mp. or live$.mp. or health$.mp. or fitness.mp. or wellbeing.mp. or quality of life.mp. or self care.mp. or impact.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
27. patient experience$.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
28. (patient adj3 view$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
29. (patient adj3 perception$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
30. (patient adj3 attitude$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
31. (patient adj5 belief$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
32. (patient adj5 concern$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
33. (patient adj5 worr$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
34. (patient adj5 burden$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
35. (patient adj5 satisf$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
36. ((patients$ adj3 dissatisf$) or (patient$ adj5 happ$) or patient$ unhapp$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

37. ((cop$ adj5 medic$) or (cop$ adj5 drug$) or (medic$ adj5 behav$) or (medic$ adj5 lifestyle) or (medic$ adj5 routin$) or (medicine adj5 lif$) or (medicine$ adj10 activities of daily living)).mp. or (medicine.mp. adj5 *day/) or (drug adj5 health$).mp. or (drug therapy adj10 fitness).mp. or (pharmaceutical therapy adj5 quality of life).mp. or (drug adj5 self care).mp. or (drug$ adj5 impact).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
38. or/27-37
39. 24 and 38
40. 25 and 39
41. limit 40 to (psycarticles journals and adulthood <18+ years> and english and human and yr='1995 - Current')
42. limit 40 to (all journals and 2220 tests & testing and '300 adulthood ' and english)
43. limit 40 to (all journals and (2200 psychometrics & statistics & methodology or 2220 tests & testing or 2222 developmental scales & schedules or 2223 personality scales & inventories or 2224 clinical psychological testing or 2225 neuropsychological assessment or 2226 health psychology testing or 2260 research methods & experimental design or 2300 human experimental psychology or 2500 physiological psychology & neuroscience or 2580 psychopharmacology or 2600 psychology & the humanities or 2800 developmental psychology or 3300 health & mental health treatment & prevention or 3310 psychotherapy & psychotherapeutic counseling or 3311 cognitive therapy or 3312 behavior therapy & behavior modification or 3315 psychoanalytic therapy or 3360 health psychology & medicine or '3361 behavioral & psychological treatment of physical illness' or '3363 medical treatment of physical illness' or '3365 promotion & maintenance of health & wellness' or 3370 health & mental health services or 3371 outpatient services or 3373 community & social services or 3900 consumer psychology or 3920 consumer attitudes & behavior) and adulthood <18+ years> and '300 adulthood ' and english and human)
44. from 43 keep 31,57
45. limit 43 to (('0400 empirical study' or '0410 experimental replication' or '0430 followup study' or '0450 longitudinal study' or '0451 prospective study' or '0453 retrospective study' or '0600 field study' or '0700 interview' or '0750 focus group' or 1600 qualitative study or 1800 quantitative study) and ('0100 journal' or '0110 peer-reviewed journal' or '0120 non-peer-reviewed journal' or '0130 peer-reviewed status unknown'))
46. limit 45 to ('0400 empirical study' or '0430 followup study' or '0450 longitudinal study' or 1800 quantitative study)
47. limit 46 to 1800 quantitative study

CINAHL Plus and MEDLINE, 1995-2015 week 16 (accessed via EBSCOHOST)

#	Query	Limiters/Expanders	Last Run Via	Results
S53	S50 AND S51	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	895
S52	S50 AND S51	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	1,645
S51	S2 OR S5 OR S7 OR S13 OR S14	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	9,379,820
S50	S46 AND S47	Limiters - Published Date: 19950101-20151231 Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	5,011
S49	S46 AND S47	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	5,331
S48	S46 AND S47	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	13,240
S47	psychometric	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	89,259
S46	S44 AND S45	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	1,855,365
S45	develop*	Expanders - Apply related words; Also search within the full text of the articles	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,230,913

		Search modes - Find all my search terms	Plus;MEDLINE	
S44	S42 AND S43	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,527,673
S43	(instrument$ or tool$ or scale* or indicator$ or technique or method$ or form$ or survey* or questionnaire$ or self report or measure or (patient adj3 report$) or outcome measure or PROM or PRO or quantif$ or rate or rating or assess$ or evaluat$ or estimat$ or develop$ or valid$ or reliab$ or psychometr$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	16,198,585
S42	S27 AND S41	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	2,888,057
S41	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	18,831,167
S40	((cop$ adj5 medic$) or (cop$ adj5 drug$) or (medic$ adj5 behav$) or (medic$ adj5 lifestyle) or (medic$ adj5 routin$) or (medicine adj5 lif$) or (medicine$ adj10 activities of daily living)).mp. or (medicine.mp. adj5 *day/) or (drug adj5 health$).mp. or (drug therapy adj10 fitness).mp. or (pharmaceutical therapy adj5 quality of life).mp. or (drug adj5 self care).mp. or (drug$ adj5 impact).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	18,550,078
S39	((patient$ adj3 happ$) or (patient$ adj3 unhapp$)).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,353,850

		any of my search terms		
S38	(patients$ adj3 dissatisf$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	5,009,958
S37	(patient adj5 satisf$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,353,411
S36	(patient adj3 burden$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,439,824
S35	patient adj3 worr$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,211,145
S34	(patient adj3 concern$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,510,950
S33	(patient adj3 belief$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,407,809
S32	(patient adj3 attitude$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,675,351

S31	(patient adj3 perception$).mp	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,657,219
S30	(patient adj3 view$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,576,537
S29	*doctor patient relation/ or *patient care/ or exp patient attitude/ or *health care quality/ or exp questionnaire/ or patient/ or exp *patient satisfaction/ or patient experience$.mp. or *psychological aspect/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	13,078,605
S28	(patient experience$ or experienc$ or view$ or perception$ or attitude$ or belief$ or concern$ or worr$ or burden$ or (medic$ adj5 burden$) or pill burden or problem or distress or (medicin$ adj3 problem) or (drug adj3 problem) or financial burden or (cost adj3 burden) or psycholog$ or social activit$ or family or friend$ or time or travel or emotion$ or satisf$ or dissatisf$ or happ$ or unhapp$ or (cop$ adj5 medic$) or (cop$ adj3 drug$) or behav$ or lifestyle or routine or life or activities of daily living).mp. or (*day/ adj3 lif$.mp.) or life.mp. or live$.mp. or health$.mp. or fitness.mp. or wellbeing.mp. or quality of life.mp. or self care.mp. or impact.mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	17,029,596
S27	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	23,635,793

	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26		Plus;MEDLINE	
S26	(medicine$ adj manag$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,311,939
S25	(self adj3 medic$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	949,167
S24	(administ$ adj3 medicine$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,251,710
S23	(taking adj3 medicine$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,436,866
S22	. (Medicine adj3 us$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,532,075
S21	(tak$ adj3 medicine$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,255,372
S20	exp Drug Therapy/ or unnecessary medicine$.mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,853,981

		terms		
S19	(excessive adj3 medicine$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,318,996
S18	exp Polypharmacy/ or exp Prescription Drugs/ or exp Drug Therapy/ or exp Coping Behavior/ or exp Treatment Compliance/ or multiple medicine$.mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	11,814,728
S17	exp 'Medical Treatment (General)'/ or exp Drug Therapy/ or regular medicine*.mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,909,446
S16	. exp Choice Behavior/ or exp Drug Therapy/ or exp Health Care Costs/ or prescription drug*.mp. or exp Consumer Attitudes/ or exp Consumer Behavior/ or exp Prescription Drugs/ or Physicians/ or Health Promotion/ or exp Drug Usage/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	14,685,952
S15	side effect/ or side effect assessment/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,236,212
S14	(Drug or medicine) adj3 dos$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	855
S13	(Drug or medicine) adj3 dos$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	0

		all my search terms		
S12	exp patient/ or *attitude/ or *attitude to health/ or Drug Us$ Attitude$.mp. or exp prescription/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	676,248
S11	drug seeking behavior/ or exp drug self administration/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,990
S10	. *treatment outcome/ or treatment duration/ or *treatment failure/ or exp time to treatment/ or *treatment planning/ or *treatment indication/ or *treatment refusal/ or treatment.mp. or exp treatment contraindication/ or topical treatment/ 12. (prescription adj3 medicine$).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	20,568,797
S9	polypharmacy/ or exp drug therapy/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,824,202
S8	(pharmaceutical adj3 therapy).	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	5,574,272
S7	. pharmaceutical therapy.mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	457,846
S6	. (therapy adj3 (drug$ or medic$)).mp.	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	8,290,732

		any of my search terms		
S5	therapy/ or drugs/ or polypharmacy/ or treatment/ or prescription drugs/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	7,659,230
S4	drug.mp. or exp drug administration/ or exp drug/ or exp drug self administration/ or 'drug toxicity and intoxication'/ or adverse drug reaction/ or drug interaction/ or exp repeated drug dose/ or exp 'drug use'/ or new drug/ or drug administration route/ or drug underdose/ or topical drug administration/ or generic drug/ or exp drug dosage form/ or exp drug effect/ or multiple drug dose/ or 'food and drug administration'/ or food drug interaction/ or exp drug labeling/ or auricular drug administration/ or herb drug interaction/ or low drug dose/ or exp prescription drug/ or long acting drug/ or acute drug administration/ or exp drug efficacy/ or exp drug dose/ or drug choice/ or exp chronic drug administration/ or exp 'drug cost'/ or drug quality/ or exp recommended drug dose/ or drug potency/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	17,932,905
S3	exp patient/ or exp inappropriate prescribing/ or exp prescription/ or prescri$.mp. or exp treatment planning/	Expanders - Apply related words; Also search within the full text of the articles Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	9,417,571
S2	medication.mp. or exp drug therapy/	Expanders - Apply related words; Also search within the full text of the articles	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8,822,890

		Search modes - Find any of my search terms	Plus;MEDLINE	
S1	medicine.mp. or exp medicine/	Expanders - Apply related words; Also search within the full text of the articles.	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus;MEDLINE	6,802,884

Appendix 2 Cognitive interview probing guide

Project title. Revising the Living with Medicines Questionnaire

[I will first explain to the participant that he/she is supposed to think (and talk out) aloud when filling in the questionnaire, and that he/she should be prepared to answer questions as he/she completes the questionnaire. I will also emphasise that the purpose of the interview is to help us in revising the questionnaire, and not to gauge the participants' beliefs, attitudes, or adherence to their medicines. I will remind them to first read the instructions (stipulated on the cover page). I will then remind them to read each statement aloud and then comment on what they think about the text and how they expect to arrive at the response.]

General probes

- What were you thinking when you answered that question?
- I noticed that you hesitated while responding to that statement, please tell me what you were thinking then.
- What does the term (e.g. 'written instructions') mean to you?
- Why do you think that…?
- Can you repeat the question I just asked in your own words?'
- What do you think of the term ''xx'?
- How did you arrive at that answer?; 'I noticed you hesitated
- Was this question hard or easy to answer?

Examples of specific probes for new and revised items

Item 'I find the written instructions on how to use my medicines easy to understand.'

- What do you think about when reading the words '*written instructions on how to use my medicines*'?

Item 'I would be worried if I forgot to take my medicines.'

- If you should rephrase this item, what words would you use?

Item 'My pharmacist tells me enough about my medicines.'

- What do you understand by this statement?

Item 'My doctor tells me enough about my medicines.'

- What does this statement mean to you?

Item 'My medicines interfere with my social activities'

Item 'My medicines interfere with my social relationships'

- Do you think there is any difference between these two statements

Item 'I have to pay more than I can afford for my medicines'

- If you were to rephrase this statement, what words would you use?

Item 'The side effects I get from my medicines are bothersome'

- What does term ' bothersome' mean to you?

Item 'The side effects I get from my medicines interfere with my day-to-day life (e.g. work, sleep, work, housework, sleep & wellbeing).'

- What does the phrase 'interfere with my day-to-day life' mean to you?

Item 'The side effects I get are worse than the problem for which I take medicines'

- If you were to rephrase this statement, what words would you use?

Item 'The side effects are worth it for the benefits I get from my medicines'

- What does this statement mean to you?

Concluding probes

- What do you think of the instructions on the cover page of the questionnaire? *(To probe for clarity)?*
- What did you think about the response options (i.e. strongly agree, agree, neutral opinion, disagree, and strongly disagree?
- Was there anything that you perceived as difficult or uncomfortable when you filled in the questionnaire? Which one was that? Why is that?
- Overall, what did you think about this questionnaire? Do you feel it covers most of the issues that concern people using medicines on a regular basis?

How did you feel about the interview? Is there anything you would like to add?

Thank you for participating.

Appendix 3 Application for amendments to the LMQ-1 & School Ethics approval

Application for proposal amendment to the Ethics Committee

13 May 2014,

Dear Research Ethics Committee,

I wish to notify you of proposed amendments to the study protocol entitled "Measuring the burden of polypharmacy: a methodological study".

The following changes are being proposed:

- **Inclusion of an additional researcher to the project**; Barbra Katusiime, PhD student, Medway School of Pharmacy
- **Amendments to the study protocol:**

a. **Termination of the Flyer-Questionnaire method for recruitment of study participants** (See Recruitment Method **a**, under Methodology, in the study protocol). This method has been unsuccessful (17.3% overall response rate), as well as wasteful of the paper questionnaires. It will not be employed any further.

b. **Target sample size increased for the two recruitment methods employing face-to-face distribution of questionnaires.** Increased from 200 to 500 per recruitment method (Refer to sections d and e under Recruitment Methods in the study protocol). Although the preliminary phase of this project has been completed, the current sample size for the two methods (n=161) is insufficient for accurate evaluation (psychometric testing) of the questionnaire. A further 839 participants will need to be recruited, in the next 4-6 months, to attain the target sample in the continuation phase of this study.

c. **Section d of 'Specific Procedures' under Methodology:** Inclusion of provisions for personal safety where a student is working alone off-campus: "Where one student will be working alone, precautions will be taken to ensure personal safety; such as sending of text messages to colleagues and/or supervisor on arrival and departure from the site."

d. **Amendment of Appendix 5; Invitation letter to community pharmacists**. Changes to this letter include: current date, current researcher's name and student status (Barbra Katusiime, Postgraduate student), and follow-up procedures. At least 10 community pharmacies within the Medway towns allowed two undergraduate pharmacy students (Temitope Ojikutu and Chandrakant Vaghji) to distribute questionnaires within their premises during the preliminary phase of this study. Only these shall be contacted and revisited by the current researcher to continue with data collection.

e. **Amendment of Appendix 6;** Pharmacist Information Sheet. Inclusion of Barbra Katusiime, as a researcher on this project. The following documents have been provided with this submission;

- **Revised protocol**
- **A revised Appendix 5**; Invitation letter to community pharmacists
- **A revised Appendix 6**; Pharmacist Information Sheet

Thank you,

Professor Janet Krska

medway school of pharmacy

22nd May 2014

Your application for amendments to the project entitled ***measuring the burden of polypharmacy: a methodology study*** has now been considered on behalf of the Medway School of Pharmacy School Research Ethics Committee (SREC).

I am pleased to inform you that all amendments have been approved, with immediate effect.

I must remind you of the following:

1. that if you are intending to work unaccompanied with children or with vulnerable adults, you will need to apply for a CRB check; the project must be conducted under the supervision of someone who has an up-to-date CRB check; you must not be in the presence of children alone except if you have completed a CRB check;
2. that you must comply with the Data Protection Act (1998);
3. that you must comply throughout the conduct of the study with good research practice standards;
4. If you are completing this project off site, you must obtain prior approval from relevant authorities and adhere to the MSOP off site protocol.
5. to refer any amendment to the protocol to the School Research Ethics Committee (SREC) for approval.
6. You are required to complete an annual monitoring report or end of project report and submit to j.mowbray@kent.ac.uk

Yours sincerely

Dr Sarah Corlett

Appendix 4 The Living with Medicines Questionnaire Version 1 (LMQ-1)

LMQ

Living with Medicines Questionnaire

Medicines and Your Day-to-Day Life

This questionnaire seeks **your** views and opinions about the prescribed medicines **you** take and how they affect **your** life.

Medicines include tablets, creams, inhalers, liquids and so on.

This booklet contains statements which cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please tick only one box for each statement.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
1.	The instructions on my medicines are **easy** to follow.	☐	☐	☐	☐	☐
2.	I find getting my prescriptions from the doctor **difficult.**	☐	☐	☐	☐	☐
3.	I find getting my medicines from the pharmacist **difficult.**	☐	☐	☐	☐	☐
4.	My medicines are **important** to me.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
5.	I find opening the packaging of my medicines **difficult.**	☐	☐	☐	☐	☐
6.	I am **concerned** about running out of medicines.	☐	☐	☐	☐	☐
7.	It is **difficult** to identify which medicine is which.	☐	☐	☐	☐	☐
8.	It is **easy** to keep to my medicines routine.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
9.	I would be **concerned** if I forgot to take my medicines.	☐	☐	☐	☐	☐
10.	I am **concerned** that I may forget to take my medicines	☐	☐	☐	☐	☐
11.	I am **concerned** about experiencing side effects.	☐	☐	☐	☐	☐
12.	I am **concerned** about possible damaging long term effects of taking medicines.	☐	☐	☐	☐	☐
13.	Taking medicines is **routine** for me.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
14.	I am **comfortable** taking the medicines I have been prescribed.	☐	☐	☐	☐	☐
15.	I am **comfortable** with the times I should take my medicines.	☐	☐	☐	☐	☐
16.	I find the patient leaflet in my medicines containers **useful**.	☐	☐	☐	☐	☐
17.	I find using my medicines **difficult.**	☐	☐	☐	☐	☐
18.	I am **satisfied** with the effectiveness of my medicines.	☐	☐	☐	☐	☐
19.	I am **concerned** that I am too dependent on my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
20.	I am **confident** speaking to my doctor(s) about my medicines.	☐	☐	☐	☐	☐
21.	I **understand** what my doctor(s) tell me about my medicines.	☐	☐	☐	☐	☐
22.	The information my doctor(s) gives me about my medicines is **useful**.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
23.	I am **confident** speaking to my pharmacist about my medicines.	☐	☐	☐	☐	☐
24.	I **understand** what my pharmacist tells me about my medicines.	☐	☐	☐	☐	☐
25.	The information my pharmacist gives me about my medicines is **useful**.	☐	☐	☐	☐	☐

Please Turn Over

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
26.	I sometimes run out of medicines.	☐	☐	☐	☐	☐
27.	I accept that I have to take medicines long term.	☐	☐	☐	☐	☐
28.	My medicines allow me to live my life as I want to.	☐	☐	☐	☐	☐
29.	My life revolves around using my medicines.	☐	☐	☐	☐	☐
30.	My medicines live up to my expectations.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
31.	My medicines prevent my condition getting worse.	☐	☐	☐	☐	☐
32.	Taking medicines interferes with my social life.	☐	☐	☐	☐	☐
33.	I trust the judgement of my doctor(s) in choosing medicines for me.	☐	☐	☐	☐	☐
34.	I have to put a lot of planning and thought into taking my medicines.	☐	☐	☐	☐	☐
35.	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies).	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
36.	I am unhappy with the extent to which my medicines interact with alcohol.	☐	☐	☐	☐	☐
37.	Taking medicines affects my driving ability.	☐	☐	☐	☐	☐
38.	I worry that I have to take several medicines at the same time.	☐	☐	☐	☐	☐
39.	The side effects I get are worse than the problem for which I take medicines.	☐	☐	☐	☐	☐
40.	I worry that my medicines may interact with each other.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
41.	I can choose whether or not to take my medicines.	☐	☐	☐	☐	☐
42.	My doctor(s) spend enough time discussing my medicines with me.	☐	☐	☐	☐	☐
43.	I know enough about my medicines.	☐	☐	☐	☐	☐
44.	I am able to balance my day to day life with taking medicines	☐	☐	☐	☐	☐
45.	There is enough sharing of information about my medicines between the different health professionals providing my care.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
46.	I have a say in the brands of medicines I use.	☐	☐	☐	☐	☐
47.	I always follow my doctor(s) advice about my medicines.	☐	☐	☐	☐	☐
48.	I sometime feel I need to get information from other sources (such as books, friends, internet).	☐	☐	☐	☐	☐
49.	I can change the times I take my medicines if I want to.	☐	☐	☐	☐	☐
50.	The health professionals providing my care know enough about me and my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
51.	My medicines are working.	☐	☐	☐	☐	☐
52.	I can adapt my medicine-taking to my lifestyle.	☐	☐	☐	☐	☐
53.	My doctor(s) listen to my opinions and concerns about my medicines.	☐	☐	☐	☐	☐
54.	I can vary the dose of the medicines I take.	☐	☐	☐	☐	☐
55.	I get too much information about my medicines.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
56.	Changes in daily routine cause problems with my medicines.	☐	☐	☐	☐	☐
57.	My doctor(s) takes my concerns about side effects seriously.	☐	☐	☐	☐	☐
58.	My medicines have an adverse effect on my sexual life.	☐	☐	☐	☐	☐
59.	The side effects are worth it for the benefits I get from my medicines.	☐	☐	☐	☐	☐
60.	The medicines I use have an adverse effect on the holidays I can take.	☐	☐	☐	☐	☐

If you have any other views about how your medicines affect your day-to-day life, please describe them here.

Finally, please answer a few questions about you and your medicines

Are you: Male ☐ Female ☐

What is your age? 18-29 ☐ 30-49 ☐ 50-64 ☐ 65-74 ☐ 75-89 ☐ over 90 ☐

Which ethnic group best describe you? *(Please tick **one** box only)*

White ☐ Mixed ☐ Asian or Asian British ☐
Black or Black British ☐ Chinese ☐ Other ☐ .....

What is the highest level of education you have completed?

None ☐ Primary/ Few years secondary ☐
Secondary completed ☐ College/Further education ☐
Bachelor degree ☐ Higher degree ☐
Still studying ☐ *(Please tell us what level are you in)*
.....

How many medicines do you take regularly? less than 4 ☐ between 4 and 8 ☐ more than 8 ☐

<u>Medicines include tablets, creams, inhalers, liquids and so on.</u>
<u>Count each different prescription as one medicine.</u>

What is your employment status? Employed ☐ Unemployed ☐ Retired ☐

Do you pay for your prescriptions? Yes ☐ No ☐

Does someone help you with using your medicines? Yes ☐ No ☐

If you answered yes, who helps you? Spouse/Partner ☐ Relative ☐ Other ☐

If you answered other, please write here who helps you. _____

Thank you for taking the time to complete this questionnaire.

Appendix 5 Phase 1- Invitation letter to the community pharmacist

May 2014

Dear pharmacist

Re: Follow-up on student project "Measuring the burden of polypharmacy"

I am Barbra Katusiime, a postgraduate student at the Medway School of Pharmacy. I am currently following up on a project about what it is like to use multiple regular medicines in the day-to-day lives of adults in Medway and Kent.

As you may remember, you recently allowed two of my school colleagues (Temi Ojikutu & Chandra Vaghji) to distribute a few questionnaires to some clients within your community pharmacy premises. Thank you for this considerable support. The preliminary findings are of interest, and indicate the need for more data to inform the Royal Pharmaceutical Society's Medicines Optimisation agenda.

I am writing to ask if you would be willing for me to distribution further questionnaires to a few customers using your pharmacy. If you are happy with this, I will visit your pharmacy for a few hours at times agreed by you and invite some of your customers to fill in this questionnaire. People can either complete the questionnaire in the pharmacy or take it away and send it back to me. You don't have to do anything.

The study uses a specially designed questionnaire called the Living with Medicines Questionnaire©. A copy of this questionnaire is enclosed. I will be distributing copies of the questionnaire to as many people as possible, not just those who are using community pharmacies. Only adults using regular prescription medicines, living in the UK will be included in this study.

I undertake not to disrupt your business in any way. An information sheet, about the study, is also enclosed. If you wish to receive a copy of the preliminary findings of this study from the questionnaires already distributed, I am happy to provide this.

I will be in contact with you in the next few weeks to follow-up this request.
Thank you for reading this letter.
Yours sincerely,

Barbra Katusiime,

Postgraduate research student

Medway School of Pharmacy

Appendix 6 Phase 1- Pharmacist information

medway school of pharmacy

PHARMACIST INFORMATION SHEET

Title of Project: Measuring the burden of polypharmacy
Name of Researcher (s): Barbra Katusiime, Professor Janet Krska

1. **What is the purpose of the study?**

This study is aimed at finding out how people who have to take medicines long-term cope with them on a day-to-day basis and how these medicines affect their lives. It is using an instrument called the Living with Medicines Questionnaire©. We are distributing these questionnaires to as many people as possible, not just those who are using pharmacies. A copy is enclosed for your information.

2. **Why have I been contacted?**

We have contacted you because you are working in a pharmacy in Kent or Medway and we would like your permission to distribute the Living with Medicines Questionnaire© to people who use your pharmacy. The questionnaire does not ask any questions about your pharmacy.

3. **Do I have to take agree?**

No. It is up to you to decide whether or not you allow us to distribute questionnaires from your pharmacy. A student will contact you in the next few weeks either by telephone or face-to-face to ask if you are willing to allow us to conduct this study in your pharmacy.

4. **What will happen if I agree?**

If you agree, a student will visit your pharmacy at an agreed time and distribute questionnaires to members of the public. The student will invite people to complete the questionnaire after they have finished their initial transaction, so that they are not interfering with your day-to-day business. People waiting for prescriptions to be dispensed may present an ideal opportunity for students to approach them, but no-one will be pressured into filling in or taking a questionnaire.

5. **How long will this take?**

The student will try to recruit a maximum of 20 people to complete the questionnaire. Some may be willing to complete it while they are waiting in your pharmacy, but others may want to take it away and send it back in the post. It is anticipated that this may take no more than three hours.

6. **Are there any risks / benefits involved?**

There are no risks to you or your business in taking part. We are not offering any payment to pharmacists for agreeing to take part.

Who should I contact if I want to know more about the study or to get a copy of the results?

Professor Janet Krska Tel: 01634 202950 e-mail: j.krska@kent.ac.uk
Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB

This project has been looked at and approved by the MSoP Research Ethics Committee

Phase 1- List of pharmacies contacted for redistribution of paper survey

Paydens Pharmacy Balmoral Gardens Gillingham Kent ME7 4PN		Osbon Pharmacy 1a Railway Street Gillingham Kent ME7 2YW
Karsons Pharmacy 33 Pattens Lane Chatham Kent ME4 6JR		Osbon Pharmacy 17 Duncan Road Gillingham Kent ME7 4LA
Karson's Pharmacy 69-71 City Way Rochester Kent ME1 2BA		Ryders 130 High Street Rochester Kent ME1 1 1JT
Williams Chemist 86 Frindsbury Road Rochester Kent ME2 4HY		ASDA Pharmacy 387 Maidstone Road Chatham Kent ME5 9SE
Paydens Ltd 139 New Road Chatham ME4 4PT		J Spensley 1 Twydall Green Gillingham Kent ME8 6JY

Appendix 7 Phase 1 - Participant information

medway school of pharmacy

PARTICIPANT INFORMATION SHEET

Title of Project: Measuring the burden of polypharmacy

Name of Researcher (s): Barbra Katusiime, Professor Janet Krska

1. **What is the purpose of the study?**
This study is aimed at finding out how people who have to take medicines long-term cope with them on a day-to-day basis and how these medicines affect their lives.

2. **Do I have to take part?**
No. It is up to you to decide whether or not you wish to take part.

3. **What will happen to me if I take part?**
If you agree to be a part of this study you will be asked to fill in a questionnaire, which will take about 10 to 15 minutes to complete. If you decide to complete the questionnaire, you should then seal it in an envelope and either give it to the researcher who gave it to you or send it in the post to Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB using the free-post envelope you were given.
Do not put your name on the questionnaire.

4. **What will happen to my questionnaire?**
Your completed questionnaire will be put together with those of all other people who have filled it in, so we can learn how many people are affected by medicines in different ways. We might publish the results of the study, but nobody will know that you took part.

5. **Are there any risks / benefits involved?**
There are no risks in taking part. We are not offering any payment for completing a questionnaire.

6. **Who will know what is in my questionnaire?**
No-one will know what is in your questionnaire, because it is anonymous.

7. **What should I do if I change my mind?**
If you change your mind before you have finished filling in a questionnaire, please tell the researcher. If you have already completed and handed in the questionnaire, it will not be possible to take out your answer, but all answers will be anonymous.

Who should I contact if I want to know more about the study?

Professor Janet Krska Tel: 01634 202950 e-mail: j.krska@kent.ac.uk
Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB

This project has been seen and approved by Medway School of Pharmacy Research Ethics Committee

Appendix 8 Phase 2 Ethics approval for a study to revise the original questionnaire

medway school of pharmacy

May 2015

Dear Barbra

Your application for ethical approval for the project entitled Revision of the Living with Medicines Questionnaire (LMQ) has now been considered on behalf of the Medway School of Pharmacy School Research Ethics Committee (SREC).

The committee has already approved an earlier version of this questionnaire, and much of the material is unchanged and does not raise ethical concerns. I am pleased to inform you that your study has been approved, with the following additions and amendments;

- Provide a statement within the protocol on how the costs will be covered (SRP student funding is £450 per student)
- Add a statement to the full application form to describe how audio/ digital recordings will be protected and participants identity safeguarded during transit between interview site and campus. (Filenames should be numerical/ coded and not include names. The files should be downloaded onto password protected computers as soon as possible after the interviews have taken place).
- Change 'hullo' to' hello' appendix 7

Please make the amendments to your original documents using track changes and submit to j.l.mowbray@gre.ac.uk .

I must remind you of the following:

1. that if you are intending to work unaccompanied with children or with vulnerable adults, you will need to apply for a CRB check; the project must be conducted under the supervision of someone who has an up-to-date CRB check; you must not be in the presence of children alone except if you have completed a CRB check;
2. that you must comply with the Data Protection Act (1998);
3. that you must comply throughout the conduct of the study with good research practice standards;
4. If you are completing this project off site, you must obtain prior approval from relevant authorities and adhere to the MSOP off site protocol.
5. to refer any amendment to the protocol to the School Research Ethics Committee (SREC) for approval.
6. You are required to complete an annual monitoring report or end of project report and submit to j.l.mowbray@gre.ac.uk

Please note that the committee also suggested that you may wish to consider contacting Kent Adult Research Unit, who have about 400 subscribers who are willing to take part in research.

Yours sincerely

Dr Sarah Corlett

medway school of pharmacy

May 2015

Dear Barbra

Your amendments to the project entitled; Revision of the Living with Medicines Questionnaire (LMQ) has now been approved on behalf of the Medway School of Pharmacy School Research Ethics Committee (SREC).

I must remind you of the following:

1. that if you are intending to work unaccompanied with children or with vulnerable adults, you will need to apply for a CRB check; the project must be conducted under the supervision of someone who has an up-to-date CRB check; you must not be in the presence of children alone except if you have completed a CRB check;
2. that you must comply with the Data Protection Act (1998);
3. that you must comply throughout the conduct of the study with good research practice standards;
4. If you are completing this project off site, you must obtain prior approval from relevant authorities and adhere to the MSOP off site protocol.
5. to refer any amendment to the protocol to the School Research Ethics Committee (SREC) for approval.
6. You are required to complete an annual monitoring report or end of project report and submit to j.l.mowbray@gre.ac.uk

Please note that the committee also suggested that you may wish to consider contacting Kent Adult Research Unit, who have about 400 subscribers who are willing to take part in research.

Yours sincerely

Dr Sarah Corlett

Appendix 9 Participant invitation letter to the cognitive interview study

May 2015

Dear << *to insert name*>>

I would like to invite you to take part in a research study that I am conducting into using medicines long-term. My name is Barbra Katusiime and I am conducting this work as part of my PhD studies at the Medway School of Pharmacy.

You have been contacted because you or a friend of yours is a member of the Public Involvement in Pharmacy Studies (PIPS) Group at the School. This group helps and advises us on a number of studies looking at medicines and pharmacy services.

In my study, I need to include people who use at least one prescription medicine regularly and have done so for at least one year. If you fall into this category, and are also over 18 and resident in England, then you could take part. If you do take part, I would like to conduct an interview with you, during which I will ask you to complete a paper questionnaire about living with medicines.

Please read the information sheet which accompanies this letter and decide whether you would like to take part in my study. If you would, then please let me know by calling 01634202920 or e-mailing me on bk231@kent.ac.uk and I will arrange a suitable time and place for the interview to take place.

If you need to know more about the study, you can contact me and I will answer any questions, or you can contact my supervisor, Professor Janet Krska on 01634 202950 or by e-mail: j.krska@kent.ac.uk.

Thank you for reading this letter and for considering taking part in my study.

Kind regards

Barbra Katusiime

PhD student, Medway School of Pharmacy, Kent, UK ME4 4TB

Appendix 10 Participant information for cognitive interviewees

medway school of pharmacy

PARTICIPANT INFORMATION SHEET

Title of Project: Revision of the Living with Medicines Questionnaire (LMQ)

Name of Researcher (s): Barbra Katusiime, Janet Krska, Sarah Corlett

You are being invited to take part in a study because you have been identified as potentially being a user of long-term medicine(s). Before you decide if you want to take part, you must understand why the study is being done and what it involves. Please take time to read the following information. Ask if anything is not clear or if you would like more information. Take time to decide if you want to take part or not.

Why is the study being done?
This study is being carried out to revise an existing questionnaire which asks people about what it is like to use regular long-term medicines. We have a version of the questionnaire already but we have found that it does not cover all the issues which people have identified as important to them, so we need to make some changes to it. The questionnaire is entirely derived from the perspective of people who use long-term medicines, therefore we need more people who take prescribed medicines regularly to help us to revise it.

Do I have to take part?
No. It is up to you to decide whether or not to take part. Even if you agree to take part, you can change your mind at any time without giving any reason. If you decide not to take part in the study, your care/medicines will not be affected in any way.

If I do take part, what would I have to do and what would be done to me?
You will be invited to take part in an interview with a researcher, at a time and place of your choosing, during which you will be asked to complete our revised questionnaire while talking out loud about what you are thinking whilst completing it. The researcher may ask you questions about how you interpret words or phrases. This is to make enable us to check that you are interpreting all parts of the questionnaire in the way that we think it should be understood. The researcher will make notes of what you say during the interview, but will also audio-record it to make sure that they don't miss anything that you have said. The interview will take no more than 1 hour to complete. If you agree to take part, you will be asked to sign a consent form, and provide contact details, so that the interview can be arranged.

Are there any risks if I take part?
There are no risks to taking part in this study. However if you wish to stop the interview at any time, the researcher will be happy to do so.

Are there any benefits if I take part?
There are no personal identifiable benefits to taking part; however travel expenses will be paid if you select to undergo an interview at the Medway School of Pharmacy.

Will anyone know that I have taken part?
We will not tell anyone that you have taken part in the study.

What will happen to the results?
The results of your interview will be used to make sure that the final version of the questionnaire is understandable. This questionnaire will then be used to measure the issues associated with using long-term medicines in a large population in England in a further study.

Any personal contact details you provide will be stored securely and will only be used for the purpose of arranging the interview and will be destroyed once all interviews have been completed.

Who is organising and funding the study?
This study is being carried out by a student at Medway School of Pharmacy, as part of a PhD research programme. It is being funded by the Medway School of Pharmacy and the Commonwealth Scholarships Commission, UK.

Who should I contact if I want to know more about the study?
Should you require further information about this study, please contact Professor

Janet Krska on 01634 202950 or by e-mail: j.krska@kent.ac.uk

Who should I contact if I have any concerns about the study or the way it has been conducted?
If you have concerns about how this research study has been conducted please contact the Head of School on K.I.Cumming@gre.ac.uk

Thank you for taking time to consider taking part in this study.

This project has been looked at and approved by the MSoP Research Ethics Committee

Appendix 11 Consent form for cognitive interview participants

medway school of pharmacy

CONSENT FORM for INTERVIEW

Revision of the Living with Medicines Questionnaire (LMQ)

Name of researchers: Barbra Katusiime, Janet Krska, Sarah Corlett

I have read and understand the information provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	Initial Here
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason. (To withdraw from the study, you can call 01634 202920 or e-mail the researcher at bk231@kent.ac.uk).	Initial Here
I understand that any personal information collected during the study will be anonymised and remain confidential	Initial Here
I understand that the interview will be digitally audio recorded and that this recording will be transcribed verbatim.	Initial Here
I agree to an interview to discuss the Living with Medicines Questionnaire with a researcher, which will last no more than 60 minutes.	Initial Here

Name of Participant (Print) Signature Date

Name of person taking consent Signature Date
(If different from the researcher)
Where possible, this is normally signed and dated in presence of the participant

Lead researcher Signature Date

Appendix 12 Participant details form for arranging cognitive interviews

medway school of pharmacy

PARTICIPANT DETAILS FORM

Please complete this form if you are:

☐ **18 years or older**
☐ **Using at least one long-term medicine (the one you get from your doctor)**
☐ **Living in England**

General Details

First Name _____ Surname _____

Address _____

Post Code: _____

Telephone _____

Mobile _____

Email address (optional)

_____

Please post the completed form, alongside the SIGNED consent form, using the free-post envelope provided.

Thank you for your interest in participating in this research study.

Appendix 13 Snowball recruitment text for cognitive interview participants

You may use the text below to talk to your friends about this study.

Hello *'...to insert of your friend here name here.....',*

As you may be aware, I am currently a member of a public engagement group, known as the Public Involvement in Pharmacy Studies (PIPS) at the Medway School of Pharmacy, in Kent. In this group, we help the School in discussing issues relating to patients and their medicines, and also help comment on some of their research ideas and study documents, such as questionnaires, written for patients or members of the general public.

I would like to invite you to participate in a study looking at patients' experiences of using medicines. The researchers have designed the Living with Medicines Questionnaire (LMQ), but the current version has been revised to include other issues that patients feel are important to them. The researchers are seeking your views on what you think of the questions in the LMQ.

Here is an information pack, you can take it and read it whenever you get a chance. You can then contact the researchers, if you are interested and they will make arrangements suitable for you to participate in this study. Please contact the researchers if you have any other questions about this study.

Thank you

Appendix 14 The intermixed version of the LMQ-2.1

LMQ

Living with Medicines Questionnaire

Medicines and Your Day-to-Day Life

This questionnaire seeks **your** views and opinions about the prescribed medicines **you** use and how they affect **your** life.

Medicines include tablets, creams, inhalers, liquids, injections and so on.

This booklet contains statements which cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please **tick only one box** for each statement. If a statement **does not apply to you,** please tick the box for **'Neutral opinion'**.

You may be **using more than one medicine**, please **think about all your medicines** when completing this questionnaire.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
1.	I find getting my **prescriptions** from the doctor difficult.	☐	☐	☐	☐	☐
2.	I find getting my **medicines** from the pharmacist difficult.	☐	☐	☐	☐	☐
3.	I find the **written instructions** on how to use my medicines easy to understand.	☐	☐	☐	☐	☐
4.	Taking medicines is **routine** for me.	☐	☐	☐	☐	☐
5.	I am **satisfied** with the effectiveness of my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
6.	I would be **worried** if I forgot to take my medicines.	☐	☐	☐	☐	☐
7.	I am **comfortable** with the times I should take my medicines.	☐	☐	☐	☐	☐
8.	I worry about **paying** for my medicines.	☐	☐	☐	☐	☐
9.	I worry that I have to take **several medicines** at the same time.	☐	☐	☐	☐	☐
10.	I would like **more say** in the brands of medicines I use.	☐	☐	☐	☐	☐
11.	I **trust** the judgement of my doctor(s) in choosing medicines for me.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
12.	It is **difficult** to identify which medicine is which.	☐	☐	☐	☐	☐
13.	My pharmacist tells me **enough** about my medicines.	☐	☐	☐	☐	☐
14.	I am concerned about possible damaging **long term effects** of taking medicines.	☐	☐	☐	☐	☐
15.	I feel I need **more information** about my medicines.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
16.	I am concerned that I may **forget** to take my medicines.	☐	☐	☐	☐	☐
17.	I can **vary the dose** of the medicines I take.	☐	☐	☐	☐	☐
18.	I find **opening the packaging** of my medicines difficult.	☐	☐	☐	☐	☐
19.	I can **choose** whether or not to take my medicines.	☐	☐	☐	☐	☐
20.	My doctor(s) **listen** to my opinions about my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
21.	My medicines **prevent** my condition getting worse.	☐	☐	☐	☐	☐
22.	I am concerned that I am too **dependent** on my medicines.	☐	☐	☐	☐	☐
23.	I am unhappy with the extent to which my medicines interact with **alcohol**.	☐	☐	☐	☐	☐
24.	I worry that my medicines may **interact** with each other.	☐	☐	☐	☐	☐
25.	My medicines interfere with my **social activities**.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
26.	I am **concerned** about experiencing side effects.	☐	☐	☐	☐	☐
27.	My doctor(s) takes my **concerns** about side effects seriously.	☐	☐	☐	☐	☐
28.	The **side effects** I get are worse than the problem for which I take medicines.	☐	☐	☐	☐	☐
29.	The **side effects** I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	☐	☐	☐	☐	☐

Please Turn Over

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
30.	I can **adapt** my medicine-taking to my lifestyle.	☐	☐	☐	☐	☐
31.	I have to put a lot of **planning and thought** into taking my medicines.	☐	☐	☐	☐	☐
32.	I **don't mind** paying for my medicines because I need them.	☐	☐	☐	☐	☐
33.	My doctor(s) tells me **enough** about my medicines.	☐	☐	☐	☐	☐
34.	My medicines live up to **my expectations.**	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
35.	I am **confident** speaking to my doctor(s) about my medicines.	☐	☐	☐	☐	☐
36.	I am **confident** speaking to my pharmacist(s) about my medicines.	☐	☐	☐	☐	☐
37.	My medicines affect what I **can eat or drink.**	☐	☐	☐	☐	☐
38.	My medicines have **an adverse effect** on the holidays I can take.	☐	☐	☐	☐	☐
39.	I can **change the times** I take my medicines if I want to.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
40.	It is **easy** to keep to my medicines routine.	☐	☐	☐	☐	☐
41.	Changes in **daily routine** cause problems with my medicines.	☐	☐	☐	☐	☐
42.	Taking medicines affects my **driving.**	☐	☐	☐	☐	☐
43.	I find **using** my medicines difficult.	☐	☐	☐	☐	☐
44.	I **accept** that I have to take medicines long term.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
45.	I **understand** what my doctor(s) tells me about my medicines.	☐	☐	☐	☐	☐
46.	I **understand** what my pharmacist(s) tells me about my medicines.	☐	☐	☐	☐	☐
47.	The side effects I get from my medicines are **bothersome.**	☐	☐	☐	☐	☐
48.	I sometimes have to **choose** between buying basic essentials or medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
49.	My medicines allow me to **live my life** as I want to.	☐	☐	☐	☐	☐
50.	I have to **pay** more than I can afford for my medicines.	☐	☐	☐	☐	☐
51.	The health professionals providing my care **know enough** about me and my medicines.	☐	☐	☐	☐	☐
52.	Taking medicines causes me problems with **daily tasks** (such as work, housework, hobbies).	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
53.	My medicines interfere with my **social relationships.**	☐	☐	☐	☐	☐
54.	My medicines interfere with my **sexual life.**	☐	☐	☐	☐	☐
55.	The **side effects** I get from my medicines adversely affect my well-being.	☐	☐	☐	☐	☐
56.	My medicines are **working.**	☐	☐	☐	☐	☐
57.	The **side effects** are worth it for the benefits I get from my medicines.	☐	☐	☐	☐	☐
58.	My **life** revolves around using my medicines.	☐	☐	☐	☐	☐

Please Turn Over

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The questions below seek your OVERALL OPINION about ALL your prescribed medicines.

For each question, please **mark on the line with an 'X'** at the position that best reflects your opinion.

1. Taking everything into account, how **satisfied** are you with your medicines?

0 _____ **10**

Not at all satisfied **Extremely satisfied**

2. How **optimal** do you feel your medicines are for you?

0 _____ **10**

Not at all optimal **Extremely optimal**

3. Overall, **how much of a burden** do you feel your medicines are to you?

0 _____ **10**

Not burden at all **Extremely burdensome**

If you have any other views about how your medicines affect your day-to-day life, please describe them here.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Finally, please answer a few questions **ABOUT YOU AND YOUR MEDICINES**

1. **How many prescription medicines do you use regularly?**

   Please write the **TOTAL** number of medicines here: ☐

   Medicines include tablets, capsules, creams, inhalers, inhalers, liquids, eye drops and so on. Count each different prescription as one medicine.

2. **Which type of medicines do you use regularly?** *You may tick one or both options*
   ☐ Tablets/Capsules ☐ Any other type

3. **How often do you use your medicine(s)?** *You may **tick one or more** options*
   ☐ Once per day ☐ Twice per day ☐ Three times per day
   ☐ More than three times per day ☐ Other, please specify.....

4. **Do you pay for your prescriptions?** ☐ Yes ☐ No

5. **Does someone help you with using your medicines?** ☐ Yes ☐ No
   If you answered yes, who helps you?

   ☐ Spouse/Partner ☐ Relative ☐ Other. If you answered other, please write here who helps you.....
   ☐ Carer/support worker ☐ Friend

6. **Are you:** ☐ Male ☐ Female

7. **What is your age?** *Please write it here in years* ☐

8. **Which ethnic group best describes you?** *(Please tick **one** box only)*

   ☐ White ☐ Asian/Asian British ☐ Other .....
   ☐ Black/Black British/African/Caribbean ☐ Mixed

9. **What is the highest level of education you have completed?**
   ☐ School ☐ Technical College/Apprenticeship ☐ University

10. **What is your employment status?**
    ☐ Employed ☐ Unemployed ☐ Retired ☐ Full-time student

11. **Please tell us your full postcode** ☐☐☐☐ ☐☐☐
    (This is to help us understand how people in different areas answer the survey. We will not be able to identify you and will never contact you or pass your details on to anyone else.)

Thank you for taking the time to complete this questionnaire

Appendix 15 Grouped/Labelled version of the LMQ-2.1

LMQ

Living with Medicines Questionnaire

Medicines and Your Day-to-Day Life

This questionnaire seeks **your** views and opinions about the prescribed medicines **you** use and how they affect **your** life.

Medicines include tablets, creams, inhalers, liquids, injections and so on.

This booklet contains statements which cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please **tick only one box** for each statement. If a statement **does not apply to you,** please tick the box for **'Neutral opinion'.**

You may be **using more than one medicine**, please **think about all your medicines** when completing this questionnaire.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

This section is about **accessing** your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
1.	I find getting my **prescriptions** from the doctor difficult.	☐	☐	☐	☐	☐
2.	I find getting my **medicines** from the pharmacist difficult.	☐	☐	☐	☐	☐

This section is about the **practical issues** you may have while using your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
3.	It is **easy** to keep to my medicines routine.	☐	☐	☐	☐	☐
4.	I find the **written instructions** on how to use my medicines easy to understand.	☐	☐	☐	☐	☐
5.	I find **opening the packaging** of my medicines difficult.	☐	☐	☐	☐	☐
6.	It is **difficult** to identify which medicine is which.	☐	☐	☐	☐	☐
7.	I find **using** my medicines difficult.	☐	☐	☐	☐	☐

This section is about the **cost** of your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
8.	I **don't mind** paying for my medicines because I need them.	☐	☐	☐	☐	☐
9.	I worry about **paying** for my medicines.	☐	☐	☐	☐	☐
10.	I have to **pay** more than I can afford for my medicines.	☐	☐	☐	☐	☐
11.	I sometimes have to **choose** between buying basic essentials or medicines.	☐	☐	☐	☐	☐

This section is about the **effectiveness** of your medicine(s) in managing your condition(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
12.	My medicines are **working.**	☐	☐	☐	☐	☐
13.	My medicines **prevent** my condition getting worse.	☐	☐	☐	☐	☐
14.	I am **satisfied** with the effectiveness of my medicines.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

This section relates to **concerns** you may have about your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
15.	I am **concerned** about experiencing side effects.	☐	☐	☐	☐	☐
16.	I am concerned about possible damaging **long term effects** of taking medicines.	☐	☐	☐	☐	☐
17.	I am concerned that I may **forget** to take my medicines.	☐	☐	☐	☐	☐
18.	I worry that my medicines may **interact** with each other.	☐	☐	☐	☐	☐
19.	I am concerned that I am too **dependent** on my medicines.	☐	☐	☐	☐	☐

This section relates to possible **side effects** of your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
20.	The side effects I get from my medicines are **bothersome.**	☐	☐	☐	☐	☐
21.	The **side effects** I get from my medicines adversely affect my well-being.	☐	☐	☐	☐	☐
22.	The **side effects** are worth it for the benefits I get from my medicines.	☐	☐	☐	☐	☐
23.	The **side effects** I get are worse than the problem for which I take medicines.	☐	☐	☐	☐	☐
24.	The **side effects** I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	☐	☐	☐	☐	☐

This section is about the **routine** of using your medicine(s) in managing your condition(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
25.	Taking medicines is **routine** for me.	☐	☐	☐	☐	☐
26.	I am **comfortable** with the times I should take my medicines.	☐	☐	☐	☐	☐
27.	My medicines allow me to **live my life** as I want to.	☐	☐	☐	☐	☐
28.	My medicines live up to **my expectations.**	☐	☐	☐	☐	☐
29.	I **accept** that I have to take medicines long term.	☐	☐	☐	☐	☐

Please Turn Over

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

This section is about possible **interference** your medicine(s) may cause to your day-to-day life.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
30.	Taking medicines causes me problems with **daily tasks** (such as work, housework, hobbies)	☐	☐	☐	☐	☐
31.	Taking medicines affects my **driving.**	☐	☐	☐	☐	☐
32.	I have to put a lot of **planning and thought** into taking my medicines.	☐	☐	☐	☐	☐
33.	I worry that I have to take **several medicines** at the same time.	☐	☐	☐	☐	☐
34.	Changes in **daily routine** cause problems with my medicines.	☐	☐	☐	☐	☐
35.	My life **revolves** around using my medicines.	☐	☐	☐	☐	☐

This section is about the potential **impact** of using your medicine(s) **on your social life.**

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
36.	My medicines interfere with my **social activities.**	☐	☐	☐	☐	☐
37.	My medicines interfere with my **social relationships.**	☐	☐	☐	☐	☐
38.	My medicines interfere with my **sexual life.**	☐	☐	☐	☐	☐
39.	My medicines affect what I **can eat or drink.**	☐	☐	☐	☐	☐
40.	I am unhappy with the extent to which my medicines interact with **alcohol.**	☐	☐	☐	☐	☐
41.	My medicines have **an adverse effect** on the holidays I can take.	☐	☐	☐	☐	☐

This section is about **your communication with your pharmacist** about your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
42.	My pharmacist tells me **enough** about my medicines.	☐	☐	☐	☐	☐
43.	I **understand** what my pharmacist(s) tells me about my medicines.	☐	☐	☐	☐	☐
44.	I am **confident** speaking to my pharmacist(s) about my medicines.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Please tick the option that applies to each of the statements.

This section is about **your communication with your doctor** about your medicines(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
45.	My doctor(s) tells me **enough** about my medicines.	☐	☐	☐	☐	☐
46.	I **understand** what my doctor(s) tell me about my medicines.	☐	☐	☐	☐	☐
47.	I am **confident** speaking to my doctor(s) about my medicines.	☐	☐	☐	☐	☐
48.	My doctor(s) **listens** to my opinions about my medicines.	☐	☐	☐	☐	☐
49.	My doctor(s) takes my **concerns** about side effects seriously.	☐	☐	☐	☐	☐
50.	I **trust** the judgement of my doctor(s) in choosing medicines for me.	☐	☐	☐	☐	☐
51.	I feel I need **more information** about my medicines.	☐	☐	☐	☐	☐
52.	The health professionals providing my care **know enough about me** and my medicines.	☐	☐	☐	☐	☐

This section is about **the control/ freedom** you feel you have over using your medicine(s).

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
53.	I can **choose** whether or not to take my medicines.	☐	☐	☐	☐	☐
54.	I can **change the times** I take my medicines if I want to.	☐	☐	☐	☐	☐
55.	I can **vary the dose** of the medicines I take.	☐	☐	☐	☐	☐
56.	I can **adapt** my medicine-taking to my lifestyle.	☐	☐	☐	☐	☐
57.	I would be **worried** if I forgot to take my medicines.	☐	☐	☐	☐	☐
58.	I would like **more say** in the brands of medicines I use.	☐	☐	☐	☐	☐

Please Turn Over

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The questions below seek your OVERALL OPINION about ALL your prescribed medicines.

For each question, please **mark on the line with an 'X'** at the position that best reflects your opinion.

1. Taking everything into account, how **satisfied** are you with your medicines?

0 _____ **10**
Not at all satisfied **Extremely satisfied**

2. How **optimal** do you feel your medicines are for you?

0 _____ **10**
Not at all optimal **Extremely optimal**

3. Overall, **how much of a burden** do you feel your medicines are to you?

0 _____ **10**
No burden at all **Extremely burdensome**

If you have any other views about how your medicines affect your day-to-day life, please describe them here.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Finally, please answer a few questions **ABOUT YOU AND YOUR MEDICINES**

1. **How many prescription medicines do you use regularly?**

   Please write the **TOTAL number of medicines** here: ☐
   Medicines include tablets, capsules, creams, inhalers, liquids, eye drops and so on.
   Count each different prescription as one medicine.

2. **Which type of medicines do you use regularly?** *You may tick one or both options*
   ☐ Tablets/Capsules ☐ Any other type

3. **How often do you use your medicine(s)?** *You may **tick one or more** options*
   ☐ Once per day ☐ Twice per day ☐ Three times per day
   ☐ More than three times per day ☐ Other, please specify.....

4. **Do you pay for your prescriptions?** ☐ Yes ☐ No

5. **Does someone help you with using your medicines?** ☐ Yes ☐ No
   If you answered yes, who helps you?

   ☐ Spouse/Partner ☐ Relative ☐ Other. If you answered other, please write here who helps you.....
   ☐ Carer/support worker ☐ Friend

6. **Are you:** ☐ Male ☐ Female

7. **What is your age?** *Please write it here in years* ☐

8. **Which ethnic group best describes you?** *(Please tick **one** box only)*

   ☐ White ☐ Asian/Asian British ☐ Other
   ☐ Black/Black British/African/Caribbean ☐ Mixed .....

9. **What is the highest level of education you have completed?**
   ☐ School ☐ Technical College/Apprenticeship ☐ University

10. **What is your employment status?**
    ☐ Employed ☐ Unemployed ☐ Retired ☐ Full-time student

11. **Please tell us your full postcode** ☐☐☐☐ ☐☐☐
    (This is to help us understand how people in different areas answer the survey. We will not be able to identify you and will never contact you or pass your details on to anyone else.)

Thank you for taking the time to complete this questionnaire.

Appendix 16 Sample analyses of cognitive interview data

Item position	Statement	General observations / Collated analysis	Comments/ Decisions
1	I find getting my prescriptions from the doctor difficult	**None of the participants had difficulty understanding this statement as posed.** However participant 9 raised an issue "*do you mean repeat prescriptions for ongoing medication or, any prescriptions. Because for new prescription,..*" P9	No ammendments
2	I find getting my medicines from the pharmacist difficult	**None of the participants had difficulty understanding this statement as posed.** Exceptions: P1 preferred positive wording (easy rather than difficult), and P5 &P7 spoke of chemist (rather than pharmacist.)	No ammendments; to add chemist to instructions box on front page for clari
3	I find the written instructions on how to use my medicines easy to understand.	**Most participants understood the statement,** except that four refered to written instructions "**on the** label, packet/packaging/box/PIL". A few refered to the patient information leaflet when answering this question.	No ammendments
4	Taking medicines is routine for me	**All participants understood this statement**	No ammendments
5	I am satisfied with effectiveness of my medicines	**All participants understood this statement.** One participant felt that *"Effectiveness can be a range of things, it could mean its working, it doesn't have side effects, and its easy to take, it could be cost effective,...the imediate reaction would be its working."P4*	No ammendments
6	I would be worried if I forgot to take my medicines.	**All participants understood this statement.**	Rewording: If I forgot to take my medicines, it would worry me.
7	I am comfortable with the times I should take my medicines	**All participants understood this statement.**	No ammendments
new 8	I worry about paying for my medicines	**All participants understood this statement.** Although only one paid for their prescriptions, all participants felt that the more items prescribed, the higher the cost- and worryabout paying. They also felt that worrying about paying depends on income levels.	No ammendments
9	I worry that I have to take several medicines at same time.	**All participants understood this statement.** One participant (P9)felt that they could worry about taking several medicines, but they were not taking them at the same time. Some had alternate interpretaions including practical issues of using many medicines at the same time, and the potential for interaction between medicines being taken at the same time.	No ammendments

Overall Analysis | Participant 1 | Participant 2 | Participant 3 | Participant 4 | Participant 5 | Participant 6 | Participant 7 | Participant 8 | Participant 9 | Participant 10 | Participant characteristics | Agreement with statements

Appendix 17 Invitation email to website managers (LMQ-2.1 on-line survey)

May 2015

Dear sir/madam,

PhD project: Patients' experiences of using medicines; revising the Living with Medicines Questionnaire©

I would like to invite you to help us with a research study looking at patients' experiences of using medicines, being conducted at Medway School of Pharmacy, in Kent, as part of my PhD studies. My name is Barbra Katusiime, a postgraduate student, and I am kindly asking you to support our study in a small way.

As you may be aware, many patients have to cope with using medicines long-term, balancing the risk of potential adverse effects against the perceived benefits, plus coping generally with the challenges of managing these on a day- to day basis. Our study is seeking the views of patients belonging to your patient organisation or forum. It will employ a specially designed Living with Medicines Questionnaire© (LMQ) that people can use to share their experiences of what it is like to use medicines on a regular basis. Patients' responses will be used to revise this questionnaire (LMQ). If you are willing, we would like you to help us distribute a link to our on-line questionnaire through your website, for up to three months. The inclusion criteria for the study are those over 18, living in England and who use regular prescription medicines. We envisage that the findings will support the Medicines Optimisation agenda developed by the Royal Pharmaceutical Society, whose objective is to enhance patients' experiences of care (and medicine use).

If you would like more information around the study you can contact my project supervisor Professor Janet Krska either by telephone (01634202950) or email (j.krska@kent.ac.uk).

Many thanks and regards,

Barbra Katusiime

PhD student, Medway School of Pharmacy, Kent, UK ME4 4TB

Appendix 18 NRES Ethics approval letter for criterion validation study

NHS
Health Research Authority
NRES Committee South Central - Oxford C
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173421334

10 August 2015

Miss Barbra Katusiime
Pharmacy Practice Research Office
Medway School of Pharmacy
The Universities of Greenwich and Kent at Medway
ME4 4TB

Dear Miss Katusiime

Study title:	**Evaluation of potential methods for measuring patient's experiences of using medicines in long-term illness; Validation of the Living with Medicines Questionnaire (LMQ)**
REC reference:	**15/SC/0505**
Protocol number:	**01**
IRAS project ID:	**174102**

The Proportionate Review Sub-committee of the NRES Committee South Central - Oxford C reviewed the above application by correspondance.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Natasha Bridgeman, nrescommittee.southcentral-oxfordc@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

The Sub-Committee requested the following changes to the PIS, Invitation Letters and Questionnaires.

- Include a statement of approval to state that the study has been reviewed by the Oxford C Research Ethics Committee.

  You re-submitted the PIS's, Invitation letters and questionnaires with these changes made.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	Version 1	02 August 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor insurance or indemnity (UoK)]	Version 1	02 August 2015
IRAS Checklist XML [Checklist_03082015]		03 August 2015
Letter from sponsor [ResGov 307]	Version 1	28 July 2015
Letters of invitation to participant [Invitation letter to participant (LMQ3]	Version 1	02 August 2015
Letters of invitation to participant [Community Pharmacist]	1	02 August 2015
Letters of invitation to participant [GP practise managers]	1	02 August 2015
Letters of invitation to participant [Outpatient clinic manager]	1	02 August 2015
Letters of invitation to participant [Participant]	1	02 August 2015
Other [LMQ]	3	02 August 2015
Other [Validated questionnaires]	1	02 August 2015
Participant information sheet (PIS) [Clinic Manager]	1	02 August 2015
Participant information sheet (PIS) [GP Manager]	1	02 August 2015
Participant information sheet (PIS) [Participant]	1	02 August 2015
Participant information sheet (PIS) [Pharmacist]	1	02 August 2015
REC Application Form [REC_Form_30072015]		30 July 2015
Research protocol or project proposal [Protocol]	Version 1	02 August 2015
Summary CV for Chief Investigator (CI) [CV for Chief Investigator]	Version 1	02 August 2015
Summary CV for student [CVs for Undergraduate Students (LMQ3 study)]	Version 1	02 August 2015
Summary CV for supervisor (student research) [CVs for Academic Supervisors]	Version 1	02 August 2015

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol

Letter confirming receipt of documents for NRES application

NHS
Health Research Authority

NRES Committee South Central - Oxford C
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173421334

04 August 2015

Miss Barbra Katusiime
Pharmacy Practice Research Office
Medway School of Pharmacy
The Universities of Greenwich and Kent at Medway
ME4 4TB

Dear Miss Katusiime

Study title:	**Evaluation of potential methods for measuring patient's experiences of using medicines in long-term illness; Validation of the Living with Medicines Questionnaire (LMQ)**
REC reference:	**15/SC/0505**
Protocol number:	**01**
IRAS project ID:	**174102**

Thank you for your application for ethical review, which was received on 30 July 2015. I can confirm that the application is valid and will be reviewed by the Proportionate Review Sub-Committee on 10 August 2015. To enable the Proportionate Review Sub Committee to provide you with a final opinion within 10 working days your application documentation will be sent by email to Committee members.

One of the REC members is appointed as the lead reviewer for each application reviewed by the Sub-Committee. I will let you know the name of the lead reviewer for your application as soon as this is known.

Please note that the lead reviewer may wish to contact you by phone or email between 4th July and 11th July to clarify any points that might be raised by members and assist the Sub-Committee in reaching a decision.

If you will not be available between these dates, you are welcome to nominate another key investigator or a representative of the study sponsor who would be able to respond to the lead reviewer's queries on your behalf. If this is your preferred option, please identify this person to us and ensure we have their contact details.

You are not required to attend a meeting of the Proportionate Review Sub-Committee.

Please do not send any further documentation or revised documentation prior to the review unless requested.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	Version 1	02 August 2015

Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor insurance or indemnity (UoK)]	Version 1	02 August 2015
IRAS Checklist XML [Checklist_03082015]		03 August 2015
Letter from sponsor [ResGov 307]	Version 1	28 July 2015
Letters of invitation to participant [Invitation letter to participant (LMQ3]	Version 1	02 August 2015
Non-validated questionnaire [LMQ©]	Version 3	02 August 2015
Other [Invitation letter to community pharmacist]	Version 1	02 August 2015
Other [Pharmacist Information Sheet]	Version 1	02 August 2015
Other [Invitation letter to GP practice managers]	Version 1	02 August 2015
Other [General Practice Manager Information Sheet]	Version 1	02 August 2015
Other [Invitation letter to Outpatient Clinic Manager]	Version 1	02 August 2015
Other [General Practice Manager Information Sheet]	Version 1	02 August 2015
Participant information sheet (PIS) [Participant Information Sheet (LMQ3 Validation)]	Version 1	02 August 2015
REC Application Form [REC_Form_30072015]		30 July 2015
Research protocol or project proposal [Protocol]	Version 1	02 August 2015
Summary CV for Chief Investigator (CI) [CV for Chief Investigator]	Version 1	02 August 2015
Summary CV for student [CVs for Undergraduate Students (LMQ3 study)]	Version 1	02 August 2015
Summary CV for supervisor (student research) [CVs for Academic Supervisors]	Version 1	02 August 2015
Validated questionnaire [Validated Questionnaires & permission for use (TSQM & EQ-5D-5L)]	Version 1	02 August 2015

No changes may be made to the application before the meeting. If you envisage that changes might be required, you are advised to withdraw the application and re-submit it.

Notification of the Sub-Committee's decision

We aim to notify the outcome of the Sub-Committee review to you in writing within 10 working days from the date of receipt of a valid application.

If the Sub-Committee is unable to give an opinion because the application raises material ethical issues requiring further discussion at a full meeting of a Research Ethics Committee, your application will be referred for review to the next available meeting. We will contact you to explain the arrangements for further review and check they are convenient for you. You will be notified of the final decision within 60 days of the date on which we originally received your application. If the first available meeting date offered to you is not suitable, you may request review by another REC. In this case the 60 day clock would be stopped and restarted from the closing date for applications submitted to that REC.

R&D approval

All researchers and local research collaborators who intend to participate in this study at sites in the National Health Service (NHS) or Health and Social Care (HSC) in Northern Ireland should apply to the R&D office for the relevant care organisation. A copy of the Site-Specific Information (SSI) Form should be included with the application for R&D approval. You should advise researchers and local collaborators accordingly.

The R&D approval process may take place at the same time as the ethical review. Final R&D approval will not be confirmed until after a favourable ethical opinion has been given by this Committee.

For guidance on applying for R&D approval, please contact the NHS R&D office at the lead site in the first instance. Further guidance resources for planning, setting up and conducting research in the NHS are listed at http://www.rdforum.nhs.uk. There is no requirement for separate Site-Specific Assessment as part of the ethical review of this research.

Communication with other bodies

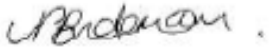
All correspondence from the REC about the application will be copied to the research sponsor and to the R&D office for Medway NHS Foundation Trust. It will be your responsibility to ensure that other investigators, research collaborators and NHS care organisation(s) involved in the study are kept informed of the progress of the review, as necessary.

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/SC/0505	Please quote this number on all correspondence

Yours sincerely



Miss Natasha Bridgeman
REC Assistant

Email: nrescommittee.southcentral-oxfordc@nhs.net

Copy to: *Nicole Palmer*
Dr Edyta McCallum, Medway NHS Foundation Trust

- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

15/SC/0505	Please quote this number on all correspondence

Yours sincerely

pp

Professor David Scott
Vice-Chair

Email: nrescommittee.southcentral-oxfordc@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Nicole Palmer*
Dr Edyta McCallum, Medway NHS Foundation Trust

NRES Committee South Central - Oxford C

Attendance at PRS Sub-Committee of the REC meeting on 10 August 2015

Committee Members:

Name	*Profession*	*Present*
Miss Gemma Davison	Solicitor	Yes
Professor David Scott (Chair)	Pharmacist	Yes
Professor Nigel Wellman	Professor of Health and Human Sciences	Yes

Appendix 19 Research governance letters for criterion validation study

NHS
National Institute for Health Research
RM&G Consortium for Kent & Medway
No 6, The Courtyard
Campus Way
Gillingham Business Park
Kent ME8 0NZ
Phone: 01634 350402
Email: rmgconsortium.km@nhs.net

Miss Barbra Katusiime
Medway School of Pharmacy
The Universities of Greenwich and Kent at Medway
Central Avenue
Chatham Maritime
Kent
ME4 4TB

28th August 2015

Dear Miss Katusiime,

Research study: assurance of governance

I am writing to inform you that we have carried out research governance in relation to the following research study. We are satisfied that there are no ethical or regulatory reasons for the study not to take place at independent primary care providers listed below. This letter only provides NHS R&D assurance to the independent primary care provider that the governance has been completed. Therefore you must ensure that you seek permission from the practice manager in the first instance and provide them with a copy of this letter (refer to condition 1 below).

It is the responsibility of the Sponsor or study team (as delegated by the sponsor) to provide your site with the correct current set of documents for use in the study.

Study details:

Study Title	Evaluation of potential methods for measuring patient's experiences of using medicines in long term illness; Validation of the Living with Medicines Questionnaire (LMQ)
Chief Investigator	Miss Barbra Katusiime
Sponsor name	University of Kent
RMG Consortium's study no.	15-072
Sponsor's reference number	N/A
IRAS number	174102
REC number, REC name	15/SC/0505, South Central - Oxford C

Participating NHS organisations and locations

Geographic area of Independent primary care provider	Date of Assurance	Site or sites to which assurance applies
All Kent & Medway CCGs	28/8/15	All GPs
All Kent & Medway CCGs	28/8/15	All pharmacies

The RM&G Consortium for Kent & Medway provides services to independent primary care providers in Kent and Medway, Kent Community Health NHS Trust, Medway Community Healthcare CIC, Kent & Medway NHS & Social Care Partnership Trust and South East Coast Ambulance NHS Trust

Amendments to date	Amendment number (local ref)
None	

Assurance is provided on the understanding that the study is conducted in accordance with the Research Governance Framework and the Data Protection Act. Assurance is only provided for the activities for which a favourable opinion has been given by the Research Ethics Committee (REC).

The following local conditions will apply

1.	**Addition of GP surgeries**	You must ensure that you obtain permission from the practice manager in the first instance and provide them with a copy of this study assurance letter.
2.	**Sponsorship of study**	The research sponsor will be the organisation named above; the management and design of the study is not the responsibility of the independent primary care provider.
3.	**Confidentiality**	You are required to ensure that all information regarding participants remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the Data Protection Act (1998) and the NHS Confidentiality Code of Practice (www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf). Furthermore, you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.
4.	**Researcher authorisation**	**Important. Only those researchers holding a Letter of Access or Honorary Research Contract, as appropriate, issued by the independent primary care provider may have direct contact with the participants of the study, unless they already hold a substantive or honorary clinical contract with the independent primary care provider.**
5.	**Urgent safety actions**	The research sponsor, or the Chief Investigator, or the Principal Investigator or members of the practice which is a research site, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. You must notify the RM&G Consortium that such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. You should notify the RM&G Consortium within the same time frame as notifying the REC and any other regulatory bodies.
6.	**Serious adverse events (SAE)**	Should an SAE occur during the course of the project, You must immediately notify the RM&G Consortium. This is in addition to your legal duty to report such events to the Sponsor.
7.	**Amendments**	All amendments (whether substantial or minor and including changes to the local research team) need to be submitted in accordance with guidance in IRAS. You should inform this office at the same time as REC is notified to avoid unnecessary delays.
8.	**Indemnity**	You must check with the Sponsor that the indemnity arrangements, as confirmed in the Sponsor's Declaration and described in the application forms, are in place before any participants are recruited.

9.	**Study progression**	You will inform us of any significant developments that occur as the study progresses. You will complete and return any report forms that we send and provide up-to-date information on the number of participants recruited when asked.
10.	**Audit of Study**	Participating sites may also be subject to a random audit of research which will involve a site visit, a requirement to view study documents and a request to interview researchers. A request to audit a research study will be made in writing to you, the Sponsor and the practice manager.
11.	**Study completion**	You will notify the Chief Investigator and this office when the study has completed recruiting participants and when the study is finally finished at your site. You will complete and return the final report that we send and inform us of any publications relating to the study.

Finally, I wish you every success with the study.

Yours sincerely,

Richard Collins

RM&G Manager, RM&G Consortium for Kent and Medway

Medway NHS
NHS Foundation Trust

MEDICAL DIRECTOR'S OFFICE

Direct Line 01634 833944

Medway Maritime Hospital
Windmill Road
Gillingham
Kent
ME7 5NY

26th August 2015

Miss Barbra Katusiime
Pharmacy Practice Research Office
Medway School of Pharmacy
The Universities of Greenwich and Kent at Medway
ME4 4TB

PROJECT TITLE:	Evaluation of potential methods for measuring patient's experiences of using medicines in long-term illness; Validation of the Living with Medicines Questionnaire (LMQ)
R&D Reference:	759
REC Reference:	15/SC/0505
CSP ref:	N/A
Sponsor:	Medway School of Pharmacy
Host site:	Medway Maritime Hospital
Principal Investigator (PI):	Miss Barbra Katusiime

Notification of host site approval

Dear Miss Katusiime

I am writing to inform you that the research approval process for the above named project has been completed successfully. This approval includes the amendments listed at the end of this letter. The documents reviewed this proposal, and approved for use, are shown at the end of this letter.

The conditions for host site approval are as follows:

- The PI must ensure compliance with protocol and advise the host of any change(s) to the protocol. Failure of notification may affect host approval status.
- Under the terms of the Research Governance Framework, the PI is obliged to report any Serious Adverse Events to the Sponsor and the Trust, in line with the protocol and Sponsor requirements. Adverse events must also be reported in accordance with the Trust Policy & Procedures.
- The PI must ensure appropriate procedures are in place to action urgent safety measures.
- The PI must ensure the maintenance of a Trial Master File (TMF) as described in the tables at the end of this document.
- The PI must undergo regular, monitoring, audit and review.
- The PI must ensure that all named staff are compliant with the Data Protection Act, Human Tissue Act 2005, Mental Capacity Act 2005 and all other statutory guidance and legislation (where applicable).
- The PI must report any cases of suspected research misconduct and fraud.
- The PI must provide an annual report to the relevant authorities for all research.
- The PI must give notice of clinical trial closure.
- If there are any changes to the study then please inform the R&D office as these may require R&D approval before they are implemented.

All research carried out at Medway NHS Foundation Trust must be in accordance with the principles set out in the Research Governance Framework for Health and Social Care (2005, second edition, Department of Health).

Please note that on 1st April every year a PI is required to submit no. of patients recruited, approximate no. of staff working on the research project, name and title of any publication and whether the project contributed to a reduction in mortality for the previous financial year.

Failure to comply with the above conditions and regulations will result in the suspension of the research project.

Should you require any further guidance or information on any matter mentioned above, please contact Research & Development Manager, Dr Edyta McCallum.

We wish you every success in your research.

Yours sincerely

Dr Edyta McCallum
R&D Manager

Documents reviewed and approved for use

Name	Version	Date
Letters of invitation to participant [Invitation letter to participant (LMQ3]	1	02 August 2015
Letters of invitation to participant [Community Pharmacist]	1	02 August 2015
Letters of invitation to participant [GP practise managers]	1	02 August 2015
Letters of invitation to participant [Outpatient clinic manager]	1	02 August 2015
Letters of invitation to participant [Participant]	1	02 August 2015
Other [LMQ] 3 02 August 2015	3	02 August 2015
Other [Validated questionnaires]	1	02 August 2015
Participant information sheet (PIS) [Clinic Manager]	1	02 August 2015
Participant information sheet (PIS) [GP Manager]	1	02 August 2015
Participant information sheet (PIS) [Participant]	1	02 August 2015
Participant information sheet (PIS) [Pharmacist]	1	02 August 2015
Research protocol or project proposal [Protocol]	1	02 August 2015

For the purposes of audit and monitoring it is strongly recommended that you maintain a file of study documentation relating to your research. The list below is designed to help you put together your trial master file.

Before the clinical conduct of the trial

Topic	Located in Investigator file	Located in file of sponsor
Signed protocol and amendments, if any, and sample case report form	X	X
Information given to trial subject including Informed consent form, any other written information and advertisement for subject recruitment (if used)	X	X

Financial aspects of the trial (financial agreement between investigator/institution and sponsor)	X	X
Insurance statement (for non NHS sponsored studies)	X	X
Signed agreement between involved parties (if applicable)	X	X
Dated, documented approval of Research Ethics Committee listing documents approved for use	X	X
Other relevant regulatory approvals	X	X
CVs for research team	X	X
Decoding procedures for blinded trials	X	X
Master Randomisation List		X
Pre-trial monitoring report		X
Trial initiation monitoring report	X	X

During the clinical conduct of the trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

Topic	Located in Investigator file	Located in file of sponsor
Any revision to and ethical committee approval to the following documents: • Protocol/amendment(s) • CRF • Informed consent form • Any other written information provided to subjects • Advertisement for subject recruitment (if used) • Any other documents given approval	X	X
MHRA and other relevant regulatory approvals for amendments	X	X
Curriculum vitae for new investigator(s) and sub-investigator(s)	X	X
Updates to normal values/ranges for medical/lab tests included in the protocol	X	X
Updates of medical/lab/technical procedures/tests, certification or accreditation, established quality control or other validation	X	X
Documentation of investigational product and trial related materials shipment	X	X
Monitoring visit reports		X
Relevant communication other than site visits including letters, printed emails, meeting reports, notes of telephone calls	X	X
Signed informed consent forms	X	
Source documents	X	
Signed, dated and completed case report forms	X copy	X original
Documentation of CRF corrections	X copy	X original
Notification by originating investigator to sponsor of serious adverse events and related reports	X	X
Notification by sponsor to investigators of safety information	X	X
Interim or annual reports to independent ethics committees	X	X where required
Subject screening log	X	X where required

Topic	Located in Investigator file	Located in file of sponsor
Subject identification code list	X	
Subject enrolment log	X	
Signature sheet	X	X
Record of retained body fluids/tissue samples (if any)	X	X

After completion or termination of trial

After completion or termination of the trial, all of the documents identified above should be in the file together with the following:

Topic	Located in Investigator file	Located in file of sponsor
Completed subject identification code list	X	
Audit certificate (if available)		X
Final trial close-out monitoring report		X
Treatment allocation and decoding documentation		X
Final report by investigator to Independent ethics committee where required and regulatory authorities if applicable	X	
Clinical study report	X if applicable	X

Researcher's letter of access to Medway Maritime Hospital

Medway NHS
NHS Foundation Trust

Medway Maritime
Hospital
Windmill Road
Gillingham
Kent
ME7 5NY

Miss B Katusiime
128 Balmoral Road
Gillingham
Kent
ME7 4QR

26th August 2015

Dear Miss Katusiime

Letter of access for research

This letter confirms your right of access to conduct research through Medway NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on 26th August 2015 and ends on 31st May 2016 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Medway NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Medway NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Medway NHS Foundation Trust, you will remain accountable to your employer, but you are required to follow the reasonable instructions of Edyta McCallum, R&D Manager, in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Medway NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Medway NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Medway NHS Foundation Trust

premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Medway NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Dr Edyta McCallum
R&D Manager

cc: Karen Dobson – Out Patients Department
Professor Janet Krska University of Kent and Medway – j.krska@kent.ac.uk

Permission for NHS GP practices

NHS
National Institute for Health Research
CRN: Kent, Surrey and Sussex
No 6, The Courtyard
Campus Way
Gillingham Business Park
Kent ME8 0NZ
Phone: 01634 350402
Email: rmgconsortium.km@nhs.net

Miss Barbra Katusiime
Medway School of Pharmacy
The Universities of Greenwich and Kent at Medway
Central Avenue
Chatham Maritime
Kent
ME4 4TB

2nd November 2015

Dear Miss Katusiime,

Permission for research

I am writing to inform you that permission has been granted to the NHS organisation or organisations listed below, for the following research project, on the basis described in the application form, protocol and supporting documentation.

Study details:

Study Title	Evaluation of potential methods for measuring patient's experiences of using medicines in long term illness; Validation of the Living with Medicines Questionnaire (LMQ)
Chief Investigator	Miss Barbra Katusiime
Sponsor name	University of Kent
RM&G Consortium study number	15-072
Sponsor's reference number	N/A
IRAS number	174102
REC number (REC name)	15/SC/0505, South Central - Oxford C

NHS organisations and locations:

Organisation giving permission	Date of Permission	Site or sites to which permission applies
Medway Community Healthcare CIC	2/11/15	The Sunlight Centre & MEDOC

Amendments to date	Amendment number (local ref)
None	

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, ICH GCP (ONLY if applicable), The Data Protection Act (1998) and NHS Trust policies and procedures. Permission is only granted for the activities for which a favourable opinion has been given by the REC or university ethics committee and which have been authorised by the MHRA (ONLY if applicable).

The following local conditions will apply:

1.	**Sponsorship of study**	The research sponsor will be the organisation named above; the management and design of the study is not the responsibility of the trust or trusts giving permission.
2.	**Confidentiality**	You are required to ensure that all information regarding participants remains *secure* and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the Data Protection Act (1998) and the NHS Confidentiality Code of Practice (www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf). Furthermore, you should be aware that under the Data Protection Act (1998), unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.
3.	**Researcher authorisation**	**Important.** Only those researchers holding a Letter of Access or Honorary Research Contract, as appropriate, from the NHS organisation or organisations may have direct contact with the participants of the study or the patients' notes, unless they already hold a substantive or honorary clinical contract with the organisation or organisations.
4.	**Urgent safety actions**	The research sponsor, or the Chief Investigator, or the local Principal Investigator at a research site, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. This office should be notified that such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. This office should be notified within the same time frame of notifying the REC and any other regulatory bodies.
5.	**Serious adverse events (SAE)**	Should an SAE occur during the course of the project, this office must be notified immediately. This is in addition to your legal duty to report such events to the Sponsor.
6.	**Amendments**	All amendments (including changes to the local research team) need to be submitted in accordance with guidance in IRAS. This office should be informed at the same time as the REC or university ethics committee is notified in order to avoid unnecessary delays.
7.	**Indemnity**	You must check with the Sponsor that the indemnity arrangements, as confirmed in the Sponsor's Declaration and described in the application forms, are in place before any participants are recruited.
8.	**Study progression**	You will inform us of any significant developments that occur as the study progresses. You will complete and return any report forms that we send you and provide up-to-date information on the number of participants recruited when asked.

9.	**Audit of Study**	You may also be subject to a random audit of research which will involve a site visit, a requirement to view study documents and a request to interview researchers.
10.	**Study completion**	You will notify the Chief Investigator and this office when the study has completed recruiting participants and when the study is finally finished at your site. You will complete and return the final report that we send you and inform us of any publications relating to the study.
11.	**Presentation of findings**	Medway Community Healthcare CIC expects that the findings of this study will be presented to members of the organisation at an appropriate meeting. You should contact the clinical quality director upon completion of the study to arrange a suitable venue and time.

Finally, I wish you every success with the study.

Yours sincerely,

Richard Collins
CRN: Kent, Surrey and Sussex

copies to Medway Community Healthcare R&D

List of study sites for criterion validation study

List of GP Practices

The College Practice 50/52 College Road, Maidstone, Kent Kent, ME15 6SB	Dr. Mara HK and Partners The Elms Medical Centre Tilley Close Main Road Hoo, Rochester, Kent, ME3 9AE
The Sunlight Centre 105 Richmond Road Gillingham, Kent, ME7 1LX	Dr. Patel JRA & Partners Shorne village Surgery Shorne, Gravesend, DA12 3DY
The Kings Family Practice 30-34 Magpie Hall Road Chatham, Kent, ME4 5JY	

List of community pharmacies

*Karsons Pharmacy, Pattens Lane, Chatham	Paydens Pharmacy, Week Street, Maidstone
Paydens Pharmacy, New Road, Chatham	Williams Chemist, Frindsbury Road, Strood
*Delmergate Pharmacy, Admiral Moore Drive, Aylesford	Link Pharmacy, King Street, Maidstone.

Appendix 20 Study information for criterion validation study

PARTICIPANT INFORMATION SHEET

Title of Project: Validation of the Living with Medicines Questionnaire (LMQ3)

Name of Researcher (s): Barbra Katusiime, Shamaila Jabeen, Hina Sehrish , Humira Mahmood , Moeed Malik , Zeshan Alvi , Munesh Farmah, Tara Saaid, Roseanna Wood, Dr Sarah Corlett, and Professor Janet Krska

You are being invited to take part in a study because you have been identified as potentially being a user of long-term medicine(s). Before you decide if you want to take part, you must understand why the study is being done and what it involves. Please take time to read the following information. Ask if anything is not clear or if you would like more information. Take time to decide if you want to take part or not.

Why is the study being done?

This study is being carried out to test the usefulness of an existing questionnaire which asks people about what it is like to use regular long-term medicines. We have a version of the questionnaire already but we need to confirm if it assesses all the issues which people have previously identified as important to them. The questionnaire is entirely derived from the perspective of people who use long-term medicines, therefore we need more people who take prescribed medicines regularly to help us to complete it.

Do I have to take part?

No. It is up to you to decide whether or not to take part. Even if you agree to take part, you can change your mind at any time without giving any reason. If you decide not to take part in the study, your care/medicines will not be affected in any way.

If I do take part, what would I have to do and what would be done to me?

You will be asked to complete questionnaires, at a time and place of your choosing. Completion of all questionnaires will take no more than 30 minutes. Once completed, you will be asked to return the questionnaires in the free-post envelope provided.

Are there any risks if I take part?

There are no risks to taking part in this study. If you change your mind and decide not to complete the questionnaires you may do so at any time without giving any reason.

Are there any benefits if I take part?

There are no personal identifiable benefits to taking part. We hope you may find the questionnaires useful in expressing your views and opinions about your medicines, and how they affect your day-to-day life.

Will anyone know that I've taken part?

We will not tell anyone that you have taken part in the study.

What will happen to the results?

This questionnaire is intended to measure the issues associated with using long-term medicines in a large population in England. Your results will enable us to confirm whether this is the case.

Any personal details (especially the postcode) will be stored securely, and will only be used to study medicine use experiences of people living in different areas. All details cannot be traced to an individual and we will not contact you or share them with anyone else. Personal details will be destroyed once the research study has been closed.

Implied consent

By completing and submitting your survey responses, you are giving your consent to be part of this study and for your data to be used as described above.

Who is organising and funding the study?

This study is being carried out by students at Medway School of Pharmacy, as part of undergraduate final year projects, and as part of a PhD research programme. It is being funded by the Medway School of Pharmacy and the Commonwealth Scholarships Commission, UK.

Who should I contact if I want to know more about the study?

Should you require further information about this study, please contact Professor Janet Krska on 01634 202950 or by e-mail: j.krska@kent.ac.uk

Who should I contact if I have any concerns about the study or the way it has been conducted?

If you have concerns about how this research study has been conducted please contact the Head of School on K.I.Cumming@gre.ac.uk

Thank you for taking time to consider taking part in this study.

This project has been looked at and approved by the NRES Committee South Central - Oxford C

medway school of pharmacy

Clinic Manager's INFORMATION SHEET

Title of Project: Validation of the Living with Medicines Questionnaire (LMQ)

Name of Researcher (s): Barbra Katusiime, Shamaila Jabeen, Hina Sehrish , Humira Mahmood , Moeed Malik , Zeshan Alvi , Munesh Farmah, Tara Saaid, Roseanna Wood, Dr Sarah Corlett, and Professor Janet Krska

1. **What is the purpose of the study?**

This study aims to validate a specially-designed questionnaire, the Living with Medicines Questionnaire© (LMQ), which helps to assess the extent to which patients who have to take medicines long-term cope with them on a day-to-day basis and how these medicines affect their lives.

2. **Why have I been contacted?**

We have contacted you because you are in-charge of outpatient clinics at the Medway Maritime hospital and we would like your permission to distribute the Living with Medicines Questionnaire© to people who use your clinics. The questionnaire does not ask any questions about your clinics.

3. **Do I have to take agree?**

No. It is up to you to decide whether or not you allow us to distribute questionnaires from your clinic. A student will contact you in the next few weeks either by telephone or face-to-face to agree which clinics we can access.

4. **What will happen if I agree?**

If you agree, a student will visit your clinic at an agreed time and distribute questionnaires to your patients. The student will invite people to complete the questionnaire while waiting for their appointment, so that they are not interfering with your day-to-day activities. People waiting for appointments may present an ideal opportunity for students to approach them, but no-one will be pressured into filling in or taking a questionnaire.

5. **How long will this take?**

The student will try to recruit patients to complete the questionnaire. Some may be willing to complete it while they are waiting in your clinic, but others may want to take it away and send it back in the post. Completion of questionnaires should last no more than 30 minutes.

6. **Are there any risks / benefits involved?**

There are no risks to you or your premises in taking part. We are not offering any payment to clinicians for agreeing to take part.

7. **Who is organising and funding the study?**

This study is being carried out by students at Medway School of Pharmacy, as part of undergraduate final year projects, and as part of a PhD research programme. It is being funded by the Medway School of Pharmacy and the Commonwealth Scholarships Commission, UK.

8. **Who should I contact if I want to know more about the study or to get a copy of the results?**

Professor Janet Krska Tel: 01634 202950 e-mail: j.krska@kent.ac.uk

Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB

9. **Who should I contact if I have any concerns about the study or the way it has been conducted?**

If you have concerns about how this research study has been conducted please contact the Head of School on K.I.Cumming@gre.ac.uk

---

This project has been looked at and approved by the NRES Committee South Central - Oxford C

GENERAL PRACTICE MANAGER
INFORMATION SHEET

Title of Project: Validation of the Living with Medicines Questionnaire (LMQ3)

Name of Researcher (s): Barbra Katusiime, Shamaila Jabeen, Hina Sehrish , Humira Mahmood , Moeed Malik , Zeshan Alvi , Munesh Farmah, Tara Saaid, Roseanna Wood, Dr Sarah Corlett, and Professor Janet Krska

1. **What is the purpose of the study?**

This study aims to validate a specially-designed questionnaire, the Living with Medicines Questionnaire© (LMQ3), which helps to assess the extent to which patients who have to take medicines long-term cope with them on a day-to-day basis and how these medicines affect their lives.

2. **Why have I been contacted?**

We have contacted you because you are in-charge of a GP practice in Kent or Medway and we would like your permission to distribute the Living with Medicines Questionnaire© to people who use your practice. The questionnaire does not ask any questions about your practice.

3. **Do I have to take agree?**

No. It is up to you to decide whether or not you allow us to distribute questionnaires from your practice. A student will contact you in the next few weeks either by telephone or face-to-face to ask if you are willing to allow us to conduct this study in your practice.

4. **What will happen if I agree?**

If you agree, up to two student will visit your practice at an agreed time and distribute questionnaires to your patients. The student will invite people to complete the questionnaire while waiting for their appointments, so that they are not interfering with your day-to-day activities..

5. **How long will this take?**

The student will try to recruit patients to complete the questionnaire. Some may be willing to complete it while they are waiting in your GP practice, but others may want to take it away and send it back in the post.

6. **Are there any risks / benefits involved?**

There are no risks to you or your practice in taking part. We are not offering any payment to practices for agreeing to take part.

7. **Who is organising and funding the study?**

This study is being carried out by students at Medway School of Pharmacy, as part of undergraduate final year projects, and as part of a PhD research programme. It is being funded by the Medway School of Pharmacy and the Commonwealth Scholarships Commission, UK.

8. **Who should I contact if I want to know more about the study or to get a copy of the results?**

Professor Janet Krska Tel: 01634 202950 e-mail: j.krska@kent.ac.uk

Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB

9. **Who should I contact if I have any concerns about the study or the way it has been conducted?**

If you have concerns about how this research study has been conducted please contact the Head of School on K.I.Cumming@gre.ac.uk

---

This project has been looked at and approved by the NRES Committee South Central - Oxford C

medway school of pharmacy

PHARMACIST INFORMATION SHEET

Title of Project: Validation of the Living with Medicines Questionnaire (LMQ)

Name of Researcher (s): Barbra Katusiime, Shamaila Jabeen, Hina Sehrish , Humira Mahmood , Moeed Malik , Zeshan Alvi , Munesh Farmah, Tara Saaid, Roseanna Wood, Dr Sarah Corlett, and Professor Janet Krska

1. What is the purpose of the study?

This study aims to validate a specially-designed questionnaire, the Living with Medicines Questionnaire© (LMQ3), which helps to assess the extent to which patients who have to take medicines long-term cope with them on a day-to-day basis and how these medicines affect their lives.

2. Why have I been contacted?

We have contacted you because you are working in a pharmacy in Kent or Medway and we would like your permission to distribute the Living with Medicines Questionnaire© to people who use your pharmacy. The questionnaire does not ask any questions about your pharmacy.

3. Do I have to take agree?

No. It is up to you to decide whether or not you allow us to distribute questionnaires from your pharmacy. A student will contact you in the next few weeks either by telephone or face-to-face to ask if you are willing to allow us to conduct this study in your pharmacy.

4. What will happen if I agree?

If you agree, a student will visit your pharmacy at an agreed time and distribute questionnaires to members of the public. The student will invite people to complete the questionnaire after they have finished their initial transaction, so that they are not interfering with your day-to-day business. People waiting for prescriptions to be dispensed may present an ideal opportunity for students to approach them, but no-one will be pressured into filling in or taking a questionnaire.

5. How long will this take?

The student will try to recruit patients to complete the questionnaire. Some may be willing to complete it while they are waiting in your pharmacy, but others may want to take it away and send it back in the post. Completion of questionnaires should last no more than 30 minutes.

6. Are there any risks / benefits involved?

There are no risks to you or your business in taking part. We are not offering any payment to pharmacists for agreeing to take part.

7. Who is organising and funding the study?

This study is being carried out by students at Medway School of Pharmacy, as part of undergraduate final year projects, and as part of a PhD research programme. It is being funded by the Medway School of Pharmacy and the Commonwealth Scholarships Commission, UK.

8. Who should I contact if I want to know more about the study or to get a copy of the results?

Professor Janet Krska Tel: 01634 202950 e-mail: j.krska@kent.ac.uk

Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB

9. Who should I contact if I have any concerns about the study or the way it has been conducted?

If you have concerns about how this research study has been conducted please contact the Head of School on K.I.Cumming@gre.ac.uk

---

This project has been looked at and approved by the NRES Committee South Central - Oxford C

Appendix 21 The final instrument (LMQ-3)

LMQ

Living with Medicines Questionnaire

Medicines and Your Day-to-Day Life

This questionnaire seeks **your** views and opinions about the prescribed medicines **you** use and how they affect **your** life.

Medicines include tablets, creams, inhalers, liquids, injections and so on.

You may be **using more than one medicine**, please **think about ALL your medicines** when completing this questionnaire.

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The following statements cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please **tick only one box** for each statement.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
1.	I find getting my prescriptions from the doctor difficult.	☐	☐	☐	☐	☐
2.	I find getting my medicines from the pharmacist difficult.	☐	☐	☐	☐	☐
3.	I am satisfied with the effectiveness of my medicines.	☐	☐	☐	☐	☐
4.	I am comfortable with the times I should take my medicines.	☐	☐	☐	☐	☐
5.	I worry about paying for my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
6.	I worry that I have to take several medicines at the same time.	☐	☐	☐	☐	☐
7.	I trust the judgement of my doctor(s) in choosing medicines for me.	☐	☐	☐	☐	☐
8.	I would like more say in the brands of medicines I use.	☐	☐	☐	☐	☐
9.	I feel I need more information about my medicines.	☐	☐	☐	☐	☐
10.	I am concerned that I may forget to take my medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
11.	I can vary the dose of the medicines I take.	☐	☐	☐	☐	☐
12.	I am concerned about possible damaging long term effects of taking medicines.	☐	☐	☐	☐	☐
13.	I can choose whether or not to take my medicines.	☐	☐	☐	☐	☐
14.	My doctor(s) listen to my opinions about my medicines.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The following statements cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please tick only one box for each statement.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
15.	My medicines prevent my condition getting worse.	☐	☐	☐	☐	☐
16.	I am concerned that I am too reliant on my medicines.	☐	☐	☐	☐	☐
17.	I am concerned that my medicines interact with alcohol.	☐	☐	☐	☐	☐
18.	I worry that my medicines may interact with each other.	☐	☐	☐	☐	☐
19.	My medicines interfere with my social or leisure activities.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
20.	My doctor(s) takes my concerns about side effects seriously.	☐	☐	☐	☐	☐
21.	The side effects I get are sometimes worse than the problem for which I take medicines.	☐	☐	☐	☐	☐
22.	The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	☐	☐	☐	☐	☐
23.	I have to put a lot of planning and thought into taking my medicines.	☐	☐	☐	☐	☐
24.	I get enough information about my medicines from my doctor(s).	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
25.	My medicines live up to my expectations.	☐	☐	☐	☐	☐
26.	I can vary the times I take my medicines.	☐	☐	☐	☐	☐
27.	It is easy to keep to my medicines routine.	☐	☐	☐	☐	☐

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The following statements cover different aspects of using medicines.

Please read each statement carefully and tick the response box that is closest to your personal opinion. Please tick only one box for each statement.

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
28.	Taking medicines affects my driving.	☐	☐	☐	☐	☐
29.	I find using my medicines difficult.	☐	☐	☐	☐	☐
30.	The side effects I get from my medicines are bothersome.	☐	☐	☐	☐	☐
31.	I sometimes have to choose between buying basic essentials or medicines.	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
32.	My medicines allow me to live my life as I want to.	☐	☐	☐	☐	☐
33.	I have to pay more than I can afford for my medicines.	☐	☐	☐	☐	☐
34.	The health professionals providing my care know enough about me and my medicines.	☐	☐	☐	☐	☐
35.	My medicines interfere with my social relationships.	☐	☐	☐	☐	☐
36.	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies).	☐	☐	☐	☐	☐

		Strongly agree	Agree	Neutral opinion	Disagree	Strongly disagree
37.	My medicines interfere with my sexual life.	☐	☐	☐	☐	☐
38.	The side effects I get from my medicines adversely affect my well-being.	☐	☐	☐	☐	☐
39.	My medicines are working.	☐	☐	☐	☐	☐
40.	The side effects are worth it for the benefits I get from my medicines.	☐	☐	☐	☐	☐
41.	My life revolves around using my medicines.	☐	☐	☐	☐	☐

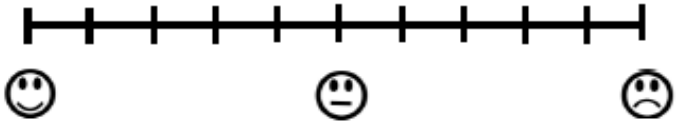
Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

The question below seeks your OVERALL OPINION about ALL your prescribed medicines.

Please mark on the line with an 'X' at the position that best reflects your opinion.

Overall, how much of a burden do you feel your medicines are to you?

0 1 2 3 4 5 6 7 8 9 10



No burden at all

Extremely burdensome

If you have any other views about how your medicines affect your day-to-day life, please describe them here.

LMQ© Version 3 2015

Medicines and Your Day-to-Day Life – Living with Medicines Questionnaire

Finally, please answer a few questions ABOUT YOU AND YOUR MEDICINES

1. **How many prescription medicines do you use regularly?**

   Please write the TOTAL number of medicines here: ☐

Medicines include tablets, capsules, creams, inhalers, inhalers, liquids, eye drops and so on.
Count each different prescription as one medicine.

2. **Which type of medicines do you use regularly?** *You may tick one or both options*
   ☐ Tablets/Capsules ☐ Any other type

3. **How often do you use your medicine(s)?** *You may **tick one or more** options*
   ☐ Once per day ☐ Twice per day ☐ Three times per day
   ☐ More than three times per day ☐ Other, please specify.....

4. **Do you pay for your prescriptions?** ☐ Yes ☐ No

5. **Does someone help you with using your medicines?** ☐ Yes ☐ No
   If you answered yes, who helps you?

   ☐ Spouse/Partner ☐ Relative ☐ Other. If you answered other, please write here who helps you.....
   ☐ Carer/support worker ☐ Friend

6. **Are you:** ☐ Male ☐ Female

7. **What is your age?** *Please write it here in years* ☐

8. **Which ethnic group best describes you?** *(Please tick **one** box only)*

   ☐ White ☐ Asian/Asian British ☐ Other
   ☐ Black/Black British/African/Caribbean ☐ Mixed .....

9. **What is the highest level of education you have completed?**
   ☐ School ☐ Technical College/Apprenticeship ☐ University ☐ Other

10. **What is your employment status?**
    ☐ Employed ☐ Unemployed ☐ Retired ☐ Full-time student

11. **Please tell us your full postcode** ☐☐☐☐ ☐☐☐
    (This is to help us understand how people in different areas answer the survey. We will not be able to identify you and will never contact you or pass your details on to anyone else.)

Thank you for taking the time to complete this questionnaire

Scoring method for the final LMQ-3

Scoring method for LMQ© Version 3 2015

Composition: 41 Likert-type statements (strongly agree to strongly disagree), one visual analogue scale, free-text open question, and participant characteristics.

Domain 1 – Relationships with HCPs /Communication with HCPs about medicines

Statement numbers: 7, 14, 20, 24, 34 (total = 5; scoring range 5 - 25)

Number	Statement	Direction	Scoring
7	I trust the judgement of my doctor(s) in choosing medicines for me.	+	1 = Strongly disagree 5 = Strongly agree
14	My doctor(s) listen to my opinions about my medicines.	+	1 = Strongly disagree 5 = Strongly agree
20	My doctor(s) take my concerns about side effects seriously	+	1 = Strongly disagree 5 = Strongly agree
24	I get enough information about my medicines from my doctor(s).	+	1 = Strongly disagree 5 = Strongly agree
34	The health professionals providing my care know enough about me and my medicines.	+	1 = Strongly disagree 5 = Strongly agree

Domain 2 – Practicalities/ Practical difficulties

Statement numbers: 1, 2, 4, 10, 23, 27, 29 (total = 7; scoring range 7– 35)

Number	Statement	Direction	Scoring
1	I find getting prescriptions from the doctor difficult	-	1 = Strongly agree 5 = Strongly disagree
2	I find getting medicines from the pharmacist difficult	-	1 = Strongly agree 5 = Strongly disagree
4	I am comfortable with the times I should take my medicines.	+	1 = Strongly disagree 5 = Strongly agree
10	I am concerned that I may forget to take my medicines.	-	1 = Strongly agree 5 = Strongly disagree
23	I have to put a lot of planning and thought	-	1 = Strongly agree

	into taking medicines		5 = Strongly disagree
27	It is easy to keep my medicines routine	+	1 = Strongly disagree 5 = Strongly agree
29	I find using my medicines difficult	-	1 = Strongly agree 5 = Strongly disagree

Domain 3 – Cost-related burden

Statement numbers: 5, 31, 33 (total = 3; scoring range 3 - 15)

Number	Statement	Direction	Scoring
5	I worry about paying for my medicines.	-	1 = Strongly agree 5 = Strongly disagree
31	I sometimes have to choose between buying basic essentials or medicines.	-	1 = Strongly agree 5 = Strongly disagree
33	I have to pay more than I can afford for my medicines.	-	1 = Strongly agree 5 = Strongly disagree

Domain 4 – Side effects

Statement numbers: 21, 22, 30, 38 (total = 4; scoring range 4 - 20)

Number	Statement	Direction	Scoring
21	The side effects I get are sometimes worse than the problem for which I take medicines.	-	1 = Strongly agree 5 = Strongly disagree
22	The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).	-	1 = Strongly agree 5 = Strongly disagree
30	The side effects I get from my medicines are bothersome.	-	1 = Strongly agree 5 = Strongly disagree
38	The side effects I get from my medicines adversely affect my well-being.	-	1 = Strongly agree 5 = Strongly disagree

Domain 5 – Effectiveness

Statement numbers: 3, 15, 25, 32, 39, 40 (total = 6; scoring range 6 - 30)

Number	Statement	Direction	Scoring
3	I am satisfied with the effectiveness of my medicines	+	1 = Strongly disagree 5 = Strongly agree
15	My medicines prevent my condition getting worse	+	1 = Strongly disagree 5 = Strongly agree
25	My medicines live up to my expectations	+	1 = Strongly

			disagree 5 = Strongly agree
32	My medicines allow me to live my life as I want to.	+	1 = Strongly disagree 5 = Strongly agree
39	My medicines are working	+	1 = Strongly disagree 5 = Strongly agree
40	The side effects are worth it for the benefits I get from my medicines.	+	1 = Strongly disagree 5 = Strongly agree

Domain 6 – Attitudes/ Concerns about medicine use

Statement numbers: 6, 8, 9, 12, 16, 17, 18 (total = 7; scoring range 7 - 35)

Number	Statement	Direction	Scoring
6	I worry that I have to take several medicines at the same time	-	1 = Strongly agree 5 = Strongly disagree
8	I would like more say in the brands of medicines I use.	-	1 = Strongly agree 5 = Strongly disagree
9	I feel I need more information about my medicines.	-	1 = Strongly agree 5 = Strongly disagree
12	I am concerned about possible damaging long term effects of taking medicines.	-	1 = Strongly agree 5 = Strongly disagree
16	I am concerned that I am too reliant on my medicines.	-	1 = Strongly agree 5 = Strongly disagree
17	I am concerned that my medicines interact with alcohol.	-	1 = Strongly agree 5 = Strongly disagree
18	I worry that my medicines may interact with each other.	-	1 = Strongly agree 5 = Strongly disagree

Domain 7 – Impact / Interference to day-to-day life

Statement numbers: 19, 28, 35, 36, 37, 41 (total = 6; scoring range 6 - 30)

Number	Statement	Direction	Scoring
19	My medicines interfere with my social or leisure activities.	-	1 = Strongly agree 5 = Strongly disagree
28	Taking medicines affects my driving.	-	1 = Strongly agree 5 = Strongly disagree
35	My medicines interfere with my social relationships.	-	1 = Strongly agree 5 = Strongly disagree
36	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies)	-	1 = Strongly agree 5 = Strongly disagree
37	My medicines interfere with my sexual life.	-	1 = Strongly agree 5 = Strongly disagree
41	My life revolves around using my medicines	-	1 = Strongly agree 5 = Strongly disagree

Domain 8 – Control/ Autonomy to vary regimen

Statement numbers: 11, 13, 26 (total = 3, scoring range 3 - 15)

Number	Statement	Direction	Scoring
11	I can vary the dose of the medicines I take.	+	1 = Strongly disagree 5 = Strongly agree
13	I can choose whether or not to take my medicines	+	1 = Strongly disagree 5 = Strongly agree
26	I can vary the times I take my medicines.	+	1 = Strongly disagree 5 = Strongly agree

Total/composite score for Likert-type statements range 41 – 205; higher scores indicate worse experiences of medicine use (higher medicine burden).

Visual Analog Scale (VAS) item, score range 0 – 10.

	Statement	Scoring
VAS item	Overall, how much of a burden do you feel your medicines are to you?	0= No burden at all 10= Extremely burdensome

All negatively phrased items are reverse scored to compute composite scores.

Based on English sample data, burden categories using LMQ-3 composite scores:
No burden at all (41-73); Minimal burden (74-106); Moderate burden(107-139);High burden(140-172); and Extremely high burden (173-205).

Burden categories based on VAS scores are: no burden at all (0.0- 2.0); minimal burden (2.1 -4.0); moderate (4.1-5.9); high burden (6.0-7.9); extremely high burden (8.0-10.0).

Participants with high or extremely high burden on both assessments can be categorised as ‘certainly’ high/extreme burden.

Appendix 22 The Treatment Satisfaction Questionnaire for Medication

TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in what you think about the effectiveness, side effects, and convenience experienced when using the medication *over the last two to three weeks, or since you last used it*. For each question, please place one tick next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes
☐$_0$ No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g. strength, energy levels)?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Somewhat Dissatisfied
☐$_4$ Slightly Dissatisfied

☐$_5$ Not at all Dissatisfied
☐$_{(5)}$ Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g. ability to think clearly, stay awake)?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Somewhat Dissatisfied
☐$_4$ Slightly Dissatisfied
☐$_5$ Not at all Dissatisfied
☐$_{(5)}$ Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g. anxiety/fear, sadness, irritation/anger)?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Somewhat Dissatisfied
☐$_4$ Slightly Dissatisfied
☐$_5$ Not at all Dissatisfied
☐$_{(5)}$ Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

Scoring **TSQM**

Quintiles, Inc.

4820 Emperor Boulevard
Durham, North Carolina 27703

Treatment Satisfaction Questionnaire for Medication (version II format b)

Scoring Algorithm: TSQM Scale scores range from 0 to 100 and no score should be lower or higher than these limits. This is computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100. (see below) *[Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent]*

EFFECTIVENESS: ([(Item 1 + Item 2) – 2] divide by 12) * 100
If one item is missing: ([(Use the completed item)) – 1] divide by 6) * 100

SIDE-EFFECTS:
(All 'NA' responses are coded as '5' indicating 'Not at all Dissatisfied')

([Sum(Item 4 to Item 6) – 3] divide by 12) * 100

If one item is missing: ([(Sum(*the two completed items*)) – 2] divide by 8) * 100

CONVENIENCE: ([Sum(Item 7 to Item 9) – 3] divided by 18) * 100
If one item is missing: ([(Sum(*the two completed items*)) – 2] divided by 12) * 100

GLOBAL SATISFACTION: ([Sum(Item 10 to Item 11) – 2] divided by 12) * 100

Permission to use the TSQM

Quintiles, Inc.
4820 Emperor Boulevard
Durham, North Carolina 27703
Telephone 919.998.2109
Fax 919.998.7838

June 26th, 2015

Medway School of Pharmacy, Universities of Kent & Greenwich, UK
Barbra Katusiime, Ms
Central Avenue, Chatham Maritime
Kent, ME4 4TB, UK
Tel: +44(0)1634 202920
E-mail: bk231@kent.ac.uk

Re: Treatment Satisfaction Questionnaire for Medication **Version II** ('TSQM') and TSQM Scoring Algorithm

Dear Barbra Katusiime (Ms),

With this letter, we are providing Barbra Katusiime with the TSQM and TSQM Scoring Algorithm, and the following translations specified in Attachment A (collectively, the 'Licensed Materials'), solely for use in connection with protocol 01/2015, titled Evaluation of potential methods for measuring patients' experiences of using medicines; Validation of the Living with Medicines Questionnaire (LMQ©).

All rights, title and interest in and to the Licensed Materials are owned by Quintiles Transnational Corp., Quintiles, Inc.'s corporate affiliate and licensor. The Licensed Materials are protected by copyright, trade secret and other laws. The TSQM may only be administered by you in connection with patients participating in the Project. The TSQM Scoring Algorithms may only be provided to your Personnel (defined below) participating in the Project for the sole purpose of scoring the TSQM.

In the event that you need a translation of the Licensed Materials which Quintiles Transnational Corp. and Quintiles, Inc. (individually and collectively, 'Quintiles') do not already have in their possession, you may, following receipt of the written consent of Quintiles, translate the Licensed Materials into the requested language; provided that the translation (a) is carried out in accordance with applicable standards for linguistic adaptation, and (b) is carried out in accordance with Quintiles' instructions and subject to Quintiles' final approval. Upon completion of the translation of the Licensed Materials pursuant to this procedure, you will promptly provide Quintiles, Inc. with a copy of the translated Licensed Materials together with a copy of the translation certificate executed by the official translator. While you will not be charged a license fee for a translation conducted under this process, any such translation will be deemed Licensed Materials under this agreement and all rights that you and any party acting on your behalf may have therein shall be assigned to Quintiles Transnational Corp.

All Licensed Materials are provided by Quintiles subject to terms regarding confidentiality as set forth in this paragraph and in the following paragraph. You will receive, maintain, and hold the Licensed Materials in strict confidence and will use at least the same level of care in safeguarding them that you use with your own confidential material. You will not reveal the Licensed Material to your employees, directors, or staff (collectively, 'Personnel') except to the extent required to administer the Project, and you will ensure that all Personnel treat the Licensed Material as strictly confidential and abide by the terms of this letter. You will not disclose the Licensed Materials to any third party or utilize Licensed Materials, except as provided herein, without first having obtained Quintiles' written consent to such disclosure or utilization.

The obligations of confidentiality set forth herein shall not apply to the Licensed Materials to the extent the Licensed Materials are required by law to be disclosed by you, provided that you notify Quintiles prior to such disclosure and offer Quintiles an opportunity to contest such disclosure.

You agree to indemnify and hold harmless Quintiles and its affiliates, and its and their directors, officers, employees and agents from and against all liabilities, losses, claims, demands, damages, costs and expenses (including but not limited to reasonable legal fees and disbursements) suffered or incurred by Quintiles and arising as a direct or indirect result of (a) any claim, proceeding, civil, criminal or administrative action, inquiry, suit or legal action instituted against Quintiles and in respect of your use of the Licensed Materials, or (b) your negligence or willful misconduct or that of any of your directors, officers, employees or agents.

Quintiles shall not be responsible for any special, incidental, consequential, exemplary or punitive damages relating to this letter or the License Materials even if Quintiles has knowledge of the possibility of such potential damages.
You will ensure that any paper, article or other publication reporting results obtained using the Licensed Materials will include the following reference:

> Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes.

2004;2:12. Those seeking information regarding or permission to use the TSQM are directed to Quintiles, Inc. at www.quintiles.com/TSQM or TSQM@quintiles.com

You agree to inform Quintiles upon the completion of the Project. Following completion of your use of the Licensed Materials as contemplated by this letter, or upon termination of your rights to such materials hereunder, you agree to provide to Quintiles all data from the Project that could be used to build the psychometric properties of the Licensed Materials. Any data provided will be used by Quintiles only to improve the psychometric properties of the Licensed Materials.

The rights granted to you hereunder are subject to your acceptance of the terms of this letter as shown below. The nonrefundable license fee is waived for your institution.

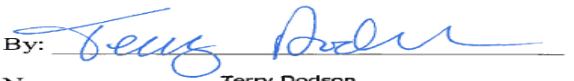
Upon completion of your use of the Licensed Materials as contemplated by this letter, or upon termination of your rights to such materials hereunder, you shall destroy all copies of the Licensed Materials and have an officer of your institution certify in writing that all Licensed Materials have been destroyed, however you may retain one copy of the Licensed Materials under seal for regulatory purposes.

The terms of this letter shall be considered effective as of the date signed by you below ('Effective Date').
This letter agreement may be executed in any number of counterparts, each of which when executed and delivered, shall constitute an original, but all of which together shall constitute one agreement binding on all parties, notwithstanding that all parties are not signatories to the same counterpart. Transmission by fax or by electronic mail of an executed counterpart of this letter agreement shall be deemed to constitute due and sufficient delivery of such counterpart. This letter agreement and any amendment or modification may not be denied legal effect or enforceability solely because it is in electronic form, or because an electronic signature or electronic record was used in its formation.

Should you have any questions, please contact us immediately. To confirm your acceptance of these terms and conditions, please sign below and return this letter electronically to TSQM@Quintiles.com.
Sincerely,

Sincerely,

Quintiles, Inc.

By: 

Name: Terry Dodson

Title: Sr. Director
Global Business Operations

Appendix 23 The EQ-5D-5L Questionnaire

🕐 Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about

I have slight problems in walking about

I have moderate problems in walking about

I have severe problems in walking about

I am unable to walk about

SELF-CARE

I have no problems washing or dressing myself

I have slight problems washing or dressing myself

I have moderate problems washing or dressing myself

I have severe problems washing or dressing myself

I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

PAIN / DISCOMFORT

I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

ANXIETY / DEPRESSION

I am not anxious or depressed

I am slightly anxious or depressed

I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

We would like to know how good or bad your health is TODAY.

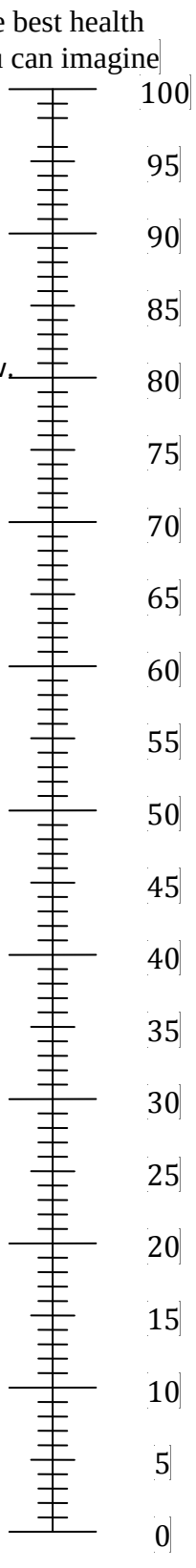
This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.



YOUR HEALTH TODAY =

Permission to use the EQ-5D-5L

26 June 2015

Dear Ms. / Mr. Barbra Katusiime,

EQ-5D registration

Thank you for registering your research at the EuroQol Research Foundation's website.

As the study 'Evaluation of potential methods for measuring patients' experiences of using medicines; Validation of the Living with Medicines Questionnaire (LMQ)' you registered involves low patient numbers (600) you may use the EQ-5D-5L instrument (Paper version) free of charge.

Please note that separate permission is required if any of the following is applicable:
- Funded by a pharmaceutical company, medical device manufacturer or other profit-making stakeholder;
- Number of respondents over 5000
- Routine Outcome Measurement;
- Developing or maintaining a Registry;
- Digital representations (e.g. PDA, Tablet or Web)

Please find attached the English (United Kingdom) EQ-5D-5L version (word format). A brief user guide is downloadable from the EuroQol website (www.euroqol.org).
Please note that over the next months the first value sets associated with the EQ-5D-5L system will be published. It will take time before 5L value sets will be available for most countries. Please check our website to see which 5L value sets are currently available. In the meantime, the EuroQol Research Foundation has developed a 'crosswalk' between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system, resulting in interim value sets for the new EQ-5D-5L descriptive system. Please find all information about the crosswalk from EQ-5D-5L data to the EQ-5D-3L value sets on-line at the EuroQol website (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html).

Kind regards,
Mandy van Reenen
Communications Officer
EuroQol Research Foundation
T: +31 88 4400190
E: vanreenen@euroqol.org
W: www.euroqol.org

Appendix 24 Ethics approval and advert for test-retest study

medway school of pharmacy

May 2016

Barbra Katusiime,

Your application for amendments to the project entitled '*Test-retest reliability of the Living with Medicines Questionnaire (LMQ- version 3)*' has now been considered on behalf of the Medway School of Pharmacy School Research Ethics Committee (SREC).

I am pleased to inform you that your study has been approved, with immediate effect.

I must remind you of the following:

1. that if you are intending to work unaccompanied with children or with vulnerable adults, you will need to apply for a DBS check; the project must be conducted under the supervision of someone who has an up-to-date DBS check; you must not be in the presence of children alone except if you have completed a DBS check;
2. that you must comply with the Data Protection Act (1998);
3. that you must comply throughout the conduct of the study with good research practice standards;
4. If you are completing this project off site, you must obtain prior approval from relevant authorities and adhere to the MSOP off site protocol.
5. to refer any amendment to the protocol to the School Research Ethics Committee (SREC) for approval.
6. You are required to complete an annual monitoring report or end of project report and submit to j.mowbray@kent.ac.uk

Yours sincerely

Dr Sarah Corlett

On 9 May 2016, at 10:43, B.Katusiime <bk231@kent.ac.uk> wrote:

Dear Dr Swift,

I hope this email finds you well.

Following our telephone conversation this morning, I am delighted to inform you that I have now obtained ethics approval for the project (letter attached).

Thank you for agreeing to help me with my PhD study, which is looking at patients' experiences of using medicines, and is being conducted at Medway School of Pharmacy.

This study aims to test the reliability of a questionnaire (known as the Living with Medicines Questionnaire, LMQ version 3) which is designed to evaluate people's experiences of using regular medicines. It will consist of repeated completion of the same survey on two occasions, separated by two weeks.

I would like your help in distributing a link to my online questionnaire (purple link below) through your participant database, the Kent Adult Research Unit (KARU) and to post this survey link to the KARU website, where possible.

https://msp.eu.qualtrics.com/SE/?SID=SV_ekEVUe3u9O4LpKB

You may copy and paste the above link in any email, website, or any other media accessible to KARU.

The inclusion criteria for this study are:

- Age 18 or over;
- Using regular prescription medicines;
- Living in England;

Participants should be willing to complete the questionnaire on two separate occasions (2 weeks apart), and be able to read English as the questionnaire is currently available in only the English language. I have included all this information in the survey link, and only those who meet the inclusion criteria will access the full survey.

People on your database who complete the survey will be requested to contact me directly, so that I can distribute the repeat survey.

I have also attached the following to this email:

a) Advertising information (also included in the survey link)
b) Participant information sheet (also included in the survey)

We will offer entry to a prize draw for a £30 shopping voucher for those who complete both surveys.

We envisage that the findings will contribute to evidence for the questionnaire's validation, for which we have already assessed construct and criterion-referenced validity. We plan to publish the work once this last stage is complete, which will allow the LMQ to be used in future studies as a patient-reported outcome measure.

If you would like more information around the study you can contact my project supervisor Professor Janet Krska (copied in this email) either by telephone (01634202950) or email (j.krska@kent.ac.uk).

Many thanks and regards,

Barbra Katusiime
PhD student

Tel: (+44) 1634 202920
E-mail: bk231@kent.ac.uk

Permission to recruit participants via the Kent Adult Research Unit

From: Hannah Swift
Sent: 21 March 2016 17:30
To: B.Katusiime
Cc: Janet Krska; Sarah Corlett

Subject: Re: Permission- Kent Adult Research Unit database

Thanks Barbra,

Apologies for not getting back to your enquiries sooner - I've been working to a number of project deadlines. When you study is ready to go I will be happy to advertise it to our volunteers - just provide me with the email you wish to send.

Look forward to hearing from you,

Hannah

Hannah Swift PhD
Eastern ARC Research Fellow

E2.10a Keynes College
School of Psychology
University of Kent
CT2 7NP

01227 824649

Living with Medicines Survey

Do you use regular medicines?

Would you like to take part in a **research study about what it's like to use regular medicines? ☑**

Are you happy to complete a survey on two separate occasions, about two weeks apart?

If you complete both surveys, you will have the chance to win a £30 shopping voucher!

To find out more about this research study, please follow the link below:

https://msp.eu.qualtrics.com/SE/?SID=SV_ekEVUe3u9O4LpKB

You may **copy and paste the link above in a new browser** or **click on the link while pressing down CTRL** on your computer key board

Appendix 25 Comments for participants with high/extremely high medicine burden

Domain	National-level sample for those completing the LMQ 2.1 (N=34) Comment	Gender	Age	No. of Meds	Form	Freq	VAS score	LMQ composite score
Int, SE, Eff, Prac, Concr	*'they make me tired, meaning that I can't get out a lot, have a social life or do a lot of activities. They also make me dizzy, so I often find it hard to be fully focused and present during conversations, making social interaction sometimes challenging. But they are mostly effective for what they were prescribed for. I find it hard to remember to take them and to fit this in to whatever activity I am doing, but this isn't really something I can avoid so I just have to get used to it.'*	F	18	1	Tablets/ capsules	bd	8.0 -10	High burden (140-172)
SE, Concr, Eff	*'They make me feel tired, I should not drink alcohol and my latest one I have been put on makes me constipated. Above all my epilepsy still isn't controlled.'*	F	38	3	Tablets/ capsules	bd	8.0 -10	High burden (140-172)
HCP, Concr	'*The doctors do not take into account how the patient actually feels, they go on blood results, with hypothyroidism they go on the TSH level, which does not reflect the true level, without taking into account the Free T4 and Free T3 and reverse T3. I have proved them wrong with my blood tests, I am not converting T4 to T3, I need T3, but they won't give it. I am now self-medicating with T3 together with T4, and feel much better. So much for the medical profession, they are criminal, ruining our lives.'*	F	60	2	Tablets/ capsules	≥qid	8.0 -10	High burden (140-172)
SE, HCP, Eff	*'started sodium valproate age 37. Menstruation stopped witout the menopause, age45. I had many serious health issues, nystagmus, tremors, spelling and mental ability, lost power in my legs, my doc. wouldn't believe me through it all but they all finishe when I was taken off it 2014. I tried 3 other drugs which all had bad effects + I''m also on Lamictal and Diazepam(I've drug resistant epilepsy and Diaz is the only med that controls them on bad days) which I suspect very much' P3*	F	60	3	Tablets/ capsules	bd	8.0 -10	High burden (140-172)
SE, Int	*'Sometimes I feel they're not worth taking due to the tiredness side effects I get. Sometimes I struggle to do anything and sometimes I worry that at work this is perceived across as being lazy.'*	F	23	1	Tablets/ capsules	bd	8.0 -10	High burden (140-172)

Domain	*Table continued* Comment	Gender	Age	No. of Meds	Form	Freq	VAS score	LMQ composite score
Concr, HCP, SE,	*'Some of the medicines are short term, others long term and one is for life. Liiothyronine treats my thyroid, and is for life - this is taken 4 - 5 times a day, is supposed to be 30 mins clear either side of eating and drinking, 4 hrs clear of anything wih iron in it - impossible; so it gets ignored. Diclofenac helps with joint and back pain which comes with fibromyalgia and Sjogrens syndrome - long term, but I can stop easily if I wish to take a break. Very unhappy this week to discover that I should hae had my kidney function tested on it, but never have in 10 years. No one ever discussed heart problems either. Gabapentin is for nerve pain due to a broken ankle, it makes me feel suicidal. I am withdrawing, but it is hard - sleeping far too much, dopey struggling to form sentences, etc. Chlorpromazin is the least used, it's for managing hypomania: it renders me unconscious quickly and takes several days to get over.'*	F	64	4	Tablets/ capsules	≥qid	8.0 -10	High burden (140-172)
SE, Int, Concr	*'severe side effects, need to be near a loo, cant do housework, having frightening experiences cant breath, make me feel worse, weight gain, cramps, exhaustion'*	F	51	3	Mixed	tid	8.0 -10	High burden (140-172)
?	*'Ruin it'*	F	42	1	Tablets/ capsules	od	8.0 -10	High burden (140-172)
SE	*'One medicine in particular (a statin) has such bad side effects that it completely wrecks my quality of life.'*	F	55	2	Tablets/ capsules	bd	6.0 -7.9	High burden (140-172)
Eff	*'My medication is not totally addressing my health issue!*	F	71	1	Tablets/ capsules	bd	6.0 -7.9	High burden (140-172)
Int, Concr	'*More of a hindrance than a help but this medication apparently is 'cheap as chips' (my doctor's comment not mine). So is the only 'recognised and accepted/licenced in the UK' so there is nothing other than this on offer. The UK is well behind USA, Canada, and Germany for example, so other patients lucky enough to live in these countries have more choice than in the UK and their health flourishes...why is this so, it's just not right???*	F	60	1	Tablets/ capsules	od	8.0 -10	High burden (140-172)
Prac, Int, Concr	*'Medicines heavily dictate my eating patterns which increase a lot of difficulty planning my day around work, classes and any social engagements. Thus, my long-term medication use leads to social exclusion - it's easier to refuse and avoid social engagemets because of when medications need to be taken, etc.'*	F	28	7	Mixed	≥qid	8.0 -10	Extremely high burden(173-205)

Table continued

Domain	Comment	Gender	Age	No. of Meds	Form	Freq	VAS score	LMQ composite score
SE, HCP	*'Medication affects my weight and has an impact on my physical activity and state of mind. Diet is very difficult and Drs are not helpful.'*	F	55	5	Mixed	≥qid	8.0 -10	High burden (140-172)
SE, Eff	*'Make me feel older than I am, suppress my already low energy levels re MS, not sure about their effectiveness. Although this is probably more about my condition and how best to manage it than the drugs I'm given to lessen the impact of my MS.'*	F	49	6	Mixed	≥qid	6.0 -7.9	High burden (140-172)
SE,	*'Make me drowsy so I tend to sleep alot. I feel that I am wasting my life away sleeping the side effects off!'*	F	52	11	Mixed	≥qid	8.0 -10	High burden (140-172)
Int, Cost,	*'it is hell!! I have very little social life, virtually no sex life, and it is a nightmare having to pay out ridiculous amounts for drugs that are essential to me being able to function!'*	F	21	7	Tablets/capsules	≥qid	8.0 -10	High burden (140-172)
SE, Concr, HCP,	*'I no longer take my medication because the side effects were making my illness worse. I was on strong pain medication for ME and FM over 20yrs and found that I was not only addicted but they were also making me sicker. I went through dreadful with drawl ad my Dr just offered me stronger medication instead. I am not on any of the medication my Dr prescribed for my illness which now makes my Dr think I'm cured. Because I won't take any more strong medication my illness is still bad but I don't have the side effects that I have lived with for so long.'*	F	52	7	Mixed	≥qid	8.0 -10	High burden (140-172)
Concr	*'I haven't a choice about taking them but no investigations have been carried out about why'*	F	44	2	Tablets/ capsules	bd	8.0 -10	High burden (140-172)
Prac	*'I have to leave considerable time after food before I take my meds, so I take them in the middle of the night.'*	F	60	2	Tablets/ capsules	bd	6.0 -7.9	High burden (140-172)
Concr	*'I have to choose between taking medication and being able to function. Either the medication or the pain/sleep problems rule my days & nights.'*	F	51	8	Tablets/ capsules	≥qid	8.0 -10	High burden (140-172)
SE, Int, Eff,	*'I have put weight on my sex life is suffering as I have lost all feelings for it and the dosage of painkiller is low as I can't cope with side effects and so the pain never goes it just gets bearable'*	F	49	7	Mixed	≥qid	6.0 -7.9	High burden (140-172)
SE, Concr	*'I have ongoing dizziness as a side effect, which increases my existing tendency to accidents. My most recent long-term prescription drug is causing weight gain - an issue as I am already 'obese'. I have gone up one dress size in spite of my efforts to los weight before this started.'*	F	64	10	Mixed	≥qid	6.0 -7.9	High burden (140-172)
Eff, SE, Concr	*'I get fed up with having to take meds that rarely solve my problems, and often create more, and having to put up with side effects. But I have no choice.'*	F	69	9	Mixed	≥qid	6.0 -7.9	High burden (140-172)

Table continued

Domain	Comment	Gender	Age	No. of Meds	Form	Freq	VAS score	LMQ composite score
HCP, SE, Concer, Cost	*'I feel that I'm the person that has to search for appropriate medication; last year Drs kept saying there was nothing they could do; took ME Association book with me and asked if I could try duloxetine ; said they'd ask psychiatrist: I asked if they could ask ME consultant. Drs reduced painkillers in March; means that I have to choose when I can cope with pain; stops activity. The nausea from duloxetine is bad, Drs told me not to take domperidone daily as it's now been shown to thicken arteries in long ter use; I've been on it for 15 years. Drs won't prescribe paracetamol or buccastem; have to buy them. After 8 yrs diagnosis finally Drs have agreed to let me have free prescriptions on the unable to get there on my own. I don't feel that I have a GP that I an talk to or who believes or supports me. I have no faith in them now.'*	F	54	9	Tablets/capsules	≥qid	6.0 -7.9	High burden (140-172)
Concr,	*'I do well on branded medication, some of the generics are not very good. I had been stable on a branded medication for over 10 years, but they have just discontinued it. So now I feel anxious that this latest generic will put me back to square one.!'*	F	55	5	Mixed	tid	6.0 -7.9	High burden (140-172)
SE, Int	'*I constantly feel tired, and spaced out I struggle to sometimes do basic tasks because I feel so tired and drained yet I am a complete insomniac. I am a totally different person since been diagnosed with epilepsy and wish it would just go away I am so depressed'*	F	38	6	Tablets/ capsules	≥qid	6.0 -7.9	High burden (140-172)
SE, Concr	*'I am on Seroxat 15 years get severe withdrawal when try to come off now I have ME my life is ruined my nervous system is shot and there is no help'*	F	57	5	Mixed	bd	8.0 -10	Extremely high burden (173-205)
Concer	*'Have no quality of life'*	F	43	26	Mixed	≥qid	8.0 -10	Extremely high burden (173-205)
Eff	'Find them ineffective , but nothing else is available for my condition'	F	53	3	Mixed	tid	6.0 -7.9	High burden (140-172)
SE	*'Depression, anxiety, tiredness, suicidal thoughts, insomnia, nausea & memory loss.'*	M	38	2	Tablets/capsules	bd	8.0 -10	High burden (140-172)

Table continued

Domain	Comment	Gender	Age	No. of Meds	Form	Freq	VAS score	LMQ composite score
SE, Int, Concer, HCP	*'Constantly feeling tired, I have no energy. They have removed my libido. I can no longer legally drive under the new laws. I cannot enjoy a glass of wine any longer. There are food interactions that the GP does not inform you of and they can change your life. Avoiding food when I go out or people cook for me etc.'*	M	59	5	Mixed	≥qid	8.0 -10	Extremely high burden(173-205)
Concr	'Change to generic Levothyroxine approximately 5 years ago has very badly adversely affected my health.'	F	69	2	Tablets/ capsules	bd	8.0 -10	High burden (140-172)
SE	*'Breathing difficulties. Attitude.'*	F	18	14	Tablets/capsules	bd	6.0 -7.9	High burden (140-172)
Concr	'*A constant reference to being ill'*	M	60	8	Mixed	bd	6.0 -7.9	High burden (140-172)
	Sample 1 completing paper questionnaires (LMQ-2.1)							
HCP	*'some doctors don't know long term damage'*	M	49	5	Tablets/Capsules	tid	8.0-10.0	High burden (140-172)
Eff	*'My life is often controlled by pain which means it is therefore controlled by my pain medication (opiates)'*	F	51	6	Tablets/Capsules	tid	6.0-7.9	High burden (140-172)
HCP, Eff	*'My GP never reviews my medication, however i do depend on them/ need them for some quality of life and staying out of hospital.'*	F	38	12	Any other type	tid	6.0-7.9	High burden (140-172)
HCP	*'I feel like my doctors are trying to kill me!'*	F	61	7	Both types	tid	8.0-10.0	High burden (140-172)
HCP	*'Doctor doesn't listen to me'*	F	49	6	Both types	tid	8.0-10.0	High burden (140-172)

Note. HCP- patient-doctor relationships and communication about medicines; Eff- Effectiveness or lack of it; Concr- General concerns about medicines; SE- Side Effects; Int- interferences with day-to-day life; Cost- Cost-related burden; Prac- Practical difficulties ; bd -twice daily; od –once daily; tid- thrice daily; qid – four times daily; F-Female; M-Male

Appendix 26 Item tracking matrix

	Original item (LMQ-1)	Statistical Recommendation	Professional judgement (Round 1)	Professional judgement (Round 2)	Interim item (LMQ-2.1)	Comments before qualitative cognitive Interviews	Decision after discussion of findings from cognitive interviews	Final item agreed after EFA & CFA data (LMQ-3)
1	The instructions on my medicines are **easy** to follow	Retain *Comment* Highly negatively skewed (ceiling effects likely)	Retain	Reword	I find the written instructions on how to use my medicines easy to understand.		Leave as is	Item dropped
2	I find getting my prescriptions from the doctor difficult	Retain	Retain	Leave as is			Leave as is	Same as original
3	I find getting my medicines from the pharmacist difficult	Retain	Retain	Leave as is			Leave as is; To define pharmacist/chemist on cover page	Same as original
4	My medicines are important to me*	Remove *Comment* Most negatively skewed item (ceiling effects).	Remove	Deletion-confirmed			Item dropped	
5	I find opening the packaging of my medicines difficult	Retain	Retain	Leave as is			Leave as is	Item dropped
6	I am concerned about running out of medicines	Remove	Remove	Deletion-confirmed	None			Item dropped
7	It is difficult to identify which medicine is which	Retain	Retain	Leave as is		Moderately skewed (ceiling effects likely)	Leave as is	Item dropped

8	It is easy to keep my medicines routine	Retain	Retain	Leave as is			Leave as is (Acknowledged repetition between with ''taking medicine is routine'. To be left in, and wait for EFA after on-line survey	Same as original .
9	I would be concerned if I forgot to take my medicines	Retain	Retain	Reword; replace 'concerned' with 'worried'	I would be **worried** if I forgot to take my medicines.	To separate ordering item 9 & 10 in revised questionnaire	**Reworded to:** If i forgot to take my medicines, it would worry me.	Item dropped
10	I am concerned that I may forget to take my medicines	Retain	Retain	Leave as is			Leave as is	Same as original item
11	I am concerned about experiencing side effects	Retain	Retain	'		†To review later when new items on side effects have been generated.	Leave as is	Item dropped
12	I am concerned about possible damaging long term effects of taking medicines	Retain	Retain	Leave as is			Leave as is	Same as original item.
13	Taking medicines is routine for me	Retain	Retain	Leave as is			Leave as is; Potential for removal after EFA as it is perceived repetitious with 'it is easy to keep my medicines routine'	Item dropped
14	I am comfortable taking medicines I have been prescribed	Remove	Remove	Deletion-confirmed		To include a global satisfaction item at a later stage.		Item dropped
15	I am comfortable with the times I should	Retain	Retain	Leave as is			Leave as is	Same as original

	take my medicines							
16	I find the patient leaflet in my medicines containers useful	Remove	Remove	Deletion-confirmed				Item dropped
17	I find using my medicines difficult	Retain	Retain	Leave as is			Leave as is	Same as original
18	I am satisfied with effectiveness of my medicines	Retain	Retain	Leave as is			Leave as is	Same as original
19	I am concerned that I am too dependent on my medicines	Retain	Retain	Leave as is			Replaced the word dependent with reliant. I am concerned that I am too reliant on medicines.	I am concerned that I am too reliant on my medicines
20	I am confident speaking to my doctor (s) about my medicines	Retain	Retain	Leave as is			Rephrase to negative wording: I am **not** confident speaking to my doctor (s) about my medicines.	Item dropped
21	I understand what my doctor(s) tell me about my medicines	Retain	Retain	Leave as is/Retain		Moderate ceiling effect	Leave as is	Item dropped
22	The information my doctor(s) give me about my medicines is useful	Retain	Retain	Deletion-confirmed	To be deleted	Thought to be redundant; & too many items in 'doctor' domain	Reworded item	I get enough information about my medicines from my doctor(s).
23	I am confident speaking to my pharmacist about my medicine	Retain	Retain	Leave as is			**Rephrase to negative wording:** I am **not** confident speaking to my pharmacist about my medicine.	Item dropped

24	I understand what my pharmacist tells me about my medicines.	Retain	Retain	Leave as is			Leave as is	Item dropped
25	The information my pharmacist gives me about my medicines is useful	Retain	Retain	Reworded	My pharmacist tells me enough about my medicines.		**Reworded to:** I get enough information about my medicines from my pharmacist.	Item dropped
26	I sometimes run out of medicines	Remove	Remove	Deletion-confirmed		Removed firstime		Item dropped
27	I accept that I have to take medicines long term	Retain Highly negatively skewed (ceiling effects likely)	Retain	Leave as is			Leave as is	Item dropped
28	My medicines allow me to live my life as I want to	Retain	Retain	Leave as is			Leave as is	Same item
29	My life revolves around using my medicines	Retain	Retain	Leave as is			Leave as is	Same as original item
30	My medicines live up to my expectations	Retain	Retain	Leave as is			Leave as is	Same item
31	My medicines prevent my condition getting worse	Retain	Retain	Leave as is			Leave as is	Same item
32	Taking medicines interferes with my **social life**	Retain	Retain	Rewording-replace 'life' with activities	My medicines interfere with my social activities	Reword for specificity	**Addition of 'social or leisure activities':** My medicines interfere with my social **or leisure** activities.	My medicines interfere with my social **or leisure** activities.
33	I trust the judgement of my doctor(s) in choosing medicines for me	Retain	Retain	Leave as is			Leave as is	Same as original item
34	I have to put a lot of	Retain	Retain	Leave as is			Leave as is	Same item

	planning and thought into taking my medicines							
35	Taking medicines causes me problems with daily tasks (such as work, housework, hobbies).	Retain	Retain	Leave as is			**Leave as is :** thought to be repetitious and as a potential side effect question	Same as original item
36	I am unhappy with the extent to which my medicines interact with alcohol	Remove (removed after CFA)	Retain	Leave as is;		Item removed by both EFA & CFA; but discussion suggested that we leave it in for the cognitive interviews & see what happens in the next phase.	**Reworded:** ***Replaced the word unhappy with concerned; deleted*** *with the extent to which:* <u>I am concerned that my medicines interact with alcohol.</u>	Reworded I am concerned that my medicines interact with alcohol.
37	Taking medicines affects my driving ability	Retain	Retain	Reword; to delete the word 'ability'	Taking medicines affects my driving.	Noted that 'driving ability' is different from 'driving'.	Leave as is	Reworded: Taking medicines affects my driving.
38	I worry that I have to take several medicines at the same time of day.	Retain	Retain	Leave as is			Leave as is	Reworded to: I worry that I have to take several medicines at the same time.
39	The side effects I get are worse than the problem for which I take medicines	Remove	Remove	<u>Retain & see what happens.</u>		Discussion suggested that we leave it in for the cognitive interviews & see what happens in the next phase alongside other new	**Addition of 'sometimes'** <u>The side effects I get are **sometimes** worse than the problem for which I take medicines</u>	The side effects I get are sometimes worse than the problem for which I take medicines.

						items on side effects.		
40	I worry that my medicines may interact with each other	Retain	Retain	Leave as is			Leave as is	Same as original item
41	I can choose whether or not to take my medicines	Retain	Retain	Leave as is			Leave as is	Same as original item
42	My doctor(s) spend enough time discussing my medicines with me.	Retain	Retain	Deletion-confirmed	Delete	Item deleted & thought to be redundant		Item dropped
43	I know enough about my medicines	Remove (Removed after CFA)	Retain	Reword item; Delete 'I know' to 'my doctor tells me..'	**My doctor tells me** enough about my medicines.	Item loaded moderately on the doctor-domain.		**Item dropped**
44	I am able to balance my day to day life with taking medicines	Remove	Remove	Deletion-confirmed	Delete			Item dropped
45	There is enough sharing of information about my medicines between the different health professionals providing my care	Remove	Remove	Deletion-confirmed	Delete			Item dropped
46	I have a say in the brands of medicines I use	Remove	Remove	Reword	**I would like more** say in the brands of medicines I use.	Item thought to be of concern in the autonomy domain. (Change of direction to a negatively worded item).	Leave as is	Item reworded: I would like more say in the brands of medicines I use.
47	I always follow my doctor (s) advice	Retain	Remove	Deletion-confirmed	Delete	Removed as it appeared to measure		Item dropped

	about my medicines					adherence		
48	I **sometimes** feel I need to get information from other sources(such as books, friends, internet) about my medicines.	Remove	Remove	Reword; Delete the word 'sometimes' & 'I 'to get' & 'from other sources(such as books, friends, internet)'	I feel I need more information about my medicines.	Items on information about medicines thought to be lacking in LMQ	Leave as is	Item reworded: I feel I need more information about my medicines.
49	I can change the times I take my medicines if I want to	Retain	Retain	Leave as is	Same		Item reworded: Replaced ' change' with vary: I can **vary** the times I take my medicines .	I can vary the times I take my medicines
50	The health professionals providing my care know enough about me and my medicines.	Retain	Retain	Leave as is	Same		Leave as is	Same as original
51	My medicines are working	Retain	Retain	Leave as is	Same		Leave as is	Same
52	I can adapt my medicine-taking to my lifestyle	Remove	Removed	Leave as is	Same		**Reworded to:** I can adapt using my medicine(s) to fit my lifestyle.	Item dropped
53	My doctor listens to my opinions **and concerns** about my medicines	Retain	Retain	Reword; Delete '**and concerns'**	My doctor listens to my opinions about my medicines.		Add an 's' to doctors: Minor rewording	My doctor(s) listen to my opinions about my medicines.
54	I can vary the dose of the medicines I take	Retain	Retain	Leave as is	Same		Leave as is	Same as original item
55	I get too much information about my medicines	Remove	Remove	Deletion-confirmed	Delete			Item dropped
56	Changes in daily	Retain	Retain	Leave as is	Same		**Add an 's' to cause:** Changes in daily	Item dropped

	routine cause problems with my medicines						routine causes problems with my medicines.	
57	My doctor (s) take my concerns about side effects seriously	Retain	Retain	Leave as is	Same		Leave as is	Same as original
58	My medicines have an **adverse effect** on my sexual life	Remove (removed after CFA)	Retain	Rewording; replaced 'have an **adverse effect** on…' with 'interfere with…'	My medicines interfere with my sexual life	Amendments proposed 12/03/15	Leave as is	Reworded: My medicines interfere with my sexual life.
59	The side effects are worth it for the benefits I get from my medicines	Remove	Remove	Retain & see what happens.		Discussion suggested that we leave it in for the cognitive interviews & see what happens in the next phase alongside other new items on side effects.	Leave as is	Same
60	The medicines I use have an adverse effect on the holidays I can take	Retain	Retain				Reword: The medicine (s) i use make it difficult to plan holidays..	Item dropped
New items	My medicines can interfere with my social relationships'			Rewording: deleted 'can'				My medicines interfere with my social relationships.
	I am concerned that my medicine(s) affect what i can eat or drink.						Item dropped	Item dropped
	I have to pay more than I can afford for my medicines.							Retained

	I sometimes have to choose between buying basic essentials or medicines.							Reained
	I worry about paying for my medicines. Dropped: I don't mind paying for my medicines because I need them dropped:							Same item
	The side effects I get from my medicines adversely affect my well-being.							Retained
	The side effects I get from my medicines are bothersome.						Leave it as but look Look in Thesaurus for alternative word to bothersome (Troublesome, inconvenient, worrisome, niggling, incommodious, difficult, vexing, annoying). Leave as 'bothersome'	
	The side effects I get from my medicines interfere with my day-to-day life (e.g. work, housework, sleep).							
	My medicines interfere with my social or leisure activities.							
	Taking everything into							Item dropped from final measure

	account, how satisfied are you with your medicines?							
	How optimal do you feel your medicines are for you?						Reworded On balance, do you feel your medicines are right for you?	Deleted from the final measure
	Overall, how much of a burden do you feel your medicines are to you?							Item retained and 10-cm visual analogue scale modified to include 1cm marks and smiley faces at anchors

Amendments/addition to instructions on cover page:
You may be using MORE THAN ONE MEDICINE, please respond to the statement with consideration to ALL your medicines.

Changes to last page on participant characteristics

No	Original question	Proposed amendments/rationale	Agreed question
1	How many medicines do you take regularly? <4 4-8 >8 (Medicines include tablets, capsules, creams, inhalers, liquids, eye drops, and so on-count each different prescription as one medicine)	To amend response option to a numeric figure rather than a category? To amend stem to include the word 'use' medicine rather than to take medicine?	How many prescription medicines do you use regularly? (please write the total number of medicines here) ……
New 2	Which type of medicines do you use? (You may tick one or more) Tablets in bottles Capsules in bottles Inhalers Injections Tablets in foil strip Capsules in strips Oral liquid Eye drops/ Ear drops Other (Please specify)……..	Can we ask the dosage form(s) of medicines used? Hypothesis: Non-oral dosage forms may be more burdensome than oral dosage forms	Which type of medicines do you use? Partially accepted: Suggested options Tablets/Capsules Any other type
New 3	How often do you use your medicine(s)? Once daily, Twice daily Thrice daily More than three times daily Other (please specify)……	Can we ask the frequency of using medicines? Hypothesis: Frequency of administration is associated with medication burden	How often do you use your medicine(s)? *Once per day Twice per day etc.*
4	What is your employment status? Employed Unemployed Retired	The categories of full or part-time employment are being proposed to assess the income (indirectly), and predict cost-related medication burden.	What is your current employment status? Added : Full-time student add Other (please specify
5	Does someone help you with your medicines? Yes No If you answered yes, who helps you? Spouse/partner Relative Other	Same question as In LMQ version 1 Propose to amend response items to include carer (or support worker), and friend	If you answered yes, who helps you? Spouse/partner Friend Relative Carer /support worker Other…….. *Added 'Friend' & 'Carer/Support worker' in options*
New 8	Please provide us with your full postcode …… Note: We will NOT pass on your details to anyone else, we will not contact you or send you junk mail. We want to study if people living in different areas have different experiences of using medicines	Proposed item to predict deprivation levels …	