‘BEYOND THE DESIRED EFFECT’: PATIENTS’ EXPERIENCES IN IDENTIFYING AND MANAGING SIDE EFFECTS FROM MEDICINES

BERNADINE O’DONOVAN

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DECLARATION

"I certify that this work has not been accepted in substance for any degree and is not concurrently being submitted for any other 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 I have not plagiarised the works of others".

Bernadine O' Donovan Professor J Krska

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ABSTRACT

Side effects from medicines can have considerable negative impact on peoples' daily lives. As a result of an aging UK population and attendant multi-morbidity, an increasing number of medicines are being prescribed for patients, leading to increased risk of unintended side effects. The aim of this study was to explore experiences and opinions of patients and the public in identifying and managing side effects from medicines. It also sought to develop a novel causality scale for use by patients to assess suspected side effects.

A mixed methods approach with four phases was selected. In Phase One surveys were distributed in pharmacies to gather information on patients' experiences of side effects and recruit potential interviewees for the following phase (935 surveys distributed; 230 returned). In-depth interviews were conducted in Phase Two with 15 people who had experienced side effects. These explored their opinions and experiences and informed Phase Three. This phase developed and validated a side effects assessment tool for patients' use (SE-PAST). The validation consisted of two strands, initial validation (by 31 assessors) followed by online validation (273 completed responses). In Phase Four 2285 patient reports to the Yellow Card Scheme were examined to learn about experiences of side effects, to investigate the value of patient reports to pharmacovigilance and to compare experiences of Yellow Card reporters to the public.

This study provided novel insights into the strategies employed by patients to identify and manage their side effects. Patients seeking side effect information used a variety of information sources and the findings suggest that a key aspect of source selection may be a hierarchy of source characteristics. The strategies used to manage side effects varied, including both cognitive and behavioural responses such as non-adherence and consultation with healthcare professionals. The findings suggest that these strategies were influenced by a range of factors including established health beliefs; previous experience of side effects and cognitive biases. Areas of similarity and difference were identified between Yellow Card reporters and the general public. There was evidence of patterns in the causative drugs, the type and impacts of effects between those who report side effects and the wider public; however there was a difference in coping strategies between these groups, with non-adherence being more prevalent among Yellow Card reporters. Most on-line users of the SE-PAST agreed it would encourage them to report their side effect or talk to a healthcare professional about it.

The thesis provides a unique and insightful perspective on patients' personal experiences of side effects, with implications for policy and practice. It has established that side effects can have noteworthy impacts with prolonged consequences on many aspects of patients' lives.

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GLOSSARY

Abbreviation	Expansion	Definition
ADR	Adverse drug reaction	An ADR is a reaction to a drug, or a combination of drugs, which is harmful and unintended and that occurs at a dose normally used for prophylaxis, diagnosis or treatment
ADRWG	Committee on safety of medicines working group	An independent advisory committee which advised the UK Licensing Authority on the quality, efficacy and safety of medicines
CHM	Commission on Human Medicines	Advisory body to UK ministers on the safety, efficacy and quality of medicinal products
CIS	Cancer Information Service	Provides up-to-date information on cancer incidence, mortality and survival rates in UK
CSM	Common Sense Model	Leventhal's common sense model (CSM) is used to understand people's responses to illness. The model suggests that illness perceptions can influence coping strategies and health outcomes
HCP	Healthcare Professional	Individual who provides preventive, curative or rehabilitative health care to people, families or communities
ICSRs	Individual case safety reports	Reports of adverse events for individual patients
IPA	Interpretative Phenomenological Approach	An approach to qualitative research with an idiographic focus
MBSS	Miller Behavioral Style Scale	A measure of coping styles that can be used in clinical settings
MeSH	Medical Subject Headings	(U.S.) National Library of Medicine's controlled vocabulary thesaurus and is used for indexing articles for MEDLINE/PUBmed/NLM databases
MOH	Medicine overuse headache	Rebound headaches which occur when analgesics are overused by people to relieve headaches
NHS	National Health Service	Publicly funded health care service in the UK
OTC	Over the counter	Medicine available to a consumer without a prescription
Patient YC	Patient reporter to YC scheme	The patient who experienced and reported the suspected ADR or their representative who made the report on his or her behalf
PIL	Patient information leaflet	Leaflet containing comprehensive information that is accessible to and understandable so that patients can use their medicine safely and appropriately
PV	Pharmacovigilance	Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of drugs

QDL	Quality of Daily Life	An assessment of the quality and well-being of an individual's daily life
SE	Side Effects	An unintended effect, as a result of using medicines which could be therapeutic or adverse
SECope	Side Effect(s) Coping Questionnaire	A measure of coping with HIV treatment side effects based on the Stress and Coping theory
SO	Superordinate	Classification of themes that represents a higher order or category
SPC	Summary of Product Characteristics	Produced by pharmaceutical companies it explains how to use and prescribe a medicine used by doctors, nurses and pharmacists
SSRs	Spontaneous reporting systems	Established to gather reports of suspected ADRs and managed by national and international regulatory bodies, drug manufacturers and drug monitoring programmes
UMC	Uppsala Monitoring Centre (Field name for WHO-UMC)	Collects and assesses information about the benefits and risks of medicines from members' pharmacovigilance centres
WHO	World Health Organisation	UN agency dealing with international public health
WHO-PIDM	World Health Organisation the Programme for International Drug Monitoring	Collects and assesses information about the benefits and risks of medicines from members' pharmacovigilance centres
WHO-UMC	World Health Organization Collaborating Centre for International Drug Monitoring.	UMC works by collecting, assessing and communicating information from member countries' national pharmacovigilance centres in regard to the benefits, harm, effectiveness and risks of medicines
YC	Yellow card report	Report made to the MHRA by HCPs or patients about problems with medicines or medical devices
YCS	Yellow Card Scheme	UK system for collecting information on suspected ADRs to medicines

CHAPTER 1: INTRODUCTION

1.1 General background

Side effects from medicines can have a considerable impact on peoples' daily lives. This impact can be significant and extend into many areas with physical, economic, social and/or psychological effects (Anderson et al., 2011; Butt et al., 2011; De Langen et al., 2008; Dibonaventura et al., 2012; Krska et al., 2011; Shet et al., 2014). Medicines are frequently the most cost effective and least invasive medical treatments available to individuals. However, an increasingly aging population and attendant multi-morbidity in combination with numerous clinical guidelines mean there are an increasing number of medicines being prescribed for people by health professionals today. This has led to an increase in the risk of unintended harmful effects or adverse drug reactions (ADRs) in the ambulatory care setting. Research into these adverse reactions identified risk factors such as age, complex medical history and low income status with older patients more likely to experience severe ADRs (Wu et al., 2003). These risk factors add to the frequent morbidity and mortality associated with ADRs (Mugosa et al., 2016). Health researchers and healthcare organisations worldwide have realised that ADRs are a public health issue which requires strategic attention and effective interventions.

1.2 Adverse Drug Reactions (ADRs)

1.2.1 Definition and characteristics

The definition of an adverse drug reaction (ADR) used by the World Health Organisation (WHO) is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (WHO, 2014). An adverse reaction is therefore a damaging and unintended response to a medicine. ADRs can be further described in the following categories: Augmented effects; Bizarre effects; Continuous effects; Delayed effects or End of Use effects (Medicines and Healthcare Products Regulatory Agency, MHRA, 2014). See *Table 1.1* on the following page for a full description of these categories.

Table 1.1: Description of ADR categories (Table adapted from Edwards & Aronson, 2000)

CATEGORIES	DESCRIPTION
A – Augmented effects	Augmentation of the drug's pharmacodynamic properties e.g. sedation with muscle-relaxant
B – Bizarre effects	Effects unrelated to drug's pharmacodynamic properties e.g. allergic reactions
C – Continuous effects	Effects that persist in the long term e.g. pharmacological dependency/ rebound effect
D – Delayed effects	Effects occur after drug discontinuation e.g. cancer/ birth defects/impaired fertility
E –End of Use effects	Effects associated with drug withdrawal e.g. insomnia/anxiety

ADRs can also be classified as expected reactions - listed in the Summary of the Product Characteristics (SPC) which is produced by manufacturers as part of the licensing process for every authorised medicinal product on the market in the UK - or unexpected reactions (Montastruc et al., 2006). ADRs encompass all types of medicine induced effects that are undesired or unpredicted. These effects are sometimes referred to as side effects (SE) and frequently the terms ADRs and SE are used interchangeably in patient information and other contexts. However, there are a number of differences between SE and ADRs:

- SE can be described as a category of ADRs (category A: Augmented ADRs)
- SE are often predictable whereas it is not possible to predict ADRs
- SE occur more frequently in patients than ADRs
- SE can be positive/beneficial but ADRs are always negative/detrimental
- SE have high morbidity rates and low mortality rates compared to ADRs
- SE has strong pharmacological foundation while less is known of the pharmacological mechanisms underlying ADRs

Previous ADR research used inclusive wording to encourage reporting of minor effects and defined ADRs as unexpected/unwanted medicine related effects which can sometimes be called 'side effects' (De Witt & Sorofman, 1999; Edwards & Aronson, 2000). Side effects can therefore be an imprecise/ambiguous term but was constructed to include beneficial as well as harmful therapeutic outcomes. Generally, SE are unintended outcomes that occur at

normal dose; go beyond the desired therapeutic effect; can be positive or negative and can be linked to the pharmacological properties of the medicine (Edwards & Aronson, 2000).

1.2.2 Prevalence rates

Research conducted into the frequency of ADRs has varied across studies with prevalence rates that range from 0.15% - 30% (Kongkaew et al., 2008). This wide variation can be explained in part by insufficient recognition of ADRs by healthcare professionals (HCPs). In addition ADR studies have employed different methodologies which could also have led to variation in their results. Overall health research indicates that ADRs when combined with numerous risk factors can be a common cause of morbidity and mortality (Mugosa et al., 2016). ADRs can frequently result in hospital admission particularly in older patients (Wu et al 2003). Numerous studies indicate that between 5% and 7% of hospital admissions are due to an ADR. In addition, 10% to 20% of all hospital in-patients experience an ADR during their stay in hospital (Alhawassi et al., 2014; Dormann et al., 2003). Up to 6.5% of acute hospital admissions in the UK were due to ADRs (Pirmohamed et al., 2004). While the prevalence rates of ADRs have varied across research studies it is suggested that these hospital figures may also reflect the rates and severity of ADRs in primary care (Pirmohamed et al., 2004). In addition, it has been calculated that approximately 50% of ADRs could be prevented (Mugosa et al., 2016). As well as statistical data, health research has also provided additional information on the impact of ADRs at individual and social levels.

1.3 Impact of ADRs

Research has established that ADRs can have a significant negative impact on healthcare costs, public health, patient safety, as well as on peoples' daily lives (Anderson et al., 2011; Butt et al., 2011; De Langen et al., 2008; Dibonaventura et al., 2012; Krska et al., 2011; Shet et al., 2014; WHO, 2014).

1.3.1 Economic costs to the NHS

ADRs have a significant impact on public health, placing significant economic burden on stretched healthcare services (Avery et al., 2011). Direct economic costs of ADRs to the National Health Service (NHS) in the UK was estimated at over £450 million annually over ten years ago (Pirmohamed et al., 2004). In 2007

the National Patient Safety Agency estimated that ADRs resulted in £770 million in costs to the NHS therefore the economic burden is likely to be greater today (Berwick review, 2013). The financial burdens of ADRs on the NHS can be considerable with increased costs in caring for patients, delays in treatment as well as prolonged hospital stays with one in seven hospital inpatients experiencing an ADR (Avery et al., 2011).

1.3.2 Patient costs

ADRs also have notable impact on patient safety in outpatient care settings often producing severe symptoms which may require hospitalisation and/or expensive visits to Accident & Emergency departments (Wu et al., 2003). ADRs have been identified as the fifth most common cause of death in developed countries (Edwards, 2012). Health research has established that 6.7% of drug reactions can be described as serious ADRs which prove fatal in 0.32% of hospital patients (Lazarou et al., 1998; Teo et al., 2016). Even if a severe ADR episode is resolved successfully patients can experience numerous long term complications (Teo et al 2016). Such complications can be multidimensional in nature often with both physical and psychological elements.

1.3.3 Psychological and social costs

Dealing with the effects of ADRs can therefore prove burdensome to patients and to healthcare systems. However, ADRs can also have profound social costs including loss of productivity; loss of confidence in healthcare systems or reduced quality of life because of long-term consequences and anxiety (Avery et al., 2011; WHO, 2014; Wu et al., 2003). The impact of ADRs on the quality of peoples' daily lives is a growing area of concern for HCPs. Individuals that experience an ADR can develop considerable anxiety and suffer psychological distress in their daily life (Reid, 2015). This depletion in their quality of life can have significant impact on health behaviours such as reduced adherence to long term treatments (Piparva et al., 2011).

It is clear therefore that there are considerable costs both direct and indirect associated with ADRs. This suggests that there is an urgent need for effective

health interventions which reduce the impact of ADRs. It also provides support for the argument that continued health research is required which looks at how people cope with ADRs as well as the outcomes of their experiences for future health behaviours.

1.4 Pharmacovigilance

The importance of researching and ensuring awareness of ADRs from the perspectives of drug development (manufacturers and licencing authorities) and actual use (prescribers and patients) has led to the development of a medical discipline known as pharmacovigilance (Singh et al., 2012). Pharmacovigilance (PV) is a description of the processes, activities and systems involved in detecting, understanding, assessing and preventing ADRs (WHO, 2014). Although all new drugs must undergo testing in clinical trials before being made available for use, processes for monitoring ADRs after licensing are essential for patient safety as most ADRs are not detected through clinical trials. These trials have several issues which can compromise ADR detection - such as limited study participants, relatively short study duration and selective recruitment of patients which can result in narrow heterogeneity amongst the trial participants (Berlin et al., 2008; Sultana et al., 2013).

The devastating effects of the thalidomide disaster in the late 1950s and early 1960s established the urgent necessity for national systems which ensured drug safety by introducing licensing and monitoring systems. In the UK, this was initially as the Dunlop Committee, which became the Committee for the Safety of Medicines and ultimately was subsumed into the Medicines and Healthcare products Regulatory Agency (MHRA). An international system for monitoring ADRs was established in the 1970s by the WHO - the Programme for International Drug Monitoring (PIDM) and the WHO Collaborating Centre for International Drug Monitoring was set up in Uppsala, Sweden. There are currently 123 countries and 28 associate members in the WHO PIDM. These member states submit ADR reports – Individual Case Safety Reports – to the WHO global database - VigiBase™. This database is managed by the Uppsala Monitoring Centre (UMC) with over 14 million reports of ADRs submitted by member countries since 1968. During 2016 a total of 1,821,051 reports were entered into the database with 1,059,738 reports entered from Jan 1st to July 2nd 2017 (“Vigibase” database, n.d.).

This large volume of data facilitates the systematic monitoring of ADRs and assists in identifying potential medicinal safety issues. The primary purpose of PV is to contribute to patient care and patient safety in relation to medicines. It also seeks to provide reliable information for the effective assessment of the risk-benefit profile of medicines as well as supporting public health programmes (WHO, 2014). Monitoring of ADRs can be conducted in a variety of ways – spontaneous reports, prescription event monitoring; cohort studies; case reports/series; post marketing surveillance; and investigation of electronic data sets (Avery et al., 2011; Singh et al., 2012).

1.4.1 National system for pharmacovigilance in the UK

National systems for the spontaneous reporting of adverse reactions have common terminologies and classifications and agreed methods of collecting, storing and analysing the data. The United Kingdom (UK) was a founding member of the WHO Programme in the 1960s and was instrumental in developing the spontaneous reporting system for ADRs. In the UK, this is managed through the Yellow Card Scheme (YCS). This scheme encourages spontaneous submission of reports of suspected ADRs to the MHRA (and its predecessor committees). If a particular symptom occurs in higher numbers than expected with a particular drug (drug-reaction pair) this can be investigated further, using case-control studies or cohort studies. Confirmed ADRs may require changes to the SPC or Patient Information Leaflet (PIL) of a product, changes to the use of a product or even withdrawal of a product from the market in a country.

1.4.2 Causality assessment of ADRs

A key element of PV is causality assessment. This is defined by the WHO-UMC as "the evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction". Causality assessment is usually carried out on the reports received by regulatory authorities by experts trained in PV. Integral to any investigation of patients' experience of ADRs are the cognitive processes employed by them in identifying ADRs. Models of health behaviours, such as Leventhal's Self-Regulation Model of Illness/Common Sense Model of Illness, can provide an effective framework to investigate the cognitive processes used by individuals in assessing the causality of ADRs (Johnson & Folkman, 2004; De Smedt et al., 2012). Patients' awareness of ADRs has been investigated to determine if a specific ADR prototype/model of cognition exists. It was found that patients displayed knowledge and accuracy in identifying ADR symptoms. The data also suggested that patients may use a prototype/model of cognition to assist in identifying ADRs (DeWitt &

Sorofman, 1999). Specific research has also been conducted which investigates the specific steps patients' take in identifying drug reactions. The large study of patient reports to the YCS conducted in 2011 found that both the timing of events and information sources were key factors influencing reporters' identification of ADRs (Avery et al., 2011). Within pharmacovigilance many methods for causality assessment of ADRs have been developed - with as many as 34 different types being available to experts (Agbabiaka, et al., 2008). Each of these methods has its own inherent strengths and weaknesses, however there is agreement that there is considerable lack of consistency across current causality assessments. These numerous methods can be divided into four categories: global introspection (GI); Bayesian approaches, focussed scales and algorithms.

1.4.2.1 Global introspection (GI)

GI, also known as expert judgement, utilises previous knowledge and experience in the field to make assessments of causality. However, this is not a standardised research tool and the structures used to generate these judgements can vary widely. Some methods use a single evaluator while others use expert groups or compare assessments across expert and non-expert groups. Thus, high levels of disagreements between experts often occur.

1.4.2.2 Bayesian approaches

Bayesian approaches work to transform previous estimations of probability of causality as increasing amounts of data become available. The previous estimation is calculated from epidemiological information while the later probability estimation uses both this background information and individual case evidence to estimate causality. Computer programmes which utilise the Bayesian Adverse Reactions Diagnostic Instrument (BARDI) have helped to increase this method's reliability. However, this method has its limitations as it requires significant investment in time and resources.

1.4.2.3 Focused scales

Further efforts to develop logical/step by step assessments have resulted in focused assessments for example, Stricker's decision tree for suspected liver injury events (Stricker, 1992). Collaboration amongst experts in the field of adverse events consensus led to the development of a new scale in the 1990's - the Roussel Uclaf Causality Assessment Method (RUCAM) (Benichou et al., 1993; Danan & Benichou., 1993). This is used for disease states such as liver and

dermatological injuries. This method gives weighted scores to causality criteria and is easy to use. However, it is focused on specific organs and would require additional work on classifications and criteria if it were to be applied in other medical areas. The Clinical Diagnostic Scale is another focused scale which evaluates suspected hepatotoxic drug reactions (Maria & Victorino, 1997). It is considered easy to apply and is frequently used in clinical settings (Aithal et al., 2000).

1.4.2.4 Algorithms

Algorithms are structured and standardised assessment methods used to identify potential ADRs. They are based on criteria such as time to ADR onset, previous medical history, previous adverse reaction history and re-challenge. Most algorithms take the form of questionnaires that allow sufficient information to be gathered to assess the probability of a suspected ADR. Various algorithms have been developed to address problems of validity and reliability as well as bias.

These include the Karch and Lasagna decision-table approach which uses three tables to (i) identify potential drug reactions, (ii) assess the certainty of the link between the drug and the event and (iii) evaluate the underlying causes of the adverse events (Karch and Lasagna 1977). This diagnostic tool is considered easy to use, however there are issues concerning its reliability. It cannot identify new/novel ADRs to a drug that has no history of ADRs and this tool requires a high level of subjective judgements which can result in bias (García-Cortéz et al., 2011).

Another decision table was designed by Blanc et al which assessed the nature of the relationship between the drug and the adverse event. It considers three factors: the role of underlying disease(s), time onset and response pattern (Blanc et al., 1979). However, this assessment method also displayed poor internal validity and variation between evaluators (Agbabiaka et al., 2008).

Kramer developed the Karch and Lasagna table into a new set of criteria for assessing ADRs (Kramer et al., 1979). The algorithm is made up of six decision tables with a scoring system for each axis. It is used to assess an adverse event that occurs after administration of a single drug. If a patient receives multiple drugs before experiencing an adverse event, then each potential drug is assessed separately (Agbabiaka et al., 2008). This method is useful therefore when more than one drug is suspected in the adverse event.

Naranjo developed an instrument for assessing ADR probability in numerous clinical settings (Naranjo et al., 1981). It is a probability scale of ten questions that can be answered as follows: “yes”, “no”, “unknown” or “inapplicable”. The Naranjo scale cannot address potential adverse reactions that may result from interactions between drugs. It is designed to assess the probability of an ADR associated with one drug only. However, it is simple to use, not time-consuming and can be applied widely across clinical settings (García-Cortéz et al., 2011).

In general, standardised methods such as algorithms offer greater reliability than GI methods. There is high inter-rater agreement in the use of algorithms within the pharmacovigilance community, but as a clinical instrument they can lack flexibility. Available data which is not required for assessment has no role within this methodology – only a finite amount of information can be considered. It is thought that failure to adopt consistent operational criteria as well as the role of confounding variables may account for the inconsistency and lack of agreement across assessment scales. Overall there is no method universally accepted for causality assessment of ADRs.

1.4.3 Yellow Card reports

As mentioned spontaneous reporting of ADRs within the UK is through the Yellow Card Scheme (YCS). When first put in place in the 1960’s, only doctors could report ADRs to the Scheme. In 1997, after much evidence had been provided to demonstrate their ability to identify and report accurately, this reporting system was extended to pharmacists and in 2002 it was further extended to allow nurses, health visitors and midwives to report suspected ADRs.

1.4.4 Problems with spontaneous reporting of ADRs

Spontaneous reporting of ADRs is an essential component of PV and is particularly important in detecting new, rare and/or serious ADRs (Giezen et al., 2009). Much of modern pharmacovigilance practice focuses on individual case safety reports (ICSRs) which are supplied by HCPs to national regulatory authorities or through pharmaceutical companies (Hazell et al, 2013). ADR reports by HCPs are a key requirement of effective PV practice and have created a considerable body of data held at the VigiBase™ database. However, research suggests that under-reporting is a significant problem within spontaneous reporting systems (SRSs). There is evidence of notable under-reporting of ADRs by HCPs to these systems. Research shows that mild or well-known ADRs are less likely to be

reported by HCPs while serious or even fatal ADRs are also under-reported (Hazell et al., 2006). Explanations for under-reporting by HCPs include lack of clinical experience, poor knowledge of over the counter (OTC) medicines and problems identifying the causative drug in patients with multiple medicines (Hughes et al., 2002). Recent research into patterns of ADR reports to VigiBase – over a nine year period - established that there is significant variation in reporting rates across high and low income countries (Aagard et al., 2012). A pattern was identified of highest reporting rates for ADRs in high-income countries with lowest reporting rates for low-income countries (Aagard et al., 2012).
It has been calculated that only between 6-10% of ADRs are reported (Edwards, 2012; Elkalmi et al., 2013). A review of ADR reports in 2006 indicated there was significant under-reporting of ADRs to SRSs which included serious/severe reactions (Hazell et al., 2006). A later review in 2009 of ADR reports identified some contributory factors linked to under-reporting by HCPs. These professionals feared they would seem ridiculous if they reported ADRs which were not proven but merely suspected. There was also a general lack of knowledge about the function of ADR reports amongst health professionals (Lopez-Gonzalez et al., 2009). Research conducted in medical practices in Scotland showed that GPs may not record in full all the symptoms that patients reported to them (Jarernsiripornkul et al., 2002). It has been proposed, however, that ADR reports by health professionals did not capture all the available information and did not fully reflect patient concerns (Edwards, 2012). Research suggested that a significant deficit existed within PV systems. An informative and useful source of additional data was being overlooked that of direct reporting by patients of ADRs.

1.4.5 Direct patient reports of ADRs

At this time, patient rights and equality were being promoted within healthcare organisations. Initially however, only a limited number of countries – such as Australia and the US – provided some opportunities for patients to report ADRs themselves within national pharmacovigilance systems. As time progressed and health care policymakers focused on ADRs, patient reporting became part of pharmacovigilance systems in several countries including the USA, Canada, Australia, New Zealand. An awareness developed - supported by the research findings - which highlighted that patient participation could prove hugely beneficial to PV systems. In 2003 UK patients could submit a report via telephone to NHS Direct, but this reporting was not publicised or genuinely considered as a contribution to PV. The Committee on Safety of Medicines formed a working group in 2004 on patient reporting of ADRs – the ADRWG. This group was composed of diverse

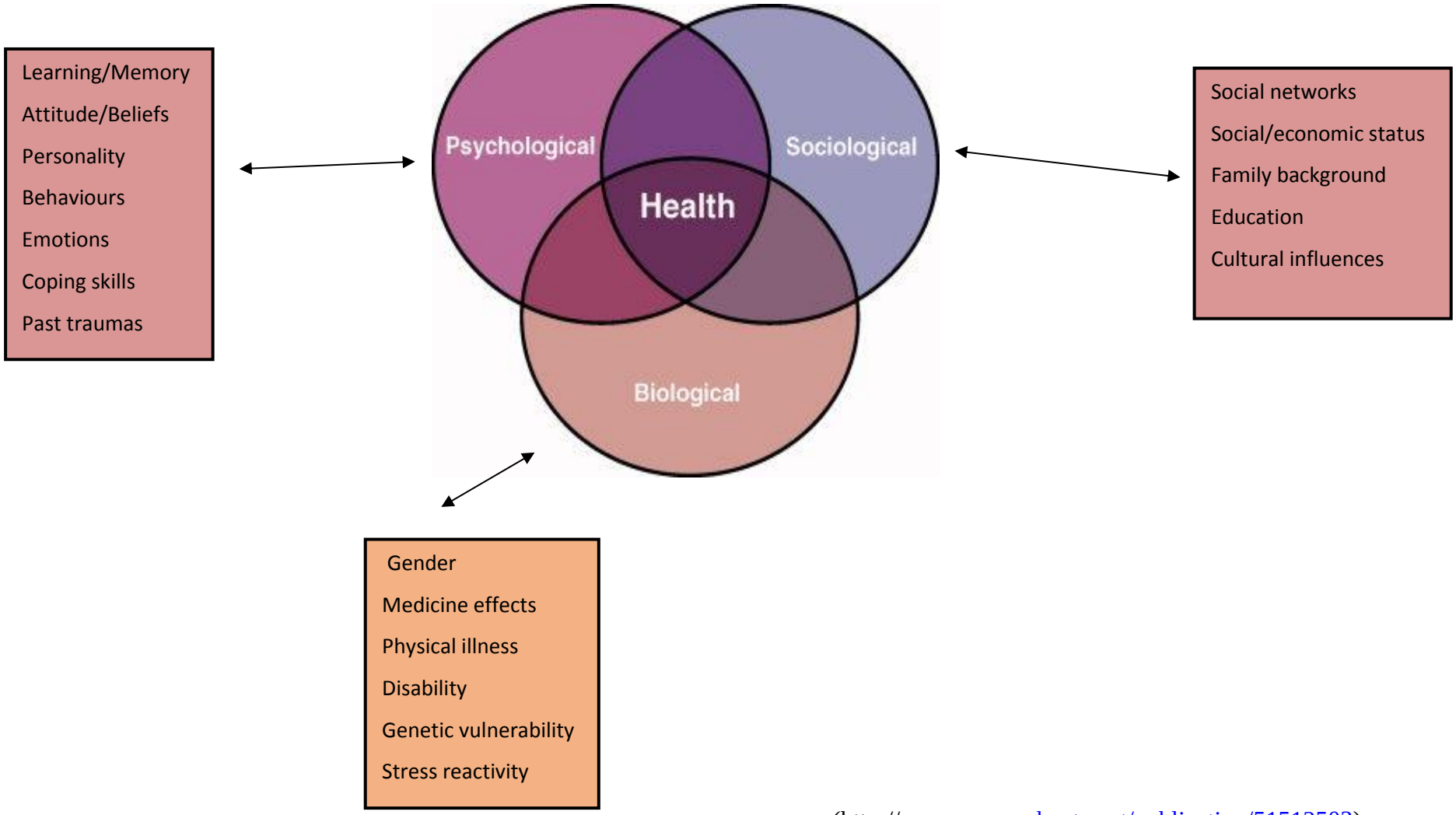
members including patients, patient organisations, pharmacists, general practitioners (GPs), clinical pharmacologists and academics. Based on recommendations from the ADRWG a patient Yellow Card (YC) for use by the public was created and piloted in 2005. This was available in electronic format on the MHRA website and a paper version Yellow Card was distributed to 4000 general practices. Over a period of nine months over 650 YC patient reports were submitted to the MHRA. When these reports were evaluated by the MHRA, it was found that they provided detailed and potentially valuable descriptions of ADRs (Avery et al., 2011). Therefore, the scheme was extended later that year and included, as well as paper and on-line systems the opportunity to report by telephone. Analysis of the reports received in the first six months was conducted. This suggested that the patient reports focused on firmly established drugs and were less complete but were of similar standard to HCP reports (Ekins-Daukes et al., 2006). The number of reports have since increased and in 2016 67,029 patient/parent/carer reports were submitted to the MHRA (MHRA Annual report 2015/2016). The MHRA records, manages and analyses the YC reports and combines them with reports from healthcare professionals.

Health research identified limitations and disadvantages of direct patient reporting within pharmacovigilance. As stated above, until recently only a limited number of countries had systems which provided opportunities for patient reports of ADRs. Over the years steps were taken to improve PV systems by facilitating patients in reporting their ADR experiences. Sufficient information was collected from countries with patient reporting systems to re-examine the potential benefits and limitations of patient reporting of ADRs. A key review was conducted in 2006 which considered the value of patient reports to PV systems world-wide. It examined published studies and patient reporting systems in six countries (Blenkinsopp et al, 2006). This review suggested that patient reports and HCPs' reports were similar in terms of quality. It found that patient reports identified possible new reactions thereby adding value to professional reports of ADRs (Blenkinsopp et al, 2006). It concluded that patient reporting could therefore complement HCP reports and contribute to SSRs. This indicated an attitudinal change from one where it was assumed that only health professionals could identify ADRs to one where the patient's experience was viewed as valuable and informative (Van Hunzel et al., 2012).

In order to explore the patient's experience further, it is important to understand patients' perspectives of ADRs and how these fit into their overall understanding of health and illness. These perspectives will in turn affect patients' behaviours in response to ADRs.

1.5 Leventhal's Self-Regulation Model of Illness/Common Sense Model of Illness

The central theory of health behaviours – the biopsychosocial (BPS) model - was developed in the 1970s by G Engel. This model views illness behaviours as a dynamic process between biological, psychological and sociocultural factors which interact to shape the person's response to pain/illness (Turk & Flor, 1999). Factors such as beliefs, coping strategies, social support, past experiences, education and other aspects can significantly impact the course of an illness. See *Figure 1.1* on the following page.



(http:// www.researchgate.net/publication/51512503)

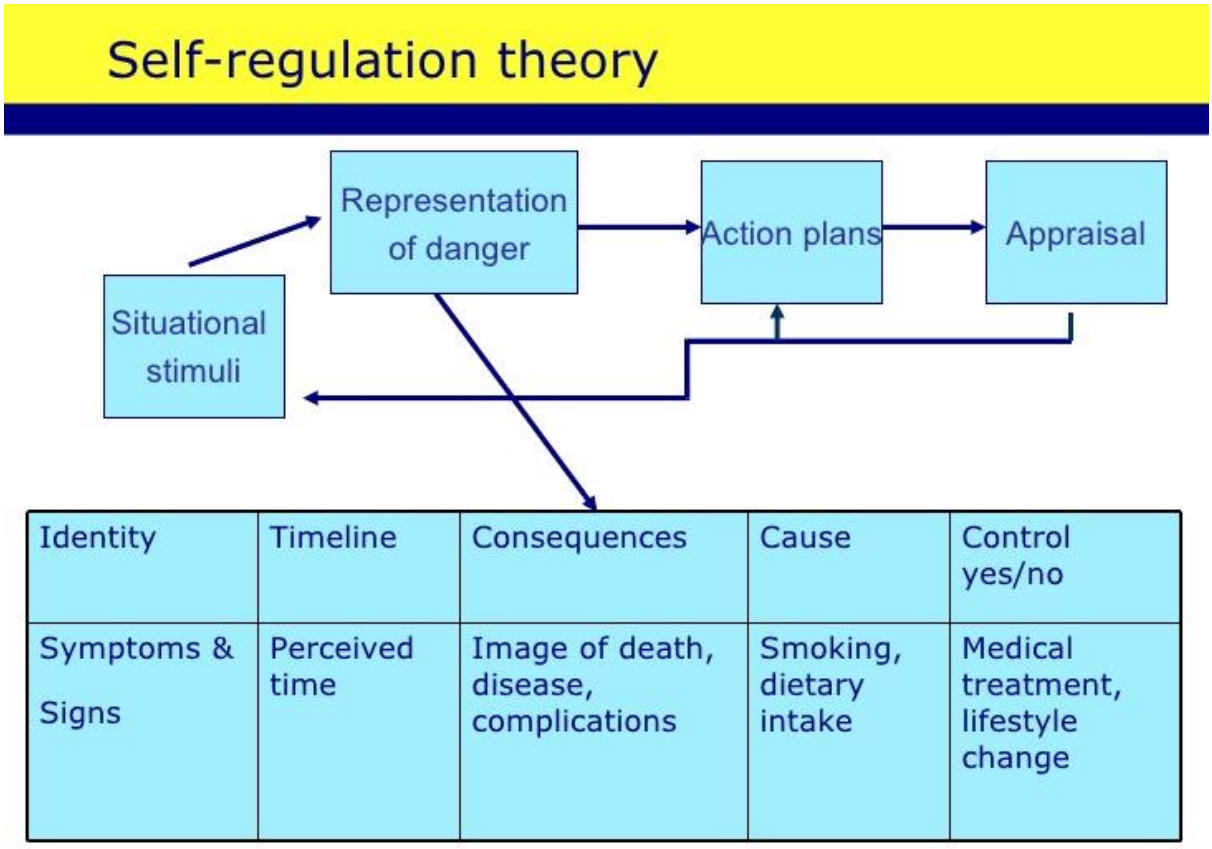
Fig 1.1: Biopsychosocial model of health (Adapted from Natale-Pereira et al., 2011)

Research was also conducted in the 1970s into the effects of fear on health-related behaviours. Leventhal developed a hierarchical model to explain how an individual processes a health-related threat. The original research identified the cognitive domains of illness representations through semi-structured interviews (Hale et al., 2007). The self-regulation aspect of the model highlights individuals' attempts to maintain their health status equilibrium and/or return their health status to normality. Leventhal's Self-Regulatory Model (1987) is composed of three main cognitive constructs:

- Representations – representations of the health-related threat which interprets the experience through cognitive representations such as symptoms, social cues, consequences.
- Coping strategies – action planning such as avoidance, information seeking, seeking medical attention.
- Appraisal - where the success or failure of coping strategies are assessed.

(Hale et al., 2007)

Leventhal's Self-Regulation model is also known as the Common Sense Model of self-regulation (CSM). Overall this model suggests that cognitive schema and a patient's illness representations influence how the individual perceives/assesses the illness situation and their subsequent health behaviour (Cameron et al., 2003). Such illness representations can be divided into five domains: identity; timeline; cause; consequences and control. Each of these domains has perceptual and semantic information about an illness threat which can be abstract and/or concrete. See *Figure 1.2* for a schematic of Leventhal's Self-Regulation model/CSM:



(http://keywordsuggest.org/gallery/583214.html)

Fig 1.2: Schematic representation of Levanthal's Self-regulation model/Common Sense model of self-regulation (CSM)

Within the self-regulation model illness cognition is stored in memory in two different representations – concrete and abstract. The illness representation of identity is therefore made up of an abstract label and concrete symptoms. There is pressure to connect abstract experience to labels known as the symmetry rule. This pressure to link is reciprocal in nature as people will seek out labels to explain their symptoms and seek symptoms to make sense of their illness/symptom labels (Hill et al., 2007). Research has provided support for the symmetry rule and found that patients linked labels and symptoms. Subjects in a study reported symptoms when informed that their blood pressure was very high (Easterling et al., 1989 as cited in Siegel et al., 2011; Bauman et al., 1989). Recent research with cancer patients identified cognitive schema and patients' expectations of side effects as important factors in terms of treatment outcomes in these patients (Von Blackenburg et al., 2013). Within the context of the self-regulation model factors such as prior experiences with side effects and symptom amplification can lead to misinterpretation of symptoms as

side effects of medications. In general, negative events generate more physiological, affective, cognitive, and behavioural activity than neutral/positive events. Once the threat of a negative event has passed, it has been found that cognitive processes engage in counterbalancing activities as they seek to minimise, reverse or undo the initial responses to an adverse event. Research using the CSM has investigated the processes employed by patients to assess their somatic changes – in terms of symptoms and daily functioning. The CSM stresses the central role that symptom interpretation plays in influencing health related coping behaviours. The theory has provided the framework for research into effective interventions in managing chronic illnesses such as psoriasis, rheumatoid arthritis and multiple sclerosis (Fortune et al., 2000; Scharloo et al., 1999; Vaughan et al., 2003). Studies have attempted to describe how patients link these somatic experiences to illness representations and how these links then influence an individual's health outcomes such as self-management and care seeking (McAndrew et al., 2008). Researchers have suggested that the self-regulation model can also be used in other health-related areas such as ADRs (see Chapter Two: Literature Review).

1.6 Sources of information about medicines

Health research has found that patients require relevant information about their medicines with appropriate medicine information often leading to positive adherence and treatment outcomes (Nahri, 2007). Information about medicine can be obtained from a variety of sources such as HCPs - particularly doctors and pharmacists. Other sources are PILs, pharmaceutical companies and drug regulatory authorities. Medicine information is also available from the print and broadcast media and medical books/guides as well as family/friends. The mass media which is designed to communicate with the general public is an important source of health information and can have a positive effect on public health (Moynihan et al., 2000). However, misgivings exist about the quality of coverage which medical matters receive. Previous research has identified issues such as inaccuracy and sensationalism (Myers, 1996; Schwarz et al., 1999). An abundance of medicine information also exists online. Patients often use the Internet to obtain information about medicines, however the sheer volume of such information available online can be overwhelming for patients (Lee et al., 2014). Reputable health-related UK websites such as electronic Medicines Compendium (eMC) and NHS Choices provide regulated up-to -date information on licensed medicines and healthcare information. Looking for health-related information was the fifth most common UK Internet activity in 2016 and has increased in

UK since 2007 by 33 percentage points to 51% in 2016 (Office for National Statistics, 2016). Evidence-based knowledge about patients' health information requirements and the sources of information that patients use could be beneficial to patient-centred care in general. Reliable information about medicines could be presented in a structured style/format that satisfies the patients' health information needs (Clarke et al., 2016). Research into patients' health information needs and sources is reviewed in the following chapter - Chapter Two: Literature Review.

1.6.1 Information seeking models

Models of information seeking were initially developed to address information problems in the fields of information science. Models were combined in the 1990s to create six general principles of information-seeking behaviour (Harris & Dewdney, 1994). These principles are as follows:

1. Information needs arise from the person's situation.
2. The decision to seek/not seek information is influenced by numerous factors.
3. People tend to seek the most accessible information.
4. People tend to first seek information from interpersonal sources, especially from people like themselves.
5. Information seekers expect emotional support.
6. People follow habitual patterns in seeking information.

Models of health information seeking behaviour

Health information seeking models were developed which incorporated these principles and which could be applied to patients. Such models describe the cognitive and affective processes involved in seeking health information (Clarke et al., 2016; Lalazaryan et al., 2014). Information seeking models include the following four models:

- Lazarus and Folkman's Stress, Appraisal, and Coping theory

This theory describes coping as a process which can employ different coping mechanisms - problem focused or emotion based coping methods. The former method uses planning and interpersonal relationships whereas the latter method seeks to pragmatically reduce the negative feelings associated with stressful situations. According to this theory personality and emotions are key influences on the evaluation and selection of these coping mechanisms. People with positive personalities would actively try to deal with the problem

while pessimistic people would underestimate their abilities and engage in avoidant behaviours.

- Lenz's Information seeking model

In this model information gathering is described as a six-stage decision making process. It begins with internal/external information seeking stimuli; setting information goals; decision-making on the necessity to seek information; search behaviours; acquiring and evaluation of information. This process will result in cognitive and behavioural changes in the information seeker. Factors such as boredom and curiosity contribute to the premature ending or extension of the information search.

- Longo's expanded model of health information seeking behaviours

This is a model applied to the sourcing and use of health information in patients with chronic disease. This model focuses on the personal and contextual factors that influence information seeking behaviours. Personal aspects include anxiety, genetics and health history while contextual components could include social support, healthcare delivery and information environment. This model describes the effects of information on increases in patients' satisfaction, perceptions of control as well as improved health status.

- Trans theoretical model (TTM) of health behaviour change (Harris & Wathen, 2005)

This is a five-stage health information seeking model, which was initially used in addictive behaviours such as smoking. It is described as a spiral shaped process, with precontemplation; contemplation; preparation; action and maintenance stages. These stages involve intermittent yet linear health behaviours with numerous stops and returns to previous stages that can be temporary or permanent.

- Miller's Monitoring and blunting hypothesis (Miller, 1989).

This is a key information seeking model which focuses on the impact of information behaviours and coping mechanisms. This hypothesis, proposes that people have distinctive coping styles/attentional styles when they are faced with threatening situations such as ADRs (Miller, 1989). When challenged by threatening conditions active information seekers or 'monitors' engage in information seeking behaviours related to their current situation. In contrast those with a non-active coping style or 'blunters' use distraction and re-interpretation techniques to lessen the threat (Miller, 1989). Active information seekers/monitors gather a large amount of information about their health status/problems and side-effects of medicines and treatments. They are quicker to identify the symptoms of diseases and more likely to visit doctors for minor problems (Miller, 1989). Monitors have high levels of anxiety and accumulating large amounts of information can help to alleviate

this anxiety and stress (Miller, 1989). Patients who do not actively seek information, blunters, generally have minimum information related to their health status and potential health issues such as ADRs (Miller, 1989). Rigid copers adhere to their coping style using either Monitoring or Blunting strategies in both controllable and uncontrollable situations. Monitors will be alert and seek information as they attempt to increase the predictability of the outcome. Blunters will employ distractive strategies even if they have the potential to influence the outcome (Voss et al., 2006). Adaptive copers change their coping style in response to different types of situations (Voss et al., 2006). Within this model coping styles are an essential component of health information seeking behaviours. Coping as a psychological construct can be mediated by factors such as gender, age, education, type and severity of illness, social support and health literacy (Lalazaryan et al., 2014).

1.6.2 Information overload

Information overload can occur when the information which is received is a barrier and not beneficial to the patients (Bawden & Robinson, 2009). As mentioned there are numerous sources of information about medicines available for patients today. Health information can now be obtained from multiple sources which can lead to an increased possibility of contradictory information as well as information overload (Carpenter et al., 2010). Information can be actively acquired by patients or passively received but both processes can result in information burden (Clarke et al., 2016). Excessive information loading can lead to delays in processing information; processing information incorrectly; accepting poor quality information and ceasing to search for required information (Miller, 1960 as cited in Clarke, 2016). Effective patient-centred heath information can be presented to patients when factors such as information overload and multiple information sources are considered.

1.7 Thesis Outline

This thesis examines patients' experiences in identifying and managing side effects from medicines. The study seeks to address the lack of information surrounding the following: patients' views on ADRs and the impact ADRs have on their lives and their behaviours. It takes a patient-centred approach to ADRs and directs the research focus on the individual's experience across physical, psychological and social domains. The thesis attempts to provide a unique and insightful perspective on patients' personal experiences of ADRs. Empirical work was conducted in four phases with these study phases divided as follows:

- Phase One - Survey development and distribution

- Phase Two - In-depth interviews with people who have experienced ADRs
- Phase Three - Development and validation of Side Effect Assessment tool
- Phase Four- Investigation of Yellow Card reports

Chapter Two supplies the context with a review of the relevant literature and research evidence in this area. This review identified deficits in knowledge and the chapter concludes with the research questions and study aims which were formulated to address these shortfalls.

Chapter Three provides a rationale for the methodological approach that has been undertaken - a mixed methods study. Each phase of the study is outlined, starting with the surveys, followed by the interviews, the assessment tool and YC study. In addition, corresponding support is offered for the inclusion of each stage of this research.

Chapter Four describes the first phase of the study: a cross-sectional survey distributed amongst pharmacy customers, exploring experiences of using information sources for finding out about ADRs.

Chapter Five reports on the second phase of the study: semi-structured interviews with survey participants from the first phase who had experienced an ADR.

Chapter Six describes the third phase of the study: the development and validation of a causality assessment tool for patients to use in identifying suspected side effects.

Chapter Seven reports on the fourth phase of the study: an investigation of a large sample of YC reports submitted by patients/the public.

Chapter Eight discusses the findings from the four phases of the study and how the research questions have been addressed. It also examines the strengths and limitations of the study, its contributions to knowledge and the implications for future research and practice.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

As part of this thesis, a literature review was conducted which examined the current research literature on patients' identification and management of ADRs. This chapter presents an overview of the research literature connected with the subject areas that inform this research. These subject areas included adverse drug reactions (ADRs); patient reporting of ADRs; cognitive processes involved in identifying ADRs; type of information sources used to identify ADRs and ADR causality assessment tools. A series of structured literature searches were carried out to identify the key issues and deficits in knowledge connected to identifying and managing ADRs. A review of these results led to development of the research questions and subsequent study design.

2.2 Aim of literature review

The literature review was undertaken to answer the search questions which were generated by initial investigation of the subject area of ADRs. These questions were as follows:

1. What cognitive processes do patients use to identify and manage ADRs?
2. What information sources do patients use to identify ADRs?
3. How do patients cope when they experience ADRs?
4. What are the characteristics of patient reporting of ADRs and is there any evidence that such reports are beneficial?
5. What motivates patients to report their ADRs?
6. What benefits would accrue from the development of a reliable ADR assessment tool specifically developed for patient use?

2.3 Search terms and methods

A broad literature search of ADR research was initially conducted using the following databases EBSCO, MEDLINE/Pubmed and PsychINFO. These databases were identified as useful resources within the Sciences and Social Sciences fields. The search terms which were initially used were broad in scope terms and generated many articles. The search terms were amended to generate project specific research articles and included Medical Subject Headings terms (MeSH) such as 'pharmacovigilance' and 'causality'. A structured literature search of ADR research from 1994 to 2017 was conducted across a wider range of electronic national and international bibliographical databases. The amended search terms included the following words/phrases:

- adverse drug reactions
- side effects
- pharmacovigilance
- patients
- reporting
- patient reporting
- information sources
- causality assessment
- patient experience

In addition, the MeSH terms ‘consumer participation’ and ‘ADR reporting systems’ were also used.

Details of these searches, the revised search terms and the paper selection process are presented in Appendix 1. The search was conducted in two phases which examined the following:

1. Relevant research publications that related to the identification and management of ADRs
2. Research publications which addressed the other search questions

Multiple databases were searched: Cochrane *Database of Systematic Reviews (CDSR);* EBSCO Host database (MEDLINE, PsychARTICLES, PsychINFO) PubMed, SAGE Journals online and ScienceDirect. This conventional search of the databases was further developed by following-up studies cited in bibliographies of relevant research papers and general internet searches. A filter which limited the search to publications from 1994 to 2017 was applied and duplicated research studies were omitted.

2.4 Inclusion and exclusion criteria

Searches were limited to article titles and abstracts and only articles which met the inclusion criteria were included in the review. See *Table 2.1* on the following page for inclusion and exclusion criteria:

Table 2.1: Inclusion and exclusion criteria used for literature search

Inclusion Criteria
Quantitative, qualitative or mixed methods research studies
Description of the research relating to the identification and management of ADRs
Assessment of the research relating to the identification and management of ADRs
Description of patients' experience of ADRs
Assessment of patients' experience of ADRs
Exclusion Criteria
ADR research relating to children
ADR research relating to non-human subjects

2.5 Selection method and data extraction

As part of the initial selection process titles and abstracts were reviewed and studies which did not meet the inclusion criteria were omitted. Studies which appeared to meet the inclusion criteria were examined in full before they were selected for review. A record of the selected studies was created which categorised each study according to the following:

- Study setting
- Study population - number of participants, demographic information
- Methodology
- Outcomes
- Summary of results

2.6 Literature review

The literature search identified papers which described qualitative, quantitative and mixed method research. This literature review has been divided into six sections with each section related to a specific research area and to the search questions outlined above (section 2.2).

2.6.1 What cognitive processes do patients use to identify and manage ADRs?

The Self-Regulation model of health behaviour/CSM

Research has suggested that the Self-Regulation model of health behaviour/CSM can be used as a framework for understanding ADRs. Within this model the five cognitive

domains – identity; timeline; cause; consequences and control - are used by patients to assist them in identifying ADRs (De Witt & Sorofman, 1999; Johnson & Folkman, 2004).

Over the years extensive research has been conducted into health behaviours and illness representations. This research has focused on the recall, evaluation and labelling of somatic changes. It found that patients process information about physical symptoms according to their prototypical perceptions about associations between diseases and particular symptoms. These prototypes are composed of cognitive processes which assist the patient to organise and evaluate information. Patients use their previous personal health experiences or knowledge of the experiences of others to identify symptoms (Bishop & Converse, 1986 as cited in De Witt & Sorofman, 1999).

Researchers considered it plausible that patients would use such preconceived perceptions about side effects to assist them in labelling and interpreting symptoms linked to adverse effects. A cognitive schema or prototype could be developed by patients which facilitates evaluation and identification of the symptoms that indicate an ADR. The elements of this prototype were described as identity (symptoms/label); cause; timeline; consequences and cure (Bishop et al., 1987 as cited in DeWitt & Sorofman, 1999).

A study was conducted to investigate if such an ADR prototype existed (De Witt & Sorofman, 1999). Self-administered questionnaires were distributed amongst 338 patients in a GP clinic to explore patients' perceptions and knowledge of ADRs. A majority of the participants were found to have previously experienced an ADR and described the reaction with reference to the five prototype elements (cause; symptom; time; consequence and cure). Results indicated that patients displayed largely accurate knowledge of ADRs and may use a prototype to assist in identification of symptoms as ADRs (De Witt & Sorofman, 1999). This study suggested that previous research into illness representations could be extended to ADRs. A specific ADR prototype existed which was composed of five elements or cognitive domains (see Figure 2.1 on the following page). These cognitive schemas were multidirectional in nature and constructed by patients to assist in organising information and identifying ADRs.

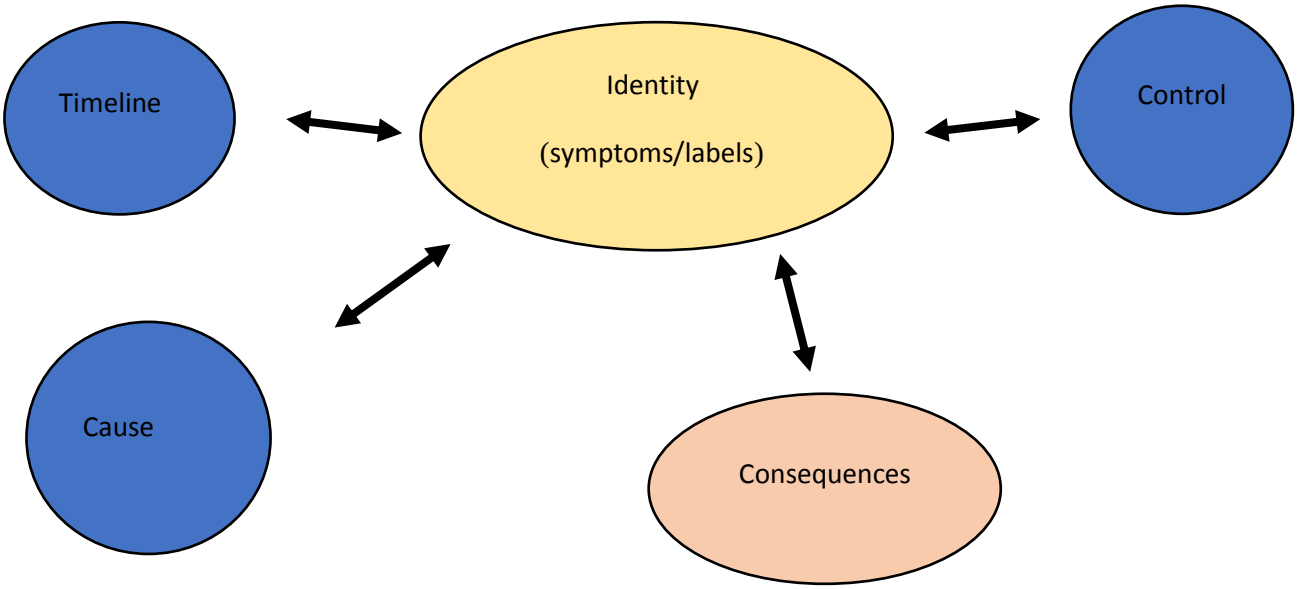


Fig 2.1: Five elements of ADR prototype used by patients to assist in recognition and evaluation of symptoms that indicate an ADR

Researchers have investigated how cognitive representations can influence coping strategies and illness outcomes in a wide range of chronic illnesses (Hale et al., 2007). A sample of 233 chronic fatigue syndrome sufferers were assessed and relationships between illness perceptions, coping, disability and psychological well-being were investigated (Moss-Morris et al., 1996). Patients who had a strong illness identity; perceived the illness to be caused by stress; as outside of their control with very severe consequences had high levels of disability and psychological impairments. These components of illness representations – identity; consequences and cure/controllability -were therefore linked to negative outcomes. In addition, disengaged coping strategies were also associated with greater disability and less psychological well-being (Moss-Morris et al., 1996). Another study was conducted among 140 UK patients with psoriasis which examined the cognitive model of their disorder. High levels of pathological worrying were associated with illness representations which perceived psoriasis as having severe consequences and being triggered by emotions (Fortune et al., 2000). A later study investigated the illness representations of 99 patients with multiple sclerosis. The relationships between these perceptions and outcomes such as depression, anxiety and levels of illness intrusion were examined (Vaughan et al., 2003). As in earlier research components of illness representations were identified which included a strong illness identity; perceived lack of

control over an illness; beliefs concerning the acute time-line and severe consequences of the illness. These illness cognitions were associated with negative outcomes such as higher levels of depression, anxiety and deficits in physical functioning (Vaughan et al., 2003). Longitudinal research was also conducted with 71 patients with rheumatoid arthritis (RA) to examine if illness perceptions and coping strategies could reliably predict health outcomes (Scharloo et al., 1999). Beliefs in adverse consequences were associated with higher anxiety, more trips to outpatient clinics and tiredness. Perceived lack of control was linked to more hospital admissions. Passive or avoidant coping strategies were connected with higher levels of anxiety, more tiredness and greater disability. Overall these research findings indicated that coping strategies and illness perceptions could significantly influence health outcomes in patients with RA (Scharloo et al., 1999).

It would be beneficial to develop this research from the broad parameters of chronic illness and focus on the specific category of ADRs. The concrete language and classifications that define ADRs could provide a solid base for research of incremental value. The CSM can therefore be used in research as a framework to investigate the cognitive processes used by individuals to identify and respond to ADRs (De Witt & Sorofman, 1999; Johnson & Folkman, 2004; De Smedt et al., 2012).
A study of 109 Human Immunodeficiency Virus patients on antiretroviral medicines suggests that the CSM can provide a useful framework to assess side effects (Johnson & Neilands, 2007). The findings indicate that patients use similar cognitive and emotional representations to evaluate side effects and symptoms related to their disease. The researchers propose that investigating these processes can provide important insight into the impact side effects can have on the quality of patients' lives and adherence to treatment (Johnson & Neilands, 2007).

Research has been conducted which investigates the cognitive processes that patients utilise to identify ADRs (Hughes et al., 2002; Krska et al., 2011; Uchaipichit et al., 2012). This research has found that overall patients displayed knowledge and accuracy in identifying ADR symptoms. The majority of patients employ temporal associations to link symptoms to medication. A proportion of patient reporters use additional information from a range of sources - such as PILs – to confirm suspected ADRs. Research has shown that reading about side effects in PILs does not create a bias in patients or encourage them to report experiences of ADRs (Krska & Morecroft, 2013). These processes for assessing causality of ADRs parallel those employed by healthcare professionals (Krska et al., 2011). These findings suggest that a standardised assessment method could be effectively used by patient reporters to produce a coherent causality profile of ADRs.

2.6.2. What information sources do patients use to identify ADRs?

2.6.2.1 Use of information sources

Research into the use of information sources by patients into ADRs has been limited. In the past health-related information was frequently passively received by patients from traditional sources such as HCPs. This 'top-down' process featured HCPs as the 'expert' who dispersed the information to patients. Now patients can actively seek information about medicines from a variety of sources (Nähri, 2007). A recent review of health information needs of patients indicated that useful and up-to-date medicine information can help patients to identify suspected ADRs (Clarke et al., 2016). However, the quality of information about medicine can vary widely and patients' information needs are not static and can change over time (Van Geffen et al., 2011). While information about medicines can be beneficial for patients, research with cancer patients has found that not all patients want information (Fallowfield 1997). In general studies have found patients' knowledge about SE and medicine toxicity to be poor even for those with chronic conditions (Gilbertson et al., 1996 as cited in Hughes et al., 2002). However, research has shown that PILs can address this knowledge deficit and can increase patients' knowledge about possible SE (Gibbs et al., 1989; Gibbs et al., 1990 as cited in Hughes et al., 2002). Research also investigated how much information patients want from their physicians regarding adverse effects from their medicines. A US study was conducted with 2500 out-patients in 2001 (Ziegler et al., 2001) which concluded that over 70% of patients wanted all the available information regarding possible adverse effects. They expected their physicians to supply complete health information about the risk of adverse effects and were reluctant to relinquish control in this area to the physician (Ziegler et al., 2001).

2.6.2.2 HCPs and PILs as information sources

A UK study in 2002 investigated patients' knowledge about SE and the information sources they used (Hughes et al., 2002). Interviews and focus groups were conducted with 32 pharmacy customers who purchased any of the following: antihistamine, decongestant or ibuprofen (Hughes et al., 2002). The findings suggested that patients accessed information about medicines from many sources including HCPs, family/friends, the media, books and the Internet (Hughes et al., 2002). Previous research proposed that patients were competent in identifying ADRs as the majority of ADRs were identified

through spontaneous patient reports to HCPs (Fisher et al., 1994; Houghton et al., 199 as cited in Hughes et al., 2002). PILs were widely accessible but rarely used by patients – unless a SE occurred or if the medicine was new (Hughes et al., 2002). This profile of PIL use by patients only after effects had occurred is supported by later studies. A Finnish study of medicine users' sources of medicine information was conducted in 2007 (Nähri, 2007). Over 1000 respondents were interviewed and the most common information sources used were PILs - 74% - followed by doctors - 68% - and pharmacists - 60%. Forty percent of respondents used television, 40% used print media, 24% used family/friends and medicine books were used by 22%. The Internet was used by 20% with the greatest Internet use reported amongst respondents aged 15-34 years (Nähri, 2007). However more recent research has focused on the aspects of health information websites which facilitate beneficial use. A study used a User Test and interviews with fifteen participants, who took medicine in the previous year, to examine the readability of information and ease of use of five websites (Nicolson et al., 2011). The design and content of the sites affected the ease with which participants located and understood the information. Web pages with too much text and/or links were considered distracting and hard to navigate. The trustworthiness of the site was frequently determined by its professional appearance (Nicolson et al., 2011). A study of 65 patients experiencing medication overuse headache (MOH) was conducted in Italy, Denmark and Germany in 2011 (Munksgaard et al., 2011). It investigated the information needs and preferences of patients beginning an MOH program of treatment. The majority – over 70% - selected personal verbal information from their HCP as their primary preference with 33% selecting PILs and 41% selecting the Internet (Munksgaard et al., 2011).

Hospital patients in six UK hospitals were surveyed in a later study regarding use of PILs and other information sources (Krska & Morecroft, 2013). Overall 1218 questionnaires were completed and it was found that 6.5% of patients only read PILs if unexpected effects occurred. However, using the PILs was beneficial for a majority of patients, helping over 80% to identify their suspected ADRs (Krska & Morecroft, 2013). A more recent study of 1044 out-patients in Thailand investigated the information sources used by patients to assess suspected ADRs respondents (Jarernsiripornkul et al., 2015). Findings indicated that the major source of information about ADRs were HCPs – used by 35.5% of respondents (Jarernsiripornkul et al., 2015). However, PILs are not widely available in Thailand and patients seldom receive information leaflets (Jarernsiripornkul et al., 2015).

The format of PILs has changed over time with increased use of consistent risk descriptors. A recent review compared the format of PILs for 100 licensed medicines in 2012 with

PILs in 2006 (Harris et al., 2015). More recent PILs are more likely to display a consistent structure and use the format recommended by the European Medicines Agency (EMA) – combined verbal and frequency information. Recent PILs are also more likely to include frequency information about SE risk (Harris et al., 2015). However, a recent study which assessed the EMA recommendations found that combined verbal and numerical information can lead to notable over-estimation of risk when compared with information presented as numerical frequency bands (Knapp et al., 2015).

2.6.2.3 Trust in information sources

In general, PILs and HCPs such as doctors and pharmacists are viewed across all age groups as trustworthy sources of information (Nähri, 2007). Trust in HCPs is associated with greater inclination in patients to follow medical recommendations. Viewing HCPs as reliable information sources can also be linked to improved attitudes in patients about their medicines (Nähri et al.,2001; Trachtenberg et al., 2005). However, research has also found that differences can exist between HCPs and patients about the type of information that is required. The types of information patients wanted to receive from their GPs about their prescribed medicines were categorised. Information about possible SE was the information category most frequently requested by patients (Berry et al., 1995 as cited in Berry et al., 2002). A later study followed on from this research and asked GPs to assess all the categories in order of importance when explaining prescription medicine to patients (Berry et al., 1997 as cited in Berry et al., 2002). A significant discrepancy was identified between the information patients wanted on possible SE and the importance GPs attached to this type of information. As stated patients often requested such information, however SE information was not considered similarly important by GPs. Inclusion of information about possible SE was not prioritised by GPs and received very low ratings from them (Berry et al., 1997 as cited in Berry et al., 2002). When such differences occur between the views of patients and GPs, the information needs of patients may not be met (Gordon et al., 2007). In addition to HCPs and PILs the news media is considered an important source of information about medicines. The media can play a positive role in public health and increase patient awareness of potential risks and benefits of medical treatments (Moynihan et al., 2000). However, there is some concern about the trustworthiness of media coverage as the quality of reporting on health can vary greatly (Kennedy & Bero, 1999; Gill et al., 2002). Research has identified issues with health reporting within news media such as

inaccuracy, an overemphasis on adverse effects/risks and sensationalism (Myers, 1996; Moynihan et al., 2000; Schwartz, 1999).

2.6.2.4 Effects of providing information

High quality health information was found to facilitate informed healthcare decision making (Clarke et al., 2016). To make such informed decisions patients need to understand the benefits and risks associated with medicines. Research into patients' information needs has indicated that they want to be informed about the possible side effects of their prescribed medicines (Berry et al., 1995; Enlund et al., 1991; Stevenson et al., 1999 as cited in Berry et al., 2002). Multiple studies have been conducted to examine the effects of supplying patients with information about side effects with mixed results (Berry et al., 1997; Gibbs et al., 1990; Myers et al., 1987 as cited in Berry et al., 2002). A study which informed patients about possible gastrointestinal SE resulted in a significant increase in reports of these SE (Myers et al., 1987). However, a later study found no evidence that supplying patients with information leaflets that described SE lead to increased reporting of SE (Gibbs et al., 1990). A study conducted by Berry et al., 2002 was composed of three experiments with 976 participants from the general public. Experiment One manipulated information about SE to observe its effects on peoples' satisfaction, adherence to medicine and their perception of risk. Experiments Two and Three examined the effects of information about negative SE and how it interacts with the perceived benefits of the medicine and the peoples' perceived level of control over SE. It found that people were less likely to take medicine associated with a small number of severe side effects than medicine linked to a large number of mild SE. Overall providing people with information on how to reduce potential SE had beneficial effects. These included increasing both peoples' perceived level of control in preventing/reducing SE and their intention to adhere to the medicine (Berry et al., 2002). This is supported by earlier research which found that supplying patients with information about possible SE – such as PILs – does not lead to increased reporting of SE (Howland et al., 1990; Myers & Calvert, 1976 as cited in Krska & Morecroft 2013).

2.6.2.5 Types of information

Research indicates that information about medicines and SE influence how people take their medicines. It is essential therefore that the information provided is both accurate and easy to understand. Studies have found that patients can misinterpret verbal and numerical

descriptors of SE and commonly overestimate the risk of SE (Berry & Hochhauser, 2006; Carrigan et al., 2008). There are advantages to using verbal descriptors which include making the information more manageable and providing a coherent picture to patients of the variation that can occur in incidence rates during clinical trials. Verbal descriptors are also a format which people find more agreeable than numerical information (Berry et al., 2003; Carrigan et al., 2008; Dickinson et al., 2016; Knapp et al., 2009). It has been suggested that giving frequency information to people about SE could address this overestimation of SE (Knapp et al., 2009). A study was conducted with 134 Cancer Research UK website users which investigated the effectiveness of SE risk information in numerical, verbal and mixed formats (Knapp et al., 2010). It found that patients generally overestimated the risk of SE and were less accurate when estimating uncommon SE. Frequencies could increase the accuracy of risk assessments and patients preferred frequencies to frequency bands (Knapp et al., 2010). A more recent study with 129 Cancer Help UK website users assessed SE risk information on tamoxifen in numerical formats alone - frequency, percentage and combined formats. The findings indicated that the type of format did not affect patients' interpretations of the information. Overall patients preferred the combined – frequency and percentage – format (Knapp et al., 2013).

Research has also indicated that patients frequently use multiple sources of information (Nähri, 2007). However, as described in Chapter One, multiple sources of information can have disadvantages for patients. There is an increased possibility of contradictory information leading to information overload (Carpenter et al., 2010). A study of over 200 patients with vasculitis found that conflicting medical information can have negative impact on patients' adherence to their medicines (Carpenter et al., 2010).

2.6.3 What coping strategies do people use when they experience ADRs?

As mentioned in Chapter One an individual's perception of a negative event - such as an ADR - can be influenced by their cognitive processes and generate specific coping strategies (Kaptein & Weinman, 2004). Coping strategies have been extensively studied in health research and can be assessed by using psychological scales such as the Miller Behavioural Style Scale (MBSS). The MBSS was developed to identify the coping styles/strategies that people use when responding to uncontrollable stressful/threatening situations (Miller et al, 1989). The scale divides people into monitors and blunters - monitoring is an information-seeking behaviour while blunting describes distraction behaviours (Miller, 1989). A review of research which used the MBSS indicated that

cancer patients with a monitoring coping style have a high degree of knowledge about their medical situation, are more anxious about their cancer risk and can experience more frequent and more severe SE from their treatment compared with blunters (Miller, 1995). Monitors in general were found to follow their HCPs' recommendations and responded to their health-related threats with greater psychological morbidity (Miller, 1995). Health research which used the MBSS also indicated that monitors can feel culpable in their health problems and responsible for the progression of the disease (Miller et al., 1995). When the MBSS was used to assess cancer patients it indicated that patients identified as monitors adapt to their situation and focus on managing their health by seeking information about prevention methods and potential outcomes (Lalazaryan et al., 2014; Miller et al., 1995; 1996; 1999; Muris et al., 1994). Cancer patients experienced better health outcomes when the information they received about their medical condition was specifically designed for their coping style (Miller, 1995; 2005). Generally, monitors cope better when given more information while blunters progress better if they receive less information (Miller, 1995; 2005). This early research was supported with later findings which found that monitors acquire a large amount of detailed information when diagnosed with cancer (Kola et al., 2013; Mancini et al., 2006; Williams-Piehota et al., 2005). However, a study in 2006 did not support the characteristics of monitors established by earlier MBSS research. Two groups of patients were examined - 217 patients from three hospital clinics (rheumatology departments/pain clinics); and 262 patients taking antihypertensive medicines from 40 community pharmacies. Monitors wanted written medical information but were not prepared to actively seek this information themselves (Koo et al., 2006). This finding may be explained by the fact that the respondents' health condition was well established and was not a new diagnosis (Koo et al., 2006). Research was also conducted across patient populations and found similar associations between the desire for information and monitoring styles of coping (Janssen et al., 2009; Meulenkamp et al., 2010; Sie et al., 2013). Monitoring is therefore associated with a desire for detailed health information as well as a desire for detailed knowledge of imminent medical procedures. Research proposes that seeking information can help to reassure monitors by reducing uncertainty (Bouckenooghe et al., 2007; Krohne & Hock, 2011; Rosen & Knauper, 2009). Monitors find information has cognitive and affective value for them and consider accessible information to be a comforting resource (Shiloh & Orgler-Shoob, 2006). The MBSS has been used with different patient groups to identify coping styles however it has not been used in research relating to ADRs to date.

2.6.4 What are the distinctive aspects of patient reporting of ADRs and is there any evidence that such reports are beneficial?

2.6.4.1 Benefits of patient reports

Patient reporting systems created datasets that could be examined to identify the potential benefits and/or limitations of patient reports and much research has been conducted in recent years on this topic. Early research in the 1980s was conducted which investigated patients' proficiency in producing useful reports on ADRs to two selected antibiotics. The researchers suggested that large scale reporting by patients could prove valuable in early detection of ADRs (Mitchell et al., 1988 as cited in Blenkinsopp et al., 2006). Later research compared the time profile of ADRs reports related to paroxetine by both patients and health care professionals. It was suggested that reporting by patients could assist in earlier detection of ADRs. These researchers suggest that optimum detection rates might be achieved by combining the information from both patients and health care professionals (Egberts et al., 1996). A later study in 2003 compared health professional reports submitted through the YCS to patient reports of suspected ADRs to paroxetine, collected via e-mails (Medawar et al., 2004). The research found that overall patient reports were more descriptive and provided greater understanding of the significance and consequences of ADRs (Medawar et al., 2004). Patients, in contrast to HCPs, provided more comprehensive explanations of their ADRs and their impact on their social and personal lives (Medawar et al., 2004). However, researchers were uncertain of the merits of direct patient reports with some in PV arguing for the desirability and value of an intermediary role for HCPs in 'filtering' patient reports (Van Grootheest et al., 2003).

Several later studies highlighted the benefits that can result from patient reporting of ADRs (De Langen et al., 2008; Hazell et al., 2013). These studies found that overall patient reports could contribute to drug safety and compliment reports by HCPs (Basch et al., 2009; Hazell et al., 2013). Patient reports were found to contain valuable information with similarities to heath professionals' reports in terms of the ADRs that were most frequently reported and most frequently reported drugs (De Langen et al., 2008; Hazell et al., 2013). Researchers suggested that patient reports could be considered as pertinent sources of information sources which provided complimentary perspectives (Basch et al., 2009). Patient reports also provided explicit detail of the effects of ADRs on the patient's life, family and/or carers. These additional details created a richer narrative and help to form a more comprehensive picture of the individual's experiences of ADRs (Avery et al., 2011; McLernon et al., 2010; Medawar et al., 2004). Despite this, a study carried out in 2011

found that 25% of community pharmacists in the UK believed that reporting of ADRs should be limited to HCPs (Krska, 2012).

A review of patient reporting of ADRs in 11 countries was conducted in 2012 (Van Hunzel et al., 2012). Most of the countries had three methods for patients to report ADRs – paper; electronic or telephone. The survey identified that personalised feedback was not offered by all countries and only the UK and The Netherlands have actively evaluated their patient reporting schemes. However all countries recognised the importance of facilitating the public in reporting ADRs and the scientific value of this data (Van Hunzel et al.,2012).

Another review compared patient reports to healthcare professionals' reports from three studies of the pharmacovigilance systems in Denmark, the UK and the Netherlands (Inch et al., 2012). This review highlighted both similarities and differences between patient reports and HCPs' reports. There were significant similarities in the category of the ADRs and the symptoms of ADRs that were reported by patients and HCPs. Both reported similar numbers of serious ADRs and similar types of causative drugs were reported in the Netherlands and UK studies. However significant differences were apparent between patient and HCPs' reports in the body systems that were affected by ADRs in the UK and Danish studies (Inch et al., 2012). Research which compares reports across pharmacovigilance systems in this manner is problematic. Recent research in Sweden of over 7000 members of the public suggested that the public experience large numbers of ADRs that are not captured by studies of hospital in-patients (Hakkarinen et al., 2013). Self-reports of ADRs from the public displayed a characteristic profile – ADRs commonly resulted in gastrointestinal symptoms with the causative drugs related to nervous system, dermatological or psychiatric disorders (Hakkarinen et al., 2013).

EU-funded reviews of patient reports identified them as valuable tools – these reports can provide information on causality, provide more detail in general and patients frequently report different types of drugs and types of reactions than healthcare professionals. The prescriber's interpretation of effects – which can differ from the patients' opinions - are not considered by patients when reporting and do not influence the patients' report. Many patient reports describe in detail the impact of ADRs on the individual's life family and/or carers (Herxheimer, 2012). These additional details create a richer narrative and help to form a more comprehensive picture of the individual's experiences of ADRs.

2.6.4.2 Evaluation of patient reporting to the Yellow Card Scheme in the UK

The reporting of ADRs has benefit in increasing knowledge and understanding of such drug effects. Patient reports can be viewed as a key component of effective PV processes.

Monitoring and evaluating patient reporting can aid in the assessment and prevention of adverse effects (Wiktorowicz et al., 2012). The MHRA has facilitated research into patient reporting by providing access to the YC dataset. A large study which reported in 2011 compared patient reports with HCP reports and evaluated the impact that direct patient reporting had on pharmacovigilance. It examined all reports to the YCS between 2005 and 2007 and also sought the opinions of the reporters and the public to patient reporting of ADRs (Avery et al., 2011). This research found that patient reports could be considered a valuable element of PV as they provided detailed descriptions of suspected ADRs; were likely to extend knowledge as they reported different drug types and reactions to HCPs and provided useful information about how they identified ADRs, the information sources they used as well as the impact of ADRs on their lives (Avery et al., 2011; Krska et al., 2011). YC reporting forms include free-text questions that seek information on the following: symptoms and how the ADR happened; details of the outcome including use of medicines and other information considered relevant. As part of this study the free-text data were analysed qualitatively and it was found that YC reports frequently provide explicit detail of the effects of ADRs on the patient's life, family and/or carers, which could be used to create a rich narrative, enabling a comprehensive picture of each individual's experiences of their ADR and their subsequent use of medicines (Avery et al., 2011). However, this qualitative work used a small, purposively selected sample of YC reports – approximately 270 patient reports. Recommendations for future study were made as part of the evaluation of the YCS, which included building on this study with an evaluation of the impact of ADRs on patients' lives and

> "the extent to which patients' views and experiences of the seriousness of ADRs concur with those of regulatory bodies, such as the MHRA"
>
> (Avery et al., 2011).

2.6.5 What motivates patients to report their ADR experiences?

Research has also focused on the motivations – conscious and unconscious – which induce patients to report ADRs. A study was conducted in the Netherlands with approximately 1300 patients who had reported an ADR (Van Hunsel et al.,2010). A web-based questionnaire was sent to canvass patients' opinions and motivations for reporting ADRs. The main motives for reporting ADRs were related to the severity of the ADR and patients' altruistic desire to share their experiences. Over 90% of reporters felt that reporting an ADR could prevent the adverse reaction happening to others (Van Hunsel et al., 2010). This finding of altruistic motivation is supported by later research which looked at patient reporting to the YCS and found the primary motivation for patients' reporting

was to describe their experiences for the benefit of others (Avery et al., 2011). The scheme allowed reporters to contribute in a significant way to PV by providing the patient perspective to manufacturers and regulators. This type of meaningful participation in improving patient safety was highlighted by reporters as an important motivating factor (Avery et al., 2011). However, another study was conducted which investigated altruistic motives for reporting ADRs amongst non-reporting patients. This examined the impact of ADRs on fifteen hospital patients and their views on reporting ADRs (Lorimer et al., 2012). Hospital patients admitted for ADRs were interviewed and asked to relate their experience of an ADR. The negative impact of an ADR – anger, fear, isolation – was apparent amongst all the patients. Patients who experienced a severe ADR following acute illness displayed negative emotions towards their HCPs. Patients with a chronic health condition coped better and experienced less negative emotions. None of these patients – acute illness or chronic illness – felt responsibility to report their ADR. Experience of a severe ADR - even if accompanied by potential motivating factors such as anger – did not routinely result in a desire in patients to report the reaction. These study findings suggest that patients who do report ADRs may not be representative of the general patient population (Lorimer et al., 2012).

2.6.6 What benefits would accrue from the development of a reliable ADR assessment tool for patients?

As outlined in Section 2.6.1, patients' cognitive processes include gathering a range of information from various sources to identify ADRs and attribute causality, in an unstructured way. In contrast pharmacovigilance centres use standardised, often highly structured methods for assessing causality, as described in Chapter 1. All the instruments available for assessing causality of ADRs are designed for use by professionals working in pharmacovigilance centres. These scales can be described as limited in their design and application as they were not created for use by general clinicians or patients (Agbabiaka et al., 2008; Théophile et al., 2013) This lack of a standardized, structured assessment tool/algorithm for patients' use could be considered as a considerable limitation of patient reporting to pharmacovigilance centres. However, some assessment tools for assessing causality are available for patients. Recent research was conducted in Thailand which developed and tested an instrument for patient self-assessment of ADRs (Jarernsiripornkul et al., 2015). This novel instrument displayed reliable psychometric properties in its preliminary testing and received positive evaluations from patients. A patient-reported adverse drug event (ADE) questionnaire was also developed and validated by researchers

in the Netherlands (De Vries et al., 2013). The questionnaire was based on checklists and it was intended to be used in clinical trials and postmarketing studies. An assessment tool - the RxISK Report - is also available on the Canadian RxISK drug safety website (htpp://rxisk.org) which helps patients establish if their side effects are linked to their medicines. Generic assessment tools could have multiple benefits and aid patients in their decisions in terms of reporting ADRs. If patients do decide to report to regulatory authorities an assessment tool specifically developed for patient use could enhance the quality of these reports. In addition, a suitable assessment tool for patient use could facilitate a productive partnership between patients and healthcare professionals. This is increasingly important, given the trend towards patient-centred consultations and their involvement in decision-making around treatments, including medicines.

2.7 Discussion

Health research has slowly come to recognise the potential of a patient-centred approach which moves past the clinical aspect of ADRs. There is genuine value to be gained by exploring the alternative viewpoint that patients can provide to ADR reporting. As part of this thesis, a literature review was conducted which examined the current research literature on patients' identification and management of ADRs.

It is clear from this research literature that there is a lack of knowledge surrounding how people cope with and manage ADRs. This review has identified key areas that merit further exploration: how patients' experience ADRs and the perspectives of patient reports; how ADRs impact on patients' lives; how patients' cope with ADRs; what information sources are used by patients to identify ADRs; and finally, the value of an ADR causality assessment tool for patients. This thesis sought to address these areas.

2.8 Aim

This research study sought to explore how people identified and managed ADRs and develop a reliable tool for patients to use to assess ADRs.

2.9 Research question

How do people identify and manage ADRs from their medicines and what impact and consequences do these ADRs have in their lives?

This central research question was developed into four sub-questions:

1. What are the personal experiences of people in managing ADRs?

   a. What are the impact and consequences of their ADR experiences?
   b. What coping strategies do people use when they experience ADRs?
2. What types of information sources do people use to find out about ADRs?
   a. What are the factors contributing to the use of these different information sources?
3. What would be the essential characteristics of a reliable assessment tool for patients to use to assess ADRs?
   a. Would patients consider such an assessment tool to be valuable and useful to them?
4. What is the value of patient reports within pharmacovigilance?
   a. Are there differences between people who report ADRs and the general public in terms of impact of ADRs and information sources used?

CHAPTER 3: GENERAL METHODS

3.1 General Introduction to methodology

The purpose of this research is to address the lack of knowledge surrounding how people cope with and manage ADRs. A variety of research methods are utilised within health research and each methodological technique presents its own inherent advantages and disadvantages. This study sought to explore the personal experiences and opinions of the general public in identifying and managing side effects from medication. It also sought to develop a novel causality scale for use by the general public to assess suspected ADRs. The Literature Review which is described in Chapter Two identified gaps in knowledge surrounding how people cope with and manage side effects. These knowledge deficits informed the research questions and the subsequent study design. A pragmatic approach to the research methodology was selected as the most beneficial way to address the research questions. This approach ensured that the most appropriate methodology was chosen for each of the four phases of the research. A mixed methods study model was therefore employed which allowed the researcher the flexibility to use any quantitative and qualitative methodological techniques that were deemed suitable. This chapter will present the alternative options that existed and the rationale for the methodological choices that were made within this study.

3.2 Justification for research

Research has established that side effects from medicines can have a significant negative impact on peoples' daily lives. This impact can be multidimensional in nature extending into many areas of peoples' lives with physical, economic, social and/or psychological effects. The literature review described in Chapter Two identified gaps in the research into patient experiences of ADRs with researchers being divided on the merits of direct patient reports. Research tended to compare health professional and patient reports of ADRs across pharmacovigilance systems or reports related to specific medicines - such as antidepressants. However recent research has highlighted the benefits that can result from patient reports in increasing knowledge and understanding of ADRs. The gaps identified in the ADR research confirm the necessity of further exploration of the personal experiences and opinions of people in identifying and managing side effects from medicines. They also support the development of a reliable assessment tool for assessing ADRs, specifically designed for patient use. A comprehensive study

was therefore needed to address the central research question set out in Chapter Two:

How do people identify and manage side effects from their medicines and what impact and consequences do these ADRs have in their lives?

3.3 Factors influencing the methodological approach

As described in Chapter Two the central research question was developed into four sub-questions. Given the range of these research questions the study design had to be structured in a manner which enabled all the required data to be collected and the following sub- questions to be fully investigated:

1. What are the personal experiences of people in managing ADRs?
    a. What are the impact(s) and consequences of their ADR experiences?
    b. What coping strategies do people use when they experience ADRs?
2. What types of information sources do people use to find out about ADRs?
    a. What are the factors contributing to the use of these different information sources?
3. What would be the essential characteristics of a reliable assessment tool for patients to use to assess ADRs?
    a. Would patients consider such an assessment tool to be valuable and useful to them?
4. What is the value of patient reports within pharmacovigilance?
    a. Are there differences between people who report ADRs and the general public in terms of impact of ADRs and information sources used?

3.4 Traditional qualitative and quantitative research

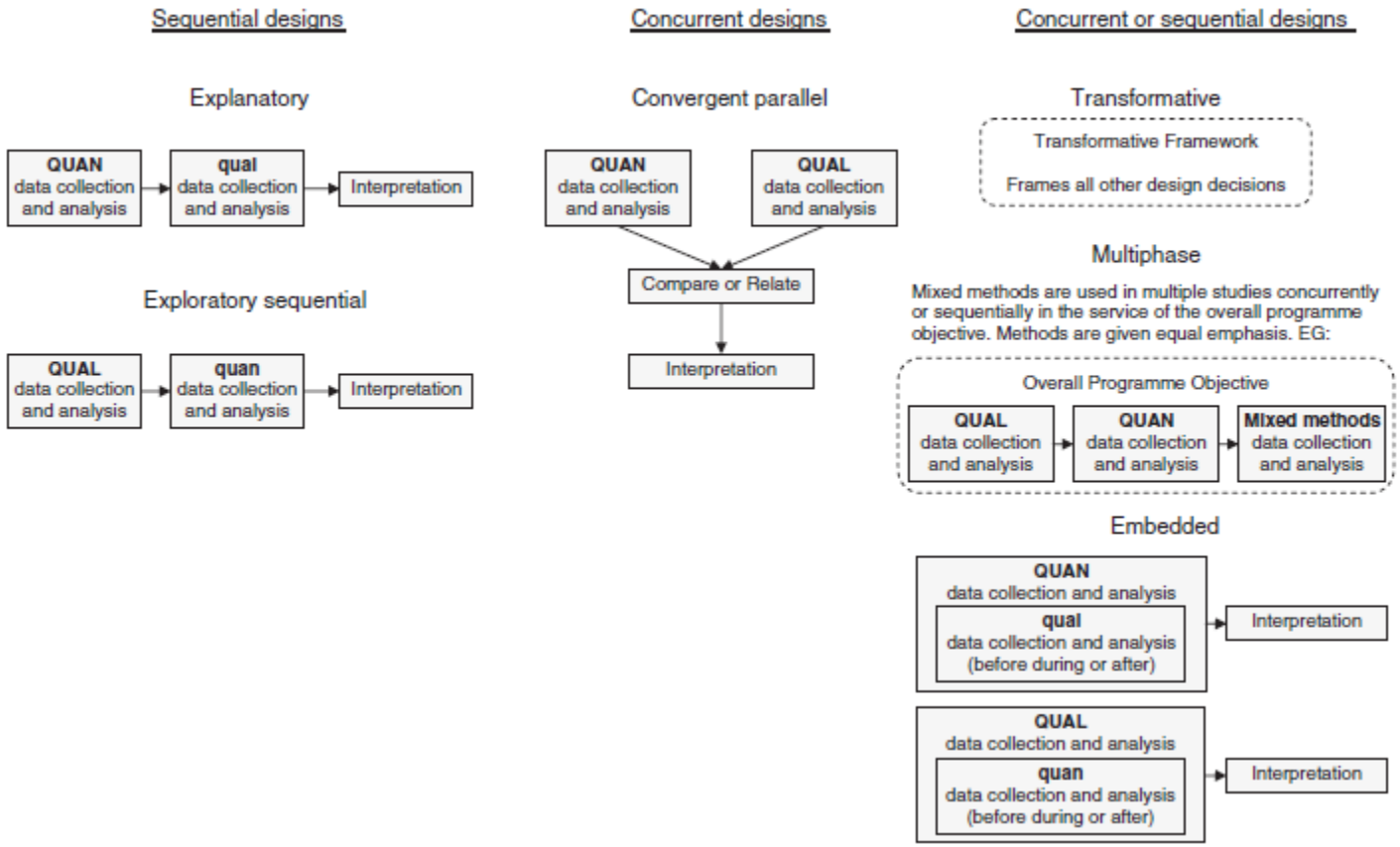
Debate between supporters of quantitative and qualitative research paradigms has existed for decades. Quantitative purists have a positivist philosophy which maintains that research should be objective with the observer separate from their observations. This ensures the researcher is without bias and can achieve stylistic neutrality (Maxwell, 2004). Qualitative purists known as constructivists/interpretivists reject this positivism approach. They contend that research is value laden with the existence of multiple-constructed realities. Explanations are generated inductively from the data and a detailed, direct informal stylistic approach is key (Smith, 1983). Both quantitative and qualitative

research approaches have many benefits as well as many disadvantages (Johnson et al., 2004). However, beyond quantitative and qualitative research arguments mixed methods research offers an additional useful research paradigm.

3.5 Mixed methods research

The combination of quantitative and qualitative research methods in a mixed methods research study can enhance the strengths of each of these approaches (Howe, 1992). The eclectic nature of the methodology is a key element of mixed methods research which can regularly result in superior research (Johnson et al., 2004). A central principle of mixed methods research is that study design is a deliberate, considered and flexible process. The key objective is to answer the research questions and not to be limited to a prescriptive list of design options (Johnson & Onwuegbuzie, 2004). It is felt that the philosophical challenges of mixed methods research can be addressed by employing pragmatist approaches (Bishop, 2015; Dures et al., 2011; Tashakkori et al., 2010). It has been argued that an optimum researcher is a pragmatic researcher who uses a needs-driven approach when selecting research methods (Johnson & Onwuegbuzie, 2004). In general pragmatist approaches accept the epistemological differences that exist between qualitative and quantitative research but suggest they are commensurable within the common aim of all research – to effect positive change in the world (Bishop, 2015). Several important features influence the procedures that are selected for a mixed methods study. These include timing, weighting, mixing and theorizing (Creswell et al., 1994; 2009). The researcher can decide to collect their quantitative and qualitative data either sequentially or concurrently. In some mixed methods studies equal priority may be given to quantitative and qualitative research or one type of research may be prioritised over the other. Mixing of the data can occur at several stages of the research. The researcher can decide to connect, integrate, or embed the databases. Finally, theoretical perspectives may be explicit or implicit within mixed methods studies (Creswell et al., 1994; 2004). Creswell and Clarke proposed six major mixed methods designs in 2011. These include exploratory, explanatory, triangulation, embedded, transformative and multiphase designs (Bishop, 2015). These can be seen in *Figure 3.1*. The transformative design describes any combination of methods used within a comprehensive transformative framework while the multiphase design describes

any combination of methods carried out within more complicated research programmes (Bishop, 2015)



**Note. QUAN indicates quantitative component; QUAL indicates qualitative component; Capitals indicate component is typically emphasised or prioritised in this design. Lower case indicates component is typically used in supportive capacity.*

(Bishop, 2015)

Figure 3.1: Six typical major mixed methods designs (Creswell & Clarke, 2011).

This study sought to explore the experiences of people and the impact of their experiences on their physical, social and psychological environments. There are five main reasons for selecting a mixed methods design: (i) triangulation - using different methods and designs to find corroboration and convergence in results; (ii) complementarity - finding clarification, enhancement and elaboration of results from one method with the results of another method; (iii) initiation - discovering any contradictions or anomalies; (iv) development - using the results from one method to inform another method and (v) expansion - expanding the width and range of the research study through the use of different methods for different elements of the research (Mark et al., 1997). In order to meet the study objectives diverse research areas needed to be covered and varied study populations investigated. It was therefore decided that an explanatory mixed method design that combined the strengths of both qualitative and quantitative research was appropriate for this study.

3.6 Study design

There is limited knowledge surrounding how people cope with and manage ADRs. This exploratory study proposed to address this deficit as well as developing a reliable assessment tool for assessing ADRs, specifically designed for patient use. Initially a mixed methods approach was selected as appropriate as both quantitative and qualitative data were required. When the study aims were considered a mixed methods design was chosen so that data could be generated from different sources and subjected to different analysis which addressed the range of research questions in varied ways (Creswell, 2004). This design also enabled the triangulation and confirmation of results across methods. The study was divided into four phases as follows:

- Phase One - Survey development and distribution
- Phase Two - In-depth interviews with people who have experienced ADRs
- Phase Three - Development and validation of Side Effect Assessment tool
- Phase Four- Investigation of Yellow Card reports

A broad outline of the methods employed in each phase follows as an overview of the study before discussion of the rationale. Full detail of the methods for each phase is provided at the appropriate chapter within the thesis. Phase One is fully described in Chapter Four: Survey; Phase Two in Chapter Five: Interviews; Phase Three in Chapter Six: Side effects Assessment tool and Phase Four in Chapter Seven: Yellow Card reports. Phase One of the study involved the development of a questionnaire to gather general information on peoples' experiences of ADRs and recruit potential interviewees for Phase Two. Survey research was chosen as an appropriate technique to gather general information from a large study population and to help prepare for the more in-depth second phase of the study. The instrument was piloted in the Medway area and amongst people known to have experienced an ADR. The results of the piloting were used to develop the final version of the Side Effects survey. These surveys were distributed to pharmacy customers in selected independent and small to medium sized multiple pharmacies within Kent and the West Midlands urban centres. Initial survey results were used to inform the Topic Guide for the interviews in the second phase. For Phase Two a phenomenological approach was selected to explore the opinions and experiences of people who had recently experienced an ADR, through in-depth interviews. Phase One and Phase Two of the study overlapped and were followed by Phase Three. Analysis of the interviews from Phase Two informed Phase Three of the research and was used to develop a causality assessment tool for the general public to use to assess suspected side effects. This phase also involved the validation of the novel assessment tool amongst members of the general public known to have experienced side effect(s) and in a larger population. Finally, an explanatory strategy was developed from the results of Phase One which informed Phase Four. In Phase Four a large sample of YC reports - submitted to the YCS by patients, parents and carers - were examined to further learn about peoples' experiences of ADRs, to investigate the potential value of data within YC reports from non-HCPs and to compare YC reporters and the wider general public. A flow diagram presents the overall methodology in *Figure 3.2* and includes the number of participants in each research phase.

	AIM	*STUDY DESIGN*	*PARTICIPANTS (N)*
Phase One	To investigate how people use information sources to help them identify ADRs and to explore peoples' experiences of ADRs	Cross-sectional survey	Pharmacy customers in Kent & Medway & Birmingham from February-November 2015 (230)
Phase Two	To explore the opinions/experiences of people who had recently experienced an ADR	In-depth interviews	People in Kent area who recently experienced an ADR from June-November 2015 (15)
Phase Three	To develop and validate a causality assessment tool for the general public to use to assess suspected side effects	Cross-sectional study	People who had experienced ADRs (Total 31: 11 Phase two interviewees & 20 novel participants) Online reports from people who suspect they have experienced ADRs (273)
Phase Four	To examine and evaluate YC reports and to compare how YC reporters and the general public identify and manage ADRs	Quantitative analysis & qualitative content analysis of free text comments in YC reports	YC reports from July-Dec 2015 (2285)

Figure 3.2: Flow diagram of Study Methodology

3.7 Rationale/Justification for study design

3.7.1 Phase One: SE Survey

It was apparent that the first phase of the research required a research technique which could gather general information from a large pre-selected study population in an effective manner and provide the researcher with access to potential interview participants for Phase Two. The survey method potentially allowed a large amount of data to be collected from a large sample, prompted by coherent questions and allowing respondents sufficient time to respond. Consideration was given to the problem of low survey response rates in health research as well as the time and resources available to the researcher (Edwards, 2002; Sax et al., 2003). Distribution of surveys in pharmacies was included in the study design to counteract anticipated low survey response rates. It was decided to distribute surveys in pharmacies, within Kent and Birmingham, amongst pharmacy customers who had used prescription medicines or non-prescribed medicines in the past six months and who satisfied the other inclusion criteria. This method of distribution was selected as the most appropriate method to gather information from a large number of people who regularly used medicines and therefore might be considered likely to frequent pharmacies, likely to have personal experience of an ADR or likely to have opinions on ADRs in general. Personal distribution of the surveys in pharmacies also afforded the researcher with opportunities not available with more blanket methods of distribution. These included the chance to initially screen the customers; to fully engage with the customers; to describe the research and its relevance in a clear manner which encouraged the customers to participate. This distribution method therefore had the potential to increase response rates and recruitment of interviewees while avoiding the necessity of accessing medical records. Development and piloting of the instrument, the final structure of the survey as well as survey distribution are described in full in Chapter 4. A sequential explanatory strategy within the mixed methods design was employed at this stage of the study.

A sequential explanatory strategy can be described as a two-phase process which initially sees the collection and analysis of quantitative data followed by the collection and analysis of qualitative data. The initial quantitative results inform the secondary qualitative phase. The two forms of data can therefore be

considered as connected yet also separate (Johnson & Onwuegbuzie, 2004). The sequential explanatory strategy that was employed during this study began with a quantitative stage - the SE survey. Analysis of this survey data was used to identify people who had recently experienced a suspected ADR. Identification of this cohort can be difficult and therefore survey data which facilitates such identification can be considered both significant and useful. This in turn led to the identification of potential participants for qualitative data collection in the secondary stage - the interviews. Because of time and resource factors the request to participate in these interviews was limited to pharmacy customers in the Kent area only. Analysis of the returned surveys was conducted to develop a Topic Guide for the secondary stage interviews.

3.7.2 Phase Two: Interviews

For Phase Two a phenomenological approach was selected as most appropriate to explore the opinions and experiences of people who had recently experienced an ADR. Interpretative Phenomenological Analysis (IPA) is an approach to qualitative research which is extensively used in psychology and based on the three key areas of phenomenology, hermeneutics and idiography (Smith, 2011). Phenomenology focuses on the 'lived experience' and IPA is based on the examination of personal 'lived experience', the meaning of experience to participants and the manner in which participants make sense of their experience (Smith, 2011). Within an IPA perspective this examination is an explicit interpretative process. IPA requires the researcher to employ a dual hermeneutic process of engagement with and interpretation of the data (Smith et al., 2008). It can be considered idiographic in its detailed analysis of each case/text. IPA is therefore a process of investigating in detail the human 'lived experience' with an iterative analytical process (Smith et al., 2008). This process is an interpretative one which situates the participants in their particular contexts and explores their personal perspectives (Smith et al., 2008). IPA involves the in-depth analysis of the personal accounts of participants and the most commonly used method of collecting these accounts is through in-depth interviews (Smith et al., 2011). While quantitative methods can be informative they cannot provide the connection that IPA does between inherent experience, talking about and reaction to the experience, as well as a participant's making sense of that experience

(Smith et al., 2008). As mentioned in Chapter Two the overall research aims of this phase of the study was to focus on the personal experience and sense-making of people who had recently experienced ADRs. Therefore, IPA was chosen as a suitable approach over other qualitative methods because it was evidently consistent with these proposed research aims (Smith et al., 2008). The difficulties that exist in identifying people who have experienced ADRs result in problems recruiting this population for research studies. Therefore, only limited qualitative research had been conducted amongst this population to date. This suggested that there was a need to increase basic understanding of their 'lived experience'. The IPA approach was therefore considered a particularly appropriate method to address this research deficit and also increase understanding of this particular phenomenon from the participants' perspective.

3.7.3 Phase Three: Side Effects Assessment Tool

The aim of this phase of the study was to develop a causality assessment tool for the general public to use to assess suspected side effects. The Side Effects -Patient Assessment tool (SE-PAST) was developed based on the findings of the research conducted in Phases One and Two. Phase Three also involved the validation of the SE-PAST amongst members of the general public known to have experienced side effects (see Appendix 2). A cross-sectional mixed methods study was selected as most appropriate as it can provide flexibility and allow the integration of complimentary perspectives (Creswell et al., 2004; Johnson & Onwuegbuzie, 2004). This research design allows the traditional objective/positivist paradigms and subjective/constructivist paradigms to be combined in research that is composed of both quantitative and qualitative research methods. This combination of quantitative and qualitative data is the key strength of mixed methods and will ensure that patient experiences will support the statistical analysis inherent in the process of developing instruments (Onwuegbuzie et al., 2010). Recent health-related research has evolved and numerous studies have used a pragmatic mixed methods approach in developing instruments (Durham et al., 2011; Onwuegbuzie et al., 2010; Willgoss et al., 2011). In the present study, initial validation of the instrument developed was sought through telephone interviews with people known to have experienced side effect(s). This was followed by placing the SE-PAST online enabling additional validation in a larger population. This helped to

increase the claims for validity and reliability, both essential components in developing a scale.

3.7.4 Phase Four: Analysis of Yellow Card reports

The aim of Phase Four was to investigate the value of YC reports as a means of confirming how people use information sources to help them identify ADRs and to further explore the experiences of ADRs among a population of people who choose to report this to the regulatory authority. The YC data included free-text comments and responses to closed questions from a large sample of Yellow Card reports. A mixed methods design was selected as the most appropriate approach to take in this exploratory stage of the study. This exploration involved an in-depth 'person-centred' focus that was a fundamental aspect of the study overall. Access to the YC reports facilitated this focus. These reports provided the researcher with the opportunity to create the personal narratives of individual experiences and combine them with quantitative data. The reports obtained included both qualitative and quantitative data and therefore analysis primarily involved both YC free-text data and content from other data fields. Using qualitative and quantitative components in a mixed methods design provided complementary insights helping to create a more comprehensive understanding of reporters' experiences of ADRs. A mixed methods approach was therefore consistent with the research aims.

3.8 Ethical considerations

Overall this study had some ethical issues to consider as it involved people who may have experienced an ADR. This experience could have left them sensitive to the subject and distressed by recalling the details for the researcher. However, each phase of the study was granted ethical approval as appropriate to the population involved. This was obtained from an NHS Research Ethics Committee (REC) which approved Phases One and Two, the Medway School of Pharmacy Research Ethics Committee (MSoP REC) which approved Phases Three, and the Independent Scientific Advisory Committee for MHRA database research (ISAC) which approved Phase Four (See Appendix 3 for approval letters: REC ref 14/NE/1053; MSoP ref 0116/2; ISAC ref GENQ-00097958).

Detailed protocols were submitted at each stage, which outlined clear research aims and objectives and comprehensive methodology. Any inherent ethical considerations were declared and robust strategies were created which ensured ethical compliance. It is incumbent for researchers to be aware when engaging with human participants if sensitivity to the research topic is displayed and participation may be a distressing process for them. In such a situation, a rigorous case for the value of such research must be made by the researcher. In this particular study, it would not have been possible to conduct research into ADRs without including participants who had experienced ADRs. The benefits of creating a more comprehensive picture of their ADR experiences outweighed any concerns about possible distress in recalling negative experiences. The researcher's background in psychology proved to be of considerable benefit during this study. The researcher's experience of working as a psychologist facilitated the survey distribution and facilitated the collection of rich narratives from interview participants. The researcher has taken care to be consistent and ethically rigorous in ensuring the confidentiality and consent of the participants. Processes and procedures dealing with participant confidentiality and consent in each of the four phases of this study are described in detail in Chapters Four-Seven.

3.9 Summary

It should be noted then that the development and approach to the study as well as the analysis and interpretation of results was shaped by the personal characteristics and previous experiences, knowledge, and general background of the researcher. Three key premises inform the study: that ADR research has been limited by focusing on clinical aspects of these effects; that ADRs can have significant impact and consequences in peoples' lives and that individuals can supply rich insight into their ADR experiences.

CHAPTER 4: SURVEY

4.1 General introduction

Chapter Two: Literature Review provided evidence of the existence of a knowledge deficit in health research in ADRs. The purpose of this study was to address the lack of knowledge surrounding how people cope with and manage ADRs. The aim of this phase – Phase One - of the research, as described in Chapter Three: General Methods, was to investigate how people use information sources to help them identify ADRs and to explore peoples' experiences of ADRs. To address some of the research questions which arose as a result of the literature review, general information on peoples' experiences of ADRs was required from a large study population. These research questions included the following:

1. What are the personal experiences of people in managing their ADRs?
    a. What are the impact and consequences of their ADR experiences?
    b. What coping strategies do people use when they experience ADRs?
2. What types of information sources do people use to find out about ADRs?
    a. What are the factors contributing to the use of these different information sources?

Phase One gathered details about these issues through a purposely designed survey which collected the required information. This survey was used as a recruitment tool to identify potential interviewees for Phase Two of the study.

4.2 Methodology

4.2.1 Introduction

The rationale which guided the design for this phase of the study was provided in Chapter Two. This phase – Phase One – sought to contribute to ADR research by collecting information through surveys on how people identify and manage their ADRs. As mentioned in the General Introduction survey data from this phase of the study was used in Phase Two to recruit interview participants and structure the subsequent interviews. This chapter will describe the instrument development and

distribution procedures, recruitment and data collection processes, the strategies for data analysis, the results and a discussion of these results.

4.2.2 Aims and objectives

The aim of this phase of the study was to investigate how people use information sources to help them identify ADRs and to explore peoples' experiences of ADRs. The objectives are as follows:

- To identify the types and value of different sources of information that people use to find out about ADRs
- To identify the factors that influence what sources of information people use to find out about ADRs
- To explore the personal experiences of people in managing their ADRs
- To investigate the impact and consequences of peoples' ADR experiences
- To investigate the coping strategies that people use when they experience ADRs
- To assess relationships between peoples' coping strategies and their experiences of ADRs

4.2.3 Ethical approval

An application was made to the NHS/HSC Research and Development (R&D) offices and the Research Ethics Committee through the Integrated Research Application System (IRAS). (See Appendix 4). A favourable opinion was obtained from the Proportionate Review Sub-committee of the NRES Committee North East - Newcastle & North Tyneside 1. However considerable delays in the research governance approval process then ensued which in turn caused significant delays to the research overall. These delays were a result of conflicting information given by the Kent and Medway Research Management and Governance (RM&G) Consortium. It was stated - incorrectly - that a research passport for the researcher with full Occupational Health (OH) and Disclosure and Barring Service (DBS) checks were required before R&D would issue a Letter of Access for the study (See Appendix 5). The delays were unnecessary and incredibly frustrating occurring at a critical time period and significantly delayed data collection. This situation continued for over three months until notification was received from Kent and Medway R&D that a research passport was not

required to distribute questionnaires and local approval for the researcher to access the pharmacy premises would now be sufficient (see Appendix 5). As part of this application process potential ethical issues that might arise during this research were identified. Key amongst these were issues of confidentiality and anonymity. The researcher structured the study as indicated below to address these crucial areas.

4.2.4 Confidentiality and Anonymity

All participating pharmacies as well as survey respondents remained anonymous. All participants were informed that the research was confidential. Lists of the pharmacies visited were generated with unique identifying numbers. These lists were written on paper and locked in a secure filing cabinet. Access to these lists was limited to named members of the research team. At the end of this study these lists will be held for period of one month and subsequently destroyed by shredding. The returned surveys were assigned unique study numbers ensuring anonymity. Consent forms which contain contact details were also assigned unique identifying numbers and stored separately from the returned surveys. All survey data collected was stored on password protected computers and memory sticks. These digital records will be destroyed five years after the final thesis has been written.

4.2.5 Instrument development

A survey was developed iteratively within the research team to gather general information on peoples' experiences of ADRs (See Appendix 6). Its structure was based on the research objectives and an effective framework was provided by previous research instruments. These surveys/questionnaires included the following: the Yellow Card Scheme Questionnaire, 2005; Side Effects Coping Questionnaire, 2012; the Hospital Inpatient Survey, 2013). Two validated instruments were also included - the MBSS abbreviated and the SECope abbreviated. Permission was obtained from the developers of these instruments to use the MBSS and SECope (see Appendix 7). These scales were included to provide additional information on the coping styles and coping behaviours of survey respondents.

4.2.5.1 Justification for using MBSS and SECope scales

An individual's perception of a negative event - such as an ADR - can be influenced by cognitive processes such as coping strategies (Kaptein & Weinman, 2004). These coping strategies can be assessed by using psychological scales. Monitoring and blunting are defined as two response modes that are utilised in stressful/threatening situations. Monitoring is an information-seeking approach while blunting describes distraction and re-interpretation of the inhibiting aspects of the situation. Most individuals will use either Monitoring or Blunting strategies in stressful situations. Monitors will be alert and seek information as they attempt to increase the predictability of the outcome. Blunters will employ distractive strategies even if they have the potential to influence the outcome (Voss et al., 2006). The abbreviated version of the Miller Behavioural Style Scale (MBSS) (Miller 1987; Steptoe, 1989) has been extensively used in psychological research to identify coping styles in stressful situations. It was used in this study to assess if coping styles influence whether and how, people with recent experience of an ADR, access information sources. The MBSS (abbreviated) consists of two controllable scenarios – going to the dentist and the threat of potential job loss. Controllability is defined as the possibility that active interventions in the situation may change the outcome. Each scenario offers the respondent eight possible behavioural choices – four will describe monitoring behaviours/styles of coping with aversive situations while the other four will describe blunting behaviours/styles of coping with aversive situations. Respondents are required to visualise the scenarios and assess if the proposed responses correspond to what they would do or think if they were in this situation. It was hypothesised that individuals that sought out information about their ADR would be assessed by the MBSS as monitors, while survey respondents that did not utilise sources of information such as PILs would be identified as blunters.

The Side Effect Coping Questionnaire (SECope) (Johnson & Neiland's, 2007) is an instrument used in health behaviour research to measure peoples' coping strategies and behaviours with treatment side effects. A revised version of the SECope questionnaire was developed composed of 16 items with four behavioural subscales - social support seeking, information seeking, non-adherence and taking additional medication (DeSmedt et al., 2011). Respondents indicate their level of agreement with statements within each of these subscales. This SECope (revised)

was further amended to 10 items, in this phase of the study, after piloting, to aid instrument clarity and reduce repetition. This amended 10 item SECope was used in this study to assess the coping behaviours of people who experience ADRs and identify potential associations between these coping strategies.

4.2.5.2 Survey structure

The survey was structured as follows (See Appendix 6):

Section A – respondents' use of sources of information

This section asked respondents how they might use information on medicines and was composed of two questions with tick box responses. Question One asked respondents about their hypothetical use of information sources if they experienced side effects. Ten potential sources of information were listed for respondents, divided into three categories:

- HCPs – GPs; Hospital doctors; Pharmacists and Nurses
- Formal sources of information – PILs; Print and Broadcast Media and Medicine books/guides
- Informal sources of information - Relatives/friends; Internet and Other

Respondents were asked to choose which of these sources they would use and could choose multiple sources by ticking multiple boxes. Question Two asked respondents to assess the information sources according to the following parameters:

- Accessibility
- Trustworthiness
- Understandable
- Relevance

Respondents were asked to consider each of the information sources and indicate if they considered them easy to access; trustworthy; easy to understand and/or relevant to them by ticking response boxes.

Section B – respondents' personal experiences of side effects

This section asked respondents for details and descriptions of their side effects' experience. It was composed of 12 questions in total with ten questions requiring tick box responses and two text box questions requiring free text comments. Questions Three to Six asked respondents if they had experienced a SE, as well as

the timing and consequences of their SE. The term 'side effect(s)' was selected as inclusive wording that would be more familiar to respondents than ADR and that would encourage reporting of minor effects. Question 7 asked respondents to rate the severity of their SE on a four-point scale ranging from Mild; Unpleasant; Serious to Very serious. Question 8 required respondents to assess the impact of the SE on their daily lives on a four-point scale ranging from No impact, Mild impact, Moderate impact to Severe impact. Question 10 also required respondents to rate their confidence that the SE was caused by their medicine on a four-point scale ranging from Not at all confident, Not very confident, Fairly confident to Very confident. Questions Nine and 11 were free text questions asking respondents to describe in their own words the impact of the SE on their daily lives and how they concluded that the medicine had caused the SE. Question 12 asked what information sources respondents used to confirm their SE. The same ten potential sources of information given in Section A in three categories were again listed for respondents. Respondents were asked to choose which of these sources they used and again could choose multiple sources by ticking multiple boxes. Questions 13 and 14 required tick box responses and sought information on adherence to medicines.

Respondents were asked if they stopped taking their medicines and if they did was it their decision to stop or the result of advice from HCPs or relatives and/or friends.

Section C – respondents' coping strategies (amended SECope)

This section sought information on how respondents cope with SE. Coping behaviours were assessed using an amended version of the SECope questionnaire (De Smedt et al., 2011), which contained 10 items in four subscales:

- Information seeking
- Taking medicines
- Social support
- Non-adherence

The 10 statements related to peoples' behaviours when they experienced SE. Respondents were asked how closely these behavioural statements corresponded with their own behaviours if they experienced a SE. They were asked to rate their possible responses on a five-point Likert-type scale ranging from Never; Rarely; Sometimes; Often to Always.

Section D – respondents' coping with stressful situations (MBSS)

This section assessed the coping styles of respondents in stressful situations using the abbreviated MBSS. The abbreviated MBSS in this section consists of two scenarios:

- Question 16 - going to the dentist
- Question 17 - threat of job loss.

Each question has eight possible behavioural choices for these aversive situations – four statements of monitoring behaviours and four statements of blunting behaviours. Respondents are asked to visualise the scenarios and choose which of the statements corresponded to what they would do or think in that situation. Respondents ticked boxes to indicate their agreement with behaviours/statements and could choose multiple responses by ticking multiple boxes.

Section E – demographic information.

This section asked respondents to provide information on their gender, age range, employment status, education level and ethnicity. They were also asked to indicate the number of prescription medicines they regularly used. In addition, they were asked to provide their postcode. These postcodes distinguished between respondents from Birmingham and Kent and Medway.

Section F - invitation to participate in interviews and Contact details form

Surveys distributed in Kent and Medway contained an additional section. This section sought to recruit interview participants who had experienced a SE in the past six months. People were invited to provide their contact details for the researcher if they were willing to talk about their SE experience.

4.2.5.3 Inclusion criteria

The inclusion criteria for survey participants were as follows:

- Adults aged 18 or over
- Resident in the UK
- Competency in written and spoken English
- People who used prescription medicines or OTC medicines in the past 6 months

4.2.5.4 First pilot

Piloting of questionnaire

Twenty people known personally to the research team, who were known to have experienced an ADR, were asked to complete and assess the questionnaire. They

were posted an envelope which contained a questionnaire, Participant Information Sheet, a pre-paid envelope, and a Feedback form (See Appendix 8). They were asked to assess the questionnaire in terms of clarity, ease of completion, face validity and overall functionality. Based on the feedback received and discussions amongst the research team, several modifications were made to the questionnaire. Question Two, which asked respondents to assess a list of information sources for their accessibility, trustworthiness, understanding and relevance, was reformatted with clearly labelled tick boxes to aid clarity. The instructions section of the SE Cope Questionnaire was re-written to enhance coherence. In addition, the perceived repetition within the SECope was addressed and the initial 16 item scale was abbreviated to 10 items which focused on the important subscales information seeking behaviours and social support seeking behaviours. A second pilot was conducted to assess the impact of these amendments.

Piloting of the distribution method

As mentioned in Chapter Three, pharmacies were selected as distribution sites for this phase - Phase One – of the study. Surveys were distributed amongst pharmacy customers who had used prescription medicines or non-prescribed medicines in the past six months. This method of distribution was selected as the most appropriate method to gather information from a large number of people who regularly used medicines. Personal distribution of the surveys in pharmacies enabled the researcher to screen and fully engage with the customers. This personal distribution method had the potential to increase response rates and recruitment of interviewees. Distribution of the initial version of the questionnaire was piloted in a local pharmacy in the Medway area. The owner of this pharmacy was known personally to the research team and was willing to participate in the pilot. Envelopes were prepared in advance and contained a questionnaire, a Participant Information Sheet and a pre-paid envelope to return completed questionnaires (See Appendix 8). During the pilot pharmacy customers were approached by the researcher who introduced herself and displayed her University ID. The researcher outlined the study and invited people to participate. If the individual indicated their willingness to participate they were asked questions to determine if they satisfied the inclusion criteria for the study. They were asked to complete the questionnaire at their leisure and return the completed questionnaire in the pre-paid envelope provided. The researcher took note of the following - the number of customers in the pharmacy over a four-hour period; the number of

customers who were approached by the researcher over this time period and the reasons given by people for refusing to take a questionnaire. This piloting of the distribution enabled the researcher to rehearse her approach to customers and calculate likely recruitment rates for the main study.

4.2.5.5 Second pilot

A novel group of people personally known to the research team and known to have experienced an ADR were contacted by the researcher. They were asked by phone or email if they were willing to participate. Those who agreed were asked to participate in the second pilot by assessing the revised questionnaire and providing feedback. Snowballing recruitment techniques were used as the pilot progressed to identify and recruit additional participants. The survey was distributed by post and included the questionnaire, a Participant Information Sheet, a pre-paid envelope and a Feedback form. This pilot enabled a final version of the survey to be developed for Phase One of the study (See Appendix 6). The final version of the survey was verified as an effective tool in investigating how people identify ADRs and gathering information about peoples' experiences of ADRs.

4.2.6 Main study design

This paragraph will describe the following stages:

- Sample size
- Recruitment of pharmacies
- Recruitment of survey participants
- Analysis of survey data

Sample size

The statistical power of a study provides a measure of the probability that its results are statistically significant. A study with good statistical power will produce accurate/precise findings which can be considered as representative of the population as a whole. Statistical power is influenced by sample size and it is good practice to estimate how many participants will be needed to achieve statistical significance. Considering sample size helps to control for Type II error and to estimate the accuracy/precision of the results. (Brace et al., 2016).
The sample size for the survey was calculated using the following equation.

$$Ss = \frac{Z^2 \times (p) \times (1-p)}{C^2}$$

where Ss= sample size; Z = 1.96 (95% confidence level); p = % accuracy expressed in decimals and C-squared = confidence interval or margin of error expressed as a decimal. C-squared is an estimate of the deviation between survey and general population parameters. Confidence intervals define the range of values which are likely to include the population parameters - margin of error set at 5% estimates that 95% of survey respondents will include the population parameter.

The calculation was based on an estimated figure for the prevalence of experiencing an ADR of 26% (/Alhawassi et al, 2014). Thus for a confidence level of 95%, a confidence interval/margin of error of 5%, the sample size required was:

$$Ss = \frac{(1.96)^2 \times (0.26) \times (1-0.3)}{(0.05)^2}$$

$$Ss = \frac{3.84 \times 0.26 \times 0.7}{0.0025} = \frac{0.698}{0.0025}$$

$$Ss = 279.5$$

The study therefore aimed to recruit approximately 300 participants. A previous study in the Kent area utilising similar methodology which sought experiences of using long-term medicines among the general public using community pharmacies found a response rate of 40%. Therefore, based on this rate, it was decided to distribute approximately 700 questionnaires (750*0.40 = 300).

4.2.6.1 Recruitment of pharmacies

This phase of the study aimed to survey members of the public through distribution of surveys in independent and small to medium sized multiple pharmacies within Kent & Medway and the West Midlands urban centres. Contacts amongst the research team (study collaborators) were used to facilitate the identification of potential small chains of pharmacies which may be willing to allow the study to take place on their premises. Large multiples were not approached as it was envisaged that seeking permission to access these premises would be too time consuming. A list of pharmacies with their contact details was compiled from the NHS Choices website. A letter of invitation to participate in the study was sent to these pharmacies and, if they could be identified, to named managers within these pharmacies (See Appendix 9). The envelope included an

information sheet for the pharmacist explaining the study and the survey (See Appendix 10). The initial postal contact was followed a week later by a telephone call to each pharmacy. The researcher asked the pharmacies for permission to access their premises to distribute surveys to the general public. The inclusion criteria for pharmacies were as follows:

- Independent pharmacies
- Small to medium sized multiples
- Pharmacies within the following geographical areas – Medway, Kent and the West Midlands

4.2.6.2 Recruitment of survey participants

Potential survey participants were identified by the researcher as pharmacy customers who had used prescription medicines or non-prescribed medicines in the past six months and satisfied the remaining inclusion criteria (see above). The researcher arrived at the pharmacy premises with prepared envelopes to distribute to the general public. Each envelope contained the following: participant information sheet, consent form, survey and a prepaid envelope to return the questionnaires. The researcher approached potential participants and outlined the study, asked questions to determine if they met the inclusion criteria and, if so, invited participation by completing the questionnaires and returning them at their leisure.

This phase – Phase One – overlapped with Phase Two of the study. Survey data continued to be collected and analysed, as interviews for Phase Two were arranged and conducted. The data collection was enhanced by the involvement of MSoP undergraduate students who contributed by distributing the survey as part of their MPharm undergraduate Research Project.

4.3 Data management

The data from the returned surveys were entered into and analysed using SPSS for Windows Statistics 23. The data were checked and cleaned - errors and inconsistencies were identified and removed and data entry quality assured through comparison with original paper surveys. For validation purposes, a 10% (n=230) sample was checked for accuracy of entries against the original questionnaires. Categorical data were described using percentages and frequencies. Respondents' age was skewed thus median and IQR

values were reported and the Kruskal-Wallis test was using to compare groups. Contingency tables and Pearson's chi-squared test was used to investigate associations between the following:

Box 4.1: List of associations investigated with contingency tables and chi-squared tests

Respondents' demographics and SE history, gender
Respondents' demographics and SE experience, SE outcomes
Use of information sources and respondents' demographics, confidence in causality
Assessment and use of information sources
Actual use of information sources and coping styles
Coping styles and SE experience and SE outcomes
Predicted coping behaviours and gender, coping styles

A significance value of $p \leq 0.05$ was set to control for type I error (a 'false positive'/incorrect rejection of the null hypothesis). A Bonferroni correction was applied for several analyses due to the large number of multiple comparisons being made. This resulted in a lower *p* value which reduced the occurrence of type I errors (adjusted *p* value=α/n). Responses to survey text box questions nine and 11 were entered in Excel and content analysis was carried out. Commonalities were identified and categories were created. The number of answers per category was noted and a frequency table was created. Then the free text responses for Survey questions were recorded in SPSS and into the data management programme NVivo (QSR NVivo 10). The responses were analysed using an iterative thematic approach.

The MBSS and SECope scale scores were analysed using the methods specified by the authors of these instruments (see below), to assess respondents' coping styles and behaviours. Factor analysis was used to investigate the underlying structure of the revised 10 item SECope. Survey data was subjected to regression analysis to examine relationships between variables and used to develop a Topic Guide for the interviews in Phase Two of the study (See Appendix 11).

4.3.1 Analysis of SECope

The SECope was scored by assigning the numerical values 1-5 to the Likert scale responses as follows: very often = 5, often = 4, sometimes = 3, rarely = 2, and never = 1. All items were positively weighted except item 8 – 'Accept the side effect and take the medication as prescribed' - which was reverse scored.

The revised 10 item SECope was subjected to Principal Component Analysis (PCA) using direct oblimin rotation with Kaiser normalisation. The internal reliability was determined with Cronbach's alpha (α). Items with loadings values greater than 0.5 on a factor were considered strong loadings and assigned to that factor. If items displayed strong loadings on more than one factor they were further examined as cross loadings components.

The amended 16 item SECope had four subscales – Information seeking subscale; Taking medicines subscale; Social support subscale and Non-adherence subscale. Positive and negatively weighted items in each subscale were scored and an average of these scores was then calculated. The percentage of individuals who engaged in information seeking behaviours; social support seeking behaviours; taking medicines and non-adherence behaviours was thus calculated. A mean percentage of each of the SECope subscales was then calculated by summing the scores for the individual items that made up the subscale and dividing by the number of items. Scores above this mean value were labelled as positive coping strategies within the subscale while those below the value were considered negative coping strategies. This further distinguished the SECope subscale results and generated percentages for positive and negative coping behaviours/strategies. Contingency tables and Pearson's chi-squared test was then used to investigate associations between the following:

- Associations between respondents' demographics and their coping behaviours
- Associations between respondents' coping styles and their coping behaviours
- Associations between respondents' use of information sources and coping behaviours

4.3.2 Analysis of MBSS

Coping styles were assessed by the abbreviated MBSS. The MBSS scoring key presents several scoring options. For this study, it was decided to calculate the total monitoring and blunting scores for each respondent. Each of the two

scenarios had eight possible responses - four monitoring and four blunting responses. Monitoring items are marked "M" on the MBSS Scoring Key and the Blunting items are marked "B" on the MBSS Scoring Key (See Appendix 12). An overall monitoring score was generated by summing endorsed monitoring items across the two scenarios. An overall blunting score was generated by summing the endorsed blunting items across the two scenarios. Subjects with a total score on the monitoring subscale of the MBSS which is greater than the median were classified as high monitors and those with scores less than the median value were classified as low monitors. Contingency tables and Pearson's chi-squared test was used to investigate associations between the following:

- Associations between respondents' demographics and their coping styles
- Associations between respondents' coping behaviours and their coping styles
- Associations between respondents' use of information sources and coping styles

4.4 Results

4.4.1 Pilot Studies

Two pilots were conducted: the first was designed to test the distribution method as well as the initial instrument, thus was intentionally large, the second was required as the instrument underwent major changes after the first pilot, thus was intentionally smaller, as there was no requirement to test the distribution method again. For the first pilot, 48 surveys were dispersed with 28 returned indicating a response rate of 58%. Approximately 40 customers were approached over four hours indicating that a 5-minute engagement with each customer was required to generate this response. The second pilot, using the amended instrument –involved the distribution of 16 surveys with 12 returned, indicating a response rate of 75%. Overall 64 surveys were distributed with 40 returned a response rate of 63%.

4.4.2 Main survey - survey distribution

In total 935 surveys were distributed to pharmacy customers - 80 distributed in pharmacies in the Birmingham region and 214 distributed in pharmacies in Kent and Medway over seven months February-July 2015. Undergraduate students distributed 641 surveys over three months from October-December 2016. An

overall response rate of 25% was achieved with 230 surveys returned. Pilot responses were not included in these totals as respondents may have differed from those in the main study, hence creating selection bias. It is generally regarded as good practice not to combine data from pilot studies with data from the main study (Lancaster et al., 2004; Peat et al., 2002).

4.4.3 Main study - Respondent characteristics

From 230 returned surveys the respondents' median (IQR) age was 61 years (51 to 70 Years), majority (141; 62%) were female and 164 (72%) were of white ethnicity. The highest proportion of respondents (102; 45%) were retired with 72 (32%) educated to University level. Demographics from pilots and main study are presented on the following page in *Table 4.1*. Comparison of pilots and main studies indicate similar demographics. The main differences were (a) education with more students in the pilots and (b) 100% of pilot respondents used medicines but 15% of survey respondents used no medicine. This was a result of recruiting people for the pilots who were known to the researcher and known to have experienced SE from their medicines. Overall 20 surveys (9%) were assessed as incomplete with item nonresponse dealt with by the conventional method of pairwise exclusion of missing data from analysis (Soley-Bori, 2013). The frequency of missing data is presented in *Table 4.2*

Table 4.1: Demographic characteristics of respondents to pilots and main survey

Demographics	**Frequency (f)**			**Percentage (%)**		
	Pilot 1(n=28)	Pilot 2 (n=12)	Main study(n=230)	Pilot 1(n=28)	Pilot 2 (n=12)	Main study(n=230)
Gender						
Male	8	2	87	29	17	38
Female	20	10	141	71	83	61
Age						
Below 40	9	1	44	32	8	19
41-50	7	3	29	25	25	13
51-60	7	3	49	25	25	21
61-70	5	3	50	18	25	22
71-80	0	2	44	0	17	19
Over 80	0	0	12	0	0	5
Prescribed medicines						
One	11	5	46	39	42	20
2-4	11	6	82	39	50	36
5-8	6	0	53	21	0	23
>8	0	1	12	0	8	5
None	0	0	35	0	0	15
Education						
School Leaver ≤16	6	2	61	21	17	27
School Leaver=17/18	6	1	36	21	8	16
Further education	6	7	60	21	58	26
University	10	2	72	36	17	31
Employment						
Full-Time	10	3	64	36	25	28
Part-Time	5	3	28	18	25	12
Retired	8	5	102	29	42	44
Student	5	1	10	18	8	4
Unemployed	0	0	12	0	0	5
Ethnicity						
White	13	8	164	46	67	71
Asian/Asian Br	5	3	36	18	25	16
Black/Black Br	10	1	11	36	8	5

Table 4.2: Frequency table of missing data per question

Survey questions (1-12)	**Missing data (freq)**	**Survey questions (13-24)**	**Missing data (freq)**
Q1 Predicted info use	2	Q13 Stopped meds	6
Q2 Assessment of info sources	1	Q14 Advice on stopping meds	4
Q3 SE experience	2	Q15 SECope	20
Q4 SE timing	2	Q16 & Q17 MBSS	6
Q5 G.P. visit	2	Q18 Medicine use	2
Q6 Hospitalisation	2	Q19 Gender	2
Q7 SE Severity	2	Q20 Age	2
Q8 SE Impact	3	Q21 Employment	2
Q9 Text box Impact on QoL	20	Q22 Education	1
Q10 Confidence on causality	3	Q23 Ethnicity	3
Q11 Text box causality	14	Q24 Postcodes	9
Q12 Actual information use	2		

QoL = quality of daily life; MBSS= Miller behavioural style scale; SECope = Side effects Coping

4.4.4 Main study - findings

Findings relating to peoples' experiences of ADRs are presented under three headings: The experience of SE; Identifying SE and Managing SE.

4.4.5 Side effect experience

The overall SE experience was composed of SE history; SE timing and SE outcomes. Outcomes were categorised for analysis by the reported severity, impact and consequences of SE.

Overall 192(85%) respondents used prescribed medicines regularly - a similar proportion of females 121(86%) and males 71(83%). The highest proportion of respondents 82(36%) took two to four medicines - 31(36%) of males and 51(36%) of females. In total 12(5%) respondents used more than eight medicines. Overall 159 respondents had experienced a SE with the timing of the SE a year ago or longer for 77(49%) respondents; past six months for 34(22%); past three months for 23(15%) and in the past month for 24(15%) of respondents.

4.4.5.1 Associations between Gender, SE history and respondents' demographics

Gender and Employment

Analysis was conducted to examine associations between Gender, SE experience and respondents' demographics. Analysis indicated that there was an association between gender and employment with a higher proportion of males 32(37%) in full time work than females 32(23%). The difference was not statistically significant at the Bonferroni adjusted probability level (p=0.005). (See *Table 4.3*).

Gender and SE history

Crosstabulation indicated that female respondents experienced more SE from their medicines than males, but the difference was not statistically significant. Overall 159 respondents – 106 females and 53 males - had experienced a SE. (Sixty eight respondents had no history of side effects). It was indicated that females 42(40%) had experienced SE once compared to 28(53%) of males. A majority of female respondents 64(60%) experienced SE more than once compared to 25(47%) of males. (See *Table 4.3*).

SE history and Age

A relationship was identified between SE history and age with a greater proportion of respondents with a history of SE 36(23%) in the 61-70 age range. The difference was not statistically significant at the Bonferroni adjusted probability level (adjusted p=0.004). Of these 26(30%) had more than one SE experience. A similar proportion of respondents 25(16%) below 40 and 41-50 years had a history of SE. However, in later age ranges there was increases in the incidence of SE to 33(21%) in those aged 51-60; 36(23%) in those 61-70 years and 31(20%) in those aged 71-80. See *Table 4.3*

SE history and medicine use

Analysis indicated an association between SE history and medicine use. However the association was not statistically significant at the Bonferroni adjusted probability level (adjusted p=0.005). Regular use of multiple prescribed medicines was linked to more than one SE experience. Overall the highest proportion of respondents 56(35%) with a history of SE used two-four medicines regularly. Over half of respondents 88(55.3%) had more than one SE experience. Amongst respondents who had experienced SE more than once 33(59%) used two-four medicines; 28(32%) used five-eight medicines and 9(10%) used more than eight medicines. (See *Table 4.3*).

SE history and Education, Employment

Overall retired respondents and those educated to further education levels had a more extensive SE history. The highest proportion of overall respondents with a history of SE were University educated 50(31%) and Retired 76(48%). A total of 89(56%) had experienced SE more than once. The highest proportion of these were Retired 48(54%) and with Further education 29(33%) (See *Table 4.3*).

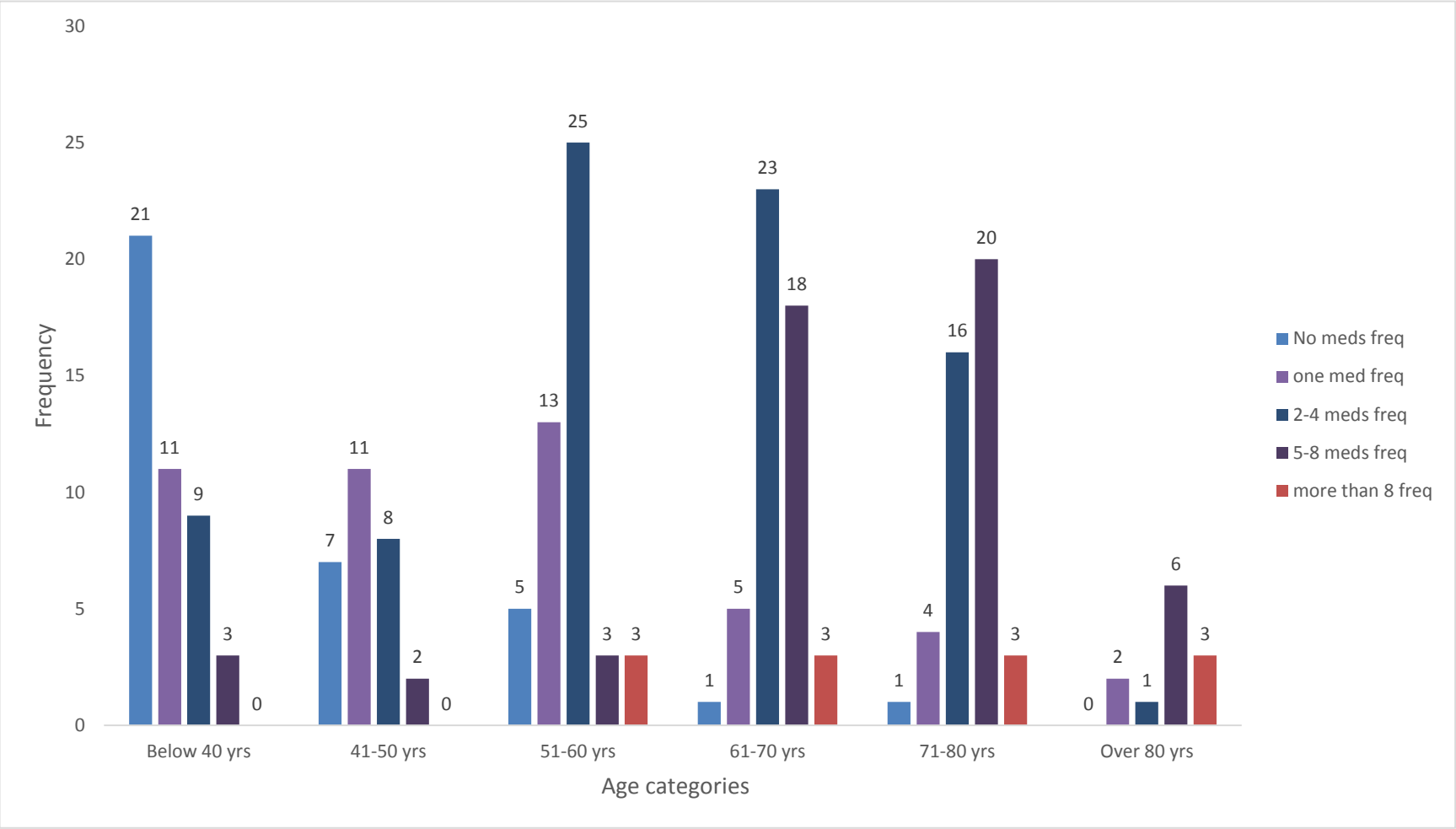
Table 4.3: Respondent characteristics by Gender/SE history n=230

Respondent characteristics	**Gender f (%) n=227**		**p-value**	**SE history f (%) n=159**		**p-value**
	Male	Female		**Once**	**More than once**	
Age			0.09			0.05*
Below 40	16(18.4)	28(20)		15(21.1)	10(11.4)	
41-50	13(14.9)	16(11.4)		12(16.9)	13(14.8)	
51-60	15(17.2)	34(24.3)		15(21.1)	18(20.5)	
61-70	22(25.3)	28(20)		10(14.1)	26(29.5)	
71-80	13(14.9)	31(22.1)		12(16.9)	19(21.6)	
Over 80	8(9.2)	3(2.1)		7(9.9)	2(2.3)	
Prescribed medicines			0.93			0.04*
None	15(17.4)	20(14.2)		12(16.9)	8(9.1)	
One	15(17.4)	30(21.3)		18(25.4)	10(11.4)	
2-4	31(36)	51(36.2)		23(32.4)	33(37.5)	
5-8	21(24.4)	32(22.7)		15(21.1)	28(31.8)	
>8	4(4.7)	8(5.7)		3(4.2)	9(10.2)	
Education			0.58			0.44
School Leaver ≤16	24(27.6)	36(25.5)		20(28.2)	23(25.8)	
School Leaver=17/18	11(12.6)	25(17.7)		11(15.5)	12(13.5)	
Further education	21(24.1)	39(27.7)		15(21.1)	29(32.6)	
University	31(35.6)	41(29.1)		25(35.2)	25(28.1)	
Employment			0.03*			0.4
Full-Time	32(37.2)	32(22.7)		20(28.2)	17(19.1)	
Part-Time	9(10.5)	19(13.5)		10(14.1)	9(10.1)	
Retired	40(46.5)	62(44)		28(39.4)	48(53.9)	
Ethnicity			0.35			0.79
White	57(65.5)	106(76.3)		54(77.1)	66(75)	
Asian/Asian Br	20(23)	16(11.5)		10(14.3)	14(15.9)	
Black/Black Br	4(4.6)	7(5)		1(1.4)	4(4.5)	
Gender						0.11
Male	N/A	N/A		28(52.8)	25(47.2)	
Female	N/A	N/A		42(39.6)	64(60.4)	

**Not significant at Bonferroni adjusted alpha levels*

Age and medicine use

Analysis indicated an association between the age range of respondents and their medicine use. Overall as the age ranges increase so too does medicine use. The highest proportion of respondents used two to four medicines 82(36%) followed by 52(23%) who used five-eight medicines. A high proportion of those who used two-four medicines were aged 51-60 and 61-70 years; 25(51%) and 23(46%) respectively. The proportion of respondents who use five-eight medicines increased from 18(36%) in those aged 61-70 to 20(46%) in 71-80 years and 6(50%) in those over 80. Half of respondents aged over 80 6(50%) use five-eight medicines. The percentages of respondents' medicine use in each age range is presented graphically see *Figure 4.1*. The association between age and medicine use was not statistically significant at the Bonferroni adjusted probability level (adjusted p=0.002).



[#] *missing data (n=3)*

Figure 4.1: Relationship between age ranges and medicine use of respondents (n=227[#])

4.4.5.2 Associations between SE severity and respondents' characteristics

The effects of respondents'characteristics on SE severity were investigated. These characteristics included demographics such as gender and medicine use.

SE severity and Gender

Analysis indicated an association between SE severity and gender of respondents. Overall a higher proportion of female respondents than males experienced 'unpleasant' or 'serious' SE, 47(44%) and 43(41%) respectively. All 'very serious' SE were reported by females 5(5%) see *Figure 4.2.*

4.4.5.3 Associations between SE consequences and respondents' characteristics

The effects of demographics and medicine use on SE outcomes such as SE severity, SE impact and SE consequences were investigated. These consequences included a GP visit and hospital admission. A GP visit was associated with gender; age and medicine use as well as employment and education. (See *Table 4.4)*

GP visit and Gender

Analysis indicated a relationship between gender and SE consequences. Gender effects were evident as 103(65%) of respondents saw a GP with the majority 76(72%) females. Overall 14(9%) respondents required hospitalisation with a higher proportion of females 11(10%) than males 3(6%). The relationship between SE consequences (GP visit) and gender was significant: X^2 (1, N = 159) = 6.01, p = 0.01. The negative association was of moderate strength: Φ = -0.2, gender accounted for just 4% of the variation in SE severity.

GP visit and age

A relationship was identified between age and SE consequences. As the age ranges increased from 41-50 to 71-80 the proportion of respondents who saw a GP also increased. The majority of respondents within these age ranges - 15(60%) of respondents aged 41-50 years; 22(67%) aged 51-60; 23(64%) aged 61-70 and 28(90%) aged 71-80 saw a GP. The highest proportion of respondents who saw a GP across the age ranges were aged 71-80 years 28(90%). The association between age and GP visits was not statistically significant at the Bonferroni adjusted probability level (adjusted p=0.004).

GP visit and medicine use

Analysis indicated an association between medicine use and SE consequences. A higher proportion of respondents using two-eight medicines saw a GP compared to other respondents. Those taking two-four medicines 43(77%) and five-eight medicines 31(74%) were compared to 17(17%) taking one medicine and 7(58%) who were using more than eight medicines. Analysis showed that one cell had expected count less than 5 so an exact significance test was selected for Pearson's chi-square. The relationship between SE consequences (GP visit) and number of prescribed medicines was significant at the Bonferroni adjusted probability level (adjusted p=0.005): X^2 (4, N = 158) = 16.22, p = 0.002. The association was of moderate strength: $\Phi = 0.3$ with medicines accounting for 10% of the variation in SE consequences (GP visit).

GP visit and Employment and Education

Retirees and those in full time employment were more likely to see a GP because of their SE when compared other respondents. Overall 104(65%) saw a GP with a higher proportion 57(76%) of these retired respondents and 23(62%) in full time employment. Early school leavers were more likely to see a GP compared to other respondents. A higher proportion of school leavers under 16 years 32(76%) and at 17/18 years 19(83%) saw a GP than other respondents.

Hospital admission and age, medicine use, employment and education

Crosstabulation indicated that those aged 41-50 (4;16%); those using 5-8 medicines (5;11.9%); retirees(5;7%); school leavers under 16 (5;12%) and University educated respondents (5;10%) experienced more hospital admissions as a consequence of their SE. However the difference was not statistically significant.

4.4.5.4 Predicting SE experience

As mentioned previously overall SE experience was composed of SE history; SE timing and SE outcomes. Outcomes were categorised for analysis by the reported severity, impact and consequences of SE.

Regression analysis was conducted to determine if SE experience could be predicted by demographic variables and medicine use. Multinomial logistic regressions were performed on 224 cases to assess the relationship between the

predictor variables - age, gender, employment status, education and number of medicines – and the dependent variable, SE experience.

It was found that age and gender significantly predicted SE history (chi-square = 25.58, df = 12, p =0.012) and SE consequences such as GP visits (chi-square = 29.2, df = 6, p <0.001). Males were less likely than females to have had more than one SE and the odds of males having had more than one SE was 63% lower than the odds of females. Respondents aged below 40 were less likely to have had more than one SE compared to those aged over 80. The odds of those aged below 40 having experienced more than one SE was 45% lower than those aged over 80. Males were less likely than females to have required a GP visit as a result of the SE with the odds of males 74% lower than the odds of females. See *Table 4.5* on the following page.

Gender also predicted SE severity (chi-square = 12.36, df = 3, p =0.006) and SE impact (chi-square = 5.6, df = 1, p =0.02). Males were less likely than females to describe their SE as serious and also less likely to report their SE as having a severe or moderate impact on their lives. Analysis indicated that the odds of males having a serious SE was 76% lower than that of females. When compared to females the odds of males reporting the impact of the SE as severe/moderate was found to be 56% lower. See *Table 4.6* and *Table 4.7.*

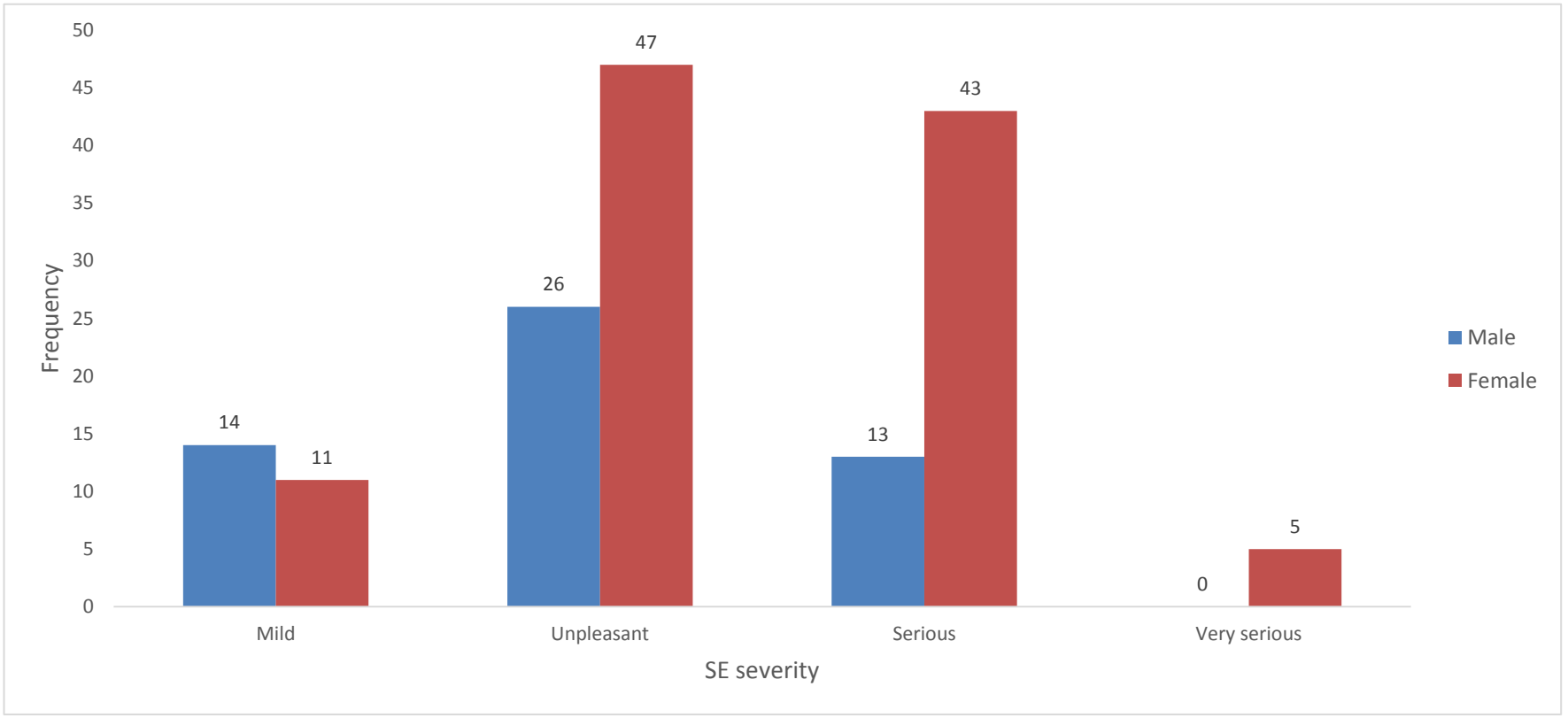


Figure 4.2: Relationship between Gender and SE severity (n=159)

Table 4.4: SE severity, SE impact and SE consequences in relation to gender and number of medicines (n=230)

SE outcomes	**Respondent characteristics**								
	Gender f (%) n=159		***p*-value**	**Prescribed medicines f (%) n=**					**p-value**
	Male	**Female**		**None**	**One**	**2-4**	**5-8**	**>8**	
SE severity			0.01[#]						0.2
Mild	14(26.4)	11(10.4)		4(15.4)	6(23.8)	8(30.8)	8(30.8)	0	
Unpleasant	26(49.1)	47(44.3)		9(12.5)	8(11.1)	30(41.7)	15(20.8)	10(13.9)	
Serious	13(24.5)	43(40.6)		7(12.5)	12(21.4)	17(30.4)	18(32.1)	2(3.6)	
Very serious	0	5(4.7)		0	2(40)	2(40)	1(20)	0	
SE impact			0.07						0.12
None	11(21.2)	11(10.5)		4(18.2)	7(31.8)	7(31.8)	4(18.2)	0	
Mild	25(48.1)	41(39)		10(14.9)	8(11.9)	24(35.8)	15(22.4)	10(14.9)	
Moderate	13(25)	37(35.2)		4(8.2)	6(12.2)	18(36.7)	19(38.8)	2(4.1)	
Severe	3(5.8)	16(15.2)		2(10.5)	7(36.8)	6(31.6)	4(21.1)	0	
SE consequences									
GP visit	27(51.9%)	76(71.7%)	0.01*	6(5.8)	17(16.3)	43(41.3)	31(29.8)	7(6.7)	0.002**
Hospital visit	3(5.8%)	11(10.4%)	0.34	0	4(28.6)	5(35.7)	5(35.7)	0	0.33

[#]*Not significant at Bonferroni adjusted alpha levels*

**Significant at p=0.05 probability level*

***Significant at Bonferroni adjusted alpha level*

Table 4.5: Multinomial regression analysis identifying predictors of SE history (n=224) and GP visits (n=156)

Predictor Variables	***B***		***df***		***Exp(B)***		***Sig***	
	SE history*	***GP visit^x^***	***SE history****	***GP visit^x^***	***SE history****	***GP visit^x^***	***SE history****	***GP visit^x^***
Gender								
Male	-0.9	-0.897	1	1	0.4	0.408	0.009**	0.021**
Female[#]	0	0	0	0	0	0	0	0
Age								
Below 40	- 0.593	-2.87	1	1	0.553	0.06	0.559	0.02**
41-50	1.362	-1.63	1	1	3.905	0.2	0.212	0.17
51-60	0.136	-1.41	1	1	1.146	0.24	0.892	0.23
61-70	0.853	-1.38	1	1	2.348	0.25	0.388	0.23
71-80	0.463	0.09	1	1	1.589	1.09	0.646	0.94
Over 80[#]	0	0	0	0	0	0	0	0

***Reference category no SE**

[x] Reference category no visit

[#]Parameter set to 0

****Significant at p<0.05 level**

Table 4.6: Multinomial regression analysis identifying predictors of SE severity (n=159)

Predictor Variables	***B*** ***Serious SE****	***df***	***Exp(B)***	***Sig***
Gender				
Male	-1.437	1	0.238	0.005**
Female#	0	0	0	0

***Reference category = mild**

#Parameter set to 0

****Significant at p<0.05 level**

Table 4.7: Multinomial regression analysis identifying predictors of SE impact (n=157)

Predictor Variables	***B*** Severe/Moderate*	***df*** Severe/Moderate*	***Exp(B)*** Severe/Moderate*	***Sig*** Severe/Moderate*
Gender				
Male	-0.83	1	0.44	0.02**
Female#	0	0	0	0

***Reference category mild/no impact**

#Parameter set to 0

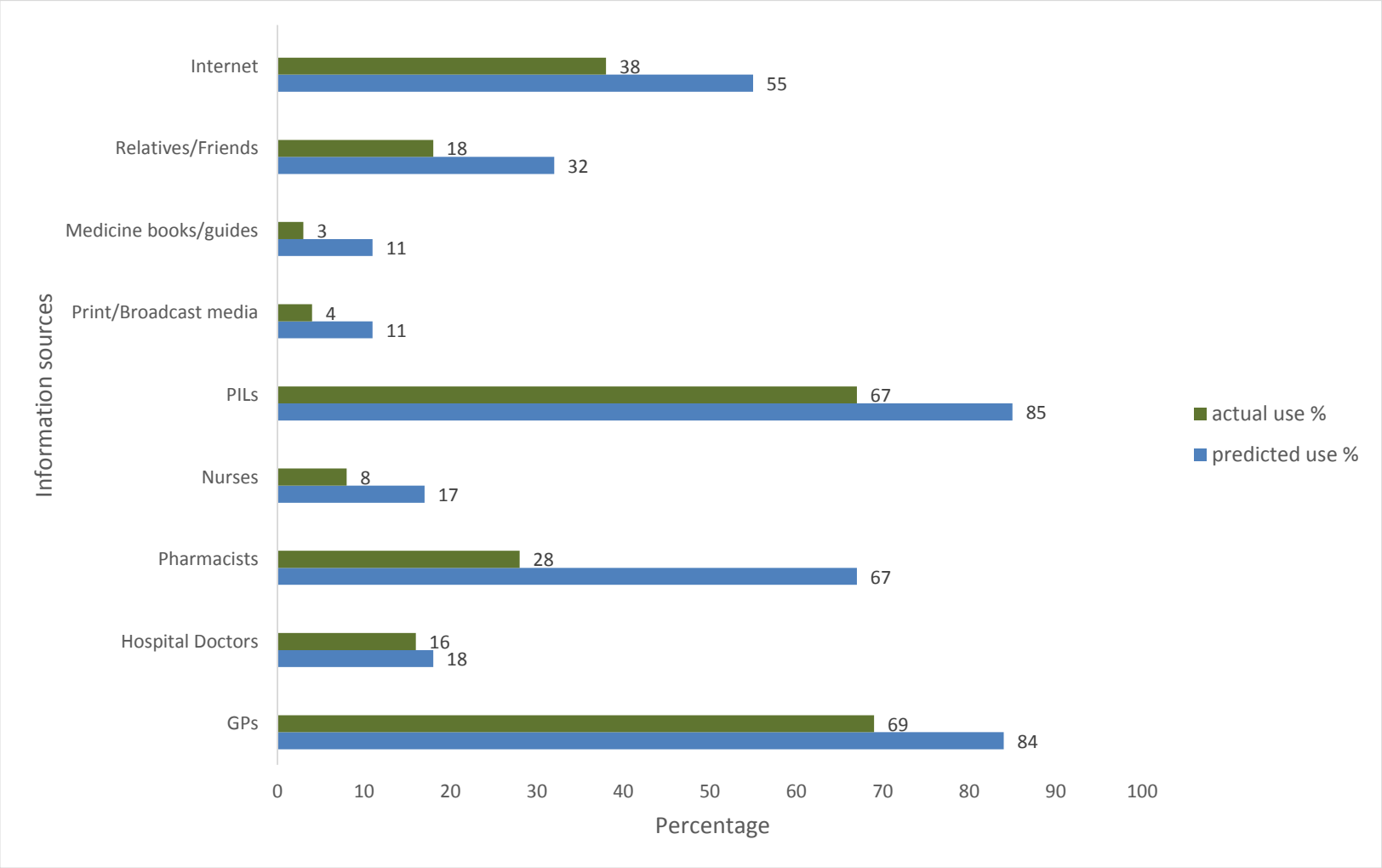
****Significant at p<0.05 level**

4.4.6 Identifying SE

4.4.6.1. Information sources

Predicted use vs actual use of information sources

In response to question 1, all survey respondents indicated the sources of information they thought they would use to find out about SE. Those who indicated they had experienced a SE also provided details of the sources they actually used, when this occurred. Respondents' actual use of information sources to confirm their SE differed from their predicted use of these sources. Analysis indicated that GPs 194(85%); PILs 192(84%) and pharmacists 153(67%) would be the information sources most likely used by respondents. In actual use GPs and PILs were the most utilised sources; 109(69%) and 106(67%) respectively. However, a higher proportion of respondents used the Internet 60(38%) than pharmacists to confirm their SE 44(28%). Overall medicine books/guides and the print/broadcast media were the least used sources across both predicted use - 25(11%); 25(11%) - and actual use – 5(3%) and 7(4%). See *Figure 4.3.*

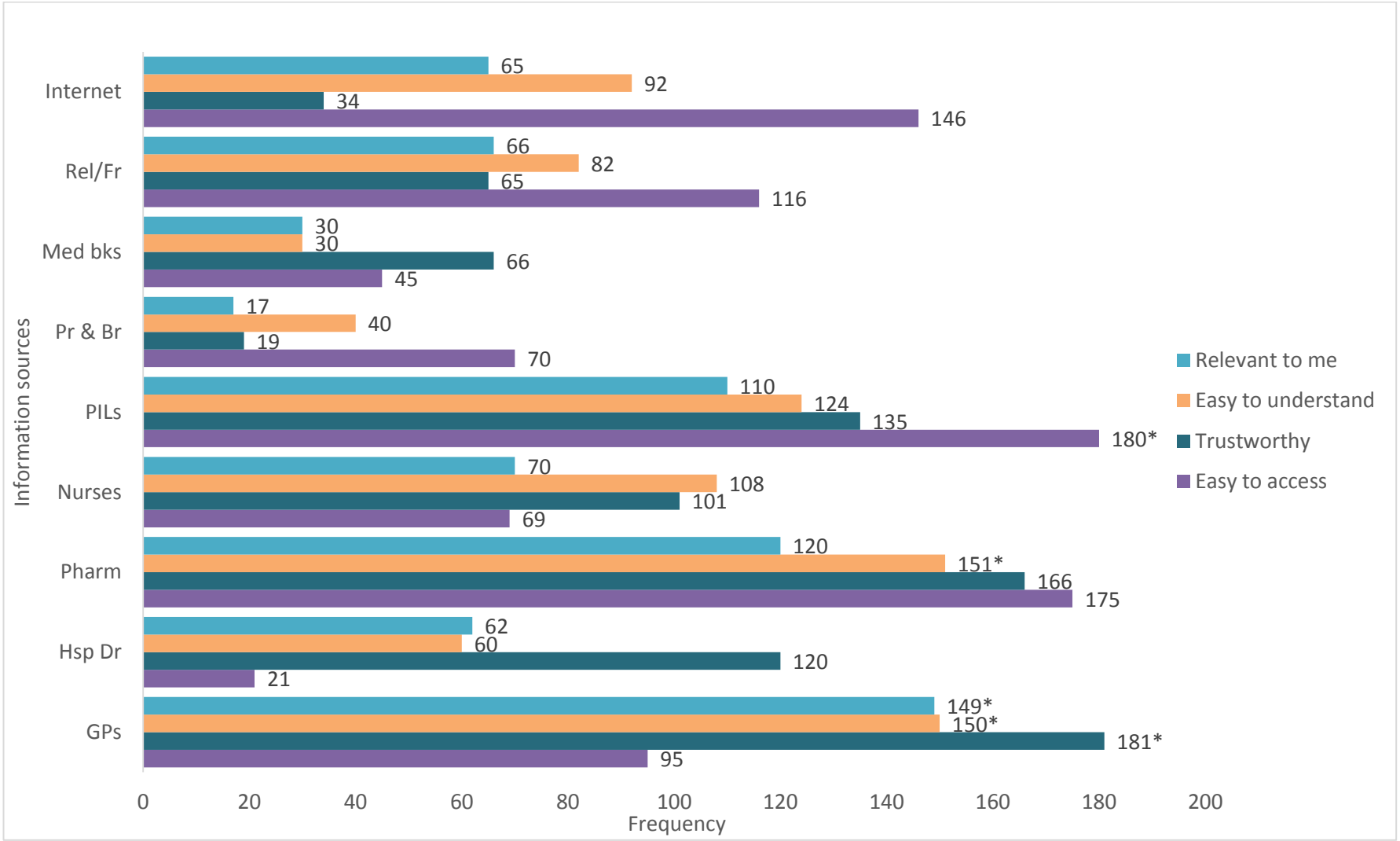


PILs-=Patient Information Leaflet; GPs=General Practitioners

Figure 4.3: Predicted use vs Actual use of information sources

4.4.6.2 Assessment of Information sources

Analysis was conducted on respondents' assessments of information sources for ease of access; ease of understanding; trustworthiness and relevance (n=229). Overall PILs were considered the most accessible source 180(79%) with medicine books/guides identified as the least accessible 45(20%). GPs were identified as the most trustworthy information source 181(79%) with the Internet considered the least trustworthy 34(15%). A similar proportion of respondents identified GPs and pharmacists as sources that were easy to understand; 150(66%) and 151(66%) respectively. However, medicine books/guides were viewed as the least understandable source 30(13%). Respondents identified GPs as the most relevant information source 149(65%) with print/broadcast media the least relevant 17(7%). See *Figure 4.4.*



Rel/Fr=Relatives/Friends; Med bks=Medicine books; Print & Broadcast media; PILs=Patient Information Leaflets; Pharm=Pharmacists; Hsp D=Hospital Doctors; GPs=General Practicioners;

*****Sources assessed by respondents as most accessible; trustworthy; easy to understand and relevant*

Figure 4.4: Assessment of Information sources by respondents (n=229)

4.4.6.3 Respondents' assessment and actual use of information sources

A logistical regression was performed to predict the actual use of information sources against respondents' assessment of these information sources. See *Table 4.8*. Use of information sources to confirm SE was the dependent variable with accessibility, trustworthiness, ease of understanding and relevance as predictor variables. This predictive analysis of 158 cases indicated that respondents' perceptions of two information sources - GPs and the Internet - could be associated with actual use of these information sources.

GPs

Assessment of GPs as easy to access and relevant information sources significantly predicted whether GPs were used to confirm SE. Accessibility variable; $b = 0.89$, Wald X^2 (1) = 4.94, $p = 0.03$ and relevance variable; $b = 1.02$, Wald X^2 (1) = 4.17, $p = 0.04$. The odds of respondents using GPs to confirm SE was 2.42 times higher and 2.77 times higher respectively if they perceived GPs as accessible and relevant (with a 95% CI 1.11-5.29; 95% CI 1.04 -7.36).

Internet

Assessment of the Internet as an accessible information source reliably predicted its use to confirm SE. Accessibility variable; $b = 1.$, Wald X^2 (1) = 6.6, $p = 0.01$. The odds of respondents using the Internet to confirm SE was 3.97 times higher if they perceived it as an accessible source (with a 95% CI 1.39 -11.37).

Table 4.8: Logistic regression analysis identifying predictors of actual use of information sources. (n = 158)

Predictor Variables	***B***	***Wald***	***df***	***Exp(B)***	***Sig***
Ease of Access					
GPs	0.89	4.94	1	2.42	0.026*
Pharmacists	0.7	1.35	1	2.02	0.25
PILs	0.29	0.36	1	1.33	0.6
Internet	1.38	6.6	1	4.0	0.01*
Trustworthy					
GPs	0.55	1.11	1	1.73	0.29
Pharmacists	0.6	1.2	1	1.81	0.27
PILs	0.6	2.0	1	1.8	0.16
Internet	0.73	1.74	1	2.08	0.19
Easy to Understand					
GPs	0.30	0.34	1	0.94	0.91
Pharmacists	0.06	0.01	1	0.94	0.91
PILs	0.7	3.3	1	2.0	0.07
Internet	0.69	2.09	1	2.0	0.15
Relevant					
GPs	1.02	4.17	1	2.77	0.04*
Pharmacists	0.45	1.07		0.64	0.3
PILs	0.42	1.01		0.32	1.5
Internet	0.02	12.81		0.2	0.97

B= coefficient; Wald= Wald chi-square test; df= degrees of freedom; Exp(B)= exponentiation of the B coefficient; Sig=significance

GPs=General Practitioners; PILs=Patient Information Leaflets

** Significance at p < 0.05 level (two-tailed)*

4.4.6.4 Use of information sources and respondents' confidence levels

Number of sources

Analysis was conducted on the effects of the number of information sources on respondents' confidence about SE causality. Overall respondents' confidence levels increased with the number of sources they used. Of the 159 respondents who experienced SE 31 (19.5%) used one source to confirm their SE; 51 (32%) used two sources, 52 (33%) three sources and 25 (16%) more than three sources. Respondents' who used two sources 36(71%); three sources 31(62%) and more than three sources 17(68%) were very confident their medicine had caused the SE. See *Figure 4.5.*

Type of sources

The types of sources used to confirm SE varied across respondents, but overall use of multiple sources or combining HCPs and PILs led to increased levels of confidence in respondents. Over half of respondents 82(52%) used multiple sources – HCPs, formal/informal sources - and 51(64%) of these were very confident that the SE was due to their medicine. Respondents who combined HCPs and PILs 37(24%) to confirm their SE were also very confident 26(70%). See *Figure 4.6.*

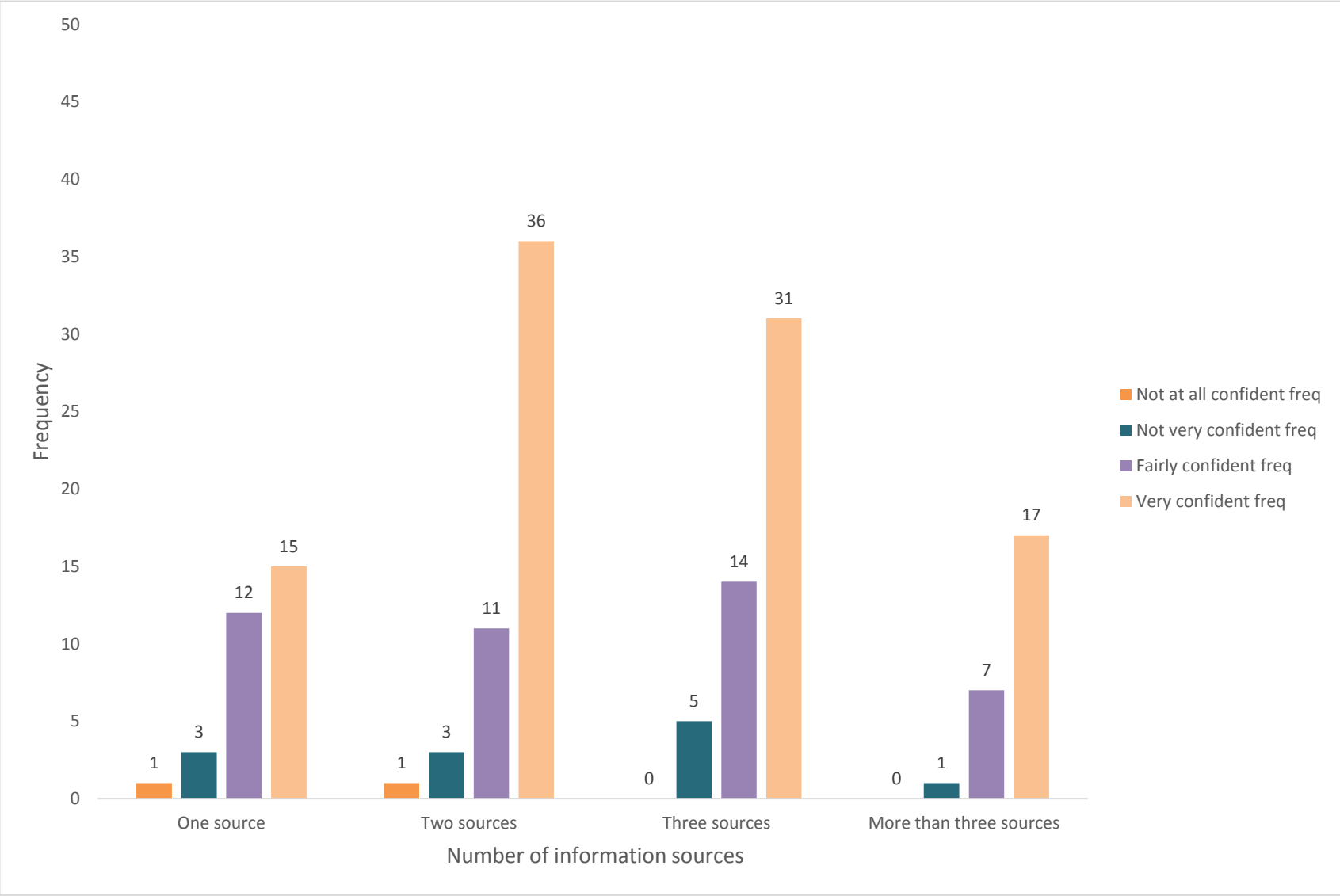


Figure 4.5: Effects of number of information sources on confidence levels (n=159)

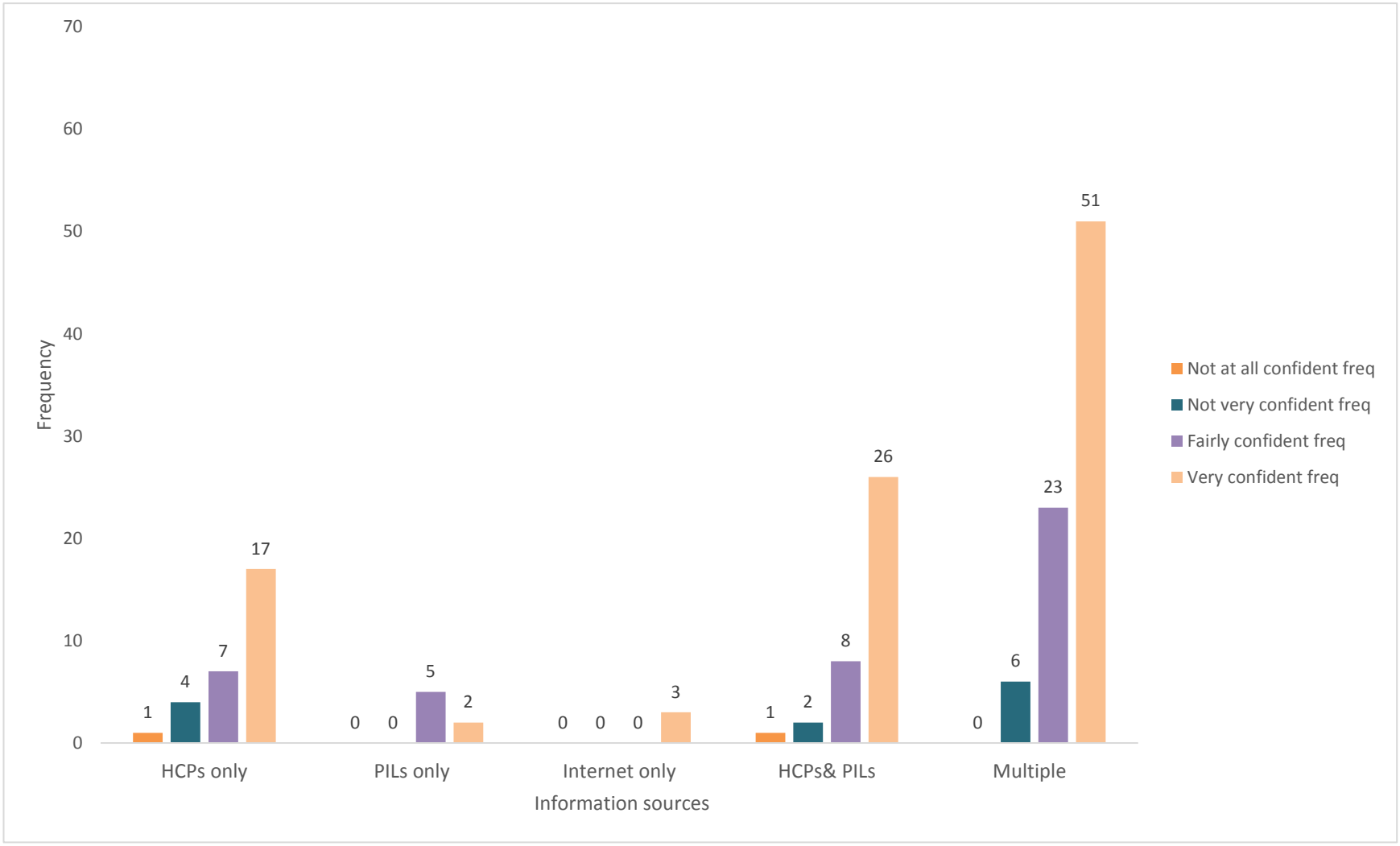


Figure 4.6: Effects of types of information sources on confidence levels (n=159)

4.4.6.5 Number and types of information sources and coping styles

Of 224 respondents 164(73%) respondents had monitoring coping styles with 28(13%) identified as Blunters and 32(14%) with neutral coping styles. Analysis was conducted on the number of information sources by respondents across these coping styles. The top three sources used by Monitors were GPs (79;72%), followed by PILs (72;66%) and the Internet (44;40%); Blunters used PILs (16;84%), GPs (11;58%) and pharmacists (8;42%). Those with neutral coping styles used PILs (16;67%) followed by GPs (14;58%) and the Internet (8;33%). See *Table 4.9.*

Table 4.9: Type of information sources used by Coping styles

	Coping Styles ***(n=153)***		
Information sources	**Monitors** ***(n=111)***	**Blunters** ***(n=19)***	**Neutral** **(*n=24*)**
Healthcare Professionals			
GPs	79(72)	11(58)	14(58)
Hospital doctors	15(58)	4(21)	7(29)
Pharmacists	31(28)	8(42)	4(17)
Nurses	12(11)	0(0)	1(4)
Formal sources			
PILs	72(66)	16(84)	16(67)
Pr & Br Media	6(6)	0(0)	0(0)
Medicine books/guides	3(3)	1()	0(0)
Informal sources			
Relatives/friends	21(19)	3(16)	4(17)
Internet	44(40)	7(37)	8(33)

Figures shown are n(%)
Pr & Br Media= Print & Broadcast Media

4.4.7 Management of SE

4.4.7.1 Coping Styles and SE experience

Data were analysed to identify any patterns between MBSS coping styles and characteristics of respondents' SE experience. The overall SE experience was composed of SE history; SE timing and SE outcomes. Outcomes were further categorised as the reported severity, impact and consequences of SE.

4.4.7.2 Coping styles and SE history and timing

A total of 160 respondents had experienced SE - 71 (44%) indicated they had experienced SE once with 89(56%) having more than one SE experience. Of those who completed the MBSS similar proportions of Monitors (49;44%) and Blunters (9;50%) had experienced a SE. The timing of SE was similar in Monitors and Blunters – 55;50% and 7;42% respectively. See *Table 4.10*.

4.4.7.3 Coping styles and SE severity

Overall 73 respondents (46%) reported their SE as 'unpleasant' and 56(35%) as 'serious'. Monitors reported their SE as 'unpleasant' or 'serious' (41;84%) compared to Blunters (15;79%) and Neutrals (16;67%). Thirty-six Monitors reported 'serious' effects compared to eight Blunters (42%) and nine neutrals (38%). Associations between coping styles and the reported severity of SE were examined. Five cells had expected count less than 5 so an exact significance test was selected for Pearson's chi-square. There was a relationship between coping styles and SE severity: X^2 (6, N = 154) = 13.97, p = 0.033. The association was of moderate strength: $\Phi = 0.3$ coping styles accounted for 9% of the variation in SE severity. See *Table 4.10.*

4.4.7.4 Coping styles and SE impact and consequences

Analysis of the impact of SE indicated that 67 respondents (42%) experienced 'mild' or 'moderate' 50(32%) impact. The highest proportion of Monitors experienced either 'moderate' (36;33%) or 'mild' impact (47;43%). The highest proportion of Blunters (7;37%) and Neutrals (11;46%) reported their impact as 'mild'. Seventeen respondents reported a 'severe' impact – 13(12%) of these were identified as Monitors. Overall a majority of respondents (104;65%) required a GP visit while 14(9%) required hospitalisation. The majority of Monitors (71;65%) and 13 Blunters (69%) required a GP

visit. Hospitalisation was required in 9(8%) of Monitors and 2 Blunters (11%) See *Table 4.10.*

Table 4.10: SE experience of respondents by Coping styles (n=154)

Coping Styles

SE Experience	**Monitors** ***(n=111)***	**Blunters** ***(n=19)***	**Neutral** ***(n=24)***	***p*-value**
SE history				0.6
Once	49(44)	10(53)	9(38)	
More than once	62(56)	9(47)	15(63)	
SE timing				0.9
Past month	13(12)	3(16%)	5(21)	
Past 3 months	16(15)	4(21%)	4(17)	
Past 6 months	26(24)	4(21%)	4(17)	
Year/Longer	55(50)	8(42%)	11(46)	
SE seriousness				0.05*
Very serious	3(3)	2(11)	0(0)	
Serious enough	36(32)	8(42)	9(38)	
Unpleasant	5(52)	7(37)	7(29)	
Mild	14(13)	2(11)	8(33)	
SE impact				0.9
Severe	13(12)	2(11)	2(8)	
Moderate	36(33)	6(32)	7(29)	
Mild	47(43)	7(37)	11(46)	
No impact	13(12)	4(17)	4(17)	
SE consequences				0.8
GP visit required	71(65)	13(68)	14(58)	
Hospitalisation required	9(8)	2(11)	3(13)	

Figures shown are n (%)

****Significance at p<0.05(two-tailed)***

4.4.7.5 SECope and coping behaviours

The revised 10 item SECope was analysed by means of a principal component analysis (PCA) with direct oblimin rotation. The various indicators of factorability were good and the residuals indicated a good solution. Four components with an eigenvalue greater than 1 were found See *Table 4.11.* These components were confirmed by visual inspection of the scree plot. See *Figure 4.7*. Parallel Analysis (PA) was then performed to further establish significant components. The same components and rotation methods were used to generate a random set of variable loadings. The PCA eigenvalues for the first four components are larger than the corresponding PA eigenvalues and are thus significant at $p = 0.05$. Retaining these components for interpretation and subsequent analysis was therefore appropriate. See *Table 4.12*.

The four extracted components corresponded with the four subscales of the original 16 item SECope. All loadings were greater than 0.5 and no clear cross-loadings were seen for the 10 items. See *Table 4.13* for the loadings of Items 1-10. The pattern of loadings indicated the following four factors/subscales:

- information seeking subscale (Items 3, 4, 9 and 10)
- non-adherence subscale (Items 1 and 8)
- social support seeking subscale (Items 2 and 6)
- taking medicines subscale (Items 5 and 7)

As with the 16 item SECope items 9 and 10 - related to requests for medicines -loaded strongly onto the information seeking subscale instead of the taking additional medicines subscale. Analysis indicated the revised 10 item scale was reliable - Cronbach's alpha (α=0.8). The subscales had acceptable internal reliability: information seeking (α=0.79); non-adherence (α=0.56); taking additional medicines(α=0.78) and social support seeking subscale (α=0.5). The exploratory analysis resulted in a 10 item scale with four subscales. This model explained 67.3% of the total variance.

Table 4.11: Eigenvalues and variance for possible Components 1-4 extracted by PCA

Possible components*	***Eigenvalues***	***Variance %***	***Cumulative loadings %***
Component 1 Information seeking	3.041	30.41	30.41
Component 2 Taking medicines	1.435	14.35	44.76
Component 3 Non-adherence	1.29	12.91	57.67
Component 4 Social support seeking	1.06	9.6	67.27

**(n=10)*

Table 4.12 Comparison of PCA and Parallel Analysis eigenvalues

Possible components*	***PCA Eigenvalues***	***Parallel Eigenvalues***
Component 1 Information seeking	3.041	1.152
Component 2 Taking medicines	1.435	1.314
Component 3 Non-adherence	1.290	1.212
Component 4 Social support seeking	1.06	0.960

**(n=10)*

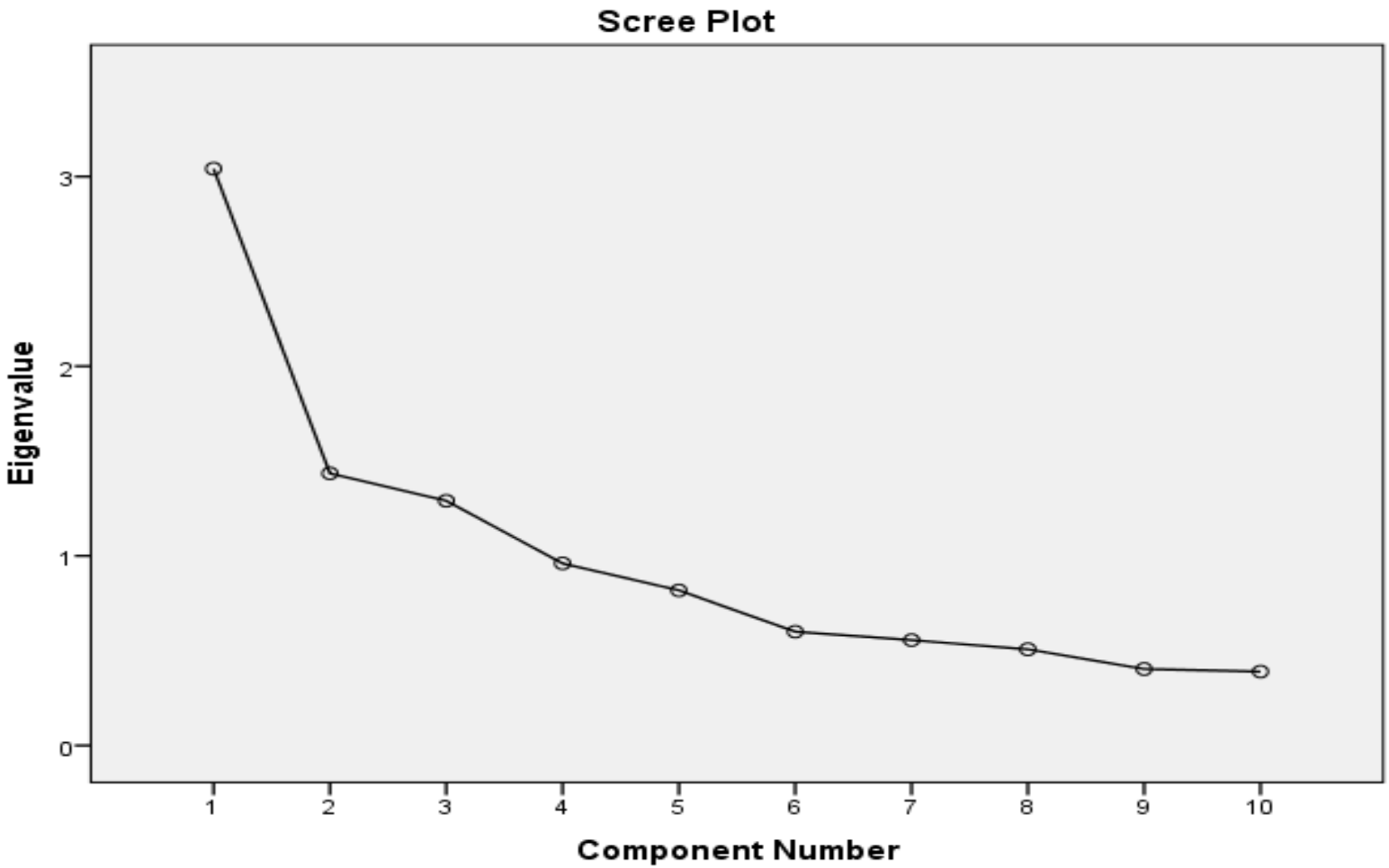


Figure 4.7: Scree plot of four components extracted by PCA

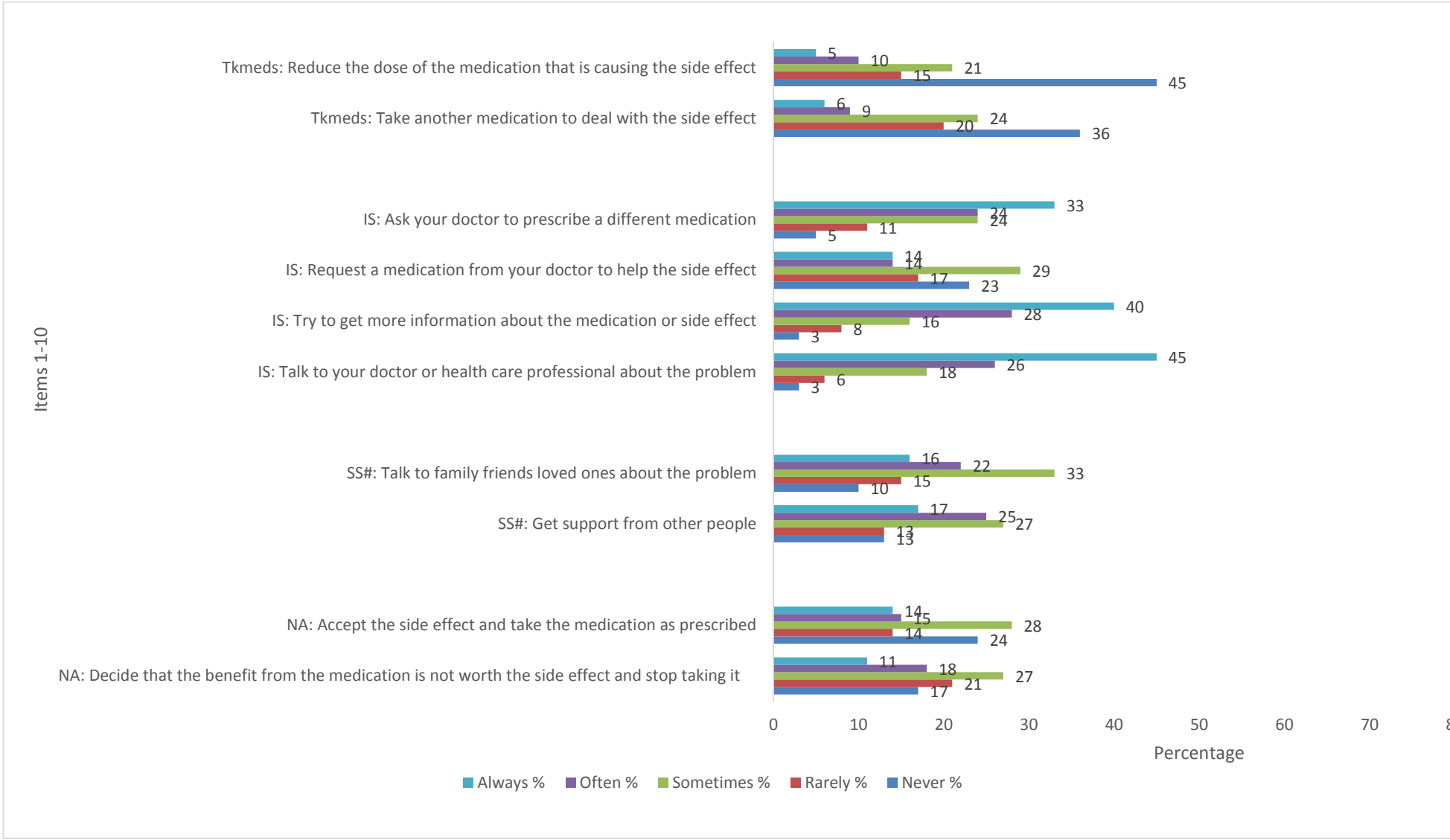
Table 4.13: PCA extracted components 1-4 and item loading

Variables 1-10	***Extracted components*** **Component 1 Information seeking**	**Component 2 Taking medicines**	**Component 3 Non-adherence**	**Component 4 Social support seeking**
Talk to your doctor or health care professional about the problem	0.783*	-0.244	0.089	-0.032
Try to get more information about the medication or side effect	0.758*	0.081	-0.078	0.031
Get support from other people	0.223	-0.044	0.035	0.715*
Ask your doctor to prescribe a different medication	0.622*	-0.242	0.370	0.018
Request a medication from your doctor to help with the side effect	0.584*	0.236	-0.051	0.035
Take another medication to deal with the side effect	0.193	0.787*	-0.067	-0.117
Accept the side effect and take the medication as prescribed	0.102	-0.158	0.801*	0.064
Reduce the dose of the medication that is causing the side effect	0.013	0.749*	0.273	0.218
Decide that the benefit from the medication is not worth the side effect and stop taking it	-0.078	0.301	0.812*	0.06
Talk to family friends loved ones about the problem	0.024	-0.026	-0.038	0.886*

** Strongest loading*

Rotation converged in 6 iterations

Analysis of the SECope item responses indicated that a high proportion of respondents would engage in information seeking strategies. Predicted strategies included information seeking with 104(45%) 'always' or 'often' 59(26%) consulting HCPs. Respondents would 'always' 93(40%) or 'often' 64 (28%) sought more information about the SE/medicine. In terms of social support, a quarter of respondents would 'often' get support from people (58;25%) while 50(22%) would 'often' talk to family/friends. Non-adherent strategies were predicted by almost 40% of respondents - 42(18%) would 'often' or 'always' (26;11%) stop taking the medicine while 55(24%) would 'never' or 'rarely' (33;14%) accept the SE and keep taking the medicine. 'Often' reducing the dose was a predicted strategy for 22(10%) while 11(5%) would 'always' engage in this behaviour. Analysis further indicated that 34(15%) would 'often' or 'always' (32;14%) accept the SE and keep taking the medicine. The responses to individual scale items can be seen in *Figure 4.8.*



IS = Information seeking subscale; NA = Non-adherence subscale; Tkmeds = Taking additional medicines subscale; SS#=Social support seeking behaviours

Figure 4.8: Responses to SECope items grouped in three SECope subscales and social seeking behaviours (n=210)

4.4.7.6 Predicted coping behaviours and gender and coping styles

Overall 210 respondents completed the SECope, mean scores for each of the four subscales were calculated see *Table 4.14* below:

Table 4.14: Descriptive statistics of SECope subscales including mean subscale scores (n=210)

SECope subscales	***N#***	***SD***	***Min-Max (items)****
Non-adherence	3.03	1.08	2-10
Information seeking	3.64	0.81	4-20
Social support seeking	3.21	1.07	2-12
Taking medicines	2.18	1.04	2-10

Mean subscale values which range from 1-5

*Range of item scores per subscale

Analysis identified positive and negative coping strategies within each subscale. A higher proportion of respondents indicated they would engage in positive information seeking behaviours (111;53%) or seek social support (107;51%). The majority of respondents predicted that they would use negative coping strategies within non-adherence and taking medicines subscales – 128(61%) and 120(57%) respectively. See *Figure 4.9*.

Gender was not a significant factor in predicted coping behaviours. Similar proportions of males (42;54%) and females (69;53%) indicated they would engage in positive information seeking behaviours. Positive social support seeking behaviours were also predicted in both males (39;50%) and females (67;52%). Monitors reported they would use positive information seeking strategies (81;52%). However they were more likely to engage in negative behaviours in relation to non-adherence (95;61%) and in relation to taking medicine(s) to cope with the SE (94;60%). A high proportion of Blunters predicted positive social support seeking (15;68%) and information seeking behaviours (13;59%). Associations between coping behaviours and coping styles were examined. The relationship between predicted non-adherent behaviours and coping styles was significant: X^2 (2, N = 206) = 7.38, p = 0.03. The association was of moderate strength: $\Phi = 0.2$ coping styles accounted for 4% of the variation in predicted non-

adherence. A summary table of predicted coping behaviours by gender and coping styles is presented in *Table 4.15.*

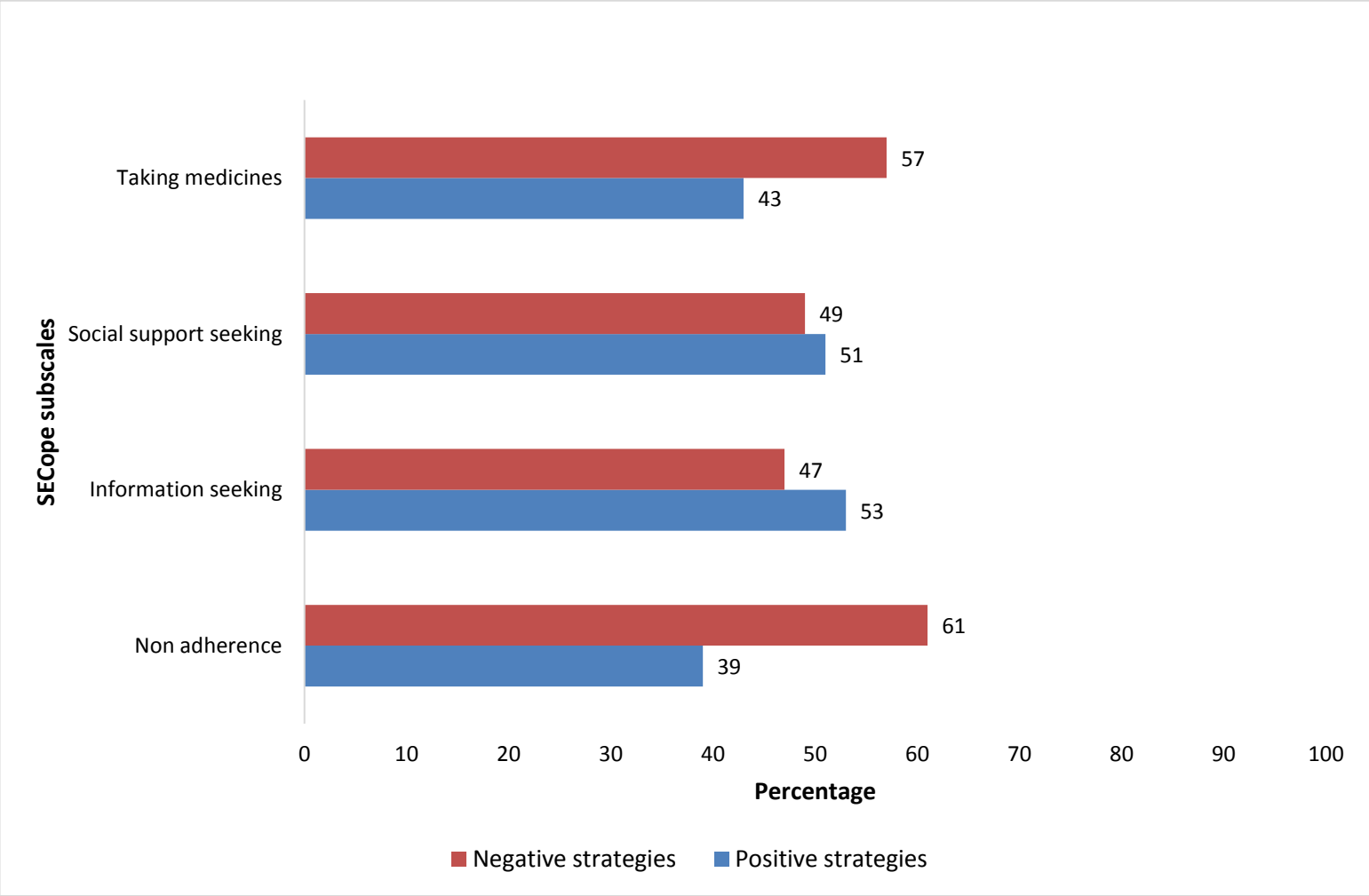


Figure 4.9: Predicted coping strategies (n=210)

Table 4.15: Predicted coping strategies vs gender and coping styles

Predicted coping strategies (n=208)	Gender			Coping styles(n=206)			
	Male (N=78)	Female (N=130)	p-value	Monitors (n=156)	Blunters (n=22)	Neutral (n=28)	p-value
Seeks Information			0.91				0.82
+ behaviours	42(54)	69(53)		61(39)	13(59)	6(21)	
- behaviours	36(42)	61(47)		95(61)	9(41)	22(79)	
Social support			0.83				0.19
+ behaviours	39(50)	67(52)		79(51)	15(68)	12(43)	
- behaviours	39(50)	63(49)		77(49)	7(32)	16(57)	
Non-adherence			0.91				0.03*
+ behaviours	30(39)	51(39)		61(39)	13(59)	6(21)	
- behaviours	48(62)	79(61)		95(61)	9(41)	22(79)	
Taking medicines			0.18				0.18
+ behaviours	38(49)	51(39)		62(40)	11(50)	16(57)	
- behaviours	40(51)	79(61)		94(60)	11(50)	12(43)	

Figures shown are n (%)

+ =positive, - = negative

****Significant at p<0.05 level***

4.4.7.7 Predicted non-adherence and actual non-adherence

Analysis of the SECope non-adherence subscale and non-adherent behaviours were conducted. This indicated that a majority of respondents who stopped taking their medicines predicted they would engage in non-adherent behaviours (49;58%). The majority of these respondents made their own decision to stop their medicines (20;77%). See *Figure 4.10.*

Blunters were more likely to engage in non-adherent behaviours as a result of HCP advice. A majority of Blunters (11;65%) with 64 Monitors (59%) and 13 Neutral (54%) stopped their medicines. HCP advice to stop medicines was received by 10 Blunters (91%); compared with 39 Monitors (58%) and 10 Neutrals (77%). Over 30% of Monitors made their own decision to stop medicines (24;36%). See *Figure 4.11*.

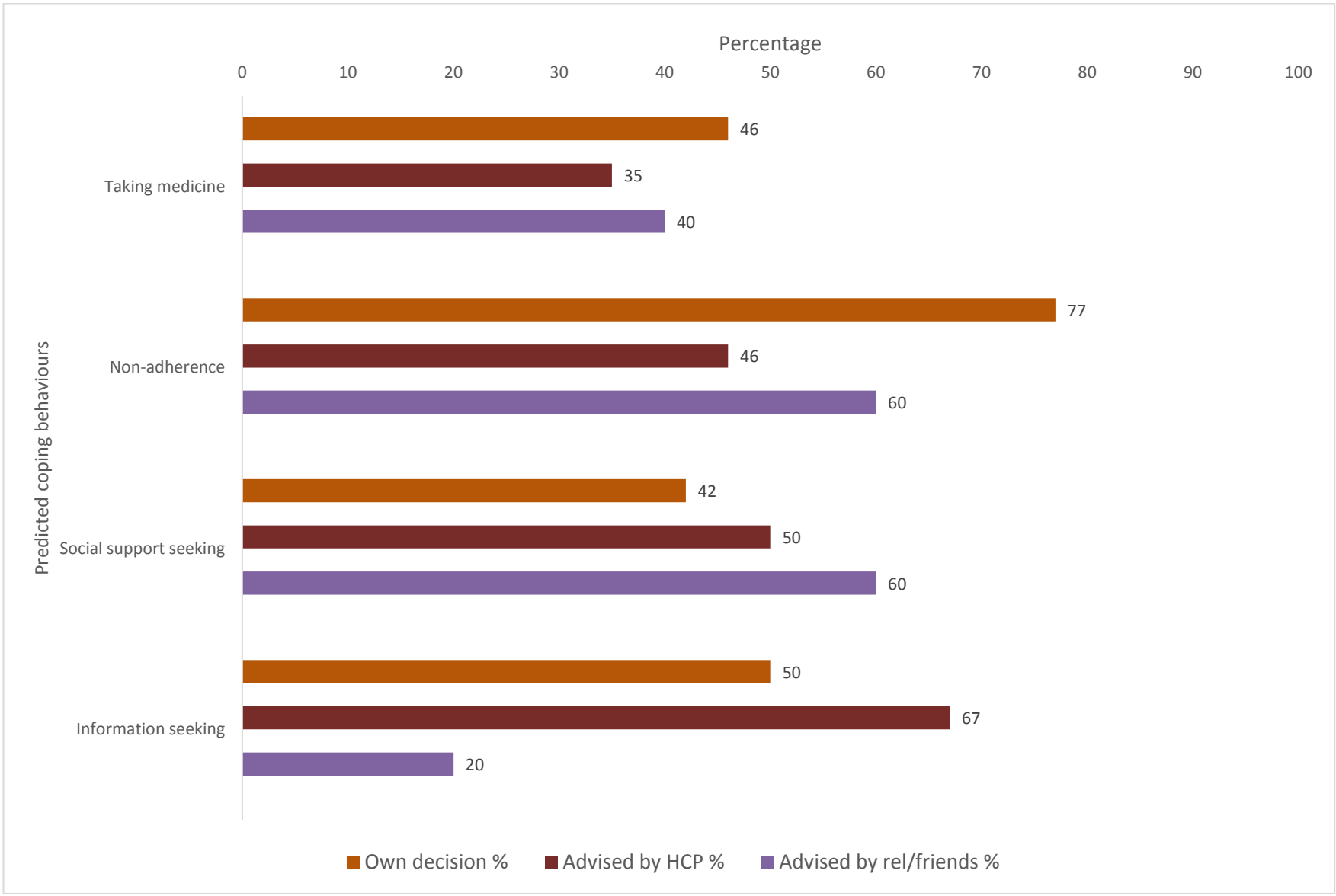
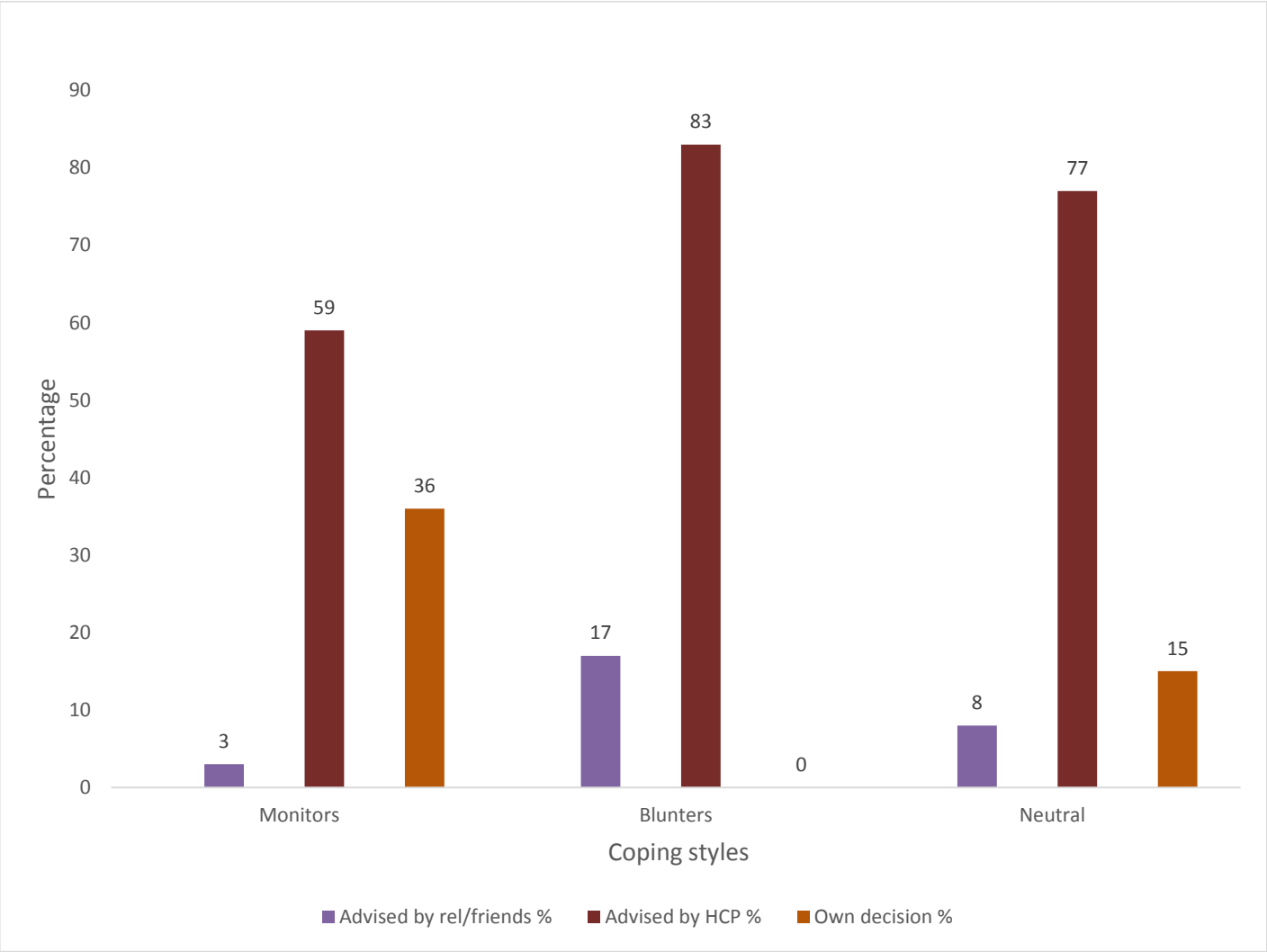


Figure 4.10: Non-adherence behaviours vs predicted coping behaviours



Rel/friends=relatives/friends; HCP=Healthcare professional

Figure 4.11: Coping styles vs advice on non-adherence

4.4.7.8 Survey text box responses

Analysis of the text box responses examined the impact of SE and the factors that aided respondents' in linking their medicines to their SE. A majority of respondents described the impact of SE in primarily physical effects (125;85%) followed by 17 (12%) describing psychological effects and 15 (10%) social effects. Respondents confirmed the SE with HCPs 43(29%) and PILs (38;26%). Factors such as the timing of the side effect, previous health experiences and knowledge (from a range of sources) were used to link the medicine to SE. See *Table 4.16.*

Table 4.16: Frequency table of text box responses to survey questions 9&10

Examples of responses to questions 9 & 10 (N=148)	**Frequency**	**%**
Q9:**Please describe in your own words how the side effect(s) affected your daily life.**		
Physical impact of SE ***"Pins & needles in my feet & hands. I also felt a bit shaky."*** ***Female, 61-70 yrs, Retired, F ed, 5- meds.*** ***"Coughing up blood and knees was[sic]painful."*** ***Male, 61-70 yrs,Retired, SL 17/18, 2-4 meds***	125	85
Psychological impact of SE ***"Methotrexate was causing my heart beat to beat faster which made me very anxious and was very unpleasant."*** ***Female, 41-50, other, F ed,1 med*** ***"Long term meds - was advised that it would take approx 3 wks for my body to get used to them. Side effects were drowsiness, confusion, numbness (feelings) woolly, disorientated - this meant I had to take extra care driving & undertaking tasks at work."*** ***Female, 41-50 yrs, Part time, SL16, 1 med***	17	12
Social impact of SE ***"Skin rashes (head & face) caused embarrassment when going out. Dizziness avoided going out of [sic]my own"*** ***Female, 61-70 yrs, retired, F ed, 1 med*** ***"Planning my route to include toilets. Worried about fainting."*** ***Male, 71-80 yrs, Retired, SL16, 5-8 meds***	15	10

Table 4.16: Frequency table of text box responses to survey questions 9&10		
Q10:**What made you think that the medicine had caused the side effect(s)?**		
Timing of the SE ***"I took it about an hour before symptoms"*** ***Female, 41-50 yrs, Part time, SL17/18, I med*** ***"A few hours (2) after taking the medicine I felt uncomfortable.."*** ***Male, 41-50 yrs, Part time, Univ, 1 med***	11	7
Dechallenge - stopped medicine(s) and SE disappeared ***"Had no symptoms before taking medicine when discontinued medicine symptons [sic]stopped"*** ***Female, 71-80 yrs, Retired, SL16, 2-4 meds*** ***"Never had this before & it started after I had taken the tabs for a week. Went away when I stopped"*** ***Female, 71-80 yrs, Retired, SL16, 5-8 meds***	23	16
Onset of symptoms linked to medicine – symptoms start when begin to take medicines ***"Had just started taking the medication"*** ***Female, below 40 yrs, Full time, F ed, 1 med*** ***"Because it started when I started the new drug"*** ***Male, 61-70 yrs, Retired, SL16, more than 8 meds***	20	14
Recall of prior health experiences – changes in health linked to medicines ***"Before I started taking the medicine I had none of the effects".*** ***Female, 61-70 yrs, Retired, F ed, 5-8 meds*** ***"Coincided with taking medication following an operation. Did not have the symptoms before or after stopping taking medication"*** ***Female, 51-60 yrs, Other, SL17/18, 2-4 meds***	2	1

Table 4.16: Frequency table of text box responses to survey questions 9&10		
Use of HCPs as information sources – confirm SE ***"Spoke to my GP and he told me it is a common side effect."*** ***Female, 71-80 yrs, Retired, F ed, 5-8 meds*** ***"Because the pharmacist told me this can happen"*** ***Female, 71-80 yrs, Retired, SL18/18, 2-4 meds***	43	29
Use of Relatives/friends as information sources to confirm SE ***"I ask my family to look into the medication"*** ***Male, 51-60 yrs, Full time, SL17/18, 2-4 meds*** ***"Talking to others on the same tablet - same side effect"*** ***Male, over 80 yrs, Retired, SL16, More than 8 meds***	5	3
Use of PILs as information sources to confirm SE ***"I look in the leaflet of the medication and one of the side effects was stomach upset"*** ***Male, 61-70 yrs, Retired, SL17/18, 1 med*** ***"I had read the leaflet and side effect was on the leaflet"*** ***Male, 71-80 yrs, Retired, SL16, 5-8 meds***	38	26
Use of the Internet to confirm SE ***"It was clearly detailed in the information leaflet. Also confirmed on various internet sites"*** ***Male, below 40 yrs, Full time, Univ, 1 med*** ***"Reading the information leaflet with the medication. Media coverage Internet"*** ***Female, 61-70 yrs, Retired, SL16, 2-4 meds***	2	1

4.5 Discussion

This phase of the study has investigated how people use information sources to help them identify ADRs and explored peoples' experiences of ADRs. Overall the survey data that were obtained has met these aims.

SE experience

The overall SE experience was composed of SE history; SE timing and SE outcomes. Outcomes were categorised for analysis by the reported severity, impact and consequences of SE.

Gender differences in respondents' SE experience

There were a greater number of females than males amongst the respondents. Results suggested that there were clear gender differences in SE experience. More females than males had experienced SE and approximately 60% of females who took 2-4 medicines had experienced more than one SE. In general females reported more SE and frequently described their experiences as both significant and negative with lasting consequences. Over 80% of females reported their SE as 'unpleasant' or 'serious'. The 5% of respondents who reported their SE as 'very serious' were female. Over twice as many females as males - 15% - reported the impact of their SE as 'severe' and 70% of those who required a GP visit were female. These findings are supported by previous research which found that that females are at higher risk of developing ADRs than males (Zopf et al., 2008). Studies suggested that older women are particularly susceptible to ADRs and reported greater impact on their QoL (Skilving et al., 2014). In addition research has indicated that females are more likely to use multiple medicines than males, increasing the likelihood that ADRs could occur (Moen et al., 2009). Females are also more interested in health information and more likely to engage in health information behaviours than males (Ek, 2013; Lorber & Moone., 2002). This body of research may explain the gender bias towards females evident in the survey respondents.

Role of age and medicine use in SE experience

Previous research has identified the prevalence of medicine use in older patients (Qato et al., 2008). These older patients have been identified as being at high risk of developing ADRs. Factors such as polypharmacy, changes in pharmacokinetics which occur in aging patients and multiple health conditions contribute to their risk (Hefner et al., 2015). Data from this study supports past findings and suggested that the incidence of SE increased as

respondents' ages increased (Martin et al., 2013). It was apparent that there was an increased risk of SE amongst older respondents. SE incidence increased from 16% in those below 40/41-50 to over 20% in 51-60; 61-70 and 71-80 age ranges. More than one SE was experienced by 30% of those aged 61-70. Over 60% of those aged 41-50; 51-60 and 61-70 and 90% of those 71-80 required a GP visit. These results suggest that the increased incidence of SE in older patients were significant events as older respondents required proportionately more GP visits than younger patients. This pattern of GP visits is supported by previous research which found that older patients value interactions with their HCPs, relying on these HCPs for information and advice on their medicines (Carter et al., 2013; Miller, 1987).

Results suggested that regular use of multiple prescribed medicines were linked to more than one SE experience. Overall the highest proportion of respondents 56(35%) with a history of SE used two-four medicines regularly. This supports previous research findings which found polypharmacy increased the risks of adverse effects. The number of older patients who present with complex health conditions that require multiple medicines increases as life expectancy rates improve. Such patients are more likely to experience SE (Rambhade et al., 2012).

Retirees and those in full time employment were more likely to see a GP because of their SE when compared to other respondents. This may be linked to less time constraints for retirees and the pressure to avoid prolonged periods off work for full time workers.

Identifying SE

Use and Assessment of Information sources

The results from this study indicated that respondents' predicted use of information sources varied from their actual use. Over 80% of respondents indicated they would use GPs and PILs with 67% indicating potential use of pharmacists. This pattern of predicted use and information preferences is supported by previous research studies (Munksgaard et a., 2011; Nähri, 2007) and was maintained in actual use for both GPs and PILs - 69% and 67% respectively.

This mirrors the respondents' assessment of GPs as the most trustworthy, and easy to understand information sources; with PILs as the most accessible source. High proportions of respondents assessed pharmacists as both trustworthy - 73% - and easy to understand information sources. Previous research has similar assessments of GPs and pharmacists as reliable and trusted information sources (Hamrosi et al., 2014). However, the positive assessments of pharmacists were not reflected in actual use as actual use of pharmacists was only 28%. Although 15% of respondents considered the Internet to be the least

trustworthy source pharmacists were used less often than the Internet (38%). This is an interesting finding and it may suggest that perceptions of information sources can be a key factor in actual use of information sources. These perceptions may in turn be mediated by a hierarchical order of characteristics. Positive assessments of pharmacists across the four source characteristics did not correspond with actual use. However, PILs, which are readily available to medicine users, were actually used by a majority of respondents despite the mixed assessments they received. If a hierarchy of characteristics exists these parameters may influence perceptions in varying degrees. Respondents' positive perception of PILs as an accessible information source seemed to mitigate the influence of the other characteristics and resulted in high usage of PILs by respondents. This is supported by the principle of information seeking behaviours which proposes an individual will seek the most accessible information available (Lalazaryan et al., 2014). Previous research identified tailorability and anonymity as salient characteristics of information sources for patients accessing health information, with a variety of factors influencing salience (Ruppel & Rains, 2012). This survey data suggested that the source characteristics of accessibility and relevance can be significant predictors of use of GPs and the Internet by respondents. Further research is required to examine the information source characteristics that are essential/relevant in information seeking on medicines. This could aid in identifying the predictive factors that are most influential in determining use of information sources relating to medicines.

Use of information sources and confidence in causality

Data from this study indicated that over 80% of respondents used two or more sources of information to confirm their SE - 32% used two, 33% used three and 16% used more than three sources. This finding is supported by previous research which found patients obtain medicine information from a variety of sources (Clarke et al., 2016; Hughes et al., 2002; Krska & Morecroft, 2013). One of the study findings was that respondents' confidence levels increased with the number of sources they used. A majority of respondents' who used two sources 36(71%); three sources 31(62%) and more than three sources 17(68%) were 'very confident' that their medicine had caused the SE. The types of sources used varied across the survey respondents and there was no significant association between the type of information source used and respondents' confidence as to causality. However, a majority of respondents who were 'very confident' either used multiple sources – 64% - or combined HCPs and PILs – 70%. These findings indicate that in practice the opportunity to access multiple sources or specific combinations of sources could prove most beneficial to patients.

Use of information sources and coping styles

The proportion of Blunters amongst survey respondents was low (28;13%) compared to Monitors (164;73%). However, analysis of the actual use of sources and coping styles identified patterns/profiles of information use. The majority of Monitors - over 70% - used GPs, followed by PILs - 66% - and the Internet – 40%. The profile of information use by Blunters was PILs (84%), GPs (58%) and pharmacists (42%). Those with neutral coping styles used PILs (67%) followed by GPs (58%) and the Internet (33%). These findings indicate that PILs and GPs are sources common across coping styles. Research has found that providing information to patients which is consistent with their coping style can be viewed as effective interventions with beneficial outcomes (Roussi & Miller, 2014). PILs and GPs may therefore have a role as mediating factors in the relationship between information use and coping styles. The findings of this survey suggest that PILs and GPs are influential information sources which are commonly used across different coping styles. Focusing on information sources which could have mediating effects on coping styles could ensure effective distribution of health information. However research has found that monitoring coping styles have specific information preferences and value health information (Carter et al., 2013; Roussi & Miller, 2014). This suggests that Monitors are more likely to engage with and complete health-related surveys. Additional research with equivalent numbers of participants with monitoring, blunting and neutral coping styles is therefore required to verify these survey findings.

Managing SE

Coping styles and coping behaviours

The majority of survey respondents who completed the MBSS were identified as Monitors – over 70%. Research has identified the specific cognitive, affective and behavioural characteristics inherent in cancer patients with monitoring coping styles (Roussi & Miller, 2014). Monitors have significant knowledge about health-related threats and attach greater value to health information then those with other coping styles. Generally, they also tend to be less satisfied about the information they receive. Monitors display more negative health beliefs, perceive greater risk and experience more negative affective consequences. Monitors demand more information and emotional support from HCPs and are more forceful in decisions related to their treatment (Rees & Bath, 2000; Roussi & Miller, 2014). A similar pattern of characteristics was identified in survey respondents with monitoring coping styles. A significant association existed between coping styles and reported severity of SE. More Monitors reported their SE as ‘unpleasant’ then either of the other two coping styles. Over 10% reported a ‘severe’ impact on QoL with a GP visit required by 65%. This

suggests that survey respondents with monitoring coping styles who experienced SE, perceived greater risks from their SE and experienced more negative consequences than respondents with blunting or neutral coping styles.

A smaller proportion of respondents – less than 30% - who completed the MBSS had blunting or neutral coping styles. A cautious approach should therefore be taken when interpreting survey results linked to the blunting/neutral coping styles. However, a significant relationship was identified between coping styles and predicted coping behaviours. Similar patterns of predicted coping behaviours were displayed by Monitors and Neutrals across the information seeking, social support seeking and non-adherence subscales. However more Blunters (21;75%) who completed the SECope, would engage in social support seeking behaviours and non-adherence behaviours (17;61%) than either of the other coping styles. These findings were not significant but the low number of Blunters amongst respondents may have been a contributory factor. Data from this survey also suggested that overall more females would employ information seeking strategies than males. This finding supports previous research which has identified females as more active seekers of information than males (Ek, 2013; Tong et al., 2014).

Predicted non-adherence behaviours and actual non-adherence behaviours

Overall predicted non-adherence behaviours were linked to actual non-adherence. Over half of respondents who indicated they would engage in these behaviours stopped their medicines when they experienced SE. These findings broadly support that of De Smedt et al., (2012) which found patients used non-adherent coping strategies to manage adverse drug events. The majority of survey respondents received advice on stopping their medicines from HCPs – which is consistent with the finding that almost 70% of respondents used GPs to find out about their SE. These findings are also supported by previous studies which found that respondents mostly accessed HCPs for medicine information (Nahri et al., 2007; Tio et al., 2007). Data from this survey indicated that the highest proportion of respondents who made their own decision to stop taking medicines had monitoring coping styles. These results confirm the association between monitoring coping styles and higher perceptions of risks identified in previous research (Miller & Roussi., 2014). In this study more Blunters (65%) stopped their medicines than either Monitors (59%) or Neutrals (54%). These findings are supported by previous research which found that avoidant/blunting coping styles were associated with non-adherence to medicines (Deschamps et al., 2004; Singh et al., 1996 as cited in Zwikker et al., 2014). However these findings should be interpreted with caution because of the low numbers of Blunters amongst survey respondents. Health research into monitoring coping styles and

non-adherence have had mixed results. Some studies have found an active coping style associated with medicine adherence (Gremigni et al., 2007; Smalls et al., 2012). However other studies with renal and cardiac patients found no relationship (Cholowski et al., 2007; Frazier et al., 1994 as cited in Zwikker et al., 2014). An interesting finding from this study was that adherence was not the preferred behaviour for Monitors – a high proportion were likely to engage in non-adherent behaviours and stop taking their medicine after experiencing SE. A possible explanation for this may be the type of information sources that Monitors used to find out about their side effects. The current study found that Monitors most commonly used GPs, PILs and the Internet as information sources. Research has found that patients who seek medicine information from independent sources were more likely to engage in non-adherent behaviours (Carter et al., 2013).

Analysis of the survey text box comments was examined and used to develop the Topic Guide for the following phase of this study - the Phase Two interviews.

This study contributes to knowledge about coping styles in patients with SE. Identifying associations or patterns of information use can assist in the delivery of tailored health information to SE patients. The objectives of this phase of the study were to identify the types and value of information sources; to identify the factors that influence their use; to investigate the SE experience, impact and consequences of SE and the coping strategies patients use. Analysis of the survey data suggests these objectives have been met.

4.6 Strengths and Limitations

This phase of the study added to previous research by exploring the types of information sources people use to find out about ADRs. In general surveys are considered to have poor validity as they are limited in their scope and do not facilitate in-depth investigation of a subject. However, one of this survey's strengths was that even respondents who had not experienced a SE could contribute to the research. This was achieved by structuring the survey to initially gather data on information sources from all respondents before moving to the specific SE experience. In addition the methods added to the strengths of this research with two pilots conducted with people known to have used medicines and to have experienced a side effect. This assisted in the development of a robust instrument, with high content validity. Postal return was selected to reduce any obsequiousness bias – the potential for respondents to indicate they would or had used a pharmacist as an information source or assess pharmacists favourably because the surveys were distributed in pharmacies.

Distributing the surveys in pharmacies was beneficial to the study as it ensured access to a pool of pharmacy customers likely to be taking medicines and by extension have potentially experienced a SE. However there was a lower response rate for the main study compared to the pilots or a previous survey using a similar distribution method. The selected distribution method also prevented the use of reminders that may have improved response rates. Respondents were required to recall and report on past events so recall bias may also have been an issue. However efforts were made to control for such bias by using a structured survey with focused questions. Respondents were also encouraged to complete the survey at their leisure, to allow them time to reflect on their past SE experiences.

A limitation of the survey structure was that respondents were not asked for details of the suspected causative medicine. This question would have contributed to the survey data and enabled investigation of different associations such as drug types and symptoms; drug types and symptom severity/impact/consequences and drug type and information use.

This phase of the study further added to previous research by investigating the coping styles of patients with SE. A key strength of the survey was the use of a gold standard psychological scale – the MBSS - to identify these coping styles. This was a novel approach as the MBSS had not been previously used in SE research. Its use reflected the multidimensional nature of SE with its cognitive, affective and behavioural components.

However, respondents with a monitoring coping style have explicit preference for information and are more likely to respond to surveys. Another issue therefore was the likelihood that there would be a high proportion of monitors amongst survey respondents. This was borne out by analysis of the surveys which indicated that the majority of survey respondents who completed the MBSS were identified, as expected, as Monitors.

An additional limitation of the survey was the presence of two scales which may have proved too onerous for some respondents. Attempts were made at the piloting stage to address this limitation. The MBSS short format was used and the SECope was revised for clarity and ease of use, by removing some items. However, respondents may still have engaged in automatic responding. Efforts were made to control for such biases and increase respondents' motivation. These included engaging with potential respondents while distributing the surveys - describing the purpose and value of the research.

4.7 Summary

A survey was developed for distribution amongst pharmacy customers to collect information on how people identify and manage their ADRs. The survey gathered

information from respondents on personal ADR experiences; the impact and consequences of these ADRs; the information sources and coping strategies people use and their demographic characteristics.

- Analysis of the 230 returned surveys was conducted and the results presented under the following headings: SE experience; identifying SE and managing SE.
- Gender differences were evident in SE history and SE severity. More females then males had SE and were more likely to report them as more severe.
- Age and medicine use were influential factors in SE history. Those using multiple medicines were likely to experience SE. Older respondents were more likely to use multiple medicines and thus more likely to experience SE.
- Actual use and predicted use of information sources varied. GPs and PILs were most used by respondents and accessed as trustworthy, relevant and accessible sources. Pharmacists were easy to understand. Source characteristics of accessibility and relevance key to predicting use of GPs and the Internet. GPs and PILs are common sources used across coping styles. Using several sources or combining HCPs with PILs increases confidence levels in respondents' about causality of SE.
- Coping styles may be related to reported severity of SE ($p = 0.05$) and non-adherent behaviours/strategies ($p = 0.03$).

As described earlier in Chapter Three: General Methods, in Phase Two of this research interviews were conducted to explore the opinions and experiences of people who had recently experienced an ADR. The recruitment procedures, analysis and findings of these in-depth interviews will be presented in the following chapter – Chapter Five: Interviews.

CHAPTER 5: INTERVIEWS

5.1 General introduction

The Literature Review described in Chapter Two provided evidence of the need to increase understanding of the personal experiences and opinions of the general public in identifying and managing side effects from medicines. Research was described which suggested that only limited qualitative research had been conducted amongst this population to date. This phase – Phase Two – of the study sought to address this deficit and thus make a novel contribution to ADR research. One of the main purposes of this phase was to form a more comprehensive picture of individuals' experiences of ADRs, but the findings were also important for aiding the development of an assessment tool for patients to assess causality.

5.2 Methodology

5.2.1 Introduction

The rationale which guided the design for this interview phase of the study was provided in Chapter Three. This chapter will describe the participant recruitment for in-depth interviews, the interview processes, the strategies for data analysis, the interview results and a discussion of these results. For this phase - Phase Two - a phenomenological approach was selected to explore the opinions and experiences of people who had recently experienced an ADR, through in-depth interviews. The surveys distributed in Kent during Phase One of the study were used to recruit interview participants. Analysis of the returned survey data was used to develop the Topic Guide for the Phase Two interviews (See Appendix 11).

5.2.2 Aims & Objectives

The aim of this phase of the study was to explore the opinions and experiences of people who had recently experienced an ADR. Objectives for this phase of the study were as follows:

- To determine how people identified their ADRs
- To investigate the impact of ADRs on peoples' daily lives
- To explore the consequences of ADRs on future health behaviours

5.2.3 Ethical approval

Approval for this phase of the study was sought from the NHS Research Ethics Service and a favourable opinion was received from the Proportionate Review Sub-committee of the NRES Committee North East - Newcastle & North Tyneside 1 (See Appendix 3: REC ref 14/NE/1053). Potential interviewees were supplied with a Participant Information sheet to facilitate their decision to participate or not in the research (See Appendix 8). Written consent was obtained from interviewees prior to interviews and they were also verbally reminded that their participation was entirely voluntary (See Appendix 13). These interviews involved participants recollecting a negative event. Sensitive issues could potentially arise and participants could become distressed in these circumstances. Suitable locations for interview were agreed between researcher and interviewee including public settings such as cafes and/or rooms in private dwellings. By selecting locations that were agreeable to participants they felt secure and/or comfortable and potential distress was avoided. Before the interview began the researcher reminded the interviewee that their participation was voluntary and if they found a question upsetting they did not have to answer. Procedures were in place in the event an interviewee became distressed. These involved an immediate suspension of the interview and recommendation that the participant contact their G.P. /pharmacist or the Patient Advice and Liaison Service (PALS).

5.2.4 Interview participant recruitment

Potential participants were identified as respondents to the Phase One survey who indicated they had experienced an ADR from their medicines, who had returned their contact details and indicated their willingness to be interviewed about their ADR experiences. All potential participants were contacted by phone/email and arrangements were made to interview them at a time and location suitable for them. Vouchers with a monetary value of £10 were offered to interviewees as an incentive to participate. Recruitment for interviewees was limited to the Kent area to facilitate ease of access for the interviewer.

Inclusion criteria were as follows:

- Pharmacy customers aged 18 years or over

- People who suspect they have experienced side effect(s) from their medicines
- Proficiency in English language (reading and speaking).

5.2.5 Study design

This phase of the study involved off campus interviews with people who had experienced an ADR from their medicines. The purpose of the interviews was to gather information on how they identified and coped with their ADR and its impact on their daily life. The interviews were in-depth and the Topic Guide for these interviews was informed by initial survey data (See Appendix 11). Interviews were audio-recorded using an Olympus Digital Voice Recorder WS-852 and were anticipated to last up to an hour. Interviewees provided written and verbal consent before the interview began. The interviews were transcribed in the Medway School of Pharmacy on the University of Kent campus with an Olympus AS-4000 Transcription Kit. Words or phrases emphasised by the interviewee were indicated by underlining in the transcripts. The interview data were then entered into the data management programme NVivo (QSR NVivo 10) to facilitate analysis.

5.2.6 Data analysis

An Interpretative Phenomenological Approach (IPA) was taken to the analysis of the transcripts. A line-by-line analysis of the transcripts was conducted. This method of analysis involved repeated readings of the transcripts and making initial notes which highlighted key areas of concerns of each participant. Connections between emergent themes were then identified through processes of abstraction, subsumption and contextualization (Smith, JA., 2008; Smith et al., 2011). See *Figure 5.1* on the following page for a schematic of the coding process. As recommended for larger sample sizes, emergent themes from analysis of initial transcripts were used to orientate further analysis.

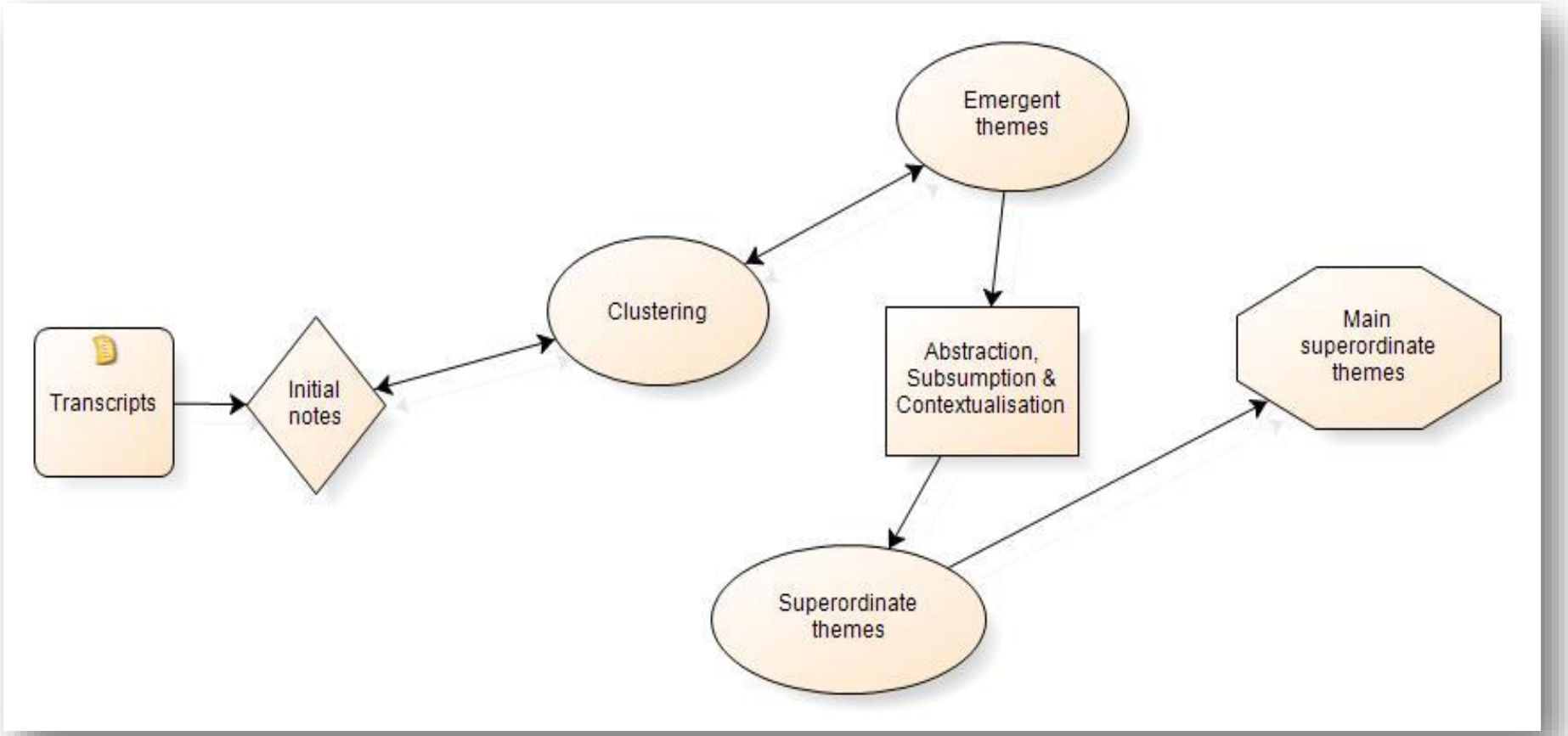


Figure 5.1: IPA Coding process (Table adapted from Smith et al., 2009)

Saturation in coding continued until no other emergent themes were being generated at which point recruitment of potential participants for interview was discontinued. Analysis of the interviews led to the creation of a Master table of themes which is presented in the Results section which follows. The main superordinate themes that were identified are supported with appropriate quotations from the interview transcripts. These distinctive/poignant quotations were selected in line with common research practice and were identified as the most representative of the research findings (Anderson, 2010; Schilling, 2006).

5.3 Results

5.3.1 Introduction

Twenty-two survey participants indicated they had recently experienced an ADR and were willing to be interviewed about their experience. They completed the Contact details section of the survey supplying their contact details and preferred method/times of contact. A response rate for interviews of 9.6% was achieved– 22 potential participants from 230 returned surveys. One participant supplied an incorrect email address and could not be contacted. The remaining 21 were contacted by telephone/email at their preferred times. In total 19 confirmed their agreement to be interviewed. Subsequently, two were not available for interview - one individual was recuperating from a car accident and the other was leaving for an extended holiday. Participants were contacted by telephone and arrangements for interview dates, times and locations were made. Fifteen participants were interviewed, by which time saturation in coding was reached and the interviews ceased. The remaining four individuals were contacted, thanked for their participation and advised they would not be interviewed. Overall 10:32:42 hours of interview data were transcribed with interview times ranging from 20.26 to 127.02 minutes (M = 42.16; SD ± 29.15). Interviewee characteristics are summarized in *Table 5.1*. See Appendix 14 for initial interview notes.

Table 5.1: Interviewee characteristics

	Gender	***Age***	***Employment***	***Education***	***Medical condition***	***No. of meds***	***Causative med***	***Coping styles***	***Interview duration***
Int1/Tpt1	Female	41-50	FT	F ed	Underactive thyroid	5-8	Carbimazole	Monitor	25.10
Int2/Tpt2	Female	41-50	FT	Univ	COPD; Lupus; MS	5-8	Hydroxychloroquine	Blunter	60.08
Int3/Tpt3	Female	51-60	Disability	SL 16	Rheumatoid arthritis	2-4	Clarithromycin	Monitor	77.02
Int4/Tpt4	Male	41-50	FT	F ed	Cardiac disease	2-4	Lisinopril	Monitor	30.23
Int5/Tpt5	Male	61-70	Retired	Fed	Hypertension	5-8	Simvastatin	Monitor	63.35
Int6/Tpt6	Female	51-60	FT	Univ	Menopause	1	HRT	Blunter	25.40
Int7/Tpt7	Male	61-70	Retired	SL 16	Chronic pain	2-4	Morphine patches	Monitor	36.17
Int8/Tpt8	Male	61-70	Retired	F ed	Arrhythmia	5-8	Amiodarone	Monitor	40.30
Int9/Tpt9	Male	61-70	FT	SL 16	Depression	2-4	Mirtazapine	Monitor	127.02
Int10/Tpt10	Female	Below 40	FT	Univ	Acne	2-4	Tetracycline	Monitor	32.80
Int11/Tpt10	Female	71-80	Retired	SL 17/18	Dental infection	2-4	Antibiotic	Neutral	24.60
Int12/Tpt12	Female	71-80	Retired	Univ	Reflux	2-4	Lamsopraole	Monitor	27.02
Int13/Tpt13	Female	61-70	Retired	Univy	Spondylosis	2-4	Co-codamol	Monitor	22.01
Int14/Tpt14	Female	61-70	Retired	SL 17/18	Asthma	1	Prednisolone	Blunter	21.06
Int15/Tpt15	Female	51-60	Disability	Univ	Fibromyalgia syndrome	More than 8	Multiple medicines	Monitor	20.26

Int = interviewee; Tpt=transcript;FT = Full time; Univ = University; F ed = Further education
COPD= Chronic obstructive pulmonary disease; MS= Multiple sclerosis; HRT= Hormone replacement therapy

These characteristics suggest that the interviewees were a reasonably diverse group. They displayed a variety of ages, education levels, coping styles and medical conditions. In addition they used a variety of medicines and numbers of medicines. This demographic information suggests that the overall interview findings could be widely applicable.

5.3.2 Themes

Analysis of the interviews identified six main superordinate (SO) themes, illustrated in Figure 5.2 and described below. These were

1. Side effect experience
2. Identification
3. Adherence
4. Information use
5. Coping
6. Body awareness.

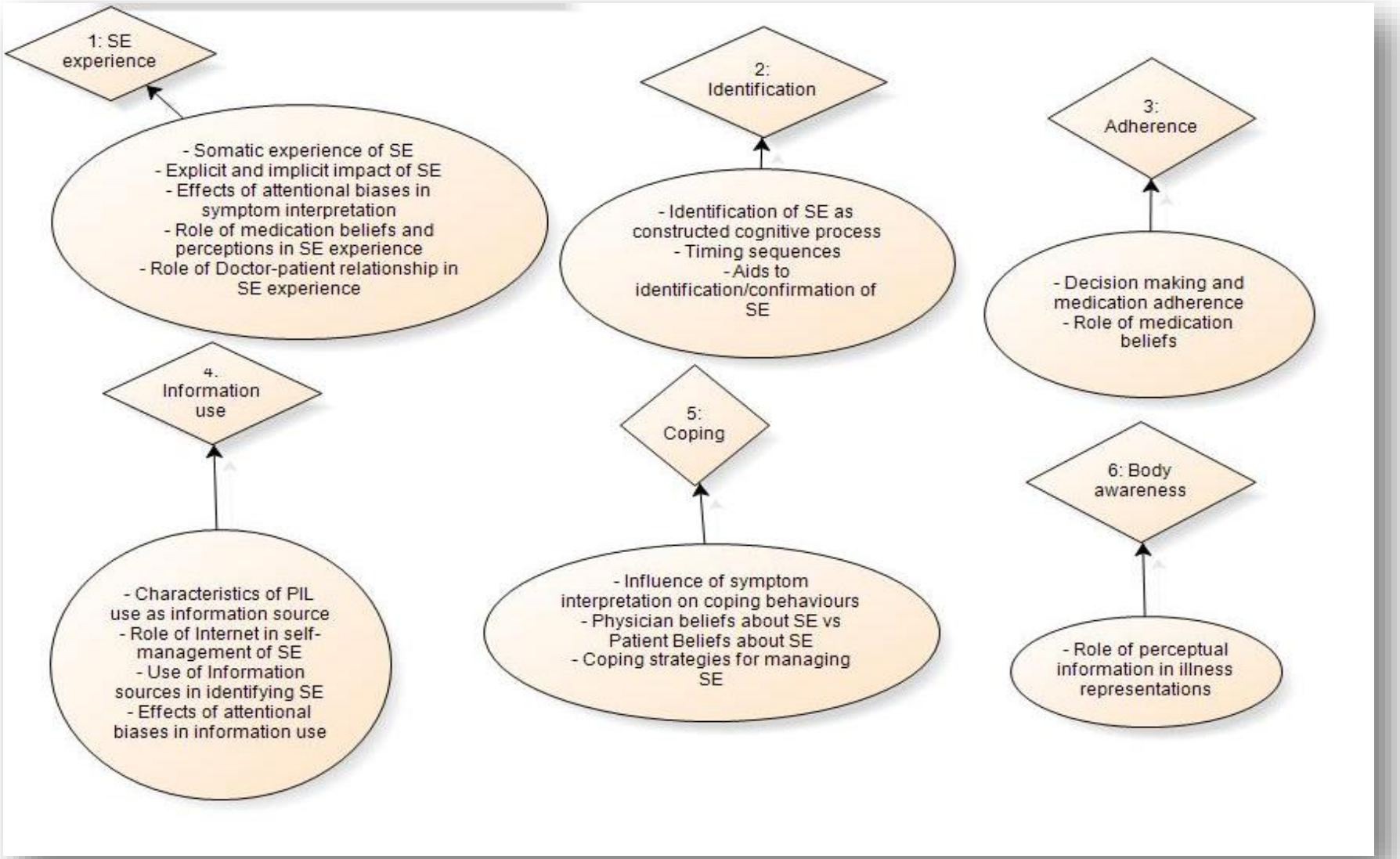


Figure 5.2 Emergent themes 'clustering' to 6 superordinate themes

5.3.2.1 Side effect experience

All the participants related the multidimensional nature of their experience of side effects. They identified a range of physical symptoms which contributed to the somatic experience of side effects:

> *T4(Transcript 4): "they prescribed me another brand I started experiencing a few side effects shaking blood palpitations"*
>
> *4.7 (page.line)*

> *T12(Transcript 12): "Yeah I mean I was having a job walking up hills..getting more and more out of breath which I was blaming it on the asthma…amh..and it wasn't just getting out of breath it was my thighs and everything walking a distance were really hurting as if there wasn't enough oxygen there"*
>
> *2.7(page.line)*

> *T6(Transcript 6): "the symptoms were like were very much like early pregnancy amh that nausea the dizziness"*
>
> *5.23(page.line)*

The side effects described also included psychological symptoms:

> *T10(Transcript 10):"the one that impacted me the most was the mini-pill reaction amh because..I was really I it was the fact it was a hormonal issue and my moods were everywhere..it was making me feel even more agitated and..depressed and..just all around horrible"*
>
> *4.8(page.line)*

> *T9(Transcript9): "Oh the change in my the change in my demeanour was was like light and shade black and white it it I went from being..nice which I think I am to being quite..not nice at all slamming things around everything was a problem"*
>
> *20.100(page.line)*

Participants described a wide range of symptoms - both physical and psychological symptoms – which had both explicit and implicit impact on their lives.

The explicit impact was primarily related to physical symptomology such as stiffness, headaches, or rashes:

> *T2(Transcript 2): "within 2 and a half weeks I was broken out head to toe in a rash..that was just massive hot lumpy dots just covering my entire body"*
>
> *4.23(page.line)*

However, participants also linked their side effect experience to explicit economic impacts:

T6(Transcript 6): "especially as you're spending you know money each month on your medication and if it's, if you're not feeling great as a result of it or it's not doing what you want it to do then… "

27.46(page.line)

T8(Transcript 8): "I'm taking co-enzyme Q10 therefore this muscle aches less….Actually am I investing wisely 15 pounds every three months"

22.98(page.line)

However, participants also emphasised the implicit impact of side effects. In general, these were linked to the psychological symptoms that they were experiencing. Most participants described these less obvious symptoms as significant in terms of impact on their lives:

T10(Transcript 10): "at the same time the fact that you're feeling these emotions that you don't usually you're not usually that much..it's not usually that much of a reaction and ..I don't know it was just the swings between it it was really bizarre it just made me feel a bit..yeah a bit scared at myself I was thinking why are you why are you being so you know so irritable all the time you're not usually like this"

9.21(page.line)

T7(Transcript 7): "I was really shocked that that just that that little tiny patch could do so much to your mental stability and the way that you felt you know the way that you felt in yourself..it was just strange…Yeah cos it was it was a total nightmare..your brain just goes wooo like that it's all over the place and you think...well what's doing this? And then you realise that the only thing that's made you do it is this this thing on your arm"

19.90(page.line)

Within the side effect experience participants echoed health research findings, reporting that attending/attentional biases towards negative symptoms could facilitate maintenance or escalation of these symptoms:

T2(Transcript 2): "you know an asthmatic attack can also be worse if you start to panic"

16.98(page.line)

T7(Transcript 7): "And then it's like a big rush that's all it is and amh then you won..then you start wondering why why that's happening aand (elongates) you think something else is wrong (laughs)...I've do I've been to the doctors quite a few times saying that I think something else is wrong"

5.25 (page.line)

Participants also indicated the priming effects which their medication beliefs had on their side effects experience. These beliefs were extensive in their range such

as positive/negative attitudes towards their medication and their own ability to manage side effects:

> *T2(Transcript 2): "So I'm really really careful, now, won't even like, won't even take anything..for pain medication unless I <u>really</u> have to because I'm so afraid I'm gonna have just an out of nowhere reaction thing"*
>
> *23.129 (page.line)*

> *T9(Transcript 9): "occasionally you do get side effects with a tablet and that's the side effect with that and it affected me you just you just have to deal with it"*
>
> *3.9(page.line)*

Participants also displayed perceptions about their health status which had significant effect on their side effect experience:

> *T6(Transcript 6): "this wasn't life-saving medication that I had to be on there there were options for me"*
>
> *9.39(page.line)*

> *T8(Transcript 8): "yes I have conditions which 50 years ago I wouldn't be here talking about....and ah so yes bottom line ah therapeutic doses of nasty toxic chemicals that you guys invent better than being dead"*
>
> *26.119 (page.line)*

The perceptions of participants towards side effects were also mediated by the doctor-patient relationship. In general, a positive relationship has a beneficial effect even if side effects occur:

> *T2(Transcript 2): "I think that he gave <u>me</u> the opportunity to say..I'm willing to take the risk take this medication because he gave me that opportunity I feel that..I can trust him with other things as well even if there's something down the road causes another reaction cos he's very open about it you know"*
>
> *33.160(page.line)*

Participants also indicated the characteristics of a positive relationship which centred on concepts of communication, engagement and accessibility:

> *T6(Transcript 6): "Yeah doctor that's it entirely amh my former we would discuss we would actually have a discussion amh it wasn't sort of an authority patient type of relationship it was more what do you think? I'll give here are a few facts what do you think? Think about them talk about them…so it was more like a dialogue amh whereas with the new GP it's a very different relationship it's well try these if they don't work come back in a month very different"*
>
> *14.60(page.line)*

> *T8(Transcript 8): "Best G.P. in the whole wide world accessible no problem if you need to see him or one of his chums that day you've got to ring at 8 o' clock on the dot and then of course it's engaged so you key 5 and then it rings you back so you can see him on the day"*
>
> *8.38 (page.line)*

5.3.2.2 Identification

Participants describe different avenues/methods in identifying their side effect. However, the system of identification was based on constructed cognitive processes. These cognitive processes are common across participants. They are constructed by participants and include eliminatory thinking, cognitive linking of medicines to symptoms and acquisition of knowledge:

> *T6(Transcript 6): "Yeah I sort of pieced it together I mean my initial my initial thoughts were perhaps I'm ill I need to go see the GP"*
>
> *17.30(page.line)*

> *T5(Transcript 5): "Suspicion was that I was getting this stiffness in my joints..and then did my research by going online..Belief was when I'd been to see my GP, when I'd spoken to a pharmacist and then further consultation with my GP…The confirmation was the fact that we then stopped my medication of any statin for 1 month..and at the end of the month when I went back to see her it was fine so it was...The thought analysis took me through..suspicion belief..confirmation…but it was the whole process from A to B"*
>
> *21.59(page.line)*

> *T2(Transcript 2): "The reading packet, amh and my GP saying yeah this is what it is (laughs) The connection was just that instant..thing of I think it could be your medications..that just..That was the bridge just hearing that I was just like mmm yeah it was just (pause) hearing..that there was like a reminder..of what I've already read"*
>
> *21.119(page.line)*

> *T1(Transcript 1): "It was new so I had been using my other four medicines and they didn't give me a problem..so I think that's one of the things that occur to me....This is a new medication..And then also...the information on the Internet people were also complaining about that. I found quite a number of patients who said they had the same problem. So I was like this is definitely it..'cos I had read about it..quite a lot"*
>
> *12.62(page.line)*

All participants used the timing of the side effect to link the medicine to the side effects. The timing of symptoms onset varied but the sequence of medication leading to symptoms was common across participants:

> *T2(Transcript 2): "And..within 2 and a half weeks I was broken out head to toe in a rash"*
>
> *4.23(page.line)*

> *T10(Transcript 10): "I took the medication..I started to get the tingliness about half an hour to an hour later? Amh and then..the really severe swelling and stuff and when I woke up that was...probably..after a little bit of sleep I'd say about about maybe five hours"*
>
> *12.27(page.line)*

T13(Transcript 13): "No..cos I said to my doctor I don't know what it is I said I just come out in this. He said what was you doing beforehand and I went well just sitting there I said I had pains in my st..tummy so I took a couple of para..of co-codamol and then about five or ten minutes later my face was started coming up like this"

6.22(page.line)

Also, common across participants was the use of aids such as PILs and HCPs to confirm the side effect:

T2(Transcript 2): "So I went to my GP and he said well it looks like measles but I don't think it is (laughs) And then I started having more breathing problems..about an hour later and he looked through all my medications and he said...he looked it up and said this..I'm pretty sure this is what it is."

6.32(page.line)

T6(Transcript 6): "I re-read the information leaflet just to confirm or not"

30.52(page.line)

5.3.2.3 Adherence

The medication beliefs of participants featured as part of the earlier theme of side effect experience. However, these beliefs also have a role in the decision-making processes surrounding adherence:

T8(Transcript 8): "So everything is status quo everything is working fine I'm not going to consider messing about with my meds"

14.68(page.line)

T2(Transcript 2): "I'm against medication I just don't think there's always a need for too much of it so before I take anything or I'm prescribed anything I just get as educated about it as I can"

19.112(page.line)

T14(Transcript 14): "I don't think I really realised you know you're sort of given this thing that is going to help you..and then you have this strange reaction and I think it took me quite a little while to make the connection because you just think given a medicine and it's going to help you and you don't really expect the other stuff to come with it…Amh but once it does happen then you just want to get it sorted out..I don't know what the time lag was amh but I do remember that..I just wanted to get rid of it basically"

7.33(page.line)

5.3.2.4 Information use

All the participants used varied information sources both formal and informal to find out about their side effects. Participants highlighted these varied sources which included healthcare professionals, the Internet as well as family/friends:

T10: (Transcript 10): "with the mini-pill amh that was because I went to the doctor's cos I was really concerned because I was there like I've been bleeding for a year now I don't know what the problem is and I've been having all these mood swings"

3.6(page.line)

T2(Transcript 2): "Yeah I just decided to stay off that and just go right to the pharmacy and see what he has to say"
14.76(page.line)

T8: "I had already spoken to my friend David amh who was already on the amh the statins and he said amh watch out for..aching limbs"

9.45(page.line)

Participants described the use of PILs as context-specific in that drug type or drug regime could determine its use. Past experiences of side effects also influenced participants' use of PILs:

T6(Transcript 6): "unless it was something like an antibiotic that I'd been prescribed for infection or something and then I wouldn't necessarily bother but something that you're taking regularly over a long period of time then yeah I would look at the information leaflet yeah"

8.15(page.line)

T10(Transcript 10): "after what happened with the tetracycline amh I always read them now because I want to be prepared in case something did happen like that again"

8.20(page.line)

T7(Transcript 7): "Yeah I always read the leaflets always read the leaflets..yeah I look for the side effects ahh quite a lot on the leaflets because there are side effects..on any drugs even paracetamol I read the leaflet now..Quite I'm quite avid (laughs) look to see the way it's going to affect me maybe"

14.66(page.line)

Participants also described the role of the Internet in the self-management of side effects. All participants approached the Internet with caution. However specific sites – such as NHS Choices - were identified as being quality trustworthy information sources. In addition, patient forums were seen by participants as useful in offering personal narratives/experiences of medical experiences:

T10(Transcript 10): "the other was through the Internet I went online and I typed in..Being sick after having the combi-pill and it came up straight away as this is a common side effect you should come off of it"

3.5(page.line)

T5(Transcript 5): "that simvastatin when I started getting this I read all the leaflets and it said this may happen..so I went onto the website about simvastatin and that was on a....NHS site I found this one out"

10.25(page.line)

T9(Transcript 9): ". Ah if you go onto the websites that are are the more professional websites amh you'll you'll get a decent sort of forum people talking about it. If you go on to say a society if you're a diabetic there's fantastic diabetic amh things out there that people go on ..They're worth looking at"

15.74(page.line)

An attentional bias is described as an increased assignment of attentional resources towards threatening stimuli relative to neutral stimuli (Cisler & Kostler, 2010; MacLeod et al., 1986). Participants described the effects of attentional biases in Internet use:

T2(Transcript 2): "Yeah amh..but I didn't go on the internet cos everytime I've gone on the internet with any symptom oh he's dying so I didn't go research that"

13.74(page.line)

T6(Transcript 6): "you can self-diagnose on the internet so easily these days and it's a similar kind of thing you can look at particularly sort of the the end of side effects that are..much more severe you might stop and wooo I was feeling like that do you know what I mean?"

32.54(page.line)

T9(Transcript 9): "What if I wanted to know anything about the tablets or whatever? Yeah everybody I think with access to the internet now [indistinct] Google. Usually if I do that I come off and phone the local funeral directors..Because you you never you always see the bad part of it or what if it was at its worst"

15.73(page.line)

5.3.2.5 Coping

Participants described the coping strategies they used to manage their side effects. These included negative thinking, excessive rumination and avoidant behaviours in social settings which impacted on the quality of their daily lives:

T7(Transcript 7): "I know that I've got at least 10 minutes before I've got enough well 10 minutes to find the loo (smiles) right down to that I look around for loos and stuff like that and I know where they are and then I can run to them if need to"

7.37(page.line)

T6(Transcript 6): "I think possibly the only thing I might do is go to bed earlier than I might usually just because you're feeling tired you've not had a great day feeling nauseous so ah sleep was probably one of the things I did more"

22.38(page.line)

Participants also identified the influential role that symptom interpretation can have on coping behaviours:

> *T7(Transcript 7): "I can walk into a shop and there's no air conditioning or something like that and I just feel claustrophobic and then that starts and you think to yourself (gasps) god and then the body temperature goes up and then half an hour later I'm rushing to the loo"*
>
> *7.36(page.line)*

> *T15(Transcript 15): "So if I get up one morning and I don't feel right I'll think hold on a minute what the hell's going off I expect to have pain I expect to have discomfort I expect to put one leg..down and [indistinct] and I go arse over tip so I'm already aware of those things and I'll prevent it every time it happens. I mean I've sticks galore there in the corner just in case I start having bad spasms"*
>
> *9.25(page.line)*

> *T4(Transcript 4): ".. when I'm not feeling well I can't do what I do..I'm aware and it's a general awareness thing that when you got a heart condition doesn't help..so when it's extra warm or I've been pushing it work wise I'll just temp my activities anyways. So I listen to what my body is telling me, slow down, ease up a little bit, sometimes I listen, I misread them and then I think I'm going into a blown panic but most of the time I kind of go: yeah! Slow down, don't do so much, you know, get a lift rather than walking if you can possibly do it, or catch a bus if you can do it, just sit down and chill out"*
>
> *8.23(page.line)*

The accounts also captured the disparity which can sometimes exist between physician beliefs about side effects versus patient beliefs about side effects:

> *T5(Transcript 5): "Where it said ah this can be quite severe and da-da-da and off it went and of course after I'd read it being told by one doctor it's 1 in 3 million and it's nothing to worry about"*
>
> *10.25(page.line)*

> *T9(Transcript 9): "I was angry that A, I hadn't read the the instructions and and B, the doctor hadn't mentioned that to me cos I thought well that's one humdinger of a possible side effect"*
>
> *21.102(page.line)*

5.3.2.6 Body awareness

The final theme which emerged was linked to body awareness. Participants indicated that attending to body signals were positive self-care health behaviours:

> *T9(Transcript 9): "cos over the years I've learned how my body is, how it works, how it feels and I know if something's not I'm not a hypochondriac or anything like that. But I know"*
>
> *18.87(page.line)*

T2(Transcript 2): "I'm very aware of what my body does because the illnesses I've had most of my life..so really..I-I don't play about I know when something is right and wrong"

8.47(page.line)

5.4 Discussion

SE experience: physical and psychological effects

The interviewees described a wide range of physical and psychological symptoms which had both explicit and implicit impact on their lives. The explicit impact was primarily related to physical symptomology such as stiffness, headaches or rashes. Participants described the implicit impact of side effects as significant and linked to psychological symptoms. This pattern of symptomatology is supported by previous research into patient reports of side effects, which found that these generally provide a detailed extensive picture of ADRs and their impact (Dobashi et al., 2016; Inch et al.,2012). In patient reports physical effects are generally the most frequently reported ADRs, with patients reporting more ADRs than HCPs (Aagaard et al., 2011; de Smedt et al.,2012; Gandhi et al., 2003; McLernon et al., 2010). This is further supported by the survey results in Chapter Four, where primarily physical effects were described in free-text comments by a majority of 230 survey respondents – 85%. Research has found that patients can have differing levels of susceptibility to psychological effects (O'Neil et al., 2012). The interview participants describe psychological effects as having a significant and debilitating impact on their lives. This is supported by research into ADRs where patients describe these changes in mood, memory and/or behaviour as distressing and persistent in nature (Avery et al., 2011; Judd et al., 2014).

SE experience: economic effects

Participants also linked their SE experience to explicit economic effects for the individual. These included medication costs, costs of treating SE and work productivity. This supports other research into ADRs which has also found general economic effects with significant costs to healthcare services and loss of productivity. (Edwards, 2012; WHO 2016).

SE experience: attentional biases to negative symptoms

Participants reported that attentional biases towards negative symptoms could facilitate maintenance or escalation of these symptoms. This is supported by health research which has found that excessive patterns of attention to negative stimuli play a central role in anxiety and depression disorders (Demeyer et al., 2012; Price et al., 2011). Research into gastrointestinal disorders has found that attentional biases can negatively impact on the subjective appraisal and perception of symptoms (Levy et al., 2006; Mogoaşe et al., 2016). This can lead in turn to symptom escalation or persistence and resulting avoidant health behaviours. These attentional biases allocate attention resources to symptom-related stimuli over neutral stimuli. This in turn can lead to impaired cognitive processing of the symptom cues, as was experienced by the interview participants.

SE experience: medication beliefs

Research has explored the impact that patients' perceptions and medication beliefs have on their health behaviours. Studies have found that negative medication beliefs can be a factor for non-adherent and information seeking behaviours (de Smedt et al., 2012; Johnson et al., 2007; Molloy et al., 2009). Interview participants indicated the significant impact which medication beliefs had on their side effects experience. These beliefs were extensive in their range and included their attitudes towards their medication, their confidence in their own ability to manage side effects, as well as their perceptions about their health status. The mediating effects of a positive doctor-patient relationship on negative medication beliefs were also mentioned by the interviewees. This suggests that current measures of medication beliefs such as the Medication Questionnaire (BMQ; Horne et al., 1999) may be limited. The BMQ covers personal and general beliefs and is widely used in health research, however it may not fully capture the wide range of factors inherent in medication beliefs.

Identification: constructed cognitive processes

Interview participants described the different processes they use to identify their side effect. The system of identification common across participants was based on constructed cognitive processes. They included eliminatory thinking, cognitive linking of medicines to symptoms and acquisition of knowledge. These results are supported by research which has identified processes where symptoms are filtered

and allocated significance through patients' cognitive systems (Eysenck et al., 2000; David et al., 2006; Mogoaşe et al., 2016). All interview participants used the timing of the side effect to link the medicine to the side effects. Previous studies support these findings and have also established that patients use temporal associations to assess suspected ADRs (Chaipichit et al., 2014; Krska et al., 2011; Lorimer et al., 2012). Also, common across interview participants was the use of aids such as PILs and HCPs to confirm the side effect. Other studies also mirror this use of PILs (Hughes et al., 2002; Krska et al., 2013). These findings are further supported by the survey results in Chapter Four: Survey. Over 80% of survey respondents used GPs or pharmacists to confirm their SE and a majority of respondents – over 70% - used PILs to confirm their SE.

Adherence: medication beliefs

Previous research investigating medication beliefs and non-adherence have shown mixed findings. Associations between medication beliefs and non-adherence have been found in a variety of patients – cardiovascular, HIV and patients with epilepsy (Bane et al., 2006; Cha et al., 2008; Nakhutina et al., 2011). However research conducted with cardiovascular and asthma patients found medication beliefs were not related to adherence (Maguire et al., 2008; Van Steemis et al., 2014)). Recent research has found that patients with negative medication beliefs could misattribute symptoms to a medication and consequently decide to stop taking their medication (de Smedt et al., 2012; Heller et al., 2015; Kelly et al., 2014). The medication beliefs of interview participants had a role in their decisions about adherence. These beliefs ranged from self-perceptions on their abilities to manage the SE, to considering whether the benefits of controlling a chronic condition outweighed the burden of SE and general beliefs that over prescribing is a current issue with HCPs.

Information use: formal and informal

Interview participants used varied information sources - both formal and informal - to find out about their side effects. This mirrors previous research which found that the majority of patients used HCPs, PILs or the Internet to find out about their SE (Chaipichit et al., 2014; Krska et al., 2013). Past experiences of side effects also influenced participants' use of PILs. Participants were also more likely to read PILs if their medicines were to be taken regularly or for a prolonged period of time. All participants considered that the Internet should be used with caution

when seeking information on SE. However specific sites – such as NHS Choices - were identified as being trustworthy. Interview participants also specifically identified on-line patient forums as useful in offering personal narratives of medical experiences. Research has shown that such interactive sites can influence patient health behaviours (Masoni et al., 2013; Weaver et al., 2009). Participants also described the tendency to over attend to negative information on the Internet. These attentional biases to negative stimuli are potential barriers to effective use of online resources and have been identified in previous research studies (Cline et al., 2001; de Raedt et al.,2010; Lee et al., 2014).

Coping: information seeking, social support seeking and non-adherent behaviours

Interview participants described the coping strategies they used to manage their side effects. The interviewees had a variety of coping styles and employed a variety of strategies. These strategies included information seeking, social support seeking and non-adherent behaviours. Previous research supports this pattern of coping, with social support seeking being the most common strategy, followed by information seeking (de Smedt et al., 2009; de Smedt et al., 2012). The SECope results reported in Chapter Four also support this pattern of coping behaviours. Social support seeking and information seeking strategies were most commonly reported predicted strategies by survey respondents (47% and 42% respectively). In addition, the predicted non-adherence of survey respondents (42%) rose to over half of actual non-adherence behaviours (56%). Research has also found that the process of obtaining information may be influenced by an individual's coping style (Case et al., 2005; Sawka et al., 2015). The levels of information that patients require varies greatly from those who require detailed medical information to those whose preference is to reduce discomfort by avoiding detail. High scores on the monitoring scale on the MBSS have been associated with specific information seeking activities. These include increased use of specialised information sources, seeking more detailed information and increased questioning of HCPs by patients (Ong et al., 1999; Timmermans et al., 2007). The majority of interviewees were monitors and their information seeking activities reflected this pattern of seeking information, particularly in accessing specialised sources of information. However recent research has found no evidence that obtaining detailed information as favoured by monitoring styles resulted in improved medical knowledge (Sawka et al., 2015).

Coping: negative thinking, excessive rumination and symptom interpretation

Interview participants also described negative coping strategies which involved cognitive factors such as negative expectations and excessive rumination. Health research has shown that affective cognitions can have significant impact on health outcomes (Taylor, 2013). Research provides evidence of the significant role that cognitive and emotional processes can have in health-protective and health-risk behaviours (Case et al., 2005; McSorley et al., 2014; Steptoe, 2006; Cameron et al., 2015). Interview participants also identified the influential role that symptom interpretation can have on coping behaviours. This central role of symptom interpretation in influencing coping behaviours is fundamentally embedded in the Self-Regulation model (Hale et al., 2007; Johnson et al., 2004; Levanthal et al.,2011).

Coping: disparity between physician and patient beliefs

Interview participants also identified the disparity which can exist between physician beliefs about side effects versus patient beliefs about side effects. Some interviewees described dismissive responses from their HCPs when they described their SE. Research studies provide supporting evidence for such dismissive attitudes amongst some HCPs. This disparity between HCPs and patients' perspectives on SE can lead to decreased SE reporting from patients (Anderson et al., 2007; Golomb et al., 2007; Gordon et al., 2007; Krska et al., 2013; van Geffen et al., 2011; van Grootheest et al., 2003).

Body Awareness: positive self-care

The final theme was linked to body awareness. Interview participants indicated that attending to body signals was an essential element of positive self-care health behaviours. This is supported by health research which has defined body awareness as an active process which involves an awareness of and attentional focus on body cues and signals (Mehling et al., 2009). Studies have identified body awareness as an adaptive process which can be helpful in managing chronic health conditions (Cioffi, 1991; Mehling et al., 2012; Watkins et al., 2004). Recent research has found that patients who ignored their bodily signals displayed lower levels of physical and psychological health (van Beugen et al., 2015). To date research has not specifically identified body awareness as a factor in terms of identifying ADRs. However this research found that body awareness and an appreciation of how the body reacts in differing circumstances is important in the

context of SE from medicines. Research has found that body awareness/sensitivity is a complicated construct which can be key to both adaptive and non-adaptive health behaviours. Hypochondriac tendency was reduced in those with high sensitivity to body symptoms that was combined with a non-catastrophising mode of attention (Ginzburg et al., 2014). Adaptive body awareness/sensitivity has been identified as occurring in combination with non-judgemental attention to the immediate sensations/effects (Mehling et al., 2009). This suggests that SE could be mediated by adopting a self-focus that directs attention to the effects in a mindful, non-judgmental manner.

5.5 Strengths and limitations

One of the main purposes of this interview phase was to address knowledge deficits in health research and form a more comprehensive picture of individuals' experiences of ADRs. This research makes a novel contribution to ADR research and increases both knowledge and understanding of the personal experiences and opinions of patients in identifying and managing side effects from medicines. It achieved this aim by collecting and investigating the detailed personal experiences of people obtained through face to face interviews. Self-selection bias may apply to the interviewees as they signalled their desire to participate from a larger survey sample. It is possible that the interview participants were particularly interested in ADRs as they had experienced significant SE which they regarded as being outside of the common SE experience. However the demographic information shows that interviewees had differing ages, education, medical conditions and number of medicines used, which suggests that participants may be likely to have a wide range of opinions and experiences. The medicines used by interview participants were also varied which suggests the results obtained could be widely applicable. The use of incentives – vouchers – may have led to bias in recruitment however the vouchers were of small monetary value which reduced their significance. Another strength of this research was that saturation in coding was reached after 15 interviews. This meant that further recruitment of interviewees was not required. A limitation of this phase of the study was the lack of independent coding considered best practice for qualitative research. Transcripts were checked by supervisor (JK) but not coded separately. This may have affected the reliability of the coding process. However the researcher had

previous experience of using IPA and had engaged in informal discussions during the coding process with an expert mentor with extensive IPA experience in health research (AK). The IPA approach to the analysis proved beneficial to this research allowing exploration of participants' subjective experience of ADRs. Its flexible interpretative processes ensured the interviews were comprehensively coded. A key finding of this phase of the research was the identification of body awareness as a key process in patients' experience of ADRs. This is a novel research finding as to date body awareness research has focused on mental health and chronic diseases.

5.6 Summary

In Phase Two of the study, in-depth interviews were conducted with 15 participants who had recently experienced an ADR. An IP approach was taken to transcript analysis and the following six main superordinate themes were identified - side effect experience; identification; adherence; information use; coping and body awareness. These themes link to recent health research, providing evidence of the significant role they have in ADR experiences. As described earlier in Chapter Three: General Methods, in Phase Three of this study a side effects assessment tool was developed which was based on the findings from these in-depth interviews. The development and validation of this assessment tool will be presented in the following chapter – Chapter Six: Side effects Assessment tool.

CHAPTER 6: SIDE EFFECT ASSESSMENT TOOL

6.1 General Introduction

Chapter One provided evidence to support the need for development of an assessment tool for use by patients to assess suspected ADRs. Scales currently in use for assessing causality of ADRs are designed for use by professionals working in pharmacovigilance centres. However, there are limited numbers of assessment tools for assessing causality available for patients (De Vries et al., 2013; Jarernsiripornkul et al., 2015). Research was described in Chapter One which suggest that a standardised assessment method could have multiple benefits. A generic assessment tool for patient use could facilitate improved reporting of ADRs by patients. It could address the current deficits within patient reporting and enhance the quality of these reports. In addition, it could empower patients to discuss their experiences of suspected ADRs with health professionals. One of the aims of this PhD was thus to develop a novel causality scale for use by the general public to assess suspected ADRs.

6.2 Methodology

6.2.1 Introduction

The rationale which guided the design for this phase of the study was provided in Chapter Three. Phase Three of the research involved the development and validation of the Side Effects Patient ASsessment Tool (SE-PAST). This chapter will describe the assessment tool development and validation procedures, the data collection processes, the strategies for data analysis, the results and a discussion of these results. The Side Effects Patient ASsessment Tool (SE-PAST) was developed based on the results obtained from research conducted in Phases One and Two – the Survey and Interview phases described in Chapters Four and Five. The Self-Regulation Model/CSM provided a theoretical framework to this phase – Phase Three – of the research. Criteria data from previous research conducted in Thailand (Jarernsiripornkul et al., 2015) and the gold standard Naranjo algorithm were used in the development of this assessment tool (Naranjo et al., 1981). This phase involved the validation of the SE-PAST amongst members of the general public known to have experienced side effect(s).

6.2.2 Aims and Objectives

The aim of this phase of the study was to develop and validate a novel assessment tool for the general public to use to assess suspected side effects. Objectives for this phase of the study were as follows:

- To develop an instrument designed to assess suspected side effects
- To validate the assessment tool amongst people known to have experienced side effect(s)
- To further validate the assessment tool in a larger population by making the assessment tool available online through links to relevant websites
- To determine whether patients consider such an assessment tool to be valuable and useful

6.2.3 Ethical approval

Two approval processes were followed. An amendment to the NHS ethics approval was sought to allow interview participants from Phase Two to be involved in the validation of the assessment tool. This was supplemented by further participants who were members of the public and the online survey also involved members of the public. Approval for the amendment to the NHS ethics protocol was obtained, and the other parts of this study phase received favourable ethical approval from the Medway School of Pharmacy Research Ethics Committee (see Appendix 3 REF 0116/2). For the initial validation stage a Participant Information Sheet, Feedback and Consent Forms were created (See Appendix 15). The Information Sheet described the aims of the study and explained exactly what participants were required to do. It also provided relevant information to participants about confidentiality, study funding as well as researcher contact details. The Feedback Forms were used to assist the participants in assessing the tool according to its structure, clarity, and usability. Consent was obtained in written form by return of completed Consent forms. Those who took part in telephone feedback also provided verbal consent at the start of each telephone engagement. Implied consent was applied to the online validation of the assessment tool. A statement which gained consent through completion of the scale was included in the online assessment tool (See Appendix 16).

6.2.4 Instrument design and development

A causality assessment tool was developed based on the Self-Regulation Model of Health Behaviours (Leventhal et al.,1980; 2011) as well as the survey and interview data collected in the earlier phases of this study. The assessment tool was primarily informed by the data and results from the Phase Two in-depth interviews conducted with people who had recently experienced an ADR. Findings from previous research, which developed a self-assessment measure for use by patients, were also used in this instrument development (Jarernsiripornkul et al., 2015). The initial tool was a paper based instrument and later an electronic version was created for use on a computer platform. The paper based tool was structured as follows (See Appendix 17):

<u>Section A – background information</u>

Respondents were asked to provide detailed descriptions of their SE experience. This section was composed of nine questions in total - five questions require tick box responses; three open-ended questions require free text comments and one question is composed of two parts with tick box response and free text comment options. Questions One to Two asked respondents to describe their suspected SE and its timing. Question Three required respondents to assess the impact of the SE on their daily lives on a four-point scale ranging from No impact, Mild impact, Moderate impact to Severe impact. Questions Four and Five required free text responses in which respondents listed their medicines at the time of the SE and indicated which medicine they suspected caused their SE. Question Six asked if respondents had allergies/pre-existing medical conditions and if they did to list them in the text box. Basic demographic information, gender, age group and highest achieved education level accounted for the remaining three questions.

<u>Section B – Assessment tool</u>

This section contained the Assessment Tool (AT), Scoring Box and SE Probability Key. The AT was composed of ten statements/items. The ten statements related to SE experiences and respondents were required to answer all the statements. They were asked to select the statements that corresponded most closely with their own SE experience. Each statement had four possible responses ‘Yes’ ‘No’ ‘Don’t know’ or ‘Not applicable’. The tool required those completing it to score their responses from 1-10, by filling in the Scoring Box with the score assigned to their selected response and then calculating the total score. This total score could then be categorised with the SE Probability Key to determine the likelihood of causal association (highly probable, probable, possible,

unlikely). Weighting of the assessment tool score for each statement was based on the widely-used Naranjo algorithm (See Appendix 18). Information about the four causality levels – ranging from unlikely to highly probable - was provided, accompanied by advice for respondents to contact a relevant health professional and consider reporting their experience to the YC Scheme, for any experience categorised as possibly, probably or highly probably a SE from a medicine. The Medway School of Pharmacy public engagement group - Public Involvement in Pharmacy Studies Group (PIPS) was approached to assess and provide feedback on the tool. Based on their assessment and suggestions amendments were made to the SE-PAST tool which was then subjected to validation.

6.2.5 Procedures to validate the instrument

A cross sectional study design was employed with initial validation by people known to have experienced side effect(s). The assessment tool was then placed online to gain additional validation in a larger population.

6.2.6 Participant recruitment

This part of the validation aimed to recruit assessors - approximately 30 people - known to have experienced side effect(s). This minimum sample size was selected based on previous research (Jarernsiripornkul et al., 2015) and to ensure the previous interview participants were balanced by an equal number of new participants. The initial validation was to be provided by the 15 interviewees who had previously participated in Phase Two of the study and 15 novel assessors. These participants were members of the general public who were known to the research team and known to have experienced SE.

The participant inclusion criteria were as follows:

- Adults aged 18 years or over
- UK residents
- Participants who suspect they have experienced side effect(s) from their medicines
- Proficient in English language (reading and speaking)

6.2.7 Distribution of draft assessment tool

6.2.7.1 Postal distribution and telephone interviews

Potential participants were approached via email or phone (See Appendix 19). They were invited to participate in the study and provided with a Participant Information Sheet, Consent Form, Assessment Tool and Feedback Form. A prepaid envelope was also included to return completed forms and tools to the Medway School (See Appendices 15 and 17). Participants were also offered the option to provide their feedback by telephone if they preferred. The Feedback form was used to structure the evaluation of the tool and to prompt the telephone interviewees. It provided some demographic information and gathered information from the assessors on the structure, clarity, and usability of the tool. Assessors were asked for their general opinion/comments on the tool overall and any suggestions for improvement.

6.2.7.2 Online distribution of assessment tool

Online distribution of the assessment tool followed this initial validation. The SE-PAST was prepared for online use in Qualtrics®. The assessment tool was mostly structured as previously described in 6.2.4 with some additional features.

This electronic version of the tool included a pre-screening component with appropriate questions used to ensure respondents satisfied the inclusion criteria. A Participant Information Page accompanied these screening questions (See Appendices 15-16). The on-line version also differed from the paper instrument as it assigned scores automatically to each response and calculated the score, so avoiding the need for respondents to do so themselves. The electronic version also requested feedback at the end of the tool. This additional feature was included to determine whether participants found the assessment tool useful, and if it would encourage them to report their side effect or talk to a HCP about it, thus meeting the final objective for this study.

A list of patient support groups and organisations with a record of encouraging patient engagement and supporting health self-management were approached via email (See Appendix 20). These organisations were asked to post a recruitment statement with a link to the assessment tool on their website.

Sample size

Robust predictive validity for a tool generally requires a large sample size to generate a lower validity coefficient (*r*) value. The sample size was calculated using the following parameters when making the power calculations;

Using a prevalence estimate of 26% (/Alhawassi et al, 2014) for experiencing an ADR

A random sample of the general population at a confidence level of 95%

Confidence interval of ±1.96 and a margin of error of 5%

Power equation

$$Ss = \frac{Z^2 \times (p) \times (1-p)}{C^2}$$

Where Ss= sample size; Z = 1.96 (95% CL); p = % accuracy expressed in decimals;

$$Ss = \frac{(1.96)^2 \times (0.26) \times (1-0.3)}{(0.05)^2}$$

$$Ss = \frac{3.84 \times 0.26 \times 0.7}{0.0025} = \frac{0.699}{0.0025}$$

Ss = 279.55

Therefore it was proposed that the study required a sample size of approximately 300 completed assessments.

To facilitate a high response rate, it was decided to maintain an active online link for five months. During this time contacts were made with appropriate people within individual organisations via email and telephone which ensured a large number of completed reports. As sufficient responses had been obtained after five months, the survey was closed.

6.2.8 Confidentiality and anonymity

All participants in the initial validation stage were informed that the research was confidential. Telephone interviewees were informed in writing and verbally of this prior to the interview. Contact details were supplied to the researcher by the assessors during the initial phone/email contact. These details were stored in paper format only and shredded by the researcher following postal and telephone feedback. No personal identifiable information was included in postal responses and telephone interviews. The study data collected online contained no personal identifiable information, ensuring anonymity.

6.2.9 Methods for data analysis

6.2.9.1 Initial validation of draft assessment tool

The postal distribution and telephone interviews generated feedback forms which helped to develop the tool. The demographic information and the overall evaluation/assessment of the tool obtained from both methods was combined. A frequency table of responses to the closed questions was created to explore the tool's clarity, ease of use, logic of the structure etc. The free text comments/suggestions for improvement were examined to identify points of commonality which needed to be addressed. Amendments were subsequently made to the tool to facilitate ease of use such as clarifying the instructions.

6.2.9.2 Online validation of SE-PAST

The Qualtrics® data were downloaded for analysis into SPSS (Windows Statistics 23) and Excel. The dataset was cleaned and checked for errors such as missing values. Missing data was dealt with by the conventional method of exclusion and was not included in the analysis (Soley-Bori, 2013). Incomplete statements in the AT were assigned a value of 0 (Brick et al., 1996). Data were then subjected to qualitative and quantitative analysis and statistical significance was set to $p \leq 0.05$. Descriptive statistics and cross-tabulations were conducted to investigate statistical differences. Categorical data were described using percentages/frequencies and as respondents' age was not normally distributed median value was reported. The SE experience of the online respondents was characterised according to the following parameters:

- impact and timing of SE
- list of medicines and causal medicine
- pre-existing conditions/allergies

Multidimensional chi-square tests were then conducted to identify associations between respondents' demographics and their SE experience. Responses to the SE-PAST text box questions were entered in Excel and the data management program QSR NVivo 10. A coding frame was created in an earlier phase of the study during the analysis of the Survey free text comments. This frame was applied to the SE-PAST free text data.

A frequency table of the feedback responses was analysed to assess the value and potential usefulness of the AT. Principal Component Analysis (PCA) with direct oblimin rotation was conducted on completed ATs to examine the factor structure of the SE-PAST. Four factors were retained based on the Eigenvalues > 1 and visual inspection of the scree plot

elbow point. An optimum structure was achieved that revealed one item had factor loadings below 0.4. This item (statement one) was excluded and PCA conducted again. The results are presented in Section *6.3.4.8. AT scores*

6.3 Results

The assessment tool was developed and initially validated by people known to have experienced SE before further validation online in a larger population. The results of the initial and online validation are presented in the following sections: respondent characteristics; their SE experience; their scoring on the AT and their feedback.

6.3.1 Initial validation – Assessor characteristics

Overall 31 assessors – 11 interviewees from Phase Two and 20 novel assessors – completed the AT and supplied feedback. Four previous interviewees were unavailable to provide feedback due to illness or holidays. The majority of assessors (21;68%) were female, median age 52 years with over half University educated (16;52%). Seventeen assessors (55%) had an existing medical condition and experienced their SE a year ago/longer. Over half used two-four medicines regularly (16;52%) and 13 (42%) rated SE impact as 'moderate'. See *Table 6.1.* A majority (20;65%) scored between 4-7 on the AT and thus their experience was categorised as 'Probable' on the SE-PAST Probability key.

6.3.2 Initial validation - Assessor feedback

Assessors provided feedback on the SE-PAST under the following criteria: ease of use; clarity; structure; length of AT and difficulties in recalling SE. The time taken to complete the SE-PAST ranged from five to forty-five minutes (M=25; SD±12). The majority (24;70%) completed it between 5-15 minutes while over 90% thought it was not too long. All assessors either agreed /strongly agreed that the SE-PAST was easy to read while a majority either agreed (13;45%) or strongly agreed (14;42%) it was easy to understand and clearly laid out (16;52% and 14;45%). Over 80% had no difficulty in recalling their SE experience. See *Table 6.2* on the following page.

Table 6.1: Characteristics of respondents involved in initial validation of the SE-PAST

Assessor characteristics (n=31)	**N(%)**	**SE experience & AT scoring (n=31)**	**N(%)**
Gender		*SE Timing*	
Male	*10(32)*	*Past mth*	*4(13)*
Female	*21(68)*	*Past 3 mths*	*5(16)*
		Past 6 mths	*5(16)*
		1 yr/longer	*17(55)*
Age		*SE impact*	
Below 40	*7(23)*	*Severe*	*7(23)*
41-50	*7(23)*	*Moderate*	*13(42)*
51-60	*5(16)*	*Mild*	*7(23)*
61-70	*6(19)*	*None*	*4(13)*
71-80	*5(16)*		
Over 80	*1(3)*		
Education		*AT scoring*	
SL 16	*6(19)*	*1-3*	*1(3)*
SL 17/18	*2(7)*	*4-7*	*20(65)*
F ed	*6(19)*	*8 or higher*	*6(19)*
Univ	*16(52)*		
Medicine use		*AT key*	
One	*6(19)*	*Possible*	*1(3)*
2-4	*16(52)*	*Probable*	*20(65)*
5-8	*5(16)*	*Highly probable*	*6(19)*
Medical condition			
Yes	*17(55)*		
No	*12(39)*		

Figures show n(%)

SL=School leaver; F ed= Further education; Univ= University; SE=Side Effects

Table 6.2: Initial feedback & evaluation by assessors of the SE-PAST

	N (%)				**N (%)**	
Feedback criteria	**Disagree**	**Agree**	**S Agree**	**Evaluation criteria**	**Yes**	**No**
Easy to read	*0*	*16(52)*	*15(48)*	*Too long*	*1(3)*	*30(97)*
Easy to understand	*4(13)*	*13(45)*	*14(42)*	*Recall difficulty*	*4(13)*	*26(84)*
Easy to complete	*2(7)*	*13(42)*	*16(52)*			
Clearly laid out	*1(3)*	*16(52)*	*14(45)*			
Logical structure	*3(10)*	*15(48)*	*13(42)*			

Figures show n (%)

S Agree= Strongly Agree

The responses from this initial validation were reviewed and used to guide amendments to the SE-PAST. Instructions were clarified to facilitate clarity and ease of use. This initial validation data was not included in further analysis.

6.3.3 Online validation

Overall 761 people accessed the SE-PAST online with 273 completed responses, a response rate of 36%. See *Table 6.3*.

A majority of online respondents were female (216;69.9%) with 35.8% aged 61-70 years. Overall over half were University educated (179;58.1%) and had experienced SE a year ago/longer 159(53.7%). A majority had an existing medical condition/allergy 273(89.8%) and used between two-four medicines at the time of the SE (122;43.1%). The SE impact was described as either moderate by 113(37.7%) or severe by 115 (38.3%) respondents.

Table 6.3: Number of responses per question/statement in online SE-PAST

SE-PAST Section A: questions 1-9	Total responses to questions	SE-PAST Section B: AT statements 1-10	Total responses to AT statements
Q1 Description of SE	304	**St1**	307
Q2 SE timing	296	**St2**	252
Q3 SE impact	300	**St3**	214
Q4 Medicine use	292	**St4**	305
Q5 Causative med	287	**St5**	306
Q6 (i) Medical conditions/allergies	304	**St6**	306
Q6 (ii) List of medical conditions/allergies	294	**St7**	286
Q7 Gender	309	**St8**	292
Q8 Age	310	**St9**	287
Q9 Education	308	**St10**	306

6.3.3.1 Gender and respondent characteristics

Over half of males (52;55.9%) and females (126;58.9%) were University educated and had experienced SE a year ago/longer - 50;59.5% and 107;51.4% respectively. There were no gender differences in the proportion of medicines used by respondents. Similar proportions of males and females used between two-four medicines 35;42.7% and 88;44% respectively. Analysis indicated an association between gender and age with a higher proportion of younger females – below 60 years - than males amongst respondents. Overall the highest proportion of each gender were aged 61-70 years – 39 males (41.9%) and 71 females (32.9%). There were a higher proportion of females aged under 40 (25;11.6%) than males (2;2.2%) and over twice as many female respondents below 60 years (96;44.4%) as males (15;16.13%). An exact Pearson's chi-square indicated a moderate association between gender and age: X^2 (5, N = 309) = 31.2, $p \leq 0.001$. Gender accounted for 10% of the variation in age ranges; $\Phi = 0.32$. See *Table 6.4.*

6.3.3.2 Gender and SE impact

Analysis indicated gender differences in SE impact. Females were more likely to describe the impact as moderate (82;39.2%) or severe (87;41.6%) This compared to moderate impact for 30 males (34.5%) and severe impact for 28 males (32.2%). The relationship between gender and SE impact was significant: X^2 (3, N=296) = 7.7, p = 0.05. The association was moderate: $\Phi = 0.2$, gender accounted for 4% of the variation in SE impact. See Table *6.4.*

6.3.3.3 Gender and medical profile

Analysis indicated a similar medical profile existed amongst respondents. The majority of males and females had two or more medical conditions - 28(52%) and 81(60%) respectively. The same proportion of females 40(71%) and males 96(71%) had no allergies. See *Figure 6.1.*

Table 6.4: Online validation of SE-PAST – gender by respondent characteristics and SE experience

Respondent characteristics	Gender f (%) n=309 **Male**	**Female**	**p-value**
Age			≤0.001*
Below 40	2(2.2)	25(11.6)	
41-50	4(4.3)	29(13.4)	
51-60	9(9.7)	42(19.4)	
61-70	39(41.9)	71(32.9)	
71-80	29(31.2)	45(20.8)	
Over 80	10(10.8)	4(1.9)	
Medicine use			0.3
One	19(23.2)	63(31.5)	
2-4	35(42.7)	88(44)	
5-8	21(25.6)	33(16.5)	
>8	7(8.5)	16(8)	
SE impact			0.05*
None	8(9.2)	8(3.8)	
Mild	21(24.1)	32(15.3)	
Moderate	30(34.5)	82(39.2)	
Severe	28(32.2)	87(41.6)	
Education			0.9
School Leaver ≤16	12(12.9)	25(11.7)	
School Leaver=17/18	8(8.6)	21(9.8)	
Further education	21(22.6)	42(19.6)	
University	52(55.9)	126(58.9)	
SE timing			0.5
Past mth	12(14.3)	45(21.6)	
Past 3 mths	8(19.5)	22(22.6)	
Past 6 mths	14(16.7)	34(16.3)	
1 yr/longer	50(59.5)	107(51.4)	

significance at ≤0.05 probability level (two-tailed)
Figures shown n(%)
Mth(s)=month(s); yr=year

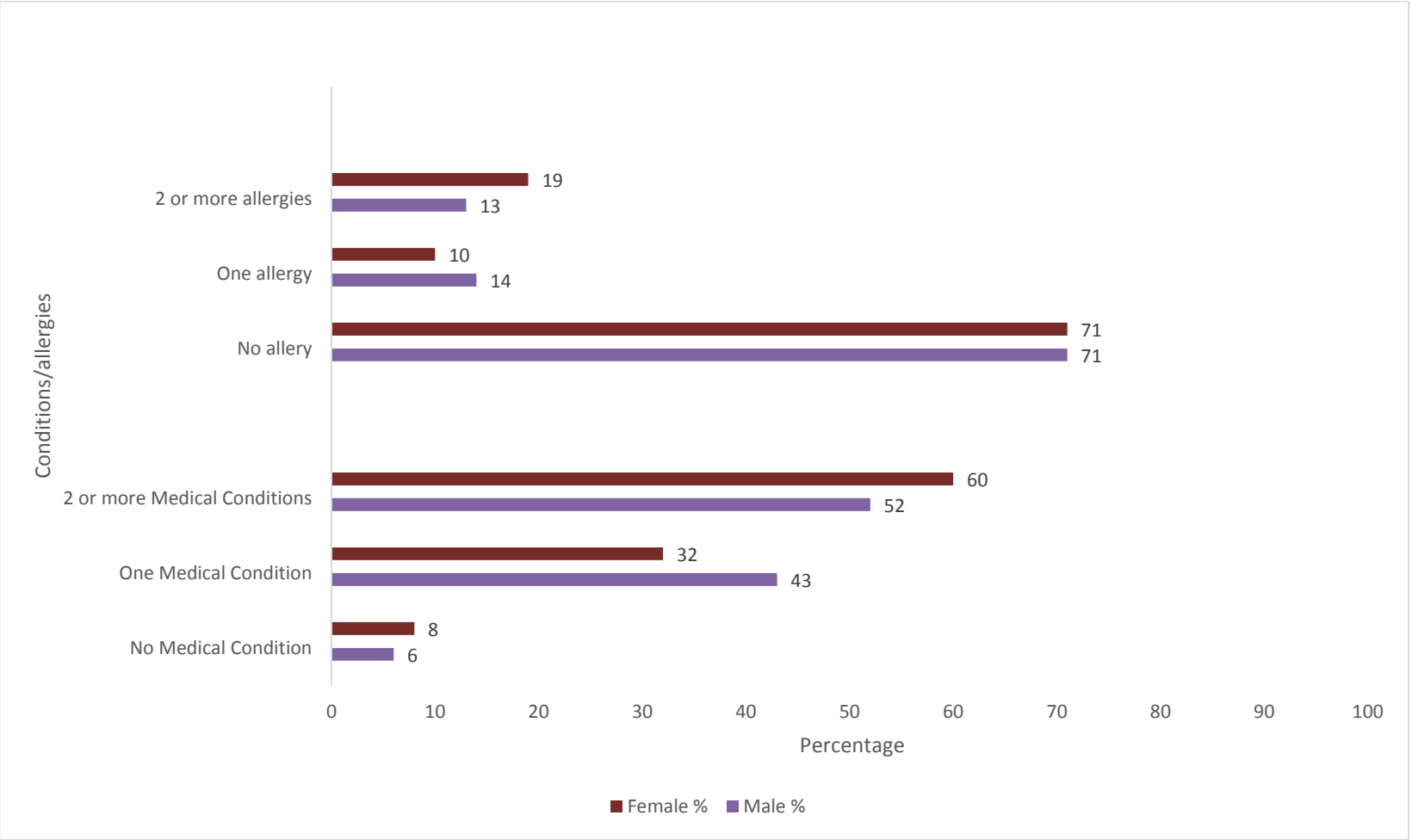
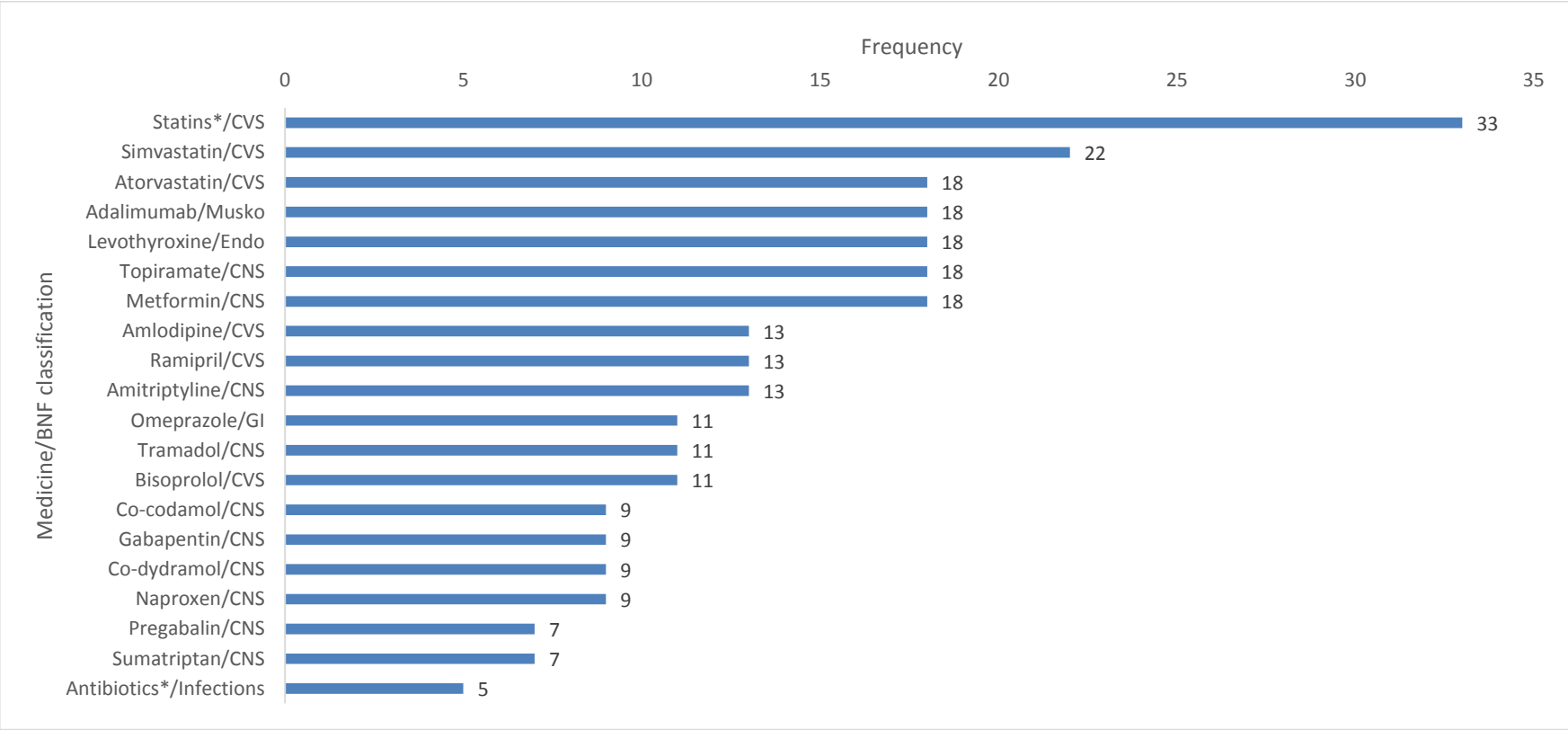


Figure 6.1: Online validation of SE-PAST – respondent gender by medical conditions (n=189) and allergies (n=191)

6.3.3.4 Categories of the top 20 causative medicines

Medicine(s) believed to have caused the SE were classified according to the British National Formulary (BNF). Overall 289 respondents supplied details with 10(3.5%) unsure what drug had caused the SE. In addition, 15.2% (44) of respondents reported combined/multiple medicines linked to BNF categories. The highest proportion of respondents (86;29.8%) reported causative medicines(s) linked to the central nervous system (CNS), followed by cardiovascular (CV) (65;22.5%), endocrine system (18;6.2%) and 14(4.8%) with gastrointestinal (GI) medicines.

The 20 most frequent causative medicines suspected of causing SE are presented in Figure *6.2.* These are BNF categorised as follows – the central nervous system (CNS) and the cardiovascular system (both systems 40%); gastrointestinal system (4%) and infections (2%).



BNF= British National Formulary; CNS= Central Nervous System; CVS=Cardiovascular system; Endo=Endocrine; GI=Gastrointestinal; Musko=Musculoskeletal

#excludes combination/multiple medicines, injections, those not sure/none

**unspecified*

Figure 6.2: 20 most frequent medicines reported by respondents as causing SE in online validation of SE-PAST (n=272#)

6.3.3.5. Medicine categories and gender, SE impact

Analysis indicated an association between gender and the category of the causative medicines. Proportionately more females (72;35.8%) identified CNS medicines as causing their SE compared to males (13;15.5%). Gastrointestinal medicines were also identified by a majority of females (11;5.5%) compared to males (2;2.4%). Similar proportions of females and males identified medicines related to infections - 9;4.5% and 4;4.8% respectively. The relationship between gender and causal drug was significant: X^2 (3, N=176) = 23.6, $p < 0.001$. The association was strong: $\Phi = 0.4$, gender accounted for 16% of the variation in the causal drug. See *Table 6.5.*

CNS and CVS medicines were linked to both 'severe' and 'moderate' impact on QoL. The highest proportions of 'severe' impact was reported for CNS (30;26.5%) and CVS medicines (19;16.8%). 'Moderate' impact was reported for CNS (37;34.9%) and CVS (27;25.5%) medicines.

Table 6.5: Categories of causative drugs reported in online validation of SE-PAST by gender and SE impact

	BNF categories (n=178)[#]				
	GI	**CVS**	**CNS**	**Infections**	**P-value**
Gender					≤ 0.001*
Male	2(2.4)	33(39.3)	13(15.5)	4(4.8)	
Female	11(5.5)	32(15.9)	72(35.8)	9(4.5)	
Impact					0.19**
Severe	5(4.4)	19(16.8)	30(26.5)	7(6.2)	
Moderate	3(2.8)	27(25.5)	37(34.9)	4(3.8)	
Mild	4(7.5)	15(28.3)	19(35.8)	2(3.8)	
No impact	2(15.4)	4(30.8)	0	0	

BNF = British National Formulary; CNS = Central Nervous System; CVS=Cardiovascular system; GI=Gastrointestinal

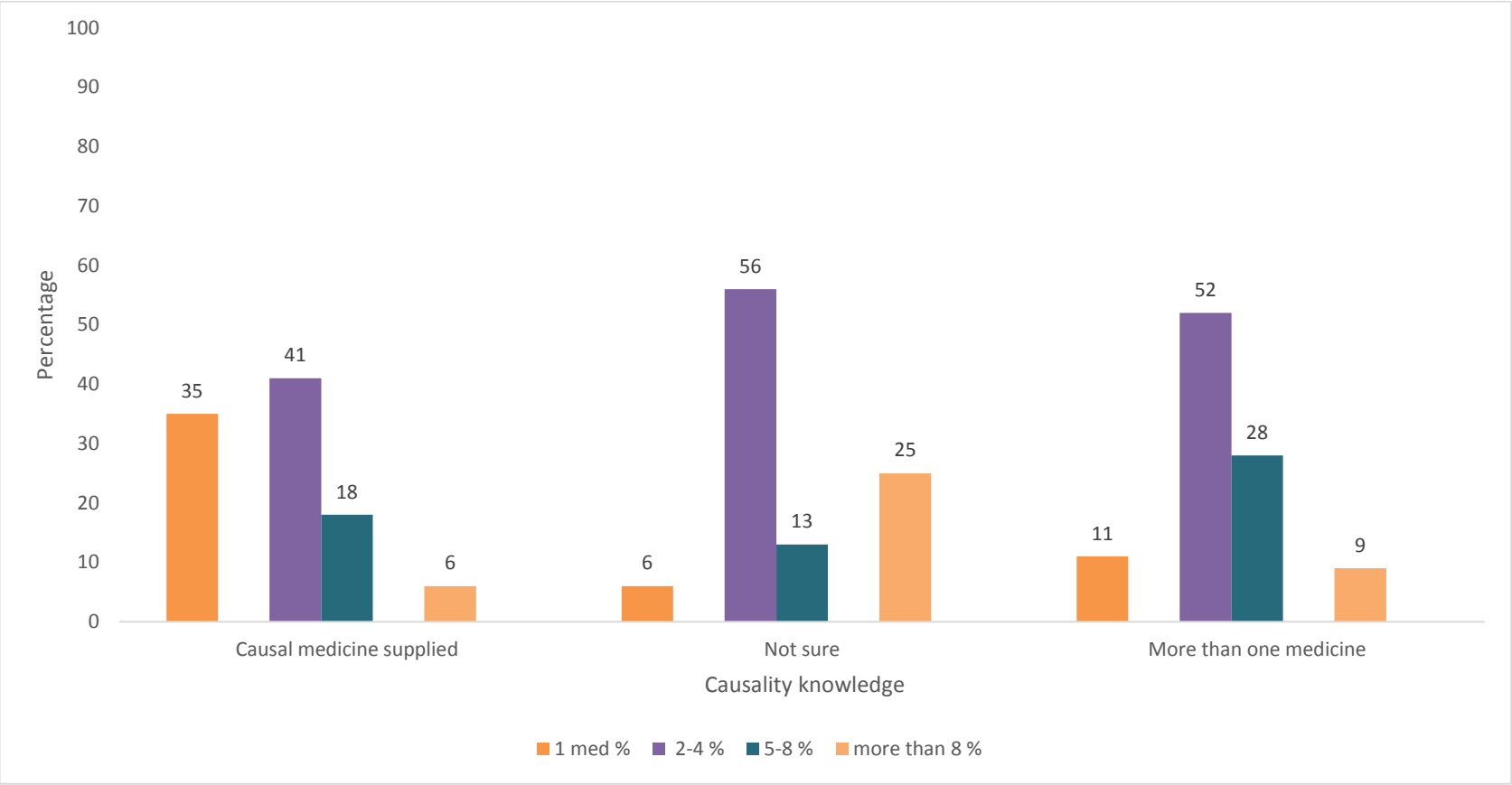
[#] Four BNF categories GI, CVS, CNS and Infections included in analysis

**significant at p< 0.05 significance level*

***p value for impact collapsed to two levels 'severe/moderate' 'mild/no impact'*

6.3.3.6 Causality knowledge and medicine use

Knowledge about causality of SE varied amongst respondents. From 280 respondents 196(70%) knew the causal medicine, 19(7%) were not sure what medicine had caused the SE and 65 (23%) thought more than one medicine was responsible. The highest proportion of those who knew the causal medicine 78(41%) or thought that more than one of their medicines could be responsible 33(52%) were using between two to four medicines. As medicine use increased, from two to four to five to eight medicines, the proportion of respondents who could identify one causal medicine dropped to 34(18%) and 18(28%) of these respondents thought that more than one medicine could be responsible. The relationship between causality knowledge and medicine use was significant: X^2 (6, N=272) = 24.7, p = 0.001. The association was moderate: Φ = 0.3, medicine use accounted for 9% of the variation in causality knowledge. See *Figure 6.3* on the following page.



Med(s)= medicine(s)

Figure 6.3: Online validation of SE-PAST - causality knowledge by medicine use in online respondents (n=272)

6.3.3.7 Description of SE

A total of 304 responses to the following text box question were analysed '*Please describe the suspected side effect(s) you experienced in detail, including any information that you think may be relevant'.*

The number of answers per category was noted and a frequency table was created. This suggested that a majority of respondents described the physical effects of the SE (255;84%) followed by social effects (74;24%) and psychological effects (46;15%). Respondents confirmed the SE with HCPs 35(37%) or PILs (4;1%). Factors such as the timing of the side effect and previous health experiences were used to link the medicine to SE. See Table *6.6.*

Table 6.6: SE-PAST - categories and frequencies of text box responses to Question 1

Responses (N=304)	Frequency	%
Categories:		
Reported physical effects	255	84
Reported psychological effects	46	15
Reported social effects	74	24
Timing of the SE#	100	33
Stopped meds & effects disappeared	69	23
Onset of symptoms linked to start of medicines	19	12
Recalled previous health experiences – changes in health linked to medicines	4	1
Talked to HCPs to confirm SE	35	37
Talked to relatives/friends to confirm SE	4	1
Used PILs to confirm SE	4	1
Used the Internet to confirm SE	2	0.7

 # specific timing of onset of symptoms described 'few hours'/'an hour later'

6.3.3.8 AT scores (SE-PAST Section B)

Overall 307(40.3%) out of 761 persons who accessed the online survey completed some or all of the AT. The number of completed statements ranged from two to 10 as some respondents failed to answer more than one statement. All ten statements were completed by 186 (60.6%) of these respondents with 75(24.4%) completing nine statements. When these incomplete statements were examined a pattern was identified - the statements most

often not completed were statement 2: '*When I stopped taking the medicine the effect(s) decreased in severity or disappeared'* (90;29.3%) and statement 3: '*I have experienced similar effect(s) from this medicine or a related medicine'* (55;17.9%).

Based on all those completing any of the AT, the majority (181; 59%) had scores of 4-7 (Probable/Likely) followed by 46(15%) who scored 8 or higher (Highly probable/Likely). The AT score ranged from -1 to 12 (M = 4.96; SD± 2.76 with skewness of -0.5 (SE=0.1) and kurtosis of -0.4 (SE=0.3). Distribution was considered approximately symmetric. A similar pattern of probability scores were identified in those who completed all of the AT, the majority (119;64%) had scores of 4-7 (Probable/Likely) followed by 38(20.4%) who scored 8 or higher (Highly probable/Likely). The AT completed by respondents were analysed using principal component analysis (PCA) with direct oblimin rotation. Sampling adequacy for the AT was acceptable (KMO = 0.6) and Barlett's Test of Sphericity $p <$ 0.05. See *Table 6.7* and *Figure 6.4.*

Table 6.7: Information about factorability of data

KMO and Bartlett's Test		
Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		0.589
Bartlett's Test of Sphericity	Approx. Chi-Square	205.127
	Df	36
	Sig.	.000

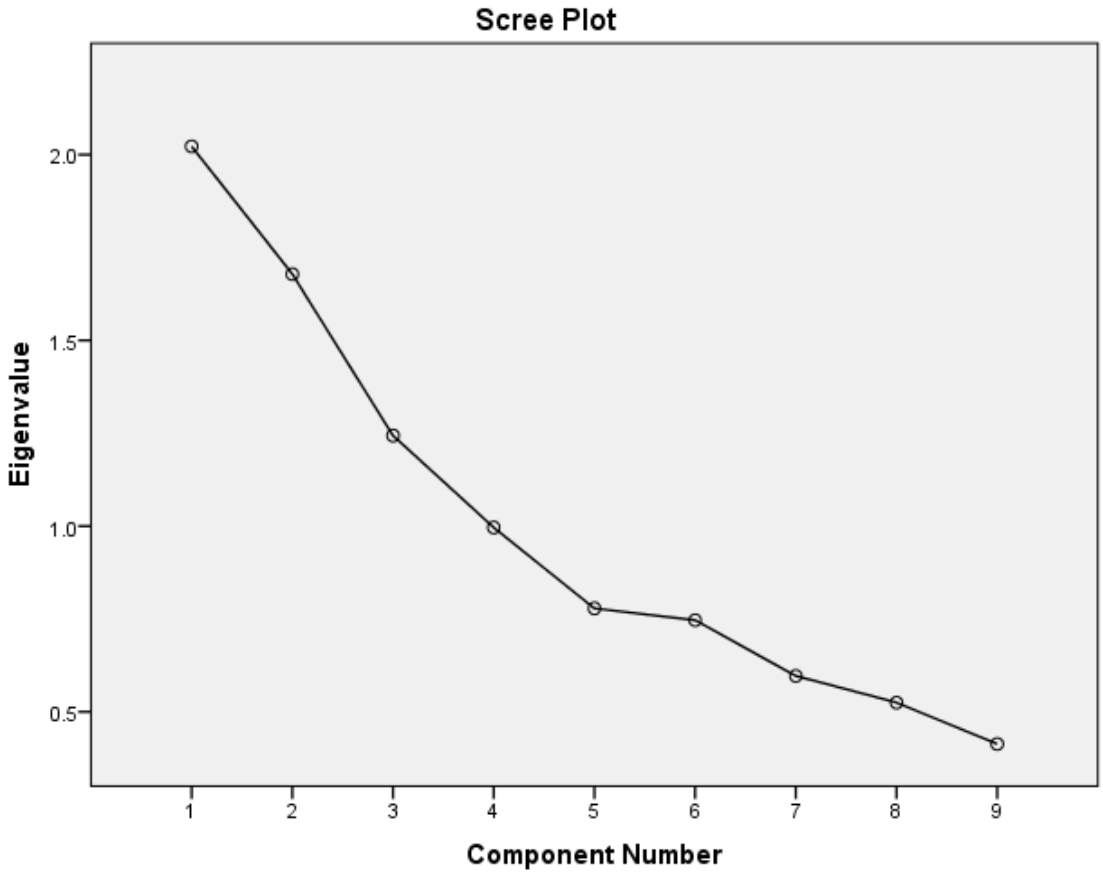


Figure 6.4: Scree plot of eigenvalues generated by PCA

The PCA revealed three components which when combined explained 54.93% of the variance. Statements 4, 5 and 6 loaded most strongly on Component 1; statements 8, 9 and 10 on Component 2 and the strongest loadings for Component 3 were statements 3 and 7. The component loadings are shown in *Table 6.8.* The components represent stages in identifying SE: component 1 -sequencing; component 2 – alternative causes and component 3 – self-directed health behaviours.

The overall scale had poor reliability (Cronbach's $\alpha = 0.53$); the three factors' reliability ranged from 0.4 - 0.7 and the items had low to moderate correlations (r^2 values ranged from 0.2 - 0.36) which indicated they were not linked to a single underlying variable.

Table 6.8: PCA components, loading variables and squared multiple correlations (n=183)

Rotated components

Component 1 (Sequencing)		R^2	**Component 2 (Alternative causes)**		R^2	**Component 3 (Self-directed health behaviours)**		R^2
Statement 6: When I decreased the dose the effect(s) became less severe.	**0.79**	0.36	Statement 9: I think an existing medical condition or conditions could have led to the effect(s).	**0.78**	0.2	Statement 3: When I stopped taking the medicine the effect(s) decreased in severity or disappeared altogether.	**0.85**	0.22
Statement 5; When I increased the dose the effect(s) became more severe.	**0.77**	0.34	Statement 8: I think that something else apart from the medicine could have caused the effect(s).	**0.74**	0.2	Statement 7: I confirmed the effect(s) with some or all of the following information sources – doctors, pharmacists, information leaflets with your medicine, the internet or medicine books.	**0.74**	0.21
Statement 4: When I took the medicine again the effect(s) reappeared.	**0.59**	0.2	Statement 10: I think that other medicine(s) that I was using at the time could have caused the effect(s).	**0.56**	0.2	Statement 2: I have experienced similar effect(s) from this medicine or a related medicine in the past.	0.4	0.20
Statement 2: I have experienced similar effect(s) from this medicine or a related medicine in the past.	0.47	0.2						

Significant loadings in bold font

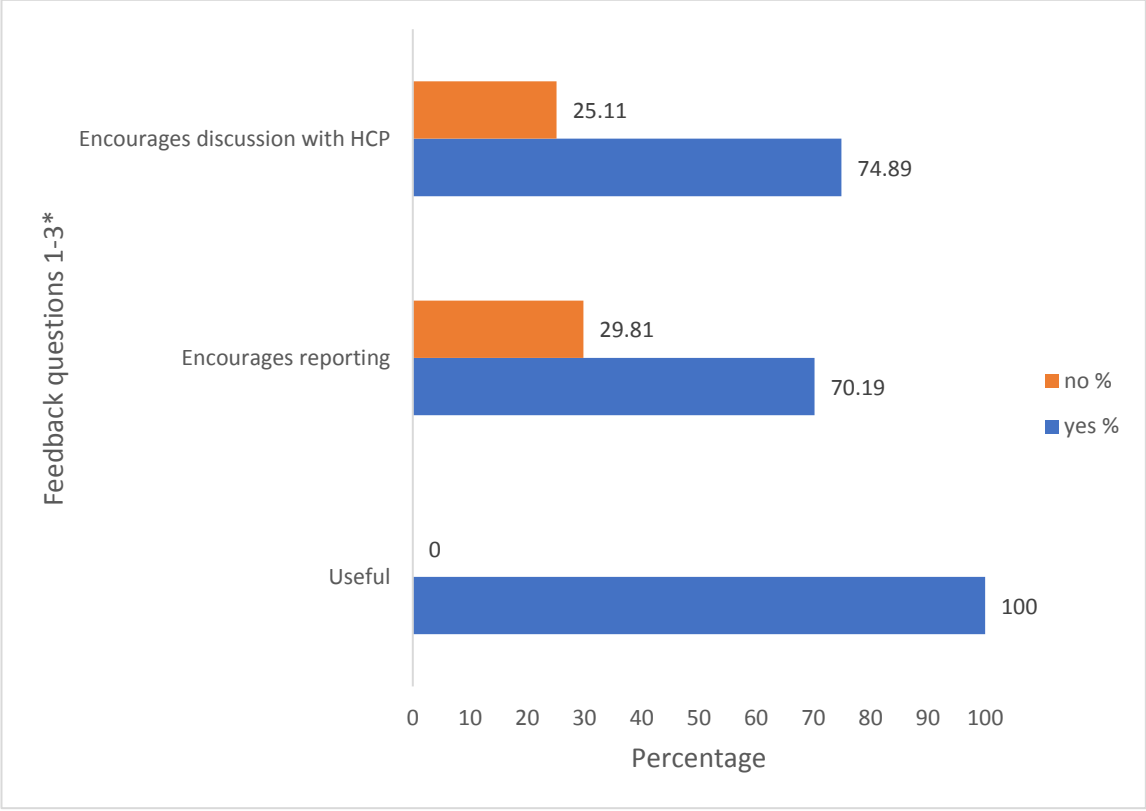
6.3.3.8 Feedback

Overall 240(91.3%) respondents agreed to provide feedback to the following questions:

1. Did you find the SE-PAST useful? (n=144)
2. Would it encourage you to report your SE to the relevant agencies? (n=208)
3. Would it encourage you to talk to a HCP about your SE? (n=227)

The 144 (100%) respondents who answered question 1 found the SE-PAST useful; 146 (70.19%) of those who answered question 2 would be encouraged to report their SE to relevant agencies and 170(74.89%) of those who answered question 3 would be motivated to discuss their SE with a HCP. See *Figure 6.5* below.

Analysis of the feedback provided by those who fully completed the 10 statements of the AT was also conducted. Overall 143 of these respondents provided feedback – a majority of those who completed the AT found the SE-PAST useful (96;67.1%); would be encouraged to report their SE (91;63.6%) and would be encouraged to discuss their SE with a HCP (105;73.4%).



**Number of respondents to feedback questions range from 144-227*

Figure 6.5: Feedback comments on SE-PAST provided by online respondents (n=240)

6.3 Discussion

SE experience of online respondents

Results suggested that there were some gender differences in SE experience. There were a majority of females amongst the online respondents and females reported greater impact on their QDL. Over 80% of females reported the impact of the SE as 'moderate' or 'severe'. These findings are supported by previous research which identified a higher risk of developing SE amongst females than males. The incidence of ADRs in females are between 50-75% more likely to occur than in males (D'Incau et al., 2014; Lucca et al., 2017; Montastruc et al., 2002; Zopf et al., 2009). Studies have also found that females generally reported greater impact on their QDL than males (Skilving et al., 2014). Most online respondents who accessed the AT were aged 61-70 years however there were twice as many females as males aged below 60 years. This higher proportion of younger females has implications as it could reflect the under-representation of the SE experience of younger males in SE research. Females are more likely to experience SE however research should be balanced and the experiences of younger males in particular are also necessary to create a comprehensive overview of SE.

As the age ranges of respondents increased this trend was reversed so there were more males – from 71 to over 80 years - than females. These results suggested that older males were more prone to engage in online health activities than younger males. This is supported by previous research into Internet use amongst older adults which found over half of these frequently used the Internet as a source of health information (Medloc et al., 2015; Tan et al., 2017; Van de Belt et al., 2013). Research suggests that tailored Internet health interventions such as the SE-PAST can be effective in reaching older adults and support adaptive health behaviours (Nes et al., 2013).

Knowledge about SE causality

The data suggested that causality knowledge amongst online respondents decreased as medicine use increased. Over 70% of respondents who took between one-four medicines could identify one causal medicine. However when medicine use increased to five-eight medicines the proportion who identified one causative medicine dropped to 18%. This could indicate that the inability to assign causality to one medicine among this high medicine use group is linked to positive health knowledge. This knowledge could include an awareness of interaction effects and good health literacy in general. Research has been conducted into the relationships between age, cognitive skills and health literacy (Berkman et al., 2011; Kiechle et al., 2013; Kobayashi et al., 2014). High medicine use does not automatically lead to negative outcomes and could have positive effects on health literacy.

An effective assessment of health literacy should include influencing factors such as medicine use. Additional research could determine the parameters of a beneficial range of medicine use for patients. Identifying when high medicine use becomes high medicine burden for patients could prove useful.

Most common drug categories

The data suggested that the most commonly reported causative medicines by online respondents were linked to the CNS, cardiovascular system and infection medicines. This finding is supported by previous research into YC reports which also found that the CNS was the most frequently reported category by patient reporters, followed by cardiovascular and anti-infection drugs (Avery et al.,2011).

The current study found an association between gender and the categories of the causative medicines. More females identified CNS medicines as their suspected causative medicine than males. Females were also more likely to report gastrointestinal medicines than males. Previous research supports these findings with females more likely to take medicines and a wider variety of medicines than males (Lucca et al., 2017; Rademaker, 2001). Females are therefore more likely to experience SE however there are fewer females than males that participate in phase 1 and 2 clinical trials. There is an awareness amongst researchers that the pharmacological status of females needs to be examined (Franconi et al., 2012; Pinnow et al., 2009). This current study built on previous research with hospital patients which found females using antibacterial and anti-inflammatory drugs experienced more ADRs than males (Zopf et al., 2009; Zopf et al., 2014). The present data were collected from a different population and provides a pattern of causative medicines in online female respondents.

SE-PAST validation

The numbers accessing the instrument were not maintained to completion and response rate was 36%. However this response rate reflects previous studies where the response rates for internet based health interventions ranged from 28% - 32% (Guttmacher et al., 2010; Wangberg et al., 2011).

The feedback from respondents about the SE-PAST was generally positive and the majority of respondents found it useful. Over 70% considered that it motivated them to report and/or discuss their SE with a HCP. These feedback comments suggest the SE-PAST has good face validity. The process of developing the instrument included a high degree of engagement by the supervisory team and an initial validation process. This ensured there was a high degree of inter-rater agreement that the SE-PAST had good content validity.

The online SE-PAST proved an effective recruitment tool as the required sample size was achieved within the estimated time period. As mentioned the overall response rate for the SE-PAST was 36% with varied completion rates across the sections. Section A was completed by 36.7% of respondents with a lower proportion - 24.4% - completing all of Section B. Previous research of completion rates for online surveys suggest the percentage of respondents who participate in full in these surveys have declined over time (Crawford et al., 2001; LaRose & Tsai, 2014). The variation in completion rates of the SE-PAST supports these research findings.

Exploratory factor analysis investigated the factor structure of the SE-PAST and the correlations between its variables. PCA identified the number of factors/components and which variables were linked to these factors/components. The three components that emerged during analysis represent stages in identifying SE: component 1 – sequencing; component 2 – alternative causes and component 3 – self-directed health behaviours. Variables were strongly loaded onto these components/factors. However, the Cronbach's alpha for the SE-PAST was below the 0.7 required for a reliable scale. This suggests problems with the tool's construct validity. This validity could be improved by rewriting items that have been revealed as inconsistent by the PCA. The validation of a measure is an iterative process and further work can be done to continue the development and increase the construct validity of the SE-PAST (Fallon et al., 2016).

6.5 Strengths and limitations

This phase of the study sought to develop and validate a novel assessment tool for the general public to use to assess suspected side effects. The online distribution of the SE-PAST was facilitated by patient support groups and organisations. This method of distribution aided the targeting of a specific population likely to have experienced SE. However online survey distribution can be limited by problems such as multiple responses or incomplete surveys. The SE-PAST was accessed by a large number of people - 761 persons - however not all these people completed the tool. A limitation of online distribution was the reduced opportunities to engage with the respondents, motivating them to progress through and complete the tool. Another limitation was the large gender bias amongst respondents - 69.9% of respondents were female. Information was gathered on causative medicines however these data are limited as it was not possible to validate the causality assigned to the individual experiences through review of medical records. However just 40% of respondents who accessed the questionnaire completed the SE-PAST. This was a considerable limitation as a large sample size of approximately 325

completed assessments were required to ensure robust predictive validity for the tool. This smaller than anticipated sample size may have contributed to the low Cronbach's alpha value for the overall scale. These limitations also extended to the PCA – the 183 responses subjected to PCA did not meet the minimum recommended sample size of 200 participants. However the requirement of 5-10 respondents per statement for effective PCA was met (Brace et al., 2016).

The structure of the questionnaire can be identified as a possible strength. Section A asked for background information from respondents before the assessment tool in Section B was presented. This design was intended to aid respondents to fully recall a particular event - their SE - before they assessed it using the AT. The SE-PAST was intended to be a balanced tool – simple yet useful. Its fundamental strength is that it has met some of those criteria and has the potential to be further developed and improved.

This phase of the study can be considered to have been of incremental value as it built upon previous research. Knowledge about the SE experience was increased and patterns of medicine use were identified. The objectives of this phase of the study were to develop and validate a novel assessment tool amongst people known to have experienced side effect(s). Further validation in a larger population was conducted by placing the assessment tool online through links to relevant websites. The following chapter - Chapter 7: YC reports - will continue to explore the experiences of people who experience SE and present the findings from analysis of the YC reports.

6.6 Summary

The SE-PAST was developed and made available online for people who suspected they had experienced SE. This assessment tool used a simple 10-item scale to assess the probability for respondents that the SE was caused by their medicines. In addition, information was collected on the impact of the SE, the suspected causative medicine(s), pre-existing medical conditions/allergies and respondents' demographic characteristics.

- Overall 761 respondents accessed the AT with 273 completed responses, a response rate of 36%. The majority were female and most online respondents were aged 61-70 years.
- Gender differences were evident in SE impact on QDL. Females were more likely than males to report the SE impact as severe ($p = 0.05$).
- Causality knowledge decreased as medicine use increased. Over 70% of respondents who took between two-four medicines could identify one causal medicine.

This ability to assign causality to one medicine drops to 18% in those taking five-eight medicines.

- The most commonly reported causative medicines were linked to the CNS, CV system, and infection medicines.
- SE-PAST has good face and content validity but poor construct validity.

CHAPTER 7: YELLOW CARD REPORTS

7.1 General Introduction

Chapter One described this PhD study as an investigation of how people cope with, identify and manage ADRs as well as the consequences of ADRs - in terms of future use of medicines and their impact on daily lives. The public have been permitted to report suspected ADRs directly to the YC Scheme since 2005. Previous research into patient Yellow Card (YC) reports was described in Chapter Two which suggested that analysis of the free-text responses and other content in a large unselected sample of patient YC reports was necessary. The analysis of existing YC data which was undertaken in this phase of the study can therefore be considered important and novel research. It will increase information about the content of the free-text data these reports include and could confirm its potential value in the field of ADR research.

7.2 Methodology

7.2.1 Introduction

Phase One of the study used a survey, distributed to patients using community pharmacies, to gather information in how people cope with and manage ADRs. Phase Two followed with in-depth interviews with a sample of survey respondents to explore their personal experiences of ADRs. These interviews informed the development of the SE-PAST in Phase Three of the study. This final phase of the study – Phase Four - involved the analysis of patient YC reports received by the MHRA with particular focus on the free-text responses. A comparison was made between YC reporters and the wider general public, through comparison of the YC reports and the Survey data collected in Phase One of the study. The results of this comparison will be discussed in Chapter 8: Discussion.

7.2.2 Aim & Objectives

The aim of this phase of the study was to explore the experiences of ADRs among the general public. The YC reports investigated were non-HCP reports from members of the general public who have reported their ADRs. The objectives were as follows:

- To investigate the free-text content of YC reports.
- To determine the different sources of information used by YC reporters in finding out about ADRs and their perceived value for this purpose.
- To assess the impact of ADRs on peoples' daily lives and the consequences of ADRs on medicines use in a large sample of YC reporters.

7.2.3 Ethical approval

This study phase received favourable ethical approval from the Independent Scientific Advisory Committee for MHRA database research (ISAC; Ref GENQ-00097958) (see Appendix 21). Accessing anonymised YC data was considered to be minimal risk. No additional information which could be considered sensitive was sought such as information about the reporter or the reporter's doctor. In addition, the Medway School of Pharmacy Research Ethics Committee was informed of the study and the ISAC approval.

7.2.4 Study Design

This study involved the analysis of YC reports received by the MHRA during a six-month period from July to December 2015. This time period was selected as it was estimated that approximately 3000 reports would be available. Vaccination reports were excluded from the data set as this sub-sample may contain confounding effects unique to vaccinations. These include confounding by indication and healthy vaccine biases which can influence vaccine effectiveness (Remschmidt et al., 2015; Jackson et al., 2013). Research has also identified associations between increased symptom/effects reports and un-informed choices to receive vaccination (Murphy et al., 2012). The remaining YC reports were subjected to qualitative and semi-quantitative analysis. Free-text comments and responses to closed questions were examined to explore the overall ADR experiences of YC reporters. The information contained in YC reports was used to address the study objectives - to establish how YC reporters identify and manage their ADR; to identify the information sources used by YC reporters as well as the impact of ADRs on their daily lives.

An application form for Permission for Access to Yellow Card data was submitted to the ISAC (See Appendix 22). A Category II request was made to the ISAC as all data fields listed in Section D.2 of the ISAC application form (except test results) were required for this study. This included both Category Ib data fields which excludes information that can identify patient/reporter and Category II data fields which are listed in *Table 7.1*. All

responses to open questions in Sections 1-3 of the YC form were also required. See *Table 7.1* which lists the requested data fields:

Table 7.1: Required data fields for YC analysis

Category Ib and Category II data fields	
Patient age (Ib)	Reaction outcomes (Ib)
Patient gender (Ib)	Reaction start/stop dates (Ib)
Suspect drug(s) (Ib)	Reaction details (Ib)
Dose of suspect drug(s) (Ib)	Past medical history (Ib)
Route of administration (Ib)	Previous drug history (II)
Drug start/stop dates (Ib)	Other: where drug(s) were obtained (II) Severity of the side effect (II)
Suspected adverse drug reaction(s) (Ib)	Other: Full free text comments provided in response to questions covering: symptoms and how it happened, more details of the outcome, any other relevant information (II)

Inclusion criteria for the YC data were as follows:

- YC reports from the general public
- YC reports generated from July – December 2015
- Category Ib & Category II data fields as specified in the ISAC application

MHRA staff extracted and cleaned the YC data, copied it into a series of Excel spreadsheets and provided these in a password protected CD format for analysis.

7.2.5 Data Analysis

All individual reports had a code number which was used to match up the data from the separate Excel spreadsheets, enabling a single dataset to be derived (by JK) which contained: reporter number, reporter status, age and gender of person experiencing ADR, reaction text, all additional free text responses and all drugs listed on the report. All individual drugs in each report were classified using BNF number 59 (March 2015) and the total number of different drugs and different products were calculated for each report (by RMR). This classification system was initially based on BNF chapter headings which were related to general body systems for example BNF Chapter 4 Central Nervous System. This

was then further broken down to show the class within the overall chapter for example BNF 4.2.1 Antipsychotic drugs. Similar mechanisms of action are usually present in drugs in a particular class and therefore these drugs may also have a similar side effect profile.

The data were transferred from Excel into SPSS and checked using simple frequencies to assess completeness of all data fields, remove any duplicate cases, detect and remove any errors and account for missing data. The cleaned data were subjected to qualitative and quantitative analysis. A significance value of $p \leq 0.05$ was set to control for Type 1 error. Content analysis was used to code the free-text responses and identify points of commonality, in addition to a semi-quantitative analysis of coded data. For the latter, free-text responses were analysed using Excel to develop a coding frame. This coding process involved the researcher and supervisor (JK) independently reading 100 different responses to identify and agree emergent themes. A further 100 responses were coded with these initial themes, to determine the need for further themes. Any differences were resolved by discussion. The final agreed themes were then used by the researcher to code the entire dataset. In addition, a subset of approximately 100 reports was selected to be coded independently by the two coders. This coding was then compared to ensure reliability in the coding process. This method has been used previously for quantitative analysis of free-text responses to questionnaires from YC reporters (Avery et al., 2011).

The data management program QSR NVivo 10 was used to further analyse the free-text responses from individual reporters qualitatively, combining them with responses to closed questions, to create narratives of individual experiences. Template analysis is a particular style of thematic analysis which focuses on hierarchical coding in a highly structured analysis process. The approach is underpinned by an established theory and permits the use of a priori themes. Unlike other thematic approaches to analysis coding levels are not ordered or set in advance. There is no distinction between descriptive and interpretive themes and no particular position assigned for each theme in the coding structure. Template analysis was chosen as an appropriate technique to examine the narratives as it was a flexible approach which used the richest data to generate themes and focused analysis on relevant aspects of the dataset (Braun & Clarke, 2006; Brooks et al., 2015). It has been used in previous studies to analyse a variety of datasets including open-ended questionnaire responses (Dornan et al., 2002; Kent, 2000). Template analysis of the narratives built on existing theory and enabled the identification of key themes relevant to the study.

This analysis involves five phases – familiarisation with the dataset; initial coding; identification and organising of themes into hierarchical clusters; reviewing and defining

themes (Braun & Clarke, 2006; Brooks et al., 2015). This is an iterative process generating a succession of templates which are refined before a final template is applied to the dataset. See *Figure 7.1* on the following page for a schematic of the coding process. The final template with the main and sub-themes is presented in the Results section which follows.

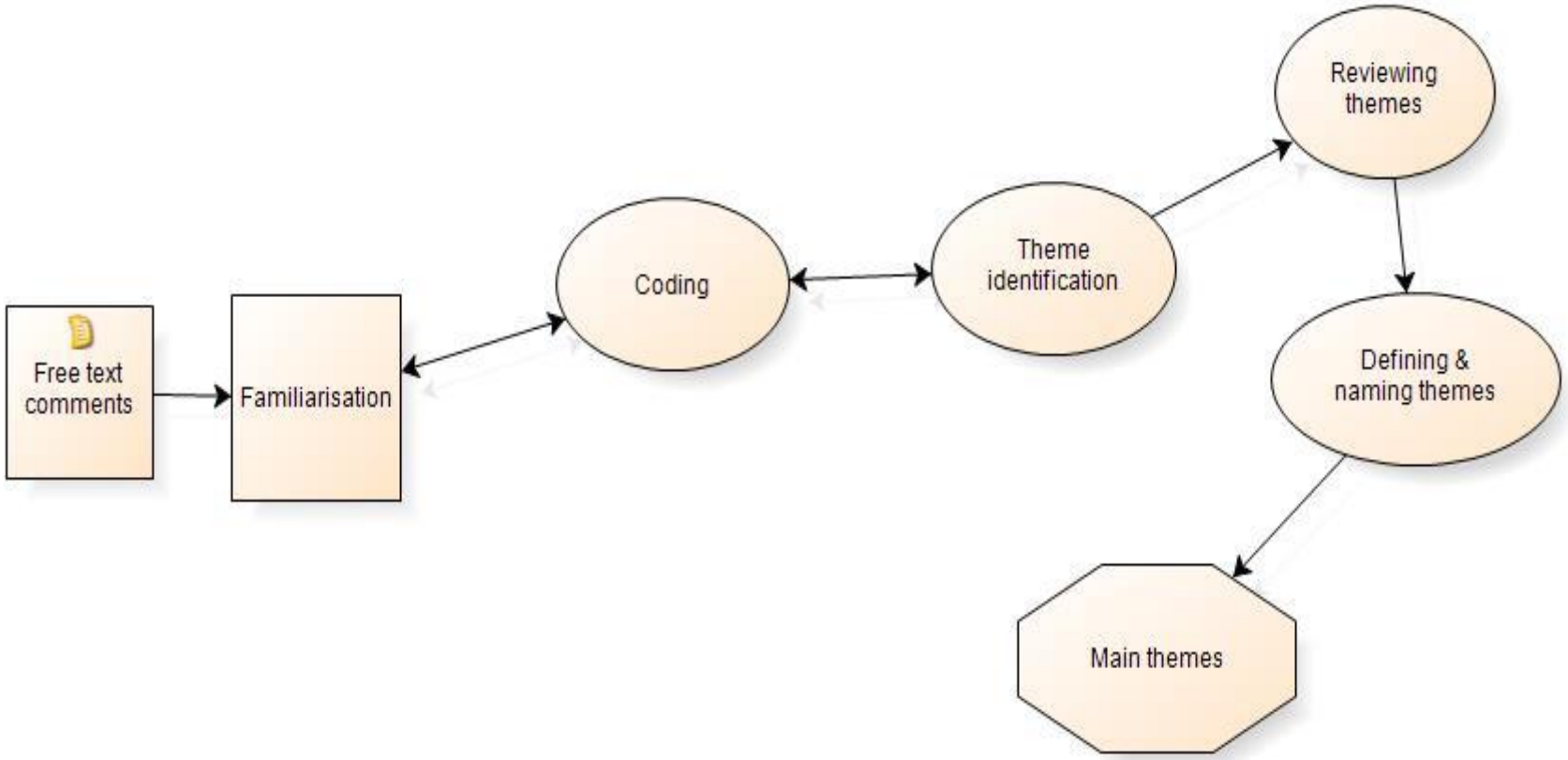


Figure 7.1: Thematic analysis coding process

The free-text responses were read to identify key narrative aspects, focusing on how the individual ADR experience was structured and actively reconstructed. The influence of social and environmental factors such as family, work, health care systems were also considered. The a priori themes focused on the processing of the ADR event and the multidimensional impact of ADRs. Narratives were selected according to the following criteria:

- reporter type
- reports coded with severe effects
- reports with elaborate narratives
- reports with a variety of drug classes

The quantitative data from responses to closed questions within the YC reports were analysed using SPSS (Windows Statistics 23). Descriptive statistics were generated covering suspect drug, indication, whether or not the drug was stopped after the ADR, reported seriousness and outcome, in relation to age and gender. For the purposes of analysis age was divided into eight categories:

1. Infants less than 1 year
2. 1-20 years
3. 21-40 years
4. 41-50 years
5. 51-60 years
6. 61-70 years
7. 71-80 years
8. Over 80 years

Reports were divided into the following three categories:

1. Patient reports/self-reports from those who had experienced the SE.
2. Carer reports submitted by carer on behalf of another person who had experienced the SE.
3. Parent reports submitted by parent on behalf of children who had experienced the SE.

The outcomes described in YC reports were divided into two categories:

1. SE outcomes.
2. Reaction outcomes.

SE outcomes were the consequences for patients of the reported SE. These were labelled as follows: incapacity, hospitalisation and/or life-threatening results.

Reaction outcomes were the assignment of categories to the current condition of the patient in relation to the SE. There were labelled as follows: effects were recovered/resolved; effects were not recovered/resolved; effects were recovering/resolving; effects were recovered/resolved with sequelae or effect outcomes were unknown.

Severity levels were divided into three categories:

1. mild symptoms/effects.
2. moderate symptoms/effects.
3. severe symptoms/effects.

Reports which used the terms ‘mild’, ‘moderate’ or ‘severe’ in their free text comments to describe symptoms/effects were flagged as self-identifying/assessing reports. These reports were then coded according to these terms. Otherwise severity levels were assessed according to the following criteria:

- the short term impact of the effects
- the long term consequences of the effects
- the number and type of effects
- the number and type of HCP interactions.

The impact of SE were divided into three categories with overlap between these classifications:

1. physical impact.
2. psychological impact.
3. social impacts.

Social impacts were assessed according to the following criteria:

- the quality of daily life was affected
- resulted in negative/avoidant social behaviours
- the result of a combination of physical and psychological impacts.

Multidimensional chi-squared, Mann-Whitney and Kruskal-Wallis tests were used to investigate associations between the following:

Box 7.1: List of associations between variables investigated in analysis of YC data

Reported demographics by gender and type of reporter
Gender and type of reporter by method of reporting and reported severity of SE
Gender and type of reporter by HCP confirmation of effects
Gender and type of reporter by SE outcomes
Gender and type of reporter by reaction outcomes
Number of drugs by gender and age
Number of drugs by reported severity and outcomes
BNF classes by gender and age
BNF classes by reported severity and outcomes

7.3 Results

7.3.1 YC sample

Reports concerning vaccinations (775) were excluded from the initial 3060 reports provided by the MHRA. Therefore, 2285 YC reports were analysed.

The results are presented in three sections: Description of YC reports; SE Causality and Managing SE.

7.3.2 Description of the YC reports

This analysis investigated reports from those who had experienced the SE - 'patient' reports/self-reports - and those who submitted the report on behalf of another individual - 'carer' and 'parent' reports. Overall 8792 reactions were reported ranging from 1-52 effects (M=3.9; SD±3.63). See Section 7.3.3 SE causality for details of these reactions/effects.

Age and gender

The reported median age of patients who experienced SE was 43 years (range 0-91). Age was not normally distributed, with skewness of -0.13 (*SE* = 0.05) and kurtosis of -0.74 (*SE* = 0.11). The majority of reports were for females (1522; 67%) compared to 752 (33%) for males. The highest proportions of reports were for those aged 21-40 years (675; 31%), followed by 368 (17%) aged 61-70 years.

There was a significant difference between gender and reported age of those who experienced SE. More younger females and older males were reported to have experienced SE. The highest proportion of these females (525; 36%) were 21-40 years while the highest proportion of males (158; 22%) were aged 61-70 years. A Mann-Whitney test indicated a significant relationship between gender and age (years): U = 393615, N_1=706, N_2=1446, p <0.001, two-tailed. The Cohen's effect size value (d = 0.4) suggested a small to moderate practical significance. See *Table 7.2.*

Type of report and reporting methods

A majority of the 2285 reports were 'patient' reports (2096; 92%), with 99 (4%) 'carer' and 90 (4%) 'parent' reports. As can be seen from *Table 7.3* the majority of SE experienced by both males (656; 87%) and females (1433; 94%) were reported via patient/self-reports*:* X^2 (2, N = 2274) = 32.56, p <0.001 with a weak association Φ = 0.12, gender accounting for 1% of the variation in reporter type. The majority of reports submitted for all age ranges apart from infants were patient reports. The highest proportion of reports for those aged 41-50 (330; 98%) and 51-60 years (355; 98%) were patient reports. As expected all reports for infants (27; 100%) and many of those aged 1-20 years (53; 36%) were parent reports. The highest proportions of carer reports were for those aged over 80 (18; 29%) followed by those aged 71-80 (17; 10%). A Kruskall-Wallis test indicated a significant relationship between reporter type and age (years): X^2 (2, N = 2159) = 263.16, p <0.001. The Cohen's effect size value (d = 0.7) suggested a large significance.

The Internet was the most common method of reporting for all reporters - 1877 'patient'/self-reporters (90%); 83 'carers' (84%) and 81 'parents' (90%). The Internet was also the most frequently used reporting method across both gender and age categories. The majority of SE reports for both males 643 (86%) and females 1388 (91%) were submitted via the Internet: X^2 (4, N = 2244) = 18.9, p <0.001 with a weak association Φ = 0.1, gender accounting for 1% of the variation in reporting methods. Over 90% of reports submitted for five of the eight age categories - 1-20; 21-40; 41-50; 51-60 and 61-70 years – were Internet reports. The lowest proportion of Internet reports were submitted for those over 80 (41; 66%).

Reported severity and HCP confirmation of SE

Severe reactions/effects were reported in 1621 (71%) reports irrespective of reporter type - patient (1481; 71%), carer (72; 73%) and parent (68; 76%) reports. The majority of SE were not confirmed with a HCP (2249; 98%). Overall SE outcomes in YC reports were as follows: incapacity (106; 5%), hospitalisation (185; 8%) and life-threatening outcomes (265; 12%). It can be seen from the data in *Table 7.3* that there was a relationship between reporter type and two SE outcomes - hospitalisation and life-threatening results. The majority of hospitalisation outcomes were reported by parents (19; 21%) and carers (18; 18%) with proportionately fewer patients (148; 7%) reporting this consequence: X^2 (2, N = 2285) = 37.04, p<0.001. There was a weak association: Φ = 0.13, thus reporter type accounted for 2% of the variation in this outcome. The majority of life-threatening results were reported by carers (13; 13%) with 8 parents (9%) and 85 patients (4%) reporting this consequence: X^2 (2, N = 2285) = 22.43, p<0.001. There was a weak association: Φ = 0.1, thus reporter type accounted for just 1% of the variation in life threatening outcomes.

7.3.2.1 Associations between Gender and age, with SE severity and SE outcomes.

Gender against SE severity and outcomes

Overall the majority of reports for both females (1113; 73%) and males (501; 67%) reported serious effects. Analysis indicated an association between gender and reported SE severity with severe/serious SE reported for more females than males. These assessments of severity were not linked to SE outcomes as a majority of both males and females experienced no incapacity (652; 87% and 1357; 89% respectively) or hospitalisation (684; 91% and 1405; 92% respectively). The relationship between gender and SE severity was significant: X^2 (1, N = 2274) = 10.34, p=0.001 with a weak association: Φ = -0.07, thus gender accounted for 0.5% of the variation in SE severity.

It can be seen from the data in *Table 7.2* that there was a relationship between gender and life-threatening outcomes. A higher proportion of males (49; 7%) than females (55; 4%) experienced life-threatening effects; X^2 (1, N = 2274) = 9.7, p=0.002 with a weak association: Φ = 0.07, thus gender accounted for 0.5% of the variation in life threatening outcomes. Although not statistically significant, there

were also slightly more males who experienced hospitalisation and disability/incapacity.

Age against SE severity and outcomes

A pattern of reported severity was evident across the older age categories with severe effects more likely to be reported for these categories. A majority of the following five age categories were reported to have experienced severe effects: 207 (68%) aged 41-50; 227 (70%) in those 51-60; increasing to 245 (73%) of those aged 61-70; 128 (72%) of those between 71-80 years and 37 (73%) aged over 80 years. A Mann-Whitney test indicated a significant relationship between reporter severity and age (years): U=405010.5, N_1=1563, N_2=593, p <0.001, two-tailed. The Cohen's effect size value (d = 0.2) suggested low practical significance. See *Table 7.4.*

Analysis indicated that 11947 reaction outcomes were linked to 2285 reports, with older patients more likely to have resolved reactions. The highest proportion of resolved effects occurred in those aged 51-60 (64; 18%) and over 80 years (15; 24%). The highest proportion of unresolved reactions occurred in 61-70 years (172; 47%). Similar proportions of reactions had unknown outcomes for infants and those over 80 – 6(22%) and 14(23%) respectively. See *Table 7.4.*

Table 7.2: Gender by reported characteristics and outcomes

Reported characteristics	Gender freq (%) n=2285		p-value
	Male	Female	
Age (yrs)			≤0.001*[1]
Infants < 1	17(2.4)	10(0.7)	
1-20	45(6.4)	102(7.1)	
21-40	145(20.5)	525(36.3)	
41-50	92(13)	244(16.9)	
51-60	111(15.7)	252(17.4)	
61-70	158(22.4)	210(14.5)	
71-80	97(13.7)	82(5.7)	
Over 80	41(5.8)	21(1.5)	
Method of reporting			0.001*
Internet	643(85.5)	1388(91.2)	
Telephone	32(4.3)	48(3.2)	
Paper	69(9.2)	75(4.9)	
YC leaflet	5(0.7)	8(0.5)	
Other	3(0.4)	3(0.2)	
Reported SE severity			0.001*
Considered serious	501(66.6)	1113(73.1)	
Not considered serious	251(33.4)	409(26.9)	
Disability/Incapacity			0.09
Yes	100(13.3)	165(10.8)	
No	652(86.7)	1357(89.2)	
Hospitalised			0.27
Yes	68(9.0)	117(7.7)	
No	684(91.0)	1405(92.3)	
Life-threatening			0.002*
Yes	49(6.5)	55(3.6)	
No	703(93.5)	1467(96.4)	
HCP confirmed			0.38
Yes	14(1.9)	21(1.4)	
No	738(98.1)	1501(98.6)	

**Denotes significance at 0.05 probability level;*

[1]*Kruskal-Wallis test*

Table 7.3: Reporter type by reported characteristics and outcomes

Reported characteristics &outcomes	**Reporter type f (%) n=2285**			**p-value**
	Patient	*Carer*	*Parent*	
Age categories				≤0.001*[1]
Infants < 1	0	0	27(100)	
1-20	92(62.6)	2(1.4)	53(36.1)	
21-40	649(96.1)	19(2.8)	7(1.0)	
41-50	330(97.9)	5(1.5)	2(0.6)	
51-60	355(97.5)	9(2.5)	0	
61-70	50(95.1)	18(4.9)	0	
71-80	162(90.5)	17(9.5)	0	
Over 80	44(71.0)	18(29.0)	0	
Gender				≤0.001*
Male	656(87.3)	48(6.4)	47(6.3)	
Female	1433(94.1)	48(3.1)	42(2.8)	
Method of reporting				0.42
Internet	1877(89.6)	83(83.8)	81(90)	
Telephone	70(3.3)	7(7.1)	3(3.3)	
Paper	131(6.3)	8(8.1)	6(6.7)	
YC leaflet	13(0.6)	0	0	
Other	5(0.2)	1(1.0)	0	
Reported SE severity				0.56
Considered serious	1481(70.7)	72(72.7)	68(75.6)	
Not considered serious	615(29.3)	27(27.3)	22(24.4)	
Disability/Incapacity				0.17
Yes	237(11.3)	12(12.1)	16(17.8)	
No	1859(88.7)	87(87.9)	74(82.2)	
Hospitalised				≤0.001*
Yes	148(7.1)	18(18.2)	19(21.1)	
No	1948(92.9)	81(81.8)	71(78.9)	
Life-threatening				≤0.001*
Yes	85(4.1)	13(13.1)	8(8.9)	
No	2011(95.9)	86(86.9)	82(91.1)	
HCP confirmed				0.8
Yes	32(1.5)	2(2.0)	2(2.2)	
No	2064(98.5)	97(98)	88(97.8)	

**Denotes significance at 0.05 probability level*

[1]*Kruskal-Wallis test*

Table 7.4: SE severity and reaction outcomes by age

	Reported severity f (%) n=2285		**p-value**	**Reaction outcomes n=11947[#]**				
	Serious	*Not serious*		*Resolved*	*Not resolved*	*Resolving*	*Rseq*	*Unknown*
Age (years)			≤0.001*[1]					
Infant< 1	123(74.1)	43(25.9)		4(14.8)	12(44.4)	2(7.4)	3(11.1)	6(22.2)
1-20	267(72.6)	101(27.4)		23(15.6)	62(42.2)	28(19)	13(8.8)	21(14.3)
21-40	387(69.2)	172(30.8)		115(17.0)	312(46.2)	109(16.1)	29(4.3)	110(16.3)
41-50	207(67.6)	99(32.4)		54(16.0)	152(45.1)	60(17.8)	11(3.3)	60(17.8)
51-60	227(70.1)	97(29.9)		64(17.6)	148(40.7)	68(18.7)	26(7.1)	58(15.9)
61-70	245(73.4)	89(26.6)		63(17.1)	172(46.7)	50(13.6)	19(5.2)	64(17.4)
71-80	128(72.3)	49(27.7)		31(17.3)	80(44.7)	25(14.0)	13(7.3)	30(16.8)
Over 80	37(72.5)	14(27.5)		15(24.2)	20(32.3)	10(16.1)	3(4.8)	14(22.6)

[#]*Multiple effects*

Rseq=resolved with sequelae

**Denotes significance at 0.05 probability level*

[1]*Mann-Whitney test*

7.3.2.2 Associations between reported severity by SE outcomes and reaction outcomes

There were relationships between the reported severity of effects and the three SE outcomes of incapacity, hospitalisation and life-threatening results.

Reported severity by SE and reaction outcomes

The data revealed that many effects which did not result in negative outcomes were still reported as severe. The majority of reported severe effects did not lead to incapacity (1356; 84%); hospitalisation (1436; 89%) or life- threatening outcomes (1515; 94%). However, the reports which did describe these SE outcomes always reported effects as severe effects. The relationship between reported severity and incapacity was significant with a moderate association: X^2 (1, N=2285) = 122.8, p <0.001: Φ = -0.23, severity accounted for 5% of the variation in incapacity.

Analysis indicated the relationship between reported severity and hospitalisation outcomes was significant with a moderate association: X^2 (1, N=2285) = 82.46, p <0.001: Φ = -0.2, severity accounted for 4% of the variation in hospitalisation outcomes.

The association between reported severity and life threatening outcomes was also found to be significant: X^2 (1, N=2285) = 45.5, p <0.001: Φ = -0.1, however severity accounted for just 1% of the variation in life threatening outcomes

Overall reported severity was also not influenced by reaction outcomes. Unresolved reactions did not result in increased reporting of severity. Similar proportions of resolved (272; 70%), resolving (276; 74%) and unresolved (739; 73%) reactions were all linked to severe/serious effects. (See *Figure 7.2* on the following page).

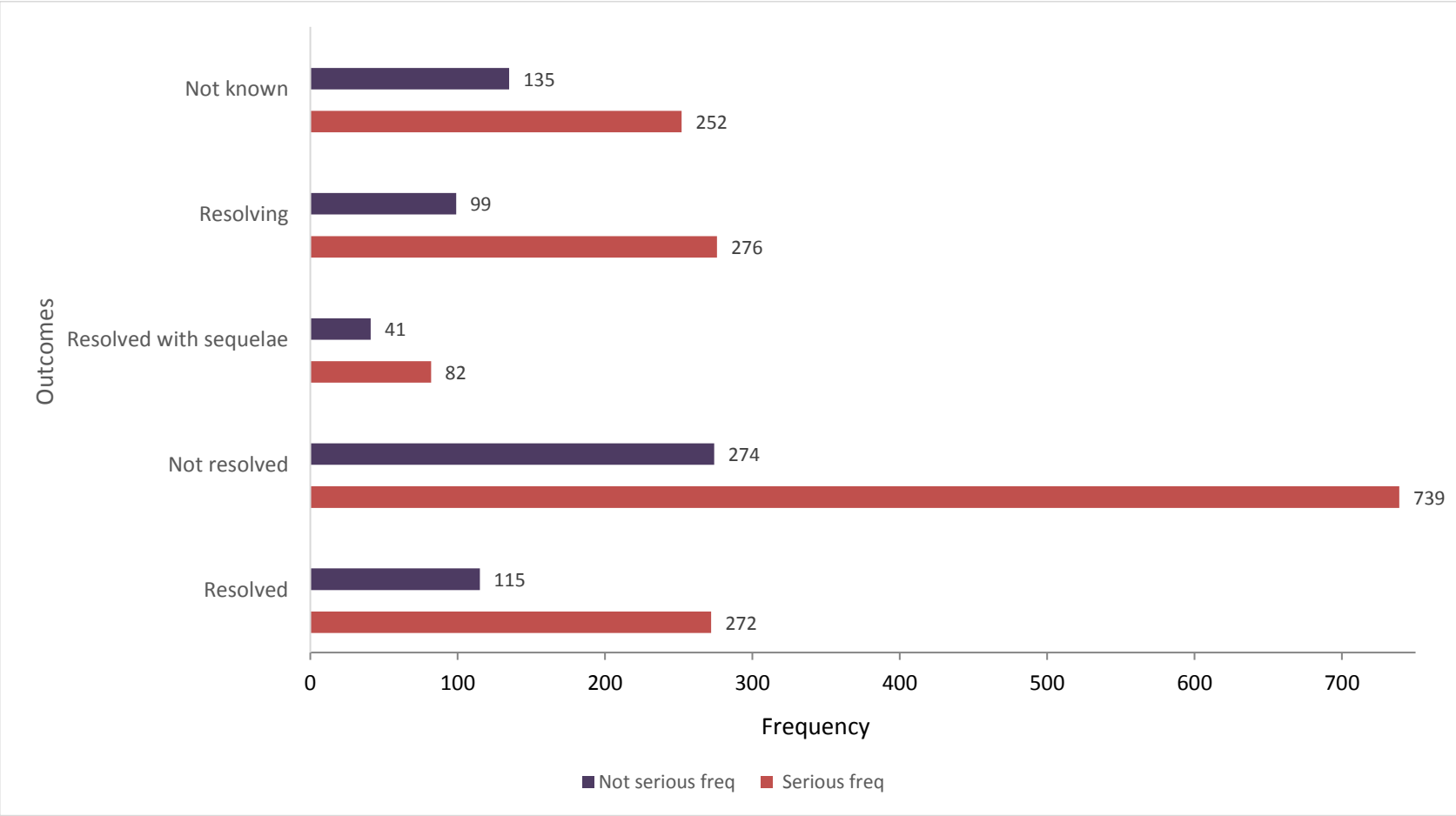


Figure 7.2: Associations between reported severity and reaction outcomes

7.3.2.4 Section summary

- Patient reports are the most common reporter type.
- The Internet is the most common method of reporting.
- SE were more frequently reported for females and older patients.
- More severe SE were reported for females and older patients.
- Reported severity of SE was not influenced by SE outcomes or reaction outcomes.

7.3.3 SE causality

7.3.3.1 Number of reported drugs and effects

Overall, within the 2285 YC reports, 2472 causative drugs were reported and linked to 8,792 SE. The number of reported drugs taken by individual patients ranged from 1 to 12; *M* = 1.08 (*SD* ± 0.45) and mode = 1. As *Table 7.5* below shows the vast majority of reports cited one drug (2168; 95%) with 79 (4%) citing two drugs.

Table 7.5: Number of reported drugs in YC reports (n=2472)

No of drugs taken	Frequency	%
1	2168	94.88
2	79	3.46
3	21	0.92
4	11	0.48
5	3	0.13
6	2	0.09
12	1	0.04

The number of reported effects per YC ranged from 1 to 52 effects (*M* = 3.9, *SD* ± 3.63). The most common number of effects reported was one effect (594; 26%) followed by 456 (20%) who reported two effects. See *Table 7.6* below.

The most frequently reported effect was pain (1060; 46%) followed by abdominal discomfort (467; 20%) headache (389; 17%) and fatigue (326; 14%). See *Figure 7.3*.

Table 7.6: Number of reported effects in YC reports (n=8792)

No of effects	Frequency	%
1	594	26.00
2	456	19.96
3	329	14.40
4	243	10.63
5	178	7.79
6	127	5.56
7	97	4.25
8	76	3.33
9	42	1.84
10	44	1.93
>10	99	4.33

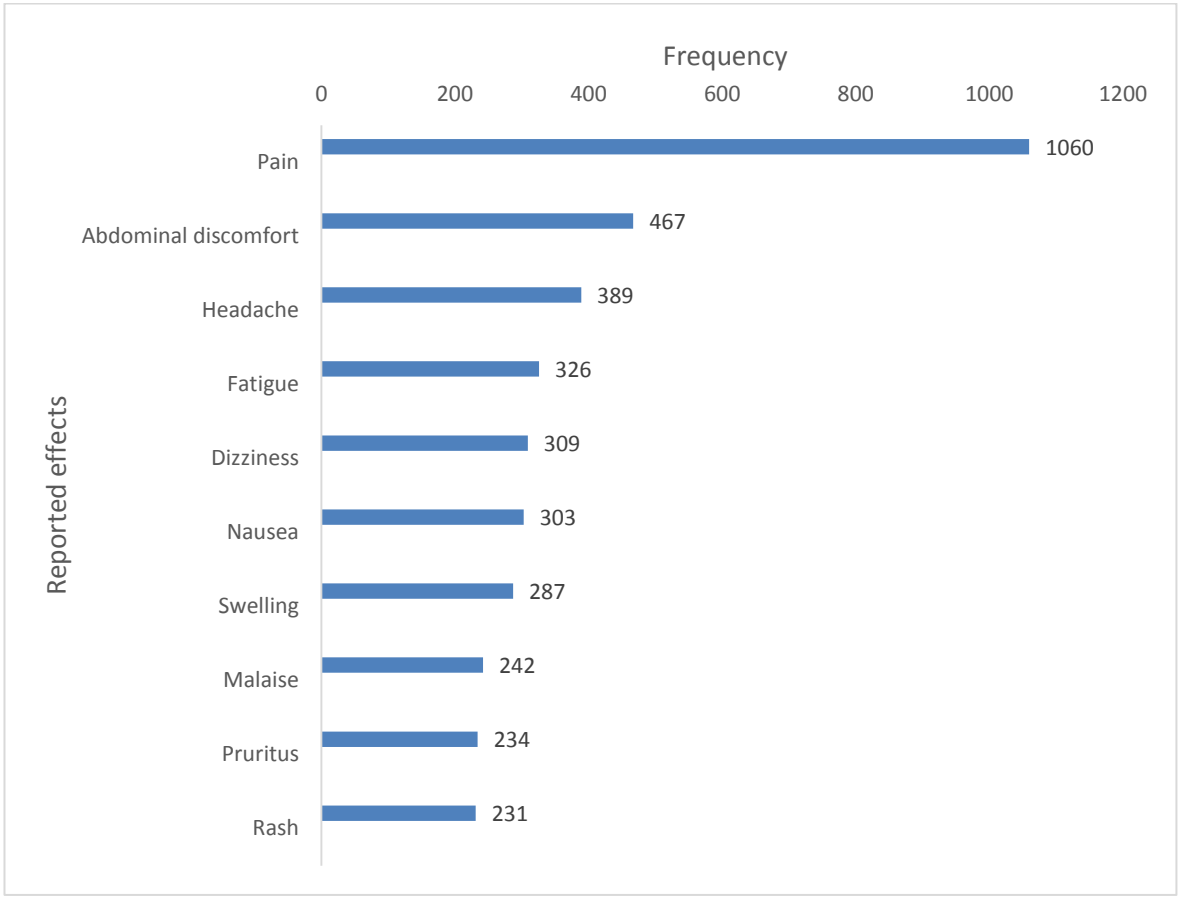
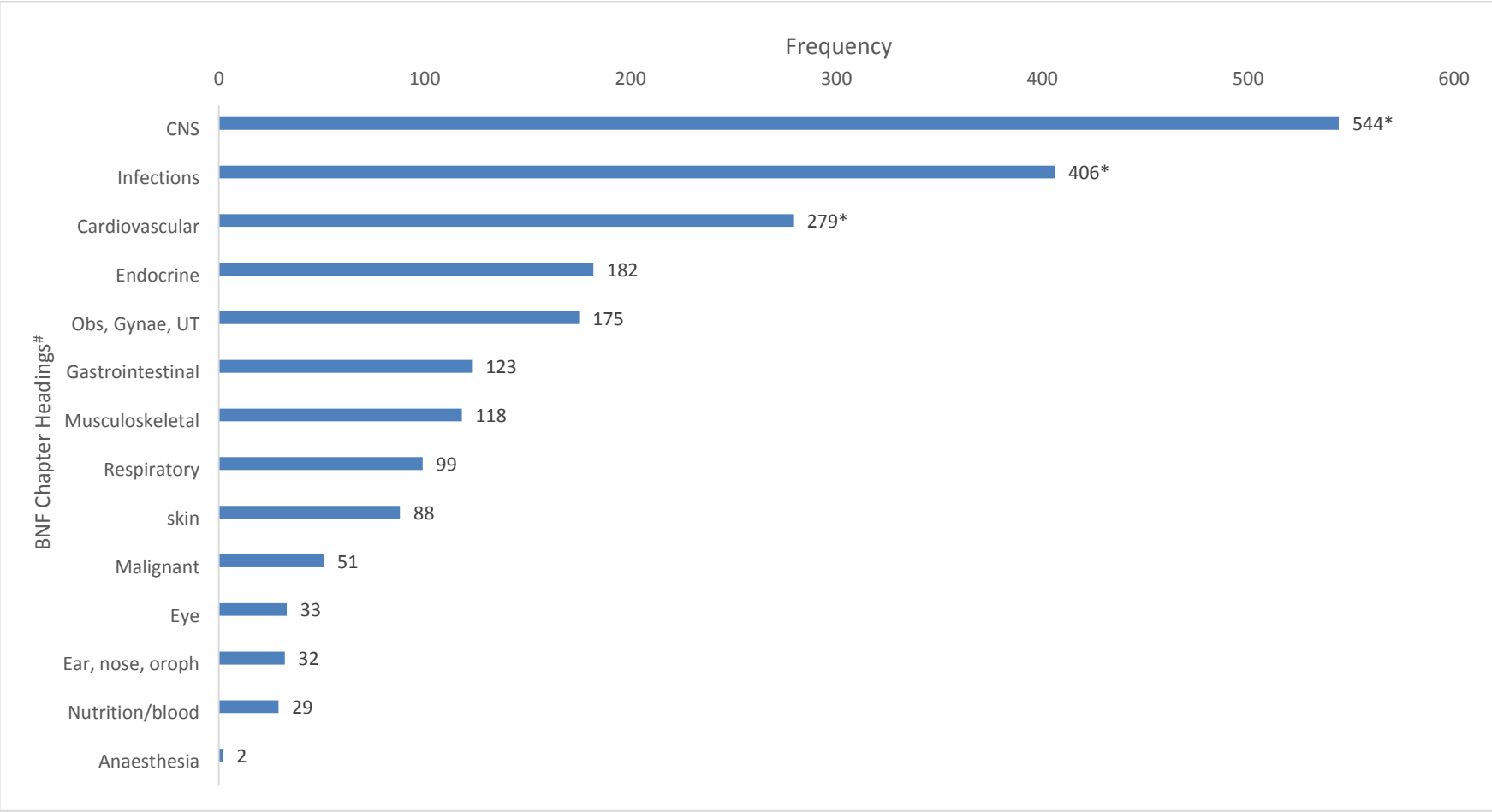


Figure 7.3: Top 10 reported effects (n=8792)

7.3.3.2 Reported causative drugs

Initial classification of the 3060 reports found that 2936 involved drugs which could be classified according to the British National Formulary (BNF), however there were also 124 reports which involved drugs/products which constituted discontinued/unclassified items. From 2285 reports, 2472 causative drugs were reported, with the highest proportion of drugs linked to the central nervous system (CNS) (544; 22%), infections (406;16.42%) and cardiovascular system (CVS) drugs (279;11.29%).

See on the following page *Figure 7.4.*



#Excludes Vaccinations/Immunological products;

**Indicates highest proportions of drugs*

Figure 7.4: Reported drugs in YC reports by BNF categories (n=2472)

The 20 most frequently reported individual drugs are presented on the following page in *Figure 7.5.* The top five drugs were as follows:

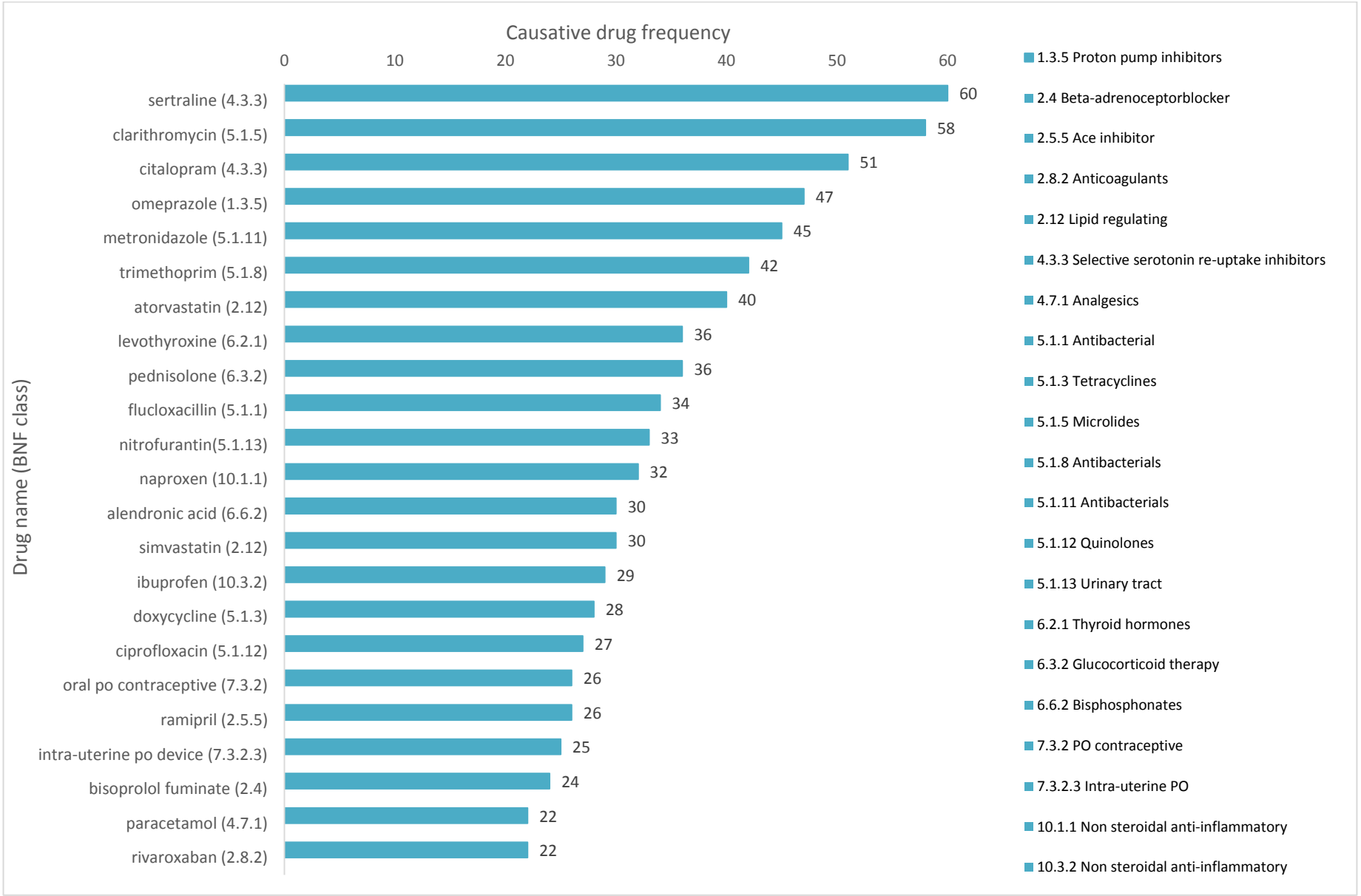
Sertaline (60; 2.43%) – BNF 4.3 Selective serotonin re-uptake inhibitors

Clarithroymcin (58; 2.35%) – BNF 5.1 Antibacterial drugs

Citalopram (51; 2.06%) - BNF 4.3 Selective serotonin re-uptake inhibitors

Omeprazole (47; 1.9%) - BNF 1.3 Proton pump inhibitors

Metronidazole (45; 1.8%) - BNF 5.1 Antibacterial drugs.



Po=progesterone only; (BNF classification number)

Figure 7.5: 20 most frequently reported drugs in YC reports (n=2472)

7.3.3.3 Associations between number of drugs and gender, age, reported severity, and outcomes

Analysis was conducted to identify relationships between age, gender, reported SE severity and the number of drugs reported to have caused the SE.

Number of drugs by gender and age, reported severity

The majority of reports for both males (704; 94%) and females (1453; 96%) related to taking one drug. The data revealed a similar pattern across the eight age categories with a majority – over 85% - reporting one causative drug. As *Table 7.7* shows the seriousness of SE did not vary with number of drugs. There were similar proportions of severe effects linked to one drug (1539; 71%); two (66; 70%) and three drugs (15; 71%).

Table 7.7: Number of drugs in YC reports by gender and age

	Number of reported drugs f (%) n=2472							p-value
	One drug	**2 drugs**	**3 drugs**	**4 drugs**	**5 drugs**	**6 drugs**	**12 drugs**	
Gender								0.37
Male	704(93.6)	33(4.4)	10(1.3)	4(0.5)	1(0.1)	0	0	
Female	1453(95.5)	46(3.0)	11(0.7)	7(0.5)	2(0.1)	2(0.1)	1(0.1)	
Age (categories)								0.37
Infants < 1	24(88.9)	3(11.1)	0	0	0	0	0	
1-20	138(93.9)	6(1.4)	1(0.7)	1(0.7)	0	1(0.7)	0	
21-40	645(95.6)	22(3.3)	2(0.3)	2(0.3)	1(0.1)	0	0	
41-50	323(95.8)	11(3.3)	0	0	1(0.3)	0	1(0.3)	
51-60	342(94)	13(3.6)	3(0.8)	3(0.8)	1(0.3)	0	0	
61-70	347(94.3)	15(4.1)	1(0.3)	1(0.3)	0	0	0	
71-80	168(93.9)	6(3.4)	2(1.1)	2(2.1)	0	1(0.6)	0	
Over 80	58(93.5)	2(3.2)	1(1.6)	1(1.6)	0	0	0	
Reported SE severity								0.98
Considered serious	1539(71)	66(69.6)	15(71.4)	10(63.6)	3(66.7)	0	0	
Not considered serious	629(29)	24(30.4)	6(28.6)	4(36.4)	1(33.3)	0	0	
Disability/Incapacity								0.86
Yes	252(95.1)	11 (4.2)	1(0.4)	1(0.4)	0	0	0	
No	1916(94.9)	68(3.4)	20 (1)	10(0.5)	3(0.1)	2(0.1)	1(0)	
Hospitalised								0.25
Yes	174(94.1)	6(6.3)	2(1.4)	1(0.5)	1(0.5)	1(0.5)	0	
No	1994(95.0)	73(3.5)	19(0.9)	10(0.5)	2(0.1)	1(0.5)	1(0.5)	
Life-threatening								0.1
Yes	104(98.1)	1(0.9)	0	0	0	1(0.9)	0	
No	2064(94.7)	78(3.6)	21(1.0)	11(0.5)	3(0.1)	1(0.5)	1(0)	

7.3.3.4 Associations between BNF categories and gender, age, reported severity, and outcomes

Analysis was conducted to identify relationships between BNF chapter categories and gender, age, reported severity and outcomes.

BNF categories by gender and age

The highest proportions of reports for both males (175; 26%) and females (361; 25%) were for CNS drugs. A Mann-Whitney test indicated a significant relationship between BNF categories and gender: $U = 435199.5$, $N_1=685$, $N_2=1444$, $p < 0.001$, two-tailed. The Cohen's effect size value ($d = 0.2$) suggested a small practical significance. See *Figure 7.6.* Similar proportions of CNS drugs were evident across age categories 1-20 (35;26%); those aged 21-40 (223; 35%) those aged 41-50 (86; 28%). The proportions of CVS drugs, in contrast, increased with age: 21-40 years (21;3%); 51-60 years (62;18%) to those aged over 80 (16;27%) A Kruskall-Wallis test indicated a significant relationship between BNF categories and age (years): X^2 (13, $N = 2013$) = 252.376, $p < 0.001$. The Cohen's effect size value ($d = 0.7$) suggested a moderate to high practical significance.

Table 7.8: BNF categories of reported drugs in YC reports by age

BNF categories[#]

Age categories	**CNS**	**CVS**
1-20	35(25.7)	3(2.2)
21-40	223(35.2)	21(3.3)
41-50	86(27.7)	26(8.4)
51-60	70(20.3)	62(18.0)
61-70	47(13.8)	87(25.5)
71-80	34(20.7)	42(25.6)
>80	8(13.6)	16(27.1)

 # Most frequently occurring categories in age categories

BNF categories and reported severity and outcomes

Similar proportions of CNS and CVS drugs were linked to serious effects. There were 539 effects involving CNS drugs and 412 of these reported serious effects (412;76%). Similar proportions of serious effects were reported for CV drugs

(205;74%). There were 407 reports of serious effects for infections however a lower proportion of these reports were linked to serious effects (280;69%). A Kruskall-Wallis test indicated a significant relationship between BNF categories and severity: X^2 (14, N = 2127) = 46.548, p <0.001. Cohen's effect size value (d = 0.3) suggested a small to moderate practical significance. See *Figure 7.7.*

The highest proportions of incapacity were reported for CNS drugs (81; 15%) and CVS (36; 13%). Similar proportions of GI (12; 9.8%), CNS (51; 9.5%) and CVS drugs (26; 9.4%) resulted in hospitalisation. The most life-threatening events occurred with CNS drugs (39; 7.3%). Kruskall-Wallis tests indicated significant relationships between BNF categories and all the following SE outcomes. Incapacity: X^2 (14, N = 2127) = 27.784, p =0.015; cohen's effect size value (d = 0.2) suggested low practical significance; hospitalisation: X^2 (14, N = 2127) = 24.965, p=0.035, with a value for cohen's effect size (d = 0.2) of low practical significance; and life-threatening events: X^2 (14, N = 2127) = 41.338, p <0.001, with cohen's effect size value (d = 0.3) of small to moderate practical significance. See *Figure 7.8.*

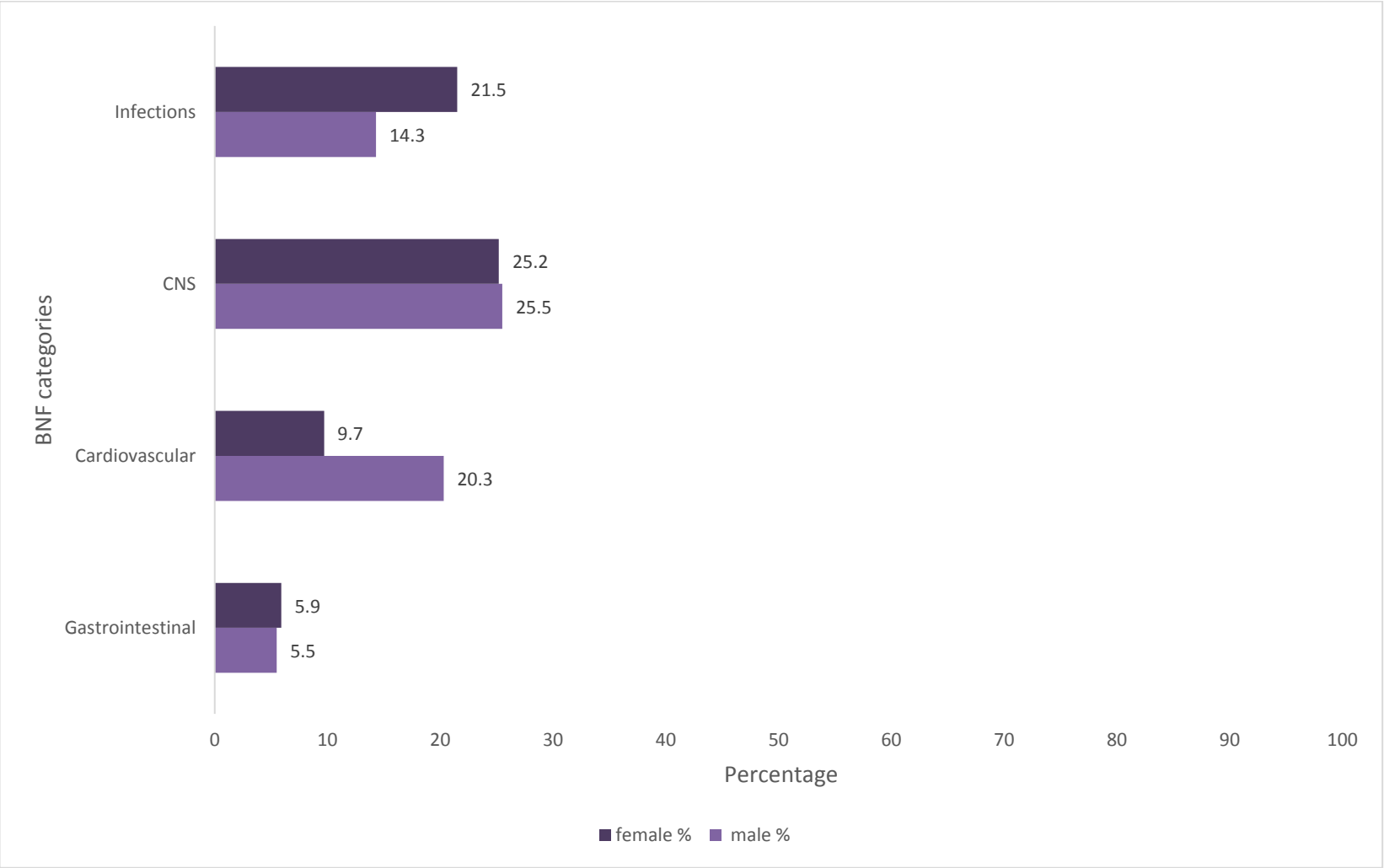


Figure 7.6: Most frequently reported BNF categories by gender

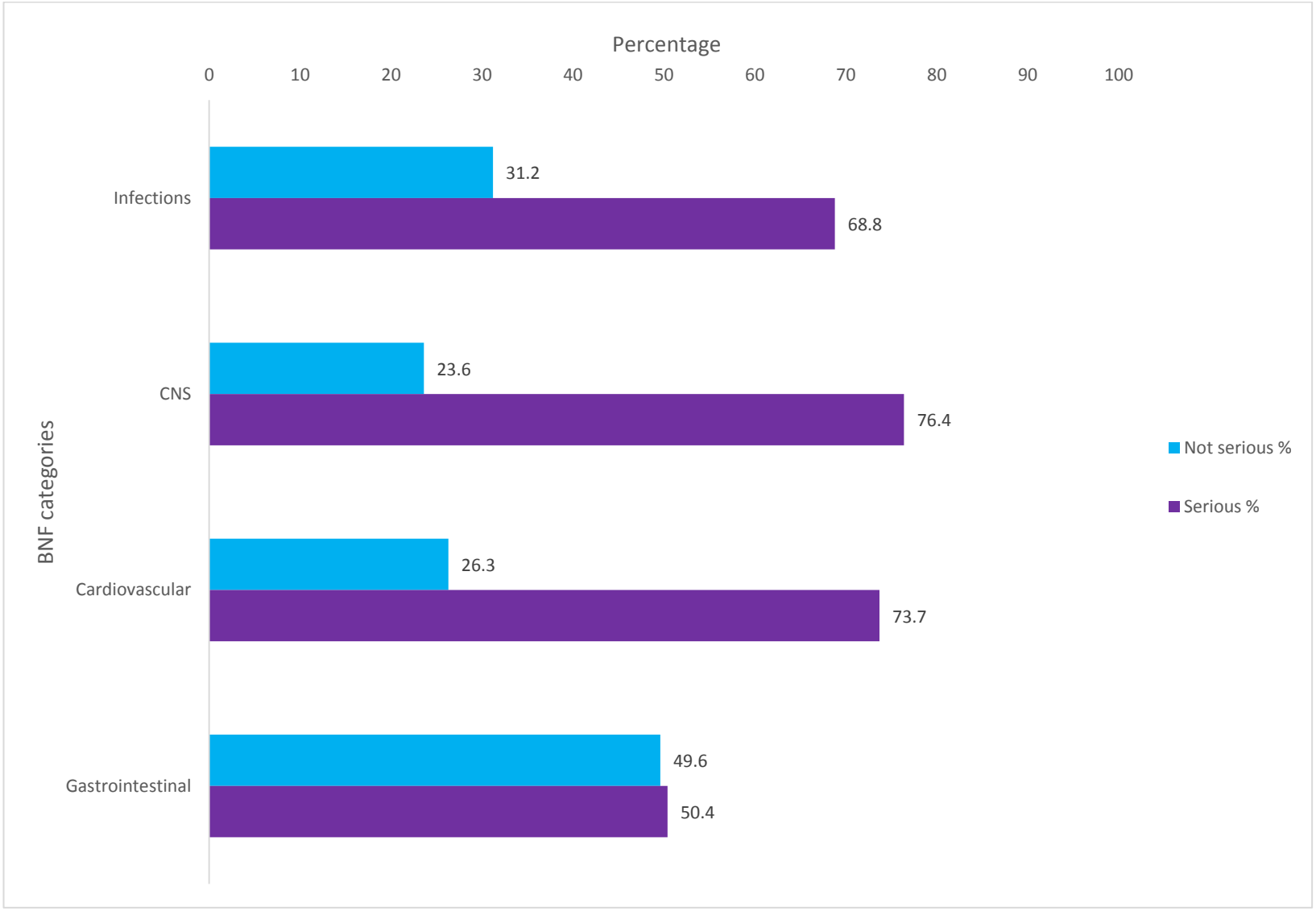


Figure 7.7: Most frequently reported BNF categories by reported severity

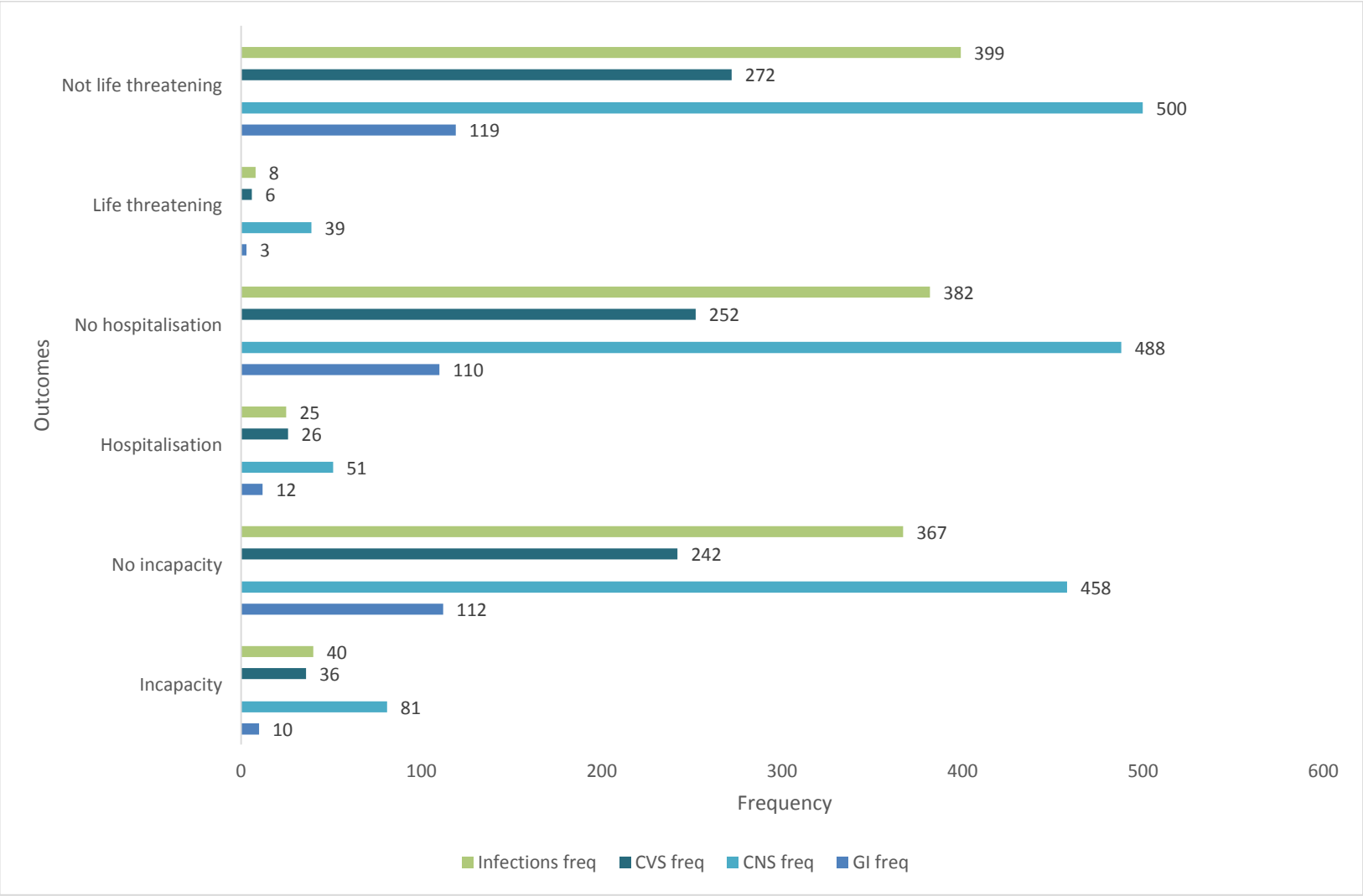


Figure 7.8: Most frequently reported BNF categories by outcomes

7.3.3.5 Section summary

• Most reported drugs were for CNS, CVS and infections

• 1-12 drugs reported; 95% reports for one drug

• SE severity did not increase with number of drugs

• 1-52 effects reported; 45% reports for 1/2 effects

• CNS drugs commonly reported across gender and age categories

• CVS drugs reports increase for older age categories

• CNS and CVS drugs linked to serious effects and incapacity

7.3.4 Managing SE

7.3.4.1 Content analysis of YC reports

The free text comments were subjected to content analysis which systematically categorised the data. From 2285 reports four duplicates and 26 blank reports were excluded from the analysis leaving 2255 reports. As outlined in the Methods chapter a Content Analysis (CA) coding frame was generated with 74 sub-categories which formed 13 hierarchical categories. These codes were applied to the YC reports and the major categories were as follows:

- SE description
- identification of SE
- management of SE
- impact of SE
- consequences of SE

See the following page for *Table 7.9*

Table 7.9: Content analysis (CA) coding frame applied to YC free text comments

Coding of sub-categories	***Hierarchical categories***	***Coding of sub-categories***	***Hierarchical categories***
Patient describing SE 1-Physical symptoms/effects	**1-Description of SE**	Suspect drug 2-Patient provides name of suspect drug	**2-Drug details**
Patient's reason for taking causative med 3-Treating long term medical condition 4-Current medical problem/general health	**3-Reason for drug use**	Impact of SE 5-Physical impact 6-Psychological impact 7-Social impact (QDL)	**4-Impact of SE on patient**
Severity of SE 8-Mild effects 9-Moderate effects 10-Severe effects	**5-Severity of SE**	Strategies employed by patient in identification of SE 11-Timing sequence of side effects 14-HCP confirmed 15-Used PILs to identify SE 16-Used Family/friends to identify SE 17-Used Internet to identify SE 18-Prior SE history (medical history) 19-Change in general health status 20-Change in brand 21-Patient makes differential diagnosis 22-Suspected possible interaction effects	**6-Identification of SE**
Knowledge of possible SE 23-Self informed prior to SE event 24-HCP informed prior to SE event 25-No knowledge of possible SE	**7-Prior knowledge of SE**	Behaviours 26-Stopping meds 27-Adhered to meds 28-Reducing dose 29-OTC remedies to counteract symptoms 30-Prescription remedies to counteract symptoms 31-Finished course 32-Reverting to original brands 33-HCP consultation 34-Self directed medicine management 35-Self directed non medicine management 36-HCP medicine management	**8-Patient behaviours**

Table 7.9: Content analysis (CA) coding frame applied to YC free text comments			
Outcome of Patient Behaviours 37-Dechallenge and SE went away 38-Took counteracting med and masked SE 39-Med taken to treat SE leads to more SE 40-Used CAMs to treat SE 41-Recorded suspect ADR in medical records (JK) 42-Used coping strategies to deal with SE	**9-Behavioural Outcomes**	Description of interactions with HCPs 43-Hospital admission 44-A&E 45-111 S service 46-GPs 47-Ambulance service 48-Pharmacist 49-Reported SE to HCP 50-Did not report SE to HCP 51-HCP not aware of SE 52-Multiple contacts with HCPs 53-Future HCP consultation likely/intended	**10- Interaction with HCPs**
Consequences 54-Accepts SE 55-Reluctant to take related med 56-Will not use med again 57-Prolonged/persistent physical effects 58-Prolonged/persistent psychological effect 59-Prolonged/persistent social effects 60-Prolonged/persistent work-related effects 61-Prolonged/persistent economic effects 62-Prolonged/persistent life-changing effects	**11-Consequences of SE**	Patient issues/concerns 63-Licensing issues 64-Issues with Prescribers 65-Issues with Pharmaceutical industry 66-Negative experience in HCP interaction 67-Specific concerns about quality/suitability of meds 68-Disagrees with HCP diagnosis/treatment 69-HCP ignored allergy 70-Perceives themselves as sensitive to meds	**12-Patient Concerns**
Characteristics of YC Reporters 71-Motivation to report described 72-Supporting documents supplied e.g. medical records/consultant letters 73-Advice requested 74-Awareness of sensitivity exhibited	**13-YC Reports**		

The frequencies of the hierarchical categories (1-13) in the YC reports were calculated. The highest proportions of reports described the SE – (2153;70%) and the impact of the SE – (2140;70%). The severity of the SE was described in 1371 reports (44%), patient behaviours in 990(32%), details of the drug were given in 751(24%) and interactions with HCPs were reported in 739(24%) reports. See *Figure 7.9.*

Analysis indicated 17 subcategories (23%) had frequencies greater than 200. These subcategories are presented in *Table 7.10.*

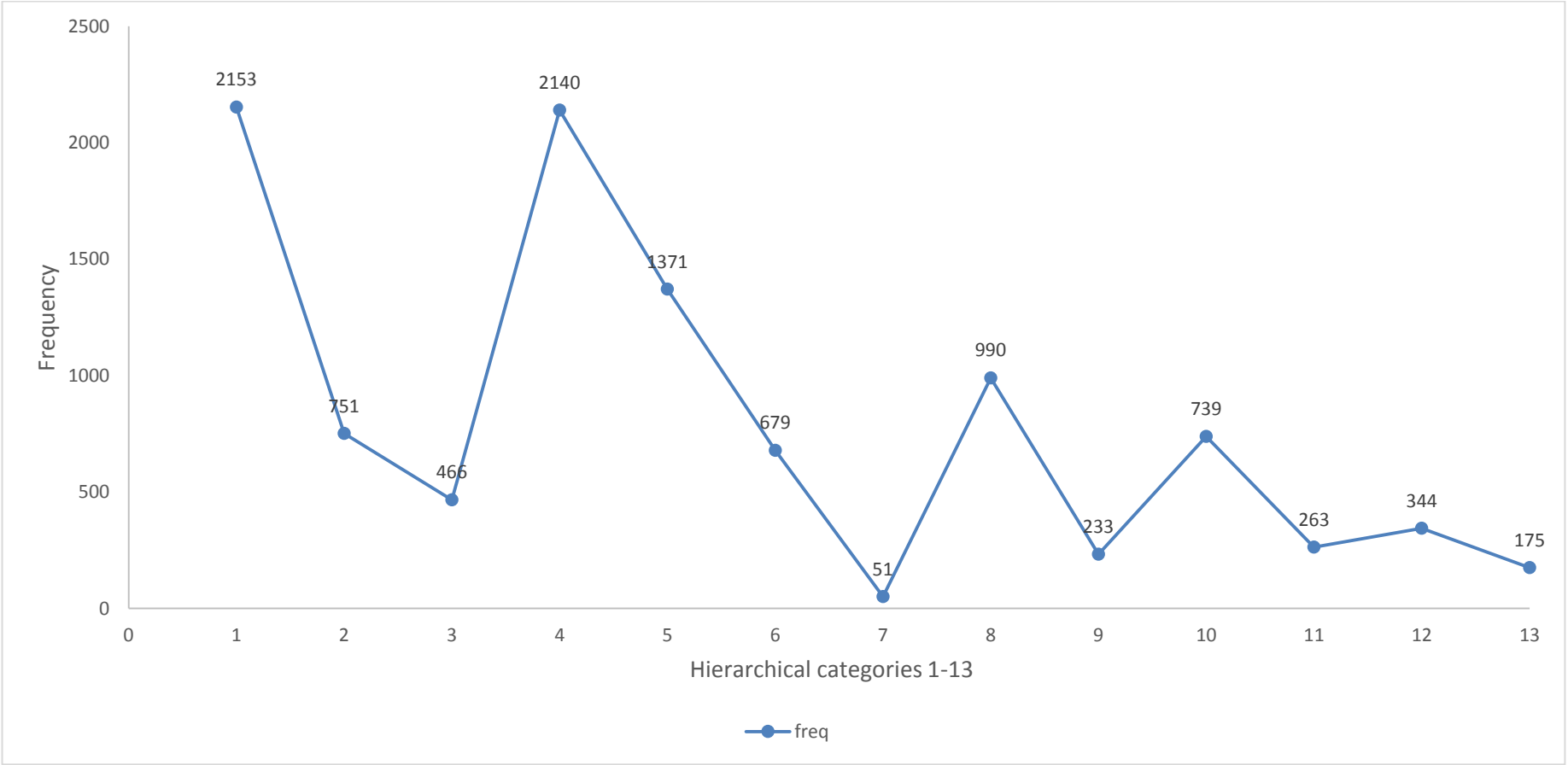


Figure 7.9: Hierarchical categories created from CA of YC free text comments (n=2255)

Table 7.10: Subcategories with frequencies greater than 200 created from CA of YC free text comments (n=2255)

Subcategories	***Frequency***
1-Physical symptoms/effects	2153
2- Patient provides name of suspect drug	751
4- Current medical problem/general health	301
5- Physical impact	2099
6-Psychological impact	532
7- Social impact (QDL)	760
8- Mild effects	290
9- Moderate effects	532
10- Severe effects	559
11- Timing sequence of side effects	313
26- Stopping meds	354
33- HCP consultation	671
36- HCP medicine management	260
46- GPs	383
52- Multiple contacts with HCPs	315
57- Prolonged/persistent physical effects	207
66- Negative experience in HCP interaction	203

7.3.4.2 Quantitative analysis and in-depth qualitative analysis of free text comments

A range of extracts have been used to describe the YC reports and demonstrate the results of the analysis. These extracts represent different reporters, drugs and reactions. Information on the gender, reporter type and method of reporting is outlined for each extract (I-Net refers to Internet reports; paper to YC forms; telephone to report via phone; MHRA to report via letter/email report). The results are based on the 13 hierarchical categories which informed the in-depth qualitative analysis. Each category is illustrated by verbatim quotations and the extracts are identified by reporter type, patient age, gender, drug type and method of reporting. The focus of the analysis is on specific sub-categories and detailed quotes are used to emphasise noteworthy themes. The analysis is divided into the following six sections:

- SE description
- Impact of SE
- Identification of SE
- Managing SE
- Consequences of SE
- YC reporters and reports

Additional quantitative analysis was conducted to create a fuller picture of the reports. Free text comments were described in relation to their characteristics, drug classes, SE severity and impact. Comments on identifying SE, HCP interactions and non-adherence were also linked to reported characteristics. A summary of this analysis is presented at the end of each section.

7.3.4.3 SE description within free text: symptoms, background information, prior knowledge of SE and severity of SE

Descriptions of SE were provided by the majority of reports (2153; 96%) with the causative drug being named in 751 (33%) reports.

Table 7.11: Frequency table of reports coded as Subcategories 1-10[#]

Sub category	Frequency	% of total	% of Hierarchical categories 1-5
Describing SE	2153	95.48	26.44
Name of suspect drug	751	33.30	9.22
Previous medical condition/medical history	167	7.41	35.84
Current medical problem/general health	301	13.35	64.59
Physical impact	2099	93.08	98.08
Psychological impact	532	23.59	24.86
Social impact (QDL)	760	33.70	35.51
Mild effects	290	12.86	21.15
Moderate effects	532	23.59	38.08
Severe effects	559	24.79	40.77

#Includes multiple effects per report

7.3.4.3.1 Physical symptoms/effects

A large majority of patients (95%; 2153) provided vivid, detailed descriptions of the physical symptoms of their SE. These ranged from lengthy lists of symptoms to single words or phrases. These frequently included descriptions of the severity, timing and consequences of their SE

> "*Movement and standing gave dragging sensation and very painful back and hip..Sleepiness then severe back pain under left shoulder blade, kidney area and right hip 3 weeks after starting. Severe back and hip pain."*
>
> *Patient, female, 67 years, atorvastatin, I-Net.*

> *"Floaters left eye, wavy flashing lights, memory blips, fainting, memory loss, loss of weight, prolonged seizures of total confusion and inability to function or speak or comprehend."*
>
> *Patient, female, 70 years, Symbicort, paper.*

7.3.4.3.2 Drug details

It was found that 751 patients (33%) also supplied details of the suspect drug within the free-text descriptions:

> *"Can't breath - asthma out of control…..Prescribed "Fostair" instead of previous asthma treatment that worked well. Within a few days asthma symptoms got much worse. I'm sitting in front of my PC and struggling to breathe."*
>
> *Patient, male, 48 years, Fostair, I-Net.*

> *"..Tight jaw, grinding of teeth, unable to relax jaw, inhibits sleep, ache in jaw. Irritating. The patient was taking Sertraline for: Anxiety and depression."*
>
> *Patient, female, 23 years, sertraline, I-Net.*

7.3.4.3.3 Reason for taking drug

Overall 20% of the reports gave reasons for taking the drug – 301 patients (13%) indicated they had taken this drug to deal with a current medical problem:

> *"Low mood, fatigue, tiredness, cold symptoms. I was regularly taking ibuprofen 400mg 3 times daily for bunions and shoulder pain for several months. I experienced extreme fatigue affecting ability to perform daily tasks, running nose, low mood."*
>
> *Patient, male, 47 years, ibuprofen, I-Net.*

> "*Swirling, flashing lights covering the whole of my right visual field. No loss of acuity. Reduced vision in right eye in low light. Started spontaneously, increasing over approximately 3 days. Had been on stable dose of 400 mg for 4 years but had increased to 700mgm due to break through of pain."*
>
> *Patient, female, 65 yrs, carbamazepine,I-Net.*

Just 167 patients (7%) reported they took the suspect drug to deal with a long term/established medical condition:

> *"Usually have a purple packet. This is a silver batch. Have noticed my old triggers in a light format starting to breakthrough. Not noticed for years. Medications have worked for 15 years. First ever symptom. Illnesses: Epilepsy. I was epileptic 20 years. Breakthrough symptoms with this silver batch. Never noticed with purple batch."*
>
> *Patient, unknown, 33 yrs, sodium valproate, I-Net*

> *"Infection. Swollen testicles and blood in urine. Very painful. Visited general practitioner who prescribed course of ciprofloxacin 500mg to be followed by course of trimethoprim 200mg. The patient was taking amiodarone for their heart condition following a number of cardiac arrests."*
>
> *Patient, male, 50 yrs, amiodarone, I-Net.*

7.3.4.3.4 Prior knowledge of SE

Two per cent or 45 patient reports indicated that they had no prior knowledge of a possible SE and consequently the effects were both negative and unexpected.

They reported their considerable dissatisfaction that they had not been informed by their HCP of the possible SE before they used the medicine:

> *"Acid reflux, bad withdrawal when coming off the medication. Doctor unaware of the full details about the medication and its side effects thus risks not explained to me."*
>
> *Patient, male, 44 years, Lyrica, I-Net.*

> *"Severe full body skin rash. Began with hives that merged. Arms, hands, legs and feet swollen. Large blisters on tops of feet. Skin turned purple and black particularly on face, legs and feet. Unable to walk for several days due to swelling on feet and legs. Shed skin all over. Felt nauseated and lost appetite…Having read the medical product information and advice associated with Omnipaque after the event, it is clear I should have been warned about side effects and asked if I was epileptic, had a brain tumour or had a history of allergic reactions to medication. All of which are documented on my medical file. I was never asked such questions or offered such advice. If I had been aware of the side effect risks, particularly to people with my history, I would have refused to have the contrast."*
>
> *Patient, male, 49 years, Omnipaque, I-Net.*

Just 2 patients (0.1%) were, in contrast, informed of the possibility of SE by their HCP prior to the SE event:

> *"Confusion, nausea, acute diarrhoea and very low temperature (e.g. 95°F)…Have great loss of appetite, but took pills with food and water, and drank absolutely no alcohol from the moment of starting the drug, as was told that it had serious side effects."*
>
> *Patient, female, 80 years, metronidazole, I-Net.*

7.3.4.4 Impact of SE

Descriptions of SE impact were divided into physical, psychological and social impacts as follows

- physical described by 2099 (93%)
- psychological described by 532 (24%)
- social described by 760 (34%)

Physical impact was reported in the majority of reports:

> *"Severe cramp and shooting pains in hands"*
>
> *Patient, female, 56 years, prednisolone, I-Net*

The SE was described as having psychological impact in 532 reports (24%) and social impact by 760(34%):

"Insomnia, suicidal thoughts, anxious depression and crying abnormal."
Patient, female, 31 years, Gedarel, I-Net

"Severe myalgia and exhaustion. Began with severe muscle pain in right calf. Gradually spread, getting worse each day, to most muscles all over body to the point that I could hardly walk and trying to lift a knife and fork to eat was an ordeal. Extreme depression caused either by medication or difficulty with daily life."
Patient, female, 59 years, Januvia, I-Net

7.3.4.5 Severity of SE

Descriptions of the severity of SE were divided into mild, moderate and severe effects as follows

- mild effects described by 290 (21%)
- moderate effects by 532 (39%)
- severe effects 559 (41%)

Severe effects were reported in 559 reports (41%) with 314 of these reports (56%) using the term "severe" to describe SE within their free text comments:

"Hands became swollen first and feet shortly after. Swollen hands and feet causing severe pain when walking, and pain when using hands for anything. Doctor prescribed strong pain killers and ibuprofen gel."
Patient, male, 67 years, Januvia, I-Net.

"Dry palms and hoarseness of voice. Hoarseness lasted several weeks and affected ability to carry out school activities. Also think it perhaps led to a severe ear infection which was difficult to clear, requiring 4 lots antibiotics.
Parent, male, 8 years, Oxybutynin hydrochloride, I-Net.

"Side effects - just like a bad flare up of irritable bowel disease/ irritable bowel syndrome - stomach pain/cramps and severe diarrhoea.. one day I was in tears at work after being stuck in the restrooms for nearly 2 hours."
Patient, female, 30 years, Xeristar, I-Net.

The SE was described as having moderate effects by 532 patients (39%) and 290 (21%) described having mild side effects:

"I feel extremely odd on this inhaler. It has not helped the wheezing and it is frightening to feel faint. Also, my mouth is very sore. I feel anxious now."
Patient, female, 67 years, Duoresp spiromax, I-Net.

"Chilled feet and lower legs, blurred vision, dizzy spells, drowsiness, poor concentration, and raised blood pressure."
Patient, male, 65 years, naproxen, I-Net.

"Applied on the area of the knee that was sore. Within about 5-10 minutes the knee joint began to get very sore and painful. Continued to suffer it for 15-20 minutes then washed it off. Gradually the pain subsided but was left with the knee joint absolutely stiff, could hardly bend it. The joint felt locked up."

Patient, male, 83 years, piroxicam, telephone

"Light-headed feeling and slightly numb around lips and face; mild tingling throughout body. Unnerving!"

Patient, female, 58 years, Ibuleve, I-Net.

"I was having the same reaction as my nutmeg allergy which alerted me - mild anaphylactic reaction (itching, disorientation and red splotches on skin)."

Patient, female, 35 years, amoxycillin, I-Net.

Associations between free text severity and the following - gender, reporter type, drug class and outcomes - were explored. Similar proportions of females (375; 41%) and males (168; 38%) experienced severe effects. The highest proportion of severe effects were linked to CNS drugs (167; 53%) and described by over half of carer reports (36; 57%) and parent reports (26; 53%). There was a significant relationship between coded severity and reporter type with a weak association: X^2 (6, N=1370) = 16.13, p =0.02: Φ = 0.11, reporter type accounted for 1% of the variation in free text severity. A Kruskal-Wallis test indicated the relationship between the coded severity and drug class was significant: X^2 (4, N = 842) = 28.51, p <0.001. The Cohen's effect size value (d = 0.4) suggested a small to moderate practical significance. Significant relationships were identified between coded severity and the outcomes of incapacity: X^2 (3, N = 1370) = 97.9, p <0.001; hospitalisation: X^2 (3, N = 1370) = 103.62, p <0.001; and life threatening consequences: X^2 (3, N = 1370) = 92.9, p <0.001. The associations were of moderate strength: Φ=0.3 with coded severity accounting for 9% of the variance. See *Table 7.12.*

Reported severity levels in free-text were compared to coded severity to establish if MHRA-assigned severity levels were reflected by the free text descriptions. As Figure 7.10 shows the reported severity levels were related to coded severity levels. A majority of effects coded as moderate (425; 82%) and severe (520; 95%) were reported as serious. Just over half of effects coded as mild (149; 51%) were reported as not serious, with 141(49%) reported as serious. See *Figure 7.10.*

Table 7.12: Coded severity by gender, reporter type and drug class.

	Coded severity f (%) n=2255				
	Mild	*Moderate*	*Severe*	*Moderate & Severe*	*p-value*
Gender					0.78
Male	95(21.5)	174(39.5)	168(38.1)	4(0.9)	
Female	192(20.9)	347(37.7)	375(40.8)	6(0.7)	
Reporter type					0.03*
Patient	268(21.3)	493(39.2)	487(38.7)	10(0.8)	
Carer	9(14.3)	18(28.6)	36(57.1)	0	
Parent	13(26.5)	10(20.4)	26(53.1)	0	
BNF class					≤0.001* [1]
GI	13(21.3)	28(45.9)	19(31.1)	1(1.6)	
CVS	30(17.1)	78(44.6)	67(38.3)	0	
Resp	21(33.9)	21(33.9)	20(32.3)	0	
CNS	46(14.6)	99(31.3)	167(52.8)	4(1.3)	
Infections	55(24.1)	89(39)	83(36.4)	1(0.4)	

**significance at ≤0.05 probability level (two-tailed)*
[1]Kruskal-Wallis test

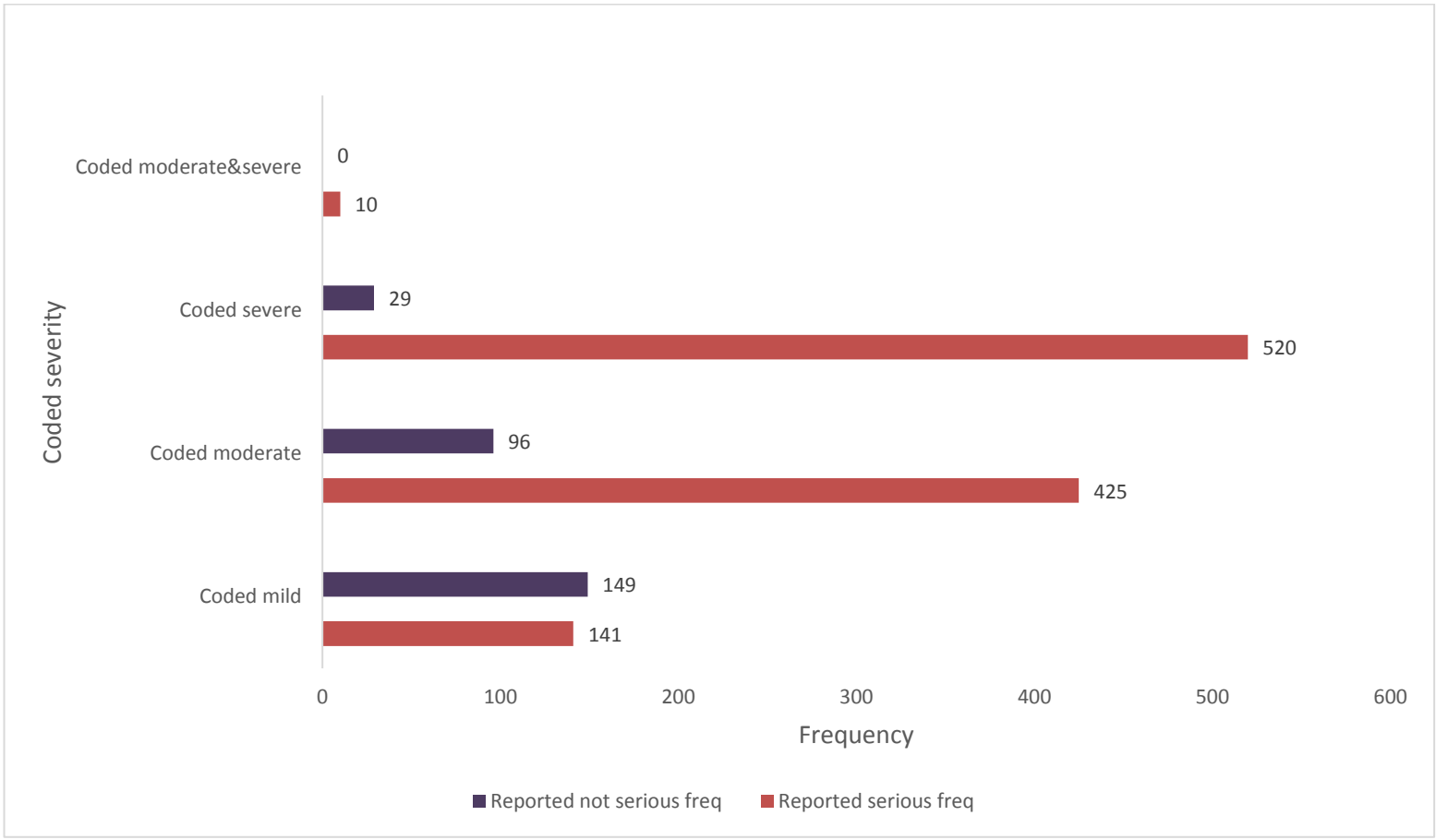


Figure 7.10: Reported severity (MHRA assigned) by free text severity (coded)

7.3.4.6 Section summary

- 22 extracts providing details of the physical symptoms; the drug and reason for taking drug; the impact and severity and previous knowledge of SE
- 21 patient reports and one parent report
- 9 reports for males; 12 for females; 1 unknown with ages ranged from 8-83 years
- Free text severity levels are 2 mild, 11 moderate and 9 severe effects
- Nine drugs linked to CNS; 3 to Respiratory; 3 to Infections; 2 CVS; 2 Endocrine; 2 Obstetrics/Gynaecological and 1 Anaesthesia
- Comments composed of 6 scant; 13 moderately elaborate and 3 elaborate narratives
- Overall comments covered descriptions of SE, their impact and severity

7.3.4.7 Impact of SE – multidimensional influences on patient lives

Descriptions of the impact of SE were divided into physical, psychological and social impacts with overlap between these classifications. Social impacts were derived from a number of criteria which included the combination of both physical and psychological impacts. In total 2098 reports reported the impact of the SE as follows:

- physical impact described by 1261 (60%)
- physical and psychological impact reported by 101 (5%)
- physical and social impact by 345 (16%)
- physical, psychological and social impact by 391 (19%)

Associations between type of impact of SE by gender, reporter type and drug class were explored. Physical impact was reported for similar proportions of males (418; 62%) and females (835; 59%). A majority of reporters – over 60% - described physical impacts with a combination of physical, psychological and social impacts reported by carers (24; 26%). The highest proportion of physical impact was reported for GI drugs (84: 72%) with a combination of physical, psychological and social impacts linked to CNS drugs (145; 30%). A Kruskal-Wallis test indicated the relationship between the type of impact and drug class was significant: X^2 (1, N = 1953) = 75.79, p <0.001. The Cohen's effect size value (d = 0.4) suggested a small to moderate practical significance. (See *Table 7.13*).

Table 7.13: Impact of SE by gender, reporter type and drug class

	Impact of SE f (%) n=2089				
	Physical	***Physical & Psychological***	***Physical & Social***	***Physical & Psychological & Social***	***p-value***
Gender					0.87
Male	418(61.6)	34(5)	109(15.9)	123(18)	
Female	835(59.4)	67(4.8)	236(16.8)	267(19)	
Reporter					0.3
Patient	1153(60.1)	92(4.8)	324(16.9)	351(18.3)	
Carer	57(61.3)	3(3.2)	9(9.7)	24(25.8)	
Parent	51(60)	6(7.1)	12(14.1)	16(18.8)	
BNF chapter classification					≤0.001*[1]
GI	84(72.4)	2(1.7)	19(16.4)	11(9.5)	
CVS	145(55.3)	15(5.7)	58(22.6)	44(16.8)	
Resp	59(71.1)	3(3.6)	10(12)	11(13.3)	
CNS	238(48.8)	31(6.4)	74(15.2)	145(29.7)	
Infections	239(64.6)	19(5.1)	67(18.1)	45(12.2)	

**significance at ≤0.05 probability level (two-tailed)*

[1]Kruskal-Wallis test

7.3.4.7.1 Physical impact of SE

The explicit impact was primarily related to physical symptomology - described by 2099 patients (93%):

> *"Felt unwell, cold, I had the most severe headache like a helmet of pain, indescribable. I will not take them again. I went out but felt cold and tired so came home. Within two hours I had a headache which got progressively worse as the evening wore on. The back of my hands, including fingers, were very blue veined. I felt as If I would have a stroke…the pain was still dreadful and had to get up 10.30pm and took a paracodol."*
>
> *Patient, female, age not supplied, Isoket, I-Net.*

> *"Red itchy rash on inside of right arm at the wrist. Rash on both underarms. Strange feeling in head and neck. Severe headache across forehead and back of head."*
>
> *Patient, female, 60 years, co-amoxiclav, I-Net.*

7.3.4.7.2 Psychological impact of SE

However the explicit psychological impact of SE was frequently experienced as increased anxiety, depression, irrational thoughts and aberrant behaviours were clearly described by 532 patients (24%):

> *"Been taking citalopram for 7 years. Had similar reaction about a year ago..with this batch experienced increased anxiety and poor sleep."*
>
> *Patient, male, 46 years, citalopram, I-Net.*

> *"Tiredness, rash and itchiness. I would like to stop taking these tablets. I feel bad taking them, headaches, severe aches in my legs and very sore hips, swollen fingers and the feeling of being constantly depressed.*
>
> *Patient, male, 58 years, ramipril, I-Net.*

> *"Balance went, cramps in leg- muscles in leg torn, ruptured achilles, feeling irritated..Very depressed and angry all the time, constant rage. Increased blood pressure. Headaches. Rage was worst. Stopped because of cramps..I also had a rather terrible irritation and a bizarre reaction were [sic] I could not stop swearing (I even used swearing words that I didn't even know that I knew)."*
>
> *Patient, female, 65 years, amlodipine, telephone.*

> *"I suffered severe irrational thoughts as well as anxiety, couldn't eat very much, feeling of impending doom, headaches, got up every morning with a very anxious upset stomach, family and friends noticed. I cannot begin to tell you how dreadful I felt. I thought I was losing the plot and worried about the effect it was having on my life, my family and friends. Everyone noticed the difference in me and would ask what was wrong as I became a completely irrational anxious person who dreaded every single day. I only realised it was the nasal spray when I stopped it for a couple of days as I had a horrendous nose bleed, it took two days and I suddenly felt me again. I can't tell you how much better I feel."*
>
> *Patient, female, 53 years, Nasonex, I-Net.*

One patient describes her fears that she would harm her family as a result of the profound psychological effects she was experiencing:

> *"Insomnia, anxiety, feeling 'fuzzy headed'. Paranoia about harming my family whilst suffering from insomnia. My head was racing, similar to if I'd drunk a lot of caffeine or was suffering from stress. I couldn't stop being scared that I might turn psychotic and kill my family. It scared the hell out of me!"*
>
> *Patient, female, 37 years, Selincro, I-Net.*

Patients described the extreme psychological impact and distress of the SE. In many cases these effects were persistent and had significant impact on their ability to function normally. The negative impact was multifaceted and experienced across numerous aspects of their lives including their concentration levels, which affected their work, social life and use of health services:

"Phobic anxiety. Ongoing high anxiety with phobias, panic, etc. Therapy and cognitive behavioural therapy for anxiety disorder with phobias (claustrophobia) and anxiety-related symptoms like palpitations that resulted in doctor's visits."

Patient, female, 27 years, Implanon, I-Net.

"Abnormal behaviour, anxiety depression, suicidal thoughts, unable to think or judge, allergic skin reaction. I feel alone and hurt and depressed. I cry a lot and need professional help."

Patient, male, 36 years, Champix, I-Net.

"Acute mania and severe depression. Insomnia and unable to eat..Made me suicidal and I had massive highs and lows. Couldn't sleep or eat and couldn't concentrate on simple tasks. Was very, very low and nearly made a suicide attempt."

Patient, female, 27 years, topiramate, I-Net.

7.3.4.7.3 Social impact of SE

Seven hundred and sixty patients (34%) also described the social impact of their SE and its implicit impact on their QoL:

"Severe muscular weakness and pain in both arms. Feels like burning and muscular spasms..Affecting my everyday life - hard to housework, pick things up. Lack of sleep due to pain in arms. Pain is still there whilst resting."

Patient, female, 60 years, amitriptyline, diclofenac sodium, Lyrica, I-Net.

"When drinking alcohol, after 2 pints of lager I blackout all the time. I cannot remember anything from a night out whatsoever, it never happened ever before in my whole life of drinking. So I stopped my social life until I come off the tablets altogether."

Patient, male, 52 years, sertraline, I-Net.

One patient reported the significant negative impact of the SE on their normal functioning at work. He experienced difficulties in concentration and stress as a result of his impaired work performance:

"It started when I was in a meeting at work - I started to get tunnel vision and eventually lost consciousness for a split second then I found it very difficult to concentrate and I felt panicky. This has got worse and worse despite my discontinuation of the drug. I constantly have blurred vision, I feel panicky and agitated in social situations (I have never suffered with panic or anxiety before), I get dizzy, I find it incredibly hard to focus and think analytically, as a result I'm developing stress and worry as it is affecting my work. I feel constantly spaced out and slightly removed from myself."

Patient, male, 26 years, omeprazole, I-Net.

Another perspective is offered by a report from a carer which describes the disabling impact of the SE on the quality of his wife's life:

> *"Her body began to inflate like a balloon. Her body became numb, two deep scars appeared at two ends of her mouth, other lines also appeared on her face and her face became flat with her high cheekbones disappearing. Such changes in her body and face made her very distressed. She could not bear her physical changes and numbness. She became disabled from her distress and lost her independence. I had to become her full-time carer."*
>
> *Carer, female, age not supplied, Seroxat, paper.*

7.3.4.7.4 Section summary

- 14 extracts providing details of the physical, psychological and social impacts of SE
- 13 patient reports and one carer report
- 5 reports for males; 9 for females with ages ranged from 26-65 years
- Free text severity levels are 3 moderate and 10 with severe effects
- Eight drugs linked to CNS; 2 to CVS; 1 to Infections; 1 to Obstetrics/Gynaecological and 1 to Ear/Nose
- Comments are composed of 6 moderately elaborate and 7 elaborate narratives
- Overall comments are related to the multidimensional impact of SE on patients' lives

7.3.4.8 Identification of SE – strategies and information sources

Strategies and information sources used to identify SE were described by 679 (30%) reports. These reports described effects for 155 males (22.83%) and 524 females (77.17%) in 635(93.52%) patient, 33(4.86%) carer and 11 (1.62%) parent reports. The highest proportions of these reports were for those in older age categories aged 51-60 (150; 22.09%); 61-70 years (128; 18.85%) and aged over 80 (25; 3.68%). The strategies employed in identifying SE included the timing sequence of SE; differential diagnosis and confirmation with information sources. Information sources included HCPs, PILs, the Internet and family/friends. Multiple sources and strategies were also used.

Table 7.14: Frequency table of Subcategories 11-22[#]

Sub category	Frequency	% total	% of Hierarchical category 6
Timing sequence of SE	313	13.88	46.1
Challenge/dechallenge	40	1.77	5.89
Reduction in dose	21	0.93	3.09
HCP confirmed	136	6.03	20.03
Used PILs to identify SE	52	2.31	7.66
Used family/friends to identify SE	12	0.53	1.77
Used internet to identify SE	28	1.24	4.12
Prior SE history	54	2.39	7.95
Change in general health status	54	2.39	7.95
Change in brand	47	2.08	6.92
Patient makes a differential diagnosis	102	4.52	15.02
Suspected possible interaction effects	40	1.77	5.89

#Includes use of multiple strategies/sources per report

7.3.4.8.1 Timing sequence

Three hundred and thirteen reports - 14% of the total population - used temporal associations including de-challenge, re-challenge, changes in dose to identify their SE:

> *"Within an hour of taking the medication I have extremely uncomfortably sweating which lasts for about 4 hours which I never had in the past. I have tried varying the times I take it to no available [sic]. I have even tried not taking it for one day and found that I did not get the sweating. And as soon as I started it again the next day the sweating came back."*
>
> *Patient, female, 63 years, propranolol, I-Net.*

> *"Nausea from start of treatment, 2nd day I struggled to drink anything. 3rd day, unable to eat or drink and started having visual hallucinations"*
>
> *Patient, female, 20 years, clarithromycin, I-Net.*

"Bleeding, bad migraines, memory loss, insomnia, loss of appetite and premenstrual syndrome (PMS) symptoms. The effects of these tablets were readily increasing every day I took one."

Patient, female, 46 years, Cerazette, I-Net.

7.3.4.8.2 Differential diagnosis

It was found that 5% or 102 patients assessed the possible causes of their SE and made a differential diagnosis:

"Heartburn particularly bad at night. Severe enough to interrupt sleep. Only started after a couple of days of taking the medicine. I don't normally get heartburn."

Patient, female, 38 years, flucloxacillin, I-Net.

"..hives / rash on palm of left hand, wrist and between fingers. No exposure to anything new which might cause this."

Patient, male, 27 years, citalopram, I-Net.

"About 4-5 hours after taking the medication I was yawning at least 4 times a minute for about 15-20 minutes and this happened almost everyday but had not happened before taking the medication."

Patient, female, 34 years, sertraline, I-Net.

7.3.4.8.3 Confirmed with HCPs

Just over 6% or 136 reports confirmed their SE with a HCP. Effects in 64 males (49.23%) and 72 females (52.94 %) were confirmed, with the most common of these reports being for those in age categories 21-40 years (28;20.59%); 51-60(32; 23.53%); 61-70 years (20; 14.71%) and aged over 80 (25; 18.38%).

Patients confirmed with their GPs:

"I had been taking atorvastatin 10mg for 15 years..The statin dose was increased to 20mg because my total cholesterol had increased to 5.4. The skin rash started to develop approximately two weeks after starting the 20mg dose. At the following visit to my GP he told me to stop taking the atorvastatin 20mg.".

Patient, male,65 years, atorvastatin, I-Net.

"Change to sense smell. The smell was so profound I felt sick with it. Eventually it dissipated but later it returned but not so bad. Spoke to GP who advised to not take any more."

Patient, female, 59 years, doxycycline, I-Net.

"Night terrors…Having had a similar reaction when given Calpol in the past, I took my son to see the GP for advice. She suggested offering tablet form of paracetamol."

Parent, male, 4 years, Calpol, I-Net.

Others used hospital doctors:

> *"Heart attack and triple bypass. Was informed by a surgeon at hospital that he was fairly certain the diclofenac had caused some or all of the cardiovascular issues and stopped my tablets at once.".*
>
> *Patient, male, 52 years, diclofenac, I-Net.*

Some patients used pharmacists as an initial point of contact:

> *"Very itchy skin for a few hours after taking… I spoke to the pharmacist at [anonymised] who has suggested I ask for another prescription".*
>
> *Patient, female, 65 years, Actavis levothyroxine, I-Net.*

> *"Increased hair loss, easy bruising and muscle twitches..Mentioned to general practitioner (GP) and to pharmacist. Pharmacist suggested I report side effects here."*
>
> *Patient, female, 53 years,vVenlafaxine, I-Net.*

One patient described how advice from his pharmacist led to a subsequent GP appointment:

> *"Within hours of applying the gel, the skin on my scalp blistered and subsequently developed crusts. After seeing the pharmacist I made an appointment to see my GP the following day who prescribed an antibiotic cream and confirmed that I should not reapply the gel…I wanted to ask a pharmacist whether I should continue applying the gel and was told not to."*
>
> *Patient, male, 78 years, Picato, I-Net.*

However another patient highlighted the lack of privacy that can be part of pharmacy interactions:

> *"I went to the pharmacy to collect my prescription, I receive my medications weekly. When collecting my last prescription one of my medications, ramipril capsules were 5mg and previously were in a red and yellowish capsule. This week it was a green and grey capsule. I have memory problems at the best of times and when sorting my many medications into my weekly planner pill boxes I was getting further confused. My prescriptions are on electronic repeat yet the pharmacy states at times that my prescription has not been filled by the general practitioners [sic] surgery and expect me to have an explanation of why this is. I find it difficult not to lose my temper with the staff as this treatment is degrading and I'm expected to discuss my private medical details in front of other customers."*
>
> *Patient, male unknown, ramipiril, MHRA.*

7.3.4.8.4 Confirmed with PILs

A smaller number of patients 52 (2%) used PILs to identify their SE:

"Although I am somewhat prone to mouth ulcers, this is usually after a specific event such as abrasion. After the third ulcer without obvious cause, I checked the patient information leaflet (PIL) for naproxen, which I had been taking for about a week, and noted it was a possible side effect."

Patient, male, 64 years, naproxen, I-Net.

7.3.4.8.5 Confirmed with the Internet

It was found that just 28 patients (1%) used the Internet to identify their SE:

"I suffered severe irrational thoughts as well as anxiety, couldn't eat very much…I went on internet to see side effects and couldn't believe the amount of people who felt exactly how I did."

Patient, female, 53 years, Nasonex, I-Net.

7.3.4.8.6 Confirmed with family/friends

However reporters were least likely to use family or friends to confirm their SE – just 0.5%:

"Diarrhoea got progressively worse as the weeks went on..I was unsure if it was related to my sensitive stomach..I was advised to stop the cough syrup by a friend who is a physiotherapist who knows my medical history and suspected I was having a reaction."

Patient, female, 34 years, Robitussin chesty cough, I-Net.

7.3.4.8.7 Confirmed with multiple sources

Reporters also used multiple information sources to assist them in identifying their SE:

"Erectile dysfunction discovered on starting new relationship. Not really made aware of this possible side effect when put on tablets but it is in the leaflet but not listed with other side effects. Search on internet immediately flagged up the issue."

Patient, male, 64 years, simvastatin, I-Net.

"Very severe aplastic anaemia. Had eye drops prescribed by general practitioner and used them for 2 days only..The leaflet enclosed in drops stated in rare cases can cause aplastic anaemia. It states on some research on the internet that it should not be used in children under 2 years of age."

Parent, male 1 year, chloramphenicol, I-Net.

"Dizziness, drowsiness, hallucinations, headache, rapid heart rate, shaking, sleep disturbance, vertigo, vomiting. After speaking to a nurse and basic searches on the internet, the patient was told they should never have been given such a high dose.."

Carer, female, 49 years, Zamadol SR, I-Net.

7.3.4.8.8 Section summary

- 20 extracts providing details of the timing sequence; differential diagnosis and information sources used to identify SE
- 17 patient reports, one carer and 2 parent reports
- 9 reports for males; 11 for females with ages ranged from 1-78 years
- Free text severity levels are 5 mild, 7 moderate and 8 severe effects
- Seven drugs linked to CNS; 3 to CVS; 3 to Infections; 2 Obstetrics/Gynaecological; 1 Muskoloskeletal; 1 Eye; 1 Ear/Nose; 1 Skin and 1 Anaesthesia
- Comments composed of 2 scant; 13 moderately elaborate and 5 elaborate narratives
- Overall comments related to the strategies and information sources used to identify SE

7.3.4.9 Managing SE – behaviours and outcomes

Overall 990 (41%) reports provided details of their behaviours as they sought to manage their SE. These details were present in reports for 282 (28.48%) of males and 708 females (71.52%), in 810(81.82%) patient, 95(9.6%) carer and 85 (8.59%) parent reports. The highest proportions of these reports were for those in older age categories aged 51-60 (378; 38.18%); 61-70 years (277; 28%); 71-80 (9; 9.2%) and aged over 80 (38; 3.84%).

Behaviours were described in 334 (61%) reports with severe effects, with the highest proportions of reports linked to Endocrine drugs (101; 58%). These are followed by CVS drugs (146; 53%); drugs for malignant disease (25; 50%) and respiratory drugs (43; 48%). The behaviours included HCP consultation, self-directed interventions - both medical and non-medical - and stopping medicine(s).

Table 7.15: Frequency table of Subcategories 26-36[#]

Sub category	Frequency	% of total	% of hierarchical category 8
Stopping meds	354	15.7	35.76
Adhered to meds	64	2.84	6.46
Reducing dose	30	1.33	3.03
OTC remedies to counteract symptoms	95	4.21	9.6
Prescription remedies to counteract symptoms	157	6.96	15.86
Finished course	27	1.2	2.73
Reverting to original brands	23	1.02	2.32
HCP consultation	671	29.76	67.78
Self directed medicine management	164	7.27	16.57
Self directed non medicine management	26	1.15	2.63
HCP medicine management	260	11.53	26.26

#Includes multiple behaviours per report

7.3.4.9.1 Patient behaviours

Analysis found that 671 patients (30%) consulted with a HCP. These reports were composed of 615 (91.65%) patient, 29 (4.32%) carer and 27 (4.02%) parent reports. Among 196 males (29.21%) and 475 females (70.79%) the highest proportion described severe effects (249; 37.11%). Consultation with HCP was linked to the following drug classes: endocrine (78; 44%); malignant disease (19; 38%); CVS (95; 35%); muskoskeletal (80; 31%) and CNS (146; 28%). Those in the older age categories were more likely to consult with HCPs – 132 (37%) aged 51-60; 121 (33%) aged 61-70; 52 (29%) aged 71-80 and 20 (33%) aged over 80 years:

> *"Increased hair loss, easy bruising and muscle twitches..Mentioned to general practitioner (GP) and to pharmacist."*
>
> *Patient, female,53 years, venlafaxine, I-Net.*

"Visited GP about painful feet and other symptoms. Said I thought it was due to ciprofloxacin. GP not so sure but to stop taking medicine anyway. Have been referred for neurological opinion.".

Patient, female, 67 years, ciprofloxacin, I-Net.

Within HCP interactions 315 patients (14% of the total sample) had multiple contacts with HCPs:

"Increased blurred vision, increased sweating and heated body. I have type 2 diabetes controlled by metformin 500mg twice daily and Zicron 40mg twice daily. I am also on ramipril 5 mg daily…I have seen two dermatologists from two different hospitals; a neurologist and most recently an endocrinologist."

Patient, male, 76 years, ramipril, I-Net.

Analysis of the reports indicate that over 380 patients (17%) interact with GPs. One carer described the symptoms their patient experienced which prompted a consultation with the patient's GP:

"Patient has Parkinson's disease and symptoms deteriorated significantly following uptake of drug. Worsened cognition, significantly reduced mobility and inability to hold items..Asked general practitioner who prescribed medication to stop use of the drug."

Carer, male, 75 years, gabapentin, I-Net.

However these HCP consultations do not always appear to result in corresponding medicine management by HCPs. Just 260 patients (12%) described a HCP managed medicine intervention:

"Tingling of facial muscles, and increasing twitching of the right side of face...prescribed the medication by diabetic specialist nurse by phone. Side effects developed by second day..telephoned her and told to stop taking it."

Patient, female, 70 years, Januvia, I-net.

"Breathlessness. spoke to general practitioner about the side effect - was particularly concerned as I am asthmatic. general practitioner removed me from the medication with immediate effect and switched me to gabapentin."

Patient, female, 33 years, topiramate, I-net.

Analysis of the reports indicated that overall 190 (8%) of patients engaged in independent behaviours to manage their SE. These behaviours included self-directed medicine management (164; 7%) as described by patients in the following extracts:

"Shortness of breath on exertion, muscle pains, headaches and sleeplessness. Been on statins for years. General practitioner took me off tablets but when restarted symptoms recurred. I have taken myself off tablets after several restarts on a reduced level."

Patient, male, 72 years, atorvastatin, I-Net.

"The consequences of stopping the statin were immediately noticeable. I lost most of my aches and pains that I suffer overnight and the pain in my elbows cleared up…I have stayed off atorvastatin for 5 weeks..and I have no more aches or pains."

Patient, male, 60 years, atorvastatin, I-Net.

Patients also engaged in self-directed behaviours to manage their SE that did not not involve medicines (26;1%). One patient described a simple intervention to manage her SE which did not require medicine:

"After the second dose on my first day of treatment I experienced moderate to severe heart burn that lasted all evening. I drank milk to neutralise the acid and this did make the burning sensation less painful however it still felt very uncomfortable."

Patient, female, 24 years, co-codamol, I-Net.

It was found that when patients experienced SE, 354 (16%) of them stopped taking their medicine or removed the medical device. Analysis indicated that the majority of these were female (238; 67.23%) compared to 116 (32.77%) males. Those more likely to stop their medicine were aged 21–40 (80; 22.6%); 51-60 (66; 18.64%) and 61-70 years (74; 20.9%). Analysis indicated that 235 (35.02%) of those who consulted HCPs stopped their medicines (235; 35.02%). Non-adherent behaviours were linked to the following drug classes: CNS (74; 22%); infections (65; 19%) and CVS (62; 19%).

"Constant urge to urinate and irritation, rash on face and lower legs plus over torso to a lesser extent, intermittent explosive diarrhoea and swelling of face (eye lids, brow, lips)..I realised that all the symptoms probably related to taking omeprazole as they are listed side effects. I stopped taking the drug.."

Patient, female, 57 years omeprazole, I-Net.

"Stopped taking by patient due to pain in kidney. Pain not at same level now."

Patient, male, 56 years, losartan, paper.

"Flickering at the side of my eye briefly. Then 2 weeks later rippling vision over half of my field of vision lasting about 15 minutes. I stopped taking the amlodipine in case they were causing the problem."

Patient, female, 67 years, amlodipine, paper.

"Abdominal bloating, pelvic pain. Pelvis felt like it was on fire, it felt like I had a terrible infection, paracetamol did not work, had to stay in bed all day. This was very upsetting, so I also felt emotionally low..Lots of little blister like spots. Then several painful large ones appeared..I should also have mentioned that I found the side effects so unbearable that I took the Mirena out myself."

Patient, female, 43 years, Mirena, I-Net.

7.3.4.9.2 Behavioural outcomes

Overall 233 patients (10%) provided details of the results of their SE management. These outcome details were for 131(56.22%) females and 102(43.78%) males contained outcome details in 218 (93.56%) patient, 9 (3.86%) carer and 6 (2.58%) parent reports. Those aged 61-70 years (51; 21.89%) and 71-80 (21; 9.01%) were more likely to provide details on outcomes. Outcomes were described in 73 (13%) reports with severe effects, with the highest proportions of reports linked to CVS drugs (46;17%) 27 (15%) with Endocrine and 15(13%) GI drugs. The outcomes described in these reports included de-challenge, taking counteracting medicine and recording SE in medical records.

Table 7.16: Frequency table of Subcategories 37-42[#]

Sub category	Frequency	% of total	% of Hierarchical category 9
Dechallenge and SE went away	124	5.5	53.22
Took counteracting med and masked SE	40	1.77	17.17
Med taken to treat SE leads to more SE	21	0.93	9.01
Used cams to treat SE	29	1.29	12.45
Recorded suspect ADR in medical records	16	0.71	6.87
Used coping strategies to deal with SE	22	0.98	9.44

#Includes multiple outcomes per report

A positive dechallenge was undertaken by 124 (6%) patients with the SE disappearing:

"First muscle pain then terrible pain in abdomen during the last year of taking..after I stopped taking it almost straight away things calmed down"

Patient, female, 56 years, atorvastatin, I-Net.

"Swelling of knees, groin swelling, swelling of legs and throbbing pain. I didn't realise the effects were from the naproxen until I stopped taking them. As soon as I stopped taking it the swelling, throbbing, heavy sensation stopped and my legs returned to normal size."

Patient, female, 55 years, naproxen, I-Net.

"Pain in my leg muscles, pain in my shoulders and reduced movability in shoulder also couldn't raise my arm above my head..When I came off the atorvastatin the pain in my legs disappeared and muscle wastage stopped and the pain in shoulders also disappeared and in time the movability improved."

Patient, male, 54 years, Lipitor, I-Net.

Forty patients (2%) took counteracting medicine aimed at masking the SE:

"Dry mouth, especially during exercise. Indigestion - taking omeprazole to counter. Two instances of cystitis requiring antibiotics. The difference the medication has made to my quality of life is such that I am prepared to put up with the side effects.

Patient, female, 57 years, Betmiga, I-Net.

"Nausea, severe migraine, pain in legs and pelvic area, anxiety, persistent vomiting unable to stop for 3 days..a practice nurse made a home visit and prescribed prochlorperazine 3mg to stop the vomiting and paracetamol suppositories for the pain."

Patient, female, 48years, Esmya, I-Net.

Just 29 patients (1%) used complimentary alternative medicines (CAMs) to treat SE:

"Since stopping the medication I'm always constipated, had recurring vaginal yeast infections, need to buy and take high doses of probiotics always now."

Patient, female, 22 years, doxycycline, I-Net.

"Uncontrollable cough, vomit, behaviour alteration, worsening as medicine kept being taken, stopped as detox with homeopathy."

Parent, female, 2 years, montelukast, I-Net.

A small number of patients - 16 - (1%) describe wanting to record their SE in their medical records, to prevent it from happening again in future:

"I need this drug to help with the reflux problems caused by using drugs for my arthritis..I have also written to my doctor to add to my notes that I need to have the Jenson Product to keep my blood pressure and pain at bay."

Patient, female, 67 years, omeprazole, I-Net.

7.3.4.9.3 Section summary

- 21 extracts providing details of behaviours for managing SE such as HCP consultation, self-directed interventions and stopping medicines

- 19 patient reports, one carer and one parent report
- 6 reports for males; 15 for females with ages ranged from 2-76 years
- Severity levels are 3 mild, 4 moderate and 14 severe effects
- Eight drugs linked to CVS; 6 to CNS; 2 to Infections; 2 to Endocrine and 2 to Obstetrics/Gynaecological
- Comments composed of 2 scant, 14 moderately elaborate and 5 elaborate narratives
- Overall comments related to the behaviours used to manage SE and the outcomes of these behaviours

7.3.5 Consequences of SE

Analysis of the reports also identified the long term results of the SE for patients with over 263 patients (12%) describing the consequences of the SE. Within 229 (11%) patient, 11 (12%) carer and 23 (16%) parent reports for 175 (12%) females and 88 (12%) males consequences were mentioned. The highest proportions of these reports were for those in the younger and older age categories – infants (9; 33%); 61-70 (43; 12%) and those aged over 80 (10; 16%). Outcomes were described in 141 (26%) reports with severe effects with the highest proportions of reports linked to malignant disease (12; 24%); skin (19; 23%); obstetrics/gynaecological (25; 15%); CNS drugs (68; 13%) and CVS (30; 11%). These consequences included accepting the SE, persistent physical, psychological, social, economic, work-related and life changing effects.

Table 7.17: Frequency table of Subcategories 54-62[#]

Sub category	Frequency	% of total	% of hierarchical category 11
Accepts SE	11	0.49	4.18
Reluctant to take related med	7	0.31	2.66
Will not use med again	14	0.62	5.32
Prolonged/persistent physical effects	207	9.18	78.7
Prolonged/persistent psychological effects	65	2.88	24.71
Prolonged/persistent social effects	50	2.22	19.01
Prolonged/persistent work-related effects	22	0.98	8.37
Prolonged/persistent economic effects	19	0.84	7.22
Prolonged/persistent life-changing effects	60	2.66	22.81

#Includes multiple consequences per report

7.3.4.8.1 Consequences for patients

A small number of reporters – 0.5% - accepted the SE:

> *"The mouth ulcers occur every time I have the injection about on to three weeks after. Sometimes they last for a few days but they have lasted for three weeks. Each time I take the medicine which I've been on for two years I get one of the side effects. The mouth ulcers have been seen by my dermatologist but I had plaque psoriasis covering 85% of my body including my hair and face so I am more than happy to suffer with the occasional side effect."*
>
> *Patient, female, 36 years, Stelara, I-Net*

> *"Spoke with nurse regarding suicidal thoughts. Asked if I wished to continue. Advantages outweigh issues so remain on the treatment. I know the thoughts are hormone related and am able to fight them. Acne, acute depression, bone pain, excess sweating, hot flushes, mood swings, painful breasts, sleep disturbance and suicidal depression."*
>
> *Patient, female, 33 years, Decapeptyl SR, I-Net.*

As a result of the SE seven reporters (0.3%) indicated their reluctance to take a related medicine while fourteen (0.6%) would not use the medicine again:

"Severe constipation and abdominal pain whilst starting dexamethasone and head was worse. Upon finishing 10 day course was followed by severe diarrhoea and abdominal pain and sought help at accident and emergency. Suspected inflammatory bowel disease and reluctantly started budesonide 9mg as previous side effects of steroids. Same happened, headache got worse and constipation gas started again. The minute started dexamethasone I had severe constipation and abdominal pain."

Patient, female, 24 years, dexamethasone, I-Net

"I have had a strong reaction to nitrofurantoin, felt like I was going to pass out in the shower. I got out and sat on the toilet seat, was then very sick. I have stopped taking them and now feel fine; I would not take these tablets again."

Patient, female, unknown, nitrofurantoin, Patient(MHRA)

7.3.5.2 Persistent physical effects

It was found that 207 patients (9%) described the prolonged physical effects of the SE:

"After stopping the treatment, my cycles have become abnormally long and irregular. My husband and I are trying for a baby and it is slowing the whole process down, as instead of 12 attempts a year (for someone with a 28/30-day cycle), we will have fewer..If I had known, I would not have started using the pill or would have stopped it a couple of months earlier. Currently, I cannot be sure that they will ever get back to normal".

Patient, female, 35 years, Gedarel, I-Net.

"Fuzzy head, headache, nausea, loss of appetite (8lbs weight loss in 6 days), weakness and loss of energy, sore throat and mouth, nasal congestion. I believe the side effects I experienced are mostly common place, and this medicine should be discontinued. It did clear up the cystitis quite quickly but the side effects are still being experienced after the course has been finished."

Patient, female, 74 years, trimethoprim, I-Net.

"Hair thinning and hair loss. This side effect was not brought to my attention yet when I search on the internet, hundreds of women are complaining about it and have no information on whether the hair growth will return or what the longer term effects are…My hair is now in terrible condition and falling out."

Patient, female, 56 years, omeprazole, I-NET.

7.3.5.3 Persistent psychological effects

Patients (65; 3%) also described the long-term psychological consequences of their SE:

"I have faced severe effects from Propecia (finasteride). I was prescribed it for hair loss and I used it for 1 week, but suffered a string of side effects, including genital pain, weak and discoloured discharge, inept, and low libido. However, more seriously I took a pill and within 90 minutes I suffered acute depression and suicidal thoughts…Some side effects have stopped, such as genital aching and poor discharge [sic], but others have persisted 9 months in..No suitable advice or referral has been offered to me, and I am at a loss of what to do. It has completely changed my life for the worse."

Patient, male, 21 years, Propecia, paper.

"Couldn't run, sleeping 18 hours, change of personality, no motivation to do anything, apathy, loss of friends. Loss of jobs. The antipsychotics have nearly completely destroyed my life. I am no longer able to function like I once did. My mind is now in a total mess."

Patient, male, 20 years, Risperdal Consta, I-Net.

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"Tendon damage to Achilles tendon, musculoskeletal pain, electric shocks in arms and legs, behind eyes, in fingers, toes, coldness numbness in legs and feet, anxiety disorder, regular panic attacks and butterflies in stomach, anxiety induced nausea, constant dizziness, crushing pressure in head, subjective visual disturbances, perception altered, pain behind eyes, electric shocks behind eyes and depressive episodes…Developed more and more terrifying symptoms as time progressed..The mental side effects are crippling."

Patient, male, 34 years, Avelox, I-Net.

7.3.5.4 Persistent social effects

Fifty patients (2%) described the negative social effects they experienced as a result of their SE. Patients provided vivid accounts of significant changes to their normal social functioning:

"Acute depression, hot flushes, weeping, insomnia. 3 nights of approximately 3 hours sleep, irritable legs syndrome, depression causing dysfunction of daily life, weeping for no significant reason."

Patient, female, 67 years, Quinoric, I-Net

One patient describes the significant psychological problems he experienced including severe depression which led to a suicide attempt on his part:

"I was ok while taking the medication and I only had several of the common side effects like dry lips, nosebleeds, tiredness and aching joints. But after completing my 6 month course I have never felt right and gradually became severely depressed and made an attempt on my life around 5 years ago. I have been with the psychiatric department since then and have been diagnosed with agitated depression and severe anxiety, obsessive compulsive disorder and have recently had a relapse in my mental health. I also take medication for my mental health. I was completely different before taking this medication and was very outgoing and sociable but now I am unable to work and I do not go out."

Patient, male, 23 years, Roaccutane, I-Net

7.3.5.5 Persistent life changing effects

Analysis identified 60 patients (3%) who described their SE as a life changing event:

"Diagnosed Cushing's syndrome caused by Nasonex/Mometasone spray. High blood pressure, weight gain of 4 stones, muscle weakness, breathless, nose bleeds, fibula fracture, blood sugars…I am extremely angry that my GP prescribed this drug to me for 9 years. I am left with a list of debilitating health problems after stopping the nasal spray, needing repeat x-ray of my left ankle as it became swollen after normal activity; I am still breathless and despite a healthy diet my weight is still 4 stones heavier than it should be, I have muscle weakness and very reduced stamina and energy levels."

Patient, female, 63 years, Nasonex, I-Net.

"I suffered a retinal artery occlusion in my left eye resulting in persistent cloudy vision which remains so today. I was prescribed one daily pill of quinine sulphate...I am now totally convinced that quinine sulphate was responsible for the original diagnosis of atrial fibrillation and, after ceasing to take it, my heart rhythm returned to normal. It is also my conviction that although I was not diagnosed with atrial fibrillation until earlier this year I think it had been present for some time before and especially last year when my eye occlusion occurred. Logically quinine sulphate could again have been the culprit. "

Patient, male, 85 years, quinine sulphate, I-Net.

"Severe long-term depression, anxiety disorder, suicidal ideation and suicide attempts. I was admitted to hospital after attempting suicide. I struggled for many years, but eventually had to give up my job as a civil servant. I am now on quite a high dose of medication to get me through each day. I suffered a complete mental breakdown, at which point my husband took me to hospital. I have been under the care of the Adult Mental Health Services ever since."

Patient, female, 40 years, Roaccutane, I-Net.

7.3.5.6 Persistent economic and work related effects

Over 40 patients experienced long term work related (22; 1%) and economic effects (19; 1%) as a consequence of their SE:

"I believe I have suffered around 80 side effects ranging from tooth grinding in sleep, ruining teeth to major anger problems, general pain, intense tight chest/breathing problems, ringing in ears and loss of my job and career due to short term memory loss and confusion/concentration."

Patient, male, 27 years, citalopram, I-Net.

7.3.5.7 Section summary

- 10 extracts providing details of the consequences of SE which included persistent physical, psychological, social, economic, work-related and life changing effects
- 10 patient reports
- 2 reports for males; 8 for females with ages ranged from 26-78 years
- Severity levels are 2 mild, 5 moderate and 3 severe effects
- Two drugs linked to CNS; 2 to CVS; 2 to Infections; 1 to Endocrine; 1 to Obstetrics/Gynaecological; 1 to Eye and 1 to Skin

- Comments composed of 7 moderately elaborate and 3 elaborate narratives
- Overall comments related to the long-term consequences of the SE for patients

7.3.6 Patient concerns

Patients (344; 15%) described issues of particular concern to them in 297 (14%) patient, 24 (25%) carer and 23 (26%) parent reports for 217 (14%) females and 127 (17%) males who reported particular issues. In 159 (29%) reports with severe effects concerns were reported, with the highest proportions of reports linked to eye drugs (10; 30%); endocrine (38; 22%); GI (23;19%) and CNS drugs (93;18%). Reports for infants (10; 37%); 41-50 years (57; 17%) and those aged over 80 (15; 25%) were more likely to describe particular concerns. These concerns included negative experiences with HCPs, disagreement with HCPs' treatment/diagnoses and specific concerns about the suitability of medicine.

Table 7.18: Frequency table of Subcategories 63-70[#]

Sub category	Frequency	% of total	% within Hierarchical category 12
Licensing issues	26	1.15	7.56
Issues with prescribers	51	2.26	14.82
Issues with pharmaceutical industry	45	2.0	13.08
Negative experience in HCP interaction	203	9.0	59.0
Specific concerns about quality/suitability of med	74	3.28	21.51
Disagrees with HCP diagnosis/treatment	92	4.08	26.74
HCP ignored allergy history	20	0.89	5.81
Perceives themselves as sensitive to meds	31	1.37	9.01

#Includes multiple concerns per report

7.3.6.1 YC reporter concerns

Over 200 patients (9%) described their HCP interaction in negative terms:

"Acne and itching face. The acne started on my neck (it was similar to the hot, fizzy type rash you get from a reaction to antibiotics if allergic). The acne then spread to my face and continued to itch. It took more than two weeks after stopping the drops before my skin cleared up. The fact medical professionals discarded my concerns and told me to continue the treatment, led me to question their expertise and whether they knew what they were doing at all, so I discontinued taking the drops."

Patient, female, 30 years, FML eye drops, I-Net.

"At the time of taking Roaccutane, I was unaware of the possible link to depression. I remember being informed that it was a 'trial' for the drug and that there were possible side effects. However, I do not recall my attention being drawn to this particular link. Therefore, I had no idea that my subsequent depression, anxiety and suicidal ideation were anything to do with Roaccutane, so I did not report it at the time".

Patient, female, 40 years, Roaccutane, I-Net

"Reduced sexual drive. Inability to maintain erection. I spoke to a General Practitioner (GP) at my local practice. She said that as I was in my fifties it was probably not something to worry about - whilst inconvenient, she said, it was better than being depressed.

Patient, male, 50 years, fluoxetine, I-Net.

Analysis found that 92 patients (4%) of patients disagreed with the treatment/diagnosis of the HCP:

"Papilledema discovered due to developing idiopathic intracranial hypertension after taking metformin. Have permanent damage to sight. Constant headaches experienced. Approached out of hours general practitioner in Accident and Emergency who wrongly diagnosed pain as migraine."

Patient, female, 26 years, metformin, I-Net.

"Itching of genital area very bad itch, yeast infection genitals, oral thrush and swollen glands. I am known to get vaginal imbalances after antibiotics as well as having penicillin allergies so this medicine should had been avoided to prescribe and a more suitable… picked for my chest infection."

Patient, female, 41 years, doxycycline, I-Net.

"Weight gain despite doing 5:2 diet. Skin blisters on penis, tired all the time, severe eczema on hands, increased bruising, skin infections that dont [sic] go away. Dosage raised several times to current 1400mg. I am not convinced I am suffering epileptic seizures since I remain conscious. I think the problem is caused by a blockage in my left carotid artery."

Patient, male, 61 years sodium valproate, I-Net.

Seventy-four patients (3%) had specific concerns about the suitability of their medicine for them:

"Photosensitive reaction, itching, burning hot lumpy skin, affected sleep because of itching. Has tried to avoid sun..Leaflet says that it is not suitable for over 65's and patient feels this should be printed on the box as she did not read this until after she opened it."

Patient, female, 68 years, tetracycline, telephone.

"Only error is that there are no warnings to general practitioners (or on the leaflet) about the medication causing systemic lupus erythematosus (lupus) so as my doctor said; it should never be given to someone with the condition."

Patient, female, 68 years, amlodipine, I-Net.

7.3.6.2 Section summary

- 8 extracts providing details of reporters' concerns such as negative experiences with HCPs, disagreement with HCPs' treatment/diagnoses and specific concerns about the suitability of medicine
- 8 patient reports
- 2 reports for males; 6 for females with ages ranged from 26-68 years
- Severity levels are 2 mild, 5 moderate and 1 severe effects
- Two drugs linked to CNS; 2 to Infections; 1 to CVS; 1 to Obstetrics/Gynaecological; 1 to Eye and 1 to Skin
- Comments composed of 7 moderately elaborate and 1 elaborate narrative
- Overall comments related to the specific concerns of YC reporters on a range of issues

7.3.4.10 Other aspects of YC Reports

Analysis indicated that 175 patients (8%) submitted reports with specific characteristics/attributes including motivations to report, evidence to support their report (medical records/photos) and seeking advice. There were 150 (85.71%) patient, 12 (6.86%) carer and 13 (7.42%) parent reports for 119 (68%) females and 56 (32%) males. Reports with severe effects (73; 13%) were the most likely to display these characteristics when compared with other severity levels. The highest proportions of these reports were linked to ear/nose drugs (5; 16%); eye (4; 12%); malignant disease (5; 10%) and respiratory drugs (9; 10%). Reports for infants (5; 19%); 51-60 years (29; 8%); 71-80 (14; 8%) and those aged over 80 (5; 8%) were more likely to have specific attributes.

Table 7.19: Frequency table of Subcategories 71-74[#]

Sub category	Frequency	% total	% of subcategory
Motivation to report described	99	4.39	56.57
Supporting documents supplied	14	0.62	8
Advice requested	51	2.26	29.14
Awareness of sensitivity exhibited	37	1.64	21.14

#Includes multiple characteristics per report

7.3.4.10.1 Motivation to report

Approximately 90 patients (4%) described the motivating factors that led to their reporting the SE.

One patient identified the importance of reporting SE even if they are well-known. She believes that common SE such as insomnia can have serious negative consequences for patients with mental health difficulties:

> *"I was prescribed aripiprazole last year in the middle of a psychotic episode…However, aripiprazole caused me to sleep much less, so I wasn't sedated and I didn't recover my sleep pattern whilst being treated on this drug. The consequences of that, along with other unfortunate circumstances, were positively harmful for me. Once I was out of hospital and saw my own psychiatrist again, I suggested to him that I might report the drug for this negative effect under the yellow card system. He dissuaded me however, saying that it was already a well-known effect so no need to report it. However, I feel that insomnia is such a serious and harmful effect to be experienced by someone with psychosis, that there absolutely ought to be high profile guidelines on how to monitor for this and what action is required if it continues."*
>
> *Patient, female, no age supplied, aripiprazole, paper.*

Another patient highlights the overwhelming effects she experienced in the following extract. Her motivation for submitting the YC is to increase patient awareness of a potentially debilitating SE:

> *"Symptoms developed over treatment from the mild symptom of restless legs, painful feet and joints in my feet and legs..Started treatment of mirtazapine 15mgs...Hit a crisis point due to being in constant pain, in feet legs knees, muscle stiffness causing reduced mobility, which in turn was affecting my work, combined with other stress my depression was getting worse..I feel that the symptoms of pain in feet, knees, muscle spasms and muscle weakness should be highlighted more on the drug information and doctors made aware of it. It may be a rare side effect but it is a debilitating one, if it had not been for the support of my family the pain would have eventually driven me to take my own life."*
>
> *Patient, female, 53 years, mirtazpine, I-Net.*

This extract describes a patient's altruistic motivation to report her SE:

> *"I thought it wise to let you know of the awful side effects l have been having since taking Nefopam Hydrochloride. I was put on this medication seven weeks ago when l dislocated my new hip replacement. l was having increased sweats, feeling queasy & had awful headaches. This culminated with me starting vomiting yesterday with diarrhoea, this has continued today. I thought to check the information sheet inside the Nefopam box and alongside the side effects that may occur less frequently l am actually experiencing: being sick, diarrhoea, blurred vision, sweating,& headaches, which are actually 5 of the 9 side effects. Needless to say l am stopping taking the Nefopam immediately as its hard enough coping with the problems l have without these extra problems. I hope my experience may help others not go through the same."*
>
> *Patient, female, age not supplied, nefopam hydrochloride, paper.*

7.3.7.2 Supporting evidence

Some reports included evidence to support their experiences. This evidence was provided in 14 reports (1%) and included photographs, medical records and letters from consultants:

> *"My hair density has decreased by approximately one-third within months and it is now approximately half of its density; thus the hair loss has been sudden and dramatic. I have attached photos prior to Mirena insertion and photos taken a year ago to give you an idea of the hair loss."*
>
> *Patient, female, 35 years, Mirena, Yellow card*

> *"The spironolactone was started and developed symptoms ten days later (was in the surgery as attended for an electrocardiogram (ECG)). This is the description of the reaction documented by our practice nurse: Attended for ECG - recently commenced on spironolactone for heart failure, during consult began spasming, rapidly became more violent and commenced on oxygen, with good effect for a short while, violent spasms ongoing."*
>
> *Patient, female, 78 years, spironolactone, I-Net*

7.3.7.3 Advice requested

Analysis of reports found that 51 patients (2%) requested advice, as potential motives for submitting a YC report:

> *"Hair loss. Well I want to find out if there's anything I can do to combat the hair loss without reducing/stopping dosage!"*
>
> *Patient, male, 27 years, Lamictal, I-Net.*

> *"My sex drive has gone down and I am unable to always maintain and get an erection. Everything was normal before I started taking this medicine and want to know anything I can take to help me. I cannot obtain and get an erection and its affecting my sexual relationship."*
>
> *Patient, male, 26 years, finasteride, I-NET.*

"Her daughter was withdrawn from Epilim and given lamotrigine for epilepsy. Experienced a severe skin rash 8 weeks after all over body..Liver readings doubled. Mother would like to know if this was first stage of Stevens-Johnson syndrome. She would also like to know if Stevens-Johnson syndrome presents itself as a skin rash initially and if it is progressive."

Parent, female, age not supplied, lamotrigine, paper.

7.3.7.4 Awareness of sensitivity exhibited

Thirty seven reporters (1.6%) made explicit reference to their sensitivity to medicines:

"I am sensitive to a list of medications, they are clearly written on my National Health Service (NHS) notes, I often have to remind consultants of them. I made this very clear to the consultant that prescribed pregabalin to me, but he still prescribed it. I also wear a medical bracelet due to high level allergies."

Patient, female, 41 years, pregabalin, I-Net

"Extreme irritation of the eye, redness, itching, inflammation and burning sensation on the skin. I was originally prescribed antibiotic drops, but those did not improve my condition and made it worse. Because of that I went to the accident and emergency which I had been advised to do in that event and was given the ointment. The ointment has had a definite adverse effect which was almost instant. I applied the ointment at night when I returned from the hospital and again in the morning. Some ointment got on to my cheek and this had a burning sensation for a short time. At this present time, about four hours since the last application, my eye is very inflamed, red and painful.I am allergic to ampicillin and septrin having had very severe reaction to the same following surgery. I have to avoid these penicillins and have not been prescribe them for years.
Patient, female 66 years, chloramphenicol, I-Net.

7.3.7.5 Section summary

- 8 extracts providing details of the specific characteristics of YC reports such as motivations to report, supporting documentation and advice seeking
- 7 patient reports and 1 parent report
- 2 reports for males; 6 for females with ages ranged from 26-78 years
- Severity levels are 1 mild, 1 moderate and 6 severe effects
- Three drugs linked to CNS; 2 to CVS; and 3 to Endocrine system
- Comments composed of 1 scant, 1 moderately elaborate and 6 elaborate narratives
- Overall comments related to the specific characteristics of YC reports

7.3.8 Reports of positive SE

In addition to these specific attributes analysis of the YC reports also revealed five reports which described positive effects:

"Rapid weight gain (24kg in 3 months) so asked general practitioner to reduce dose from 600 to 300mg/day. Weight stabilised after reducing dose, at 15 kg heavier than normal weight. A positive side effect is a complete reduction in migraines, used to suffer 3-5/month but have not had any since starting pregabalin."

Patient, female, 30 years, pregabalin, I-Net

"The side effect I am reporting is a positive one. Not only has erectile dysfunction (ED) been treated, the chronic pain I have suffered is much reduced. Markedly reduced pain from my right hand, following a reverse flow radial arm flap surgery."

Patient, male, 63 years, sildenafil, I-Net

"Did feel a bit light headed. More important fact is that this medicine had a rapid, confirmed, successful additional effect on ending a dystonic storm. The storm started as I got into bed. It's a deep neurological crisis. I felt it happening in my nervous system and I lost control of limbs and entered a state of panic and utterly intolerable pain. I was in a state of forced squirming unable to sit or lie still and unable to control body properly. Other pains from my myalgia, paresthesia were exacerbated by the storm. Taking one 5 mg zolpidem in EU/ UK Stilnoct film coated tablet had a moderate effect but merely took it down from cat 4 to cat 1-2. Systems were still all involved and head, neck, back, chest, legs, feet, arms, hands, face, voice, and a deep sense of profound unease/ terror. So I took one more and it pretty much nailed the storm. The dystonia continues in its usual semi manageable way so I look forward to sleeping now. I would be delighted to explain my experience as my experience confirms that of others. This drug and similar ones of the class may be novel treatments for status dystonia: an acute flare of chronic focal and generalised dystonia."

Patient, male, 39 years, Stilnoct, I-Net

"On taking tramadol I had much more energy. On further investigation it was found that 1 tablet 50mg extended release lowered my standing heart rate by 20 beats per minute. This is great if you have postural orthostatic tachycardia syndrome (POTS). Continued use to prevent daily spikes in heart rate for POTS could be a possible treatment for those with asthma that can't take beta blockers?"

Patient, female, 34 years, tramadol hydrochloride, I-Net

"I suffer from myelofibrosis and have been having regular blood transfusion, every 3 - 4 weeks. Since being diagnosed with temporal arteritis and being prescribed prednisolone my haemoglobin is much improved and seems to hold at around 90. I only need transfusions now at extended intervals, around 8 weeks. Improved production of red cells. Is this one of the (beneficial) side effects of prednisolone? None of the professionals seems to know."

Patient, male, 76 years, prednisolone, I-Net

7.3.9 Template analysis of selected free text narratives

A range of extracts have been used to demonstrate the results of the template analysis. These extracts represent severe effects to a variety of drugs across different reporters. The findings are illustrated by verbatim quotations and the extracts identified by reporter type, patient age, gender, drug type and method of

reporting. The analysis was conducted on 12 patient, 12 carer and 12 parent reports. These reports described severe reactions across a range of drug classes - GI(3); CVS(4); respiratory(3); CNS(7); infections(4); endocrine(3); obstetrics(3); malignant(1); muskoloskeletal (2); eye(1); ear/nose(1); skin(2); and OTC(2). The focus of the analysis is on the multi-dimensional impact of severe SE. Five main themes were identified with eight subthemes. The analysis is divided into these main themes and is composed of five sections as follows:

- Reconstruction of event
- Impact of SE
- Coping with SE
- Seeking meaning
- Attitudinal change

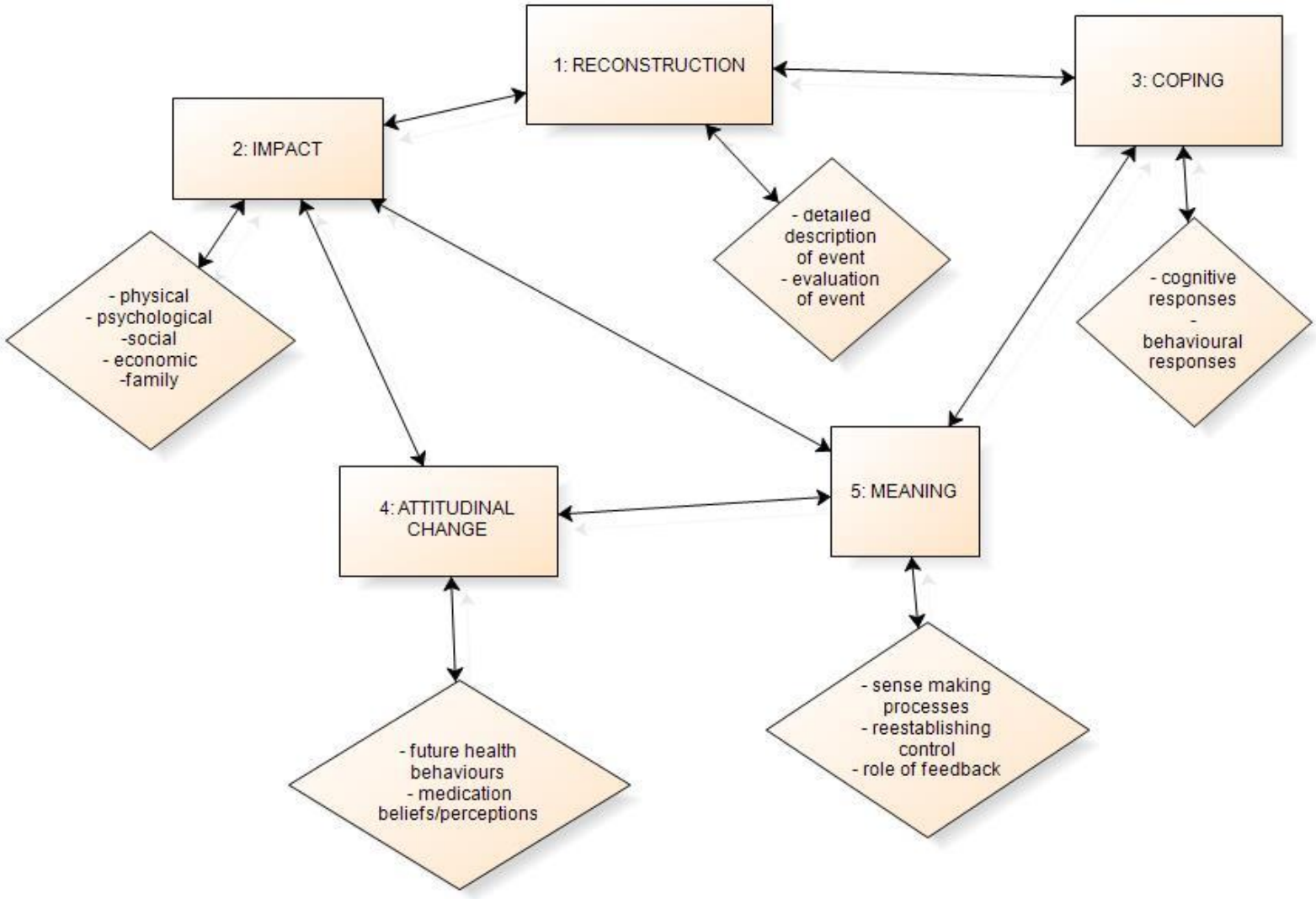

Figure 7.11: Final template of main themes and subthemes

7.3.9.1 Reconstruction of event

Description and evaluation of effects

The elaborate narratives had detailed descriptions and evaluations of SE. They relate information on the onset, progression, severity and outcomes of SE:

> *"I am e-mailing on behalf of my friend who is staying with me for a few days. She became unwell yesterday evening with a bad head cold and as she felt worse this morning she took two of the above caplets which she claims she has had before. Within a very short while she suffered from swelling of the inside of her mouth and lips, thankfully just on the left side. I took her to my local pharmacy and the pharmacist there advised that she saw a doctor. Thankfully my medical centre were able to see her and she was told that she was suffering an allergic reaction to the caffeine which obviously is one of the ingredients."*
>
> *Carer, female, unknown, Galpharm extra pain reliever, Patient(MHRA)*

> *"Red hands and feet, prickly raised rash on feet, knees, hands, elbows and eventually on the arms, pins and needles throughout the body. Dry mouth, headache and nausea. General exhaustion. He has been given antihistamine and steroid cream. Seek Advice Details: My son woke up in the night with itching and the rash burning. We called NHS Direct due to severity of the rash and places. The doctor called 3am and then we saw a doctor twice for medication."*
>
> *Parent, male, 14 years, Buscopan, I-Net*

7.3.9.2 Impact of SE

Analysis indicated that the impact of SE manifested themselves across a range of domains – physical, psychological, social and economic.

Physical, psychological, social, economic and family effects

Reporters indicated the effects had significant negative physical, psychological and economic effects:

> *"Severe acute respiratory syndrome, acute digestive discomfort, persistent chronic nausea, very tight chest and diaphragm pain ("like a 3-hour heart attack"). The effects all peaked and continued at a high level for 4.5 hours, tailing off until 3.5 hours later. I was reluctant to involve the ambulance service, and it was obviously not a time when I could consult a pharmacy or my own general practitioner. Had this happened during daylight hours, I would have probably sought professional advice or intervention. The chest tightness and breathing difficulties were extremely difficult and painful, and the chronic nausea was quite distressing."*
>
> *Patient, male, 69 years, carbocisteine, I-Net*

> *"My daughter only started to gamble when the dosage was increased, and she eventually had to sell her house to pay some debts. Having been told by the neurologist 'it was not her fault', and that gradually decreasing the dose of the agonist, changing to a levodopa drug Sinemet and having deep brain surgery the addiction would stop, but it continued in secret for some time. We were never told this is known to be a possibility. Her attempted suicide and depression was as a result of her desperate financial situation. This has led to a breakdown in family*

relationships (she is widowed with two teenage sons). She has told so many lies to so many people, there is now a total lack of trust."

Parent, female, 40 years, Requip, I-Net,

Reporters also expressed concerns about the particularly significant negative impact of effects on the family of patients:

"Aggression, agitation, anxiety, paranoia, passive suicidal ideation and violence. I am writing to report this on behalf of my deceased father. I believe that he should never have been prescribed this drug in the first place given its side effects, I feel it exacerbated problems my father already had and the GP should have flagged this when prescribing. My father was on this medication for 6 months before his death and day to day life for himself and his wife and my sisters was awful. He became aggressive, violent and suffered severe anxiety and paranoid thought. He mentioned suicide on more than one occasion."

Carer, male, 50 years, Champix, I-Net

"Ruptured post tibial tendon. Joint and tendon, muscle pain. Anxiety. Fatigue. Pins and needles. Right post tibial tendon ruptured after three days on ciprofloxacin. Left post tibial tendon also affected after three days on ciprofloxacin. All other symptoms mentioned happened gradually. From a fit and active person to disabled in three days. I rode horses and was able to do all the associated work. I am only just able to walk without crutches for short distances and still need them for rough ground. My husband had to take over the running of the house, the horses and dogs and caring for elderly relatives. This had had a catastrophic effect on our lives as a family."

Patient, female, 62 years, ciprofloxacin, I-Net

7.3.9.3 Coping with SE

Overall reporters' descriptions of coping processes involved two subthemes that divided into cognitive and behavioural responses. Effective coping strategies generally involved both cognition and adaptive health behaviours.

Cognitive and behavioural responses

These sub-themes were linked and most reporters engaged in combinations of these responses. Regardless of reporter type, coping involved cognitive and behavioural responses such as non-adherence, information seeking, differential diagnosis and social support seeking behaviours:

"Dizziness, drowsiness, hallucinations, headache, rapid heart rate, shaking, sleep disturbance, vertigo, vomiting. After speaking to a nurse and basic searches on the internet, the patient was told they should never have been given such a high dose as they have never taken this before, and should have started lower and built up over time."

Carer, female, 49 years, Zamadol SR, I-Net

"Bumps on arms a day after taking omeprazole, followed by rash spreading over body from the back. Doctor thought it was eczema but it didn't cause my child to itch and didn't respond to prescribed eczema lotions and creams. I suspected it was the medicine as I saw this was a rare side effect so I decided to stop the medicine."

Parent, female 0 years, omeprazole, I-Net

"I received a letter from a medical centre making a strong recommendation to discontinue taking quinine sulphate which I complied with shortly after my first 24 hour electrocardiogram (ECG). At that time my only thought was what could I now take to relieve my leg cramps at night. Your letter confirming your diagnosis of atrial fibrillation came as a great shock but also encouraged me and my wife to carry out detailed research into the side effects of quinine sulphate on the regular rhythm of the heart and I discovered there existed a great deal of evidence of which I am sure you are aware. At the same time I tried to convince myself into taking your recommended regime of medication but I did not succeed. After weeks of discussion with my wife, who has been a tower of strength throughout, I continued to take only my usual medication of perindopril, clopidogrel and amlodipine."

Patient, male, 85 years, quinine sulphate, Patient(MHRA)

7.3.9.4 Seeking meaning

Several processes were identified by reporters as fundamental to finding clear meaning and understanding their experiences. These included seeking to clarify/making sense of their SE event. In addition, reporters frequently tried to re-establish control with health-related decisions such as non-adherence; reporting their SE or accessing appropriate feedback:

"Three months ago my granddad passed away it was sudden and unexpected. In 2007 he suffered a stroke in result of this he was prescribed the drug warfarin. He also had an irregular heartbeat. He was doing fine on the warfarin. I was taking him for his regular blood tests. A few years later we discovered that he was losing his memory we didn't think anything of it until it started getting worse. He had dementia for 6 years prior to his death, me and my mother were looking after him. I was his full time carer and my mother helped me out. He had arthritis on his hip and knee so he had trouble walking. His dementia and arthritis rapidly went down hill so we could no longer take him to the clinic for his blood tests, meaning we had to get district nurses to come out to the house. This was fine until they started having problems extracting blood. They suggested putting him on this drug where he wouldn't need as many blood tests, the drug in question is rivaroxaban. We didn't know that rivaroxaban could cause bleeding to the brain, this is what my granddad died of. At the hospital they explained that with dementia your brain shrinks and any sudden jolt, fall or knock to the head could cause a bleed. We put my granddad in respite, went away and on arrival back we received the call from the hospital, they couldn't operate because of his dementia, age and heart condition. I don't know exactly what happened in the care home but you don't just suddenly get a bleed on the brain, something must have caused it. We were there with him in the hospital and we saw him take his final breath, this will live with in my memory for the rest of my life. Please I want your help to try and get rivaroxaban banned for good, there must be another way to thin the blood, another medicine that won't cause death. I want to leave end this email with this, warfarin is used in rat poison, it may just be in small doses but it is still a poison. Thank you for taking the time to read this".

Carer, male, unknown, Xarelto, Patient(MHRA)

"I am writing to find out whether or not a severe adverse reaction to infliximab that I suffered has been reported. I had the intravenous medication at the hospital and almost died as a result of a severe reaction resulting in liver failure, pneumonia and development of lupus. This was confirmed by severe jaundice, long stay in hospital and two liver biopsies etc. Unfortunately, the hospital office has refused to let me know if this was reported. This is a very serious incident that almost resulted in my death and should have been reported..I developed itching prior to the infusion. I explained to the rheumatology nurses who checked with the doctor who dismissed it as dermatitis although I told them I have never had dermatitis or any skin problems. He gave the nurses the go-ahead to give the infusion despite my concerns that I had the itching and my alanine aminotransferase were elevated which the same doctor also dismissed as a blip. I became extremely unwell and had to admit myself via accident and emergency to hospital with serious liver damage and close to death. I was unable to walk, became extremely jaundiced, lost my sense of tasting (was unable to taste any kind of salt or sugar totally; lost my appetite completely), became extremely swollen with cellulitis, numbness and pins and needles to both legs which were very swollen with fluid retention, the steroids burnt a hole in the side of my tongue, muscle weakness, fainting, fatigue, tinnitus, shortness of breath among other symptoms. None of the medications were working and my liver became more damaged. Following on from the liver damage, I had atelectasis and subsequently suffered from serious pneumonia. This unit does not have a liver specialist department yet I was not referred to a specialist unit and suffered unnecessarily and unduly. I have made some degree of recovery but have ongoing problems with my health generally and my liver. My alanine aminotransferase fluctuate and are presently deranged also my gamma-glutamyltransferase. I continue to suffer tremendously from ongoing problems with my health and emotional state. I was never offered any debriefing or counselling as this has had a major impact on my young family and myself. Over the last few days I have been diagnosed with possible narrowing of the carotid arteries due to syncope (continue to feel faint even when sitting and suffering from serious fatigue and exhaustion). The side effects are still ongoing as my liver function remains abnormal and I am suffering from liver pain etc. I am disappointed to learn that such a serious, adverse medication-induced liver injury occurred and almost resulted in my death yet it was not reported to the MHRA".

Patient, female, 47 years infliximab, MHRA

"My son commented three weeks into the treatment that this was affecting his sexual libido and he had noticed the change over the past few weeks following commencement of this tablet course. He has now stopped taking this medication prior to seeking further medical advice. We were aware of the listed side effects before commencement and my son experienced some headaches in the first week and the drying of skin and lips, nose, which he had expected. This was reported to the pharmacist and the skin clinic. Paracetamol x 2 were taking at the onset of a headache and emollients for the dry skin. He was not taking any other medicines. Prior to commencing with this medication we carefully read the leaflet Information for the user containing all the listed side-effects. He has later said to me that his emotions were also more emphasised. Which we were aware of as they were listed. This clearly does not mention or list male low libido or impotence condition in your leaflet. My son was concerned and searched the side effects of isotretinoin on the internet in relation to his new complaint of a low libido. Only to find this was listed and commented on frequently of sexual libido being affected as a common side effect of this drug. Prior to my son taking this medication, he had a normal sexual relationship with his girlfriends. Why was this side effect not listed on your leaflet? I cannot begin to say what implications

this can have on my child at this very important development age. Do you have any trials of testosterone levels taken before and after isotretinoin use? My son feels so sure of this side effect of impotence with the taking of isotretinoin and is willing to have the testosterone blood test to prove clinically that this is a side effect of this drug. I will be taking this matter further and await your early response. He felt he had to stop taking this medication prior to seeking further medical advice."

Parent, male, 17 years, isotretinoin, I-Net

7.3.9.5 Attitudinal change

A recurrent theme amongst the narratives was the change that occurred in health beliefs/perceptions. As a result of SE, beliefs about medicines; about their ability to manage effects; attitudes towards their general health and perceptions of HCPs were subject to change.

This report highlights a change in belief about medicine with specific concerns about future use of antibiotics:

"Felt giddy and sick. When you feel ill you don't want a drug that makes you feel sicker. Now afraid of using antibiotics."

Carer, female, 81 years, amoxicillin, I-Net

This patient is afraid to try any new medicines as a result of her effects:

"Now, just over 2 months later, the pain and weakness have continued to improve slowly, but I am by no means fully recovered. I find that if I overdo things, which could simply be a session of ironing or a shopping trip, the pains become more severe and the feeling of weakness in all my muscles returns. I still sometimes wake up from sleep screaming in pain and unable to move to a more comfortable position, but this is now less frequent. My doctor, whilst sympathetic, offered me no help for my symptoms. I am now afraid to try any new medications and am trying to control my blood sugar with diet."

Patient, female, 59 years, Januvia, I-Net

This patient describes a change in her health beliefs - the severe effects she experienced have led her to now believe she is addicted to her medicine:

"Yesterday I forgot to take my tablets (i.e. venlafaxine lisonopril and simvastatin all of which I take in the morning). I went to bed and woke at 1am thinking I was getting a migraine - I had at that time not remembered that I had missed a dose.. I took 50mg sumatriptan. Very shortly afterwards I suffered from severe vivid migraines with wakefulness/paralysis/trying to scream from which I was unable to rouse myself. I had no headache or nausea. The nightmares continued through the night, although later turned to less frightening but extremely vivid dreams. I had great difficulty waking up at my usual time, but managed it. It is now 11.22 and I still feel peculiar and extremely tired, although I have now taken my medication at 8.30am. I think that this incident was caused by either missing my venlafaxine, or otherwise by this and by subsequently taking the sumatriptan. I

hope this information is useful. It isn't pleasant to realise that one is addicted to ones [sic] medication."

Patient, female, 53 years, sumatriptan succinate, I-Net

The SE have had a negative impact on this patient's daily life and her confidence to cope with the onset of unpredictable effects:

"There is definitely good cause to prevent e-lites being smoked near people on lithium. I went shopping not so long ago and basically suddenly had to stop walking as felt terrible. My partner looked up and saw someone passing by smoking an e-lite in close proximity. I luckily always have water on me and also paused red faced and hot for a minute till I felt better and vowed never to go near the e-lites and their open air users again..The e-lite nearby must have rocketed through my system and changed my level as I couldn't even carry on walking. Lithium also affects heart rhythms which could be very serious. I think it is very unfair that random passers-by have the power to make others feel ill this way albeit accidentally. It still makes you ill whether they do it on purpose or not. I can't go to the shop the cinema or any cafes etc. because I dread a sudden health change prompted by unpredictable circumstance."

Patient, female, unknown, E-lite - electronic cigarette, MHRA

This patient believes that her medicine is necessary and worries about the impact of non-adherence on her general health. However she is unable to accept the resulting SE and has to stop taking the medicine:

"40mg atrovastatin-anxiety and depression. Tried simvastatin provastatin, now rosuvastatin reduce dose each time same problem. Took medicines for approximately 3 months. I felt unwell on them, nothing specific informed GP then woke one morning with no warning and was unable to go to work, very tearful, did not want to leave the house..Went back to 5 mg been on for nearly 4 months but have had to stopped again as I was getting the anxiety and depression coming back. I have no issues taking the medication if that's what I need to stay well, but constantly feeling like this is not good and every time I have to stopped [sic] taking them I start to worry about having a heart attack or stroke. Each dose was lowered, but side effects occurred quicker, and have taken longer to get over."

Patient, female, 60 years, rosuvastatin, I-Net

This patient's health beliefs now include his conviction that his SE were unnecessary and that his long term health may have been negatively affected by his medicine:

"The Creo Pharma lofepramine has given me severe and lingering side effects from 1 tablet taken at night-time and one tablet taken on the following morning.. The dispensing of the lofepramine was a matter of some discussion between the pharmacist and myself, when I discovered that the brand I've had two days of misery and totally unnecessary side effects from the Creo lofepramine, and with now unknown future repercussions on my already frail system by ingesting what was, to my body, nothing but utter poison in the form of Creo lofepramine."

Patient, female, 65 years, lofepramine, I-Net

These attitudinal changes were apparent across all reporter types and often were linked to negative interactions with HCPs or the SE being downplayed by HCPs:

> *"I eventually got taken to the local hospital to wait for ages to see a doctor. This doctor then referred me on to the new specialist emergency hospital, where I was admitted for tests. My blood was found to be ok and the doctor was off with me and acted like I was wasting his time! I repeated my concerns about the bad side-effects I'd experienced since taking the clarithromycin antibiotic- he didn't seem to know anything about these side-effects."*
>
> *Patient, female, 42 years, clarithromycin, I-Net*

> *"After taking Zamadol they were unable to return to work for over a week as they felt so dizzy and had a headache. When the patient tried to report this at the chemist they were told they had never heard of yellow card and go to see the doctor. The doctors surgery also told them they had never heard of yellow card so a complaint form was taken. The next day the doctor phoned to tell them that they had caused a commotion asking for the yellow card. They are reporting this effect so that no one else suffers the same as them. They were not very keen to report these effects and I am filling this in for the patient as I'm not sure if the doctor has done one. The patient contacted the doctor but was told the reaction had nothing to do with tablet prescribed. They did not suffer from this before they took the tablet and after advice from a scientist and a nurse they were advised to report this."*
>
> *Carer, female, 49 years, Zamadol SR, I-Net*

> *"Was prescribed trimethoprim for a suspected urine infection, within an hour of taking I started to feel unwell, short of breath, dizzy, heart racing. Called my general practitioner (GP) who said call an ambulance. I was admitted to hospital and kept in for 4 days but they did not believe it was connected to the Trimethoprim. Within a month I had another water infection and despite me talking through my concerns about taking trimethoprim I was prescribed again and assured I would be ok. Within 1 hour I became increasingly unwell, my vision was very blurred and I had severe pain in my legs. I immediately went to my GP. I was in agony, still my GP refused to accept it was connected. I left my GP and started severely vomiting and collapsed. An ambulance was called and I was rushed to hospital."*
>
> *Patient, female, unknown, trimethoprim, I-Net*

4.5 Discussion

The aim of this phase of the study was to investigate how YC reporters identify and manage ADRs, what type of information sources were used to aid identification, as well as the impact of ADRs. It analysed 2285 patient YC reports received by the MHRA in a six month period from July-December 2015.

YC description

Results indicated a pattern in YC reports - the majority submitted for females with more younger females and older males reported to have experienced SE. Over 30% of reports were for females aged 21-40 and over 20% for males aged 61-70. Previous YC research found a similar pattern of greater proportions of reports for females (Avery et al., 2011). ADR research which indicated that females and older patients are at higher risk of developing ADRs also supports this study's findings (Martin et al., 2013; Moen et al., 2009; Zopf et al., 2008).

Data from this study shows that the majority of reports were submitted by patients themselves, particularly among females (94%). Over 90% of reports concerning those aged 41-50 and 51-60 years were submitted by patients. As expected most parent reports were for infants and those 1-20 years; while most carer reports were for those in the oldest age categories (71-80 years and over). Although past research has suggested that older people were at greater risk of developing ADRs due to factors such as such as co-morbidity and polypharmacy (Alhawassi et al., 2014; Hefner et al., 2015; Martin et al., 2013), the distribution of reports did not reflect this.

The Internet was the most commonly used method of reporting for both genders, all age groups and for all reporter types (over 90%). These findings are consistent with previous research which found that the Internet was commonly used for health information (Clarke et al., 2016; Harvey et al., 2017). However Internet reporting dropped to 66% for those aged over 80. This finding is consistent with that of Medlock (2015) who identified HCPs as the preferred information source for older seniors seeking additional information on side effects. In contrast to this study previous YC research identified the YC form as the most frequently used method of patient reporting with just 14% using the Internet (Avery et al., 2011). Possible explanations could include increased Internet use amongst the general population. In general research has also indicated that increased numbers of patients are accessing health information online (Clarke et al., 2016). Research has also been conducted which suggested changes to the Internet form to reduce its complexity (Anderson et al., 2011). These changes may have led to enhanced Internet reporting. Frequently online health forums provide details on the YC scheme which could also result in increased Internet reporting.

This study identified over 70% of overall reports for serious effects with a higher proportion in females. These results reflect previous research which also found that more serious ADRs were reported for females and females reported greater impact on QDL (Lucca et al., 2017; Skilving et al., 2016). Consistent with previous research this study found that severe effects were more likely to be

reported for older age categories (Hefner et al., 2015). Over 60% of those aged 14-50 reported serious effects, increasing to over 70% in those aged 61-80 and over. Serious effects were not confirmed by HCPs in the majority of YC reports (90%) regardless of reporter type. The current study also found that unresolved reactions did not result in increased reporting of severity. Only a small proportion of reports described effects that caused incapacity (5%), hospitalisation (8%) or threatened life (11%). In contrast, earlier YC research found higher rates of hospitalisation (13%) and lower rates (6%) of life threatening outcomes for UK patients (Avery et al., 2011; Inch et al., 2012). It seems possible that several factors could explain these different findings including general improvements in pharmacovigilance, increased availability of health information on ADRs, increased drug potency or simply variation in individuals' experiences due to chance. Many extreme outcomes such as hospitalisation/life threatening events were experienced by the vulnerable populations - younger and older patients. The most interesting findings relate to severity and suggest that YC reporters' assessment of SE as serious, are not linked to consultation with HCPs, unresolved reactions, or outcomes such as hospitalisation/incapacity. Further research is required to examine what factors influence YC reporters' severity assessments.

A high proportion of severe reactions and polypharmacy reports were linked to multiple reactions and multiple outcomes. Older patients were more likely to have resolved reactions which could be explained by effective medical interventions. In general older patients are more likely to attend HCPs than younger patients which could in turn result in better recovery outcomes. This explanation is supported by survey findings in Phase One of this study which found that retirees were more likely to attend their GPs when experiencing SE. The findings from all the phases of this study will be compared and discussed in the following chapter – Chapter 8: Discussion.

Pattern of medicine use amongst YC reports

This study revealed a pattern of medicine use amongst YC reports. The number of reported drugs ranged from 1-12, although the majority of reports were for one drug regardless of gender or age, with most reports being linked to CNS, infections and CV systems. These findings are not unexpected - NHS statistics which examined the number of prescription items dispensed in England indicate that the top three system drugs prescribed in the community in 2015 were as follows: 98.5% were for drugs in infections; 97% for drugs in

CVS with 90% for drugs in CNS (NHS, 2016). It is reasonable therefore the YC reports would reflect this pattern of prescribing and that a large number of reported SE would be related to these systems. CNS drugs were the most commonly reported regardless of gender. They were also linked to four age categories and were highest in those aged 21-40 and 51-60 indicating similar use across age ranges. CNS drugs are used for a wide range of conditions such as anxiety, depression, nausea, pain, epilepsy, dementia and substance dependence. It is therefore not unexpected that CNS drugs were regularly reported to the YCS. In addition NHS statistics indicate that there has been an increase of 5.7 million in CNS items dispensed since 2014 (NHS, 2016). The greatest increase in prescribing in 2015 was for antidepressant drugs such as amitriptyline, mirtazapine and citalopram (NHS, 2016). Increased volume of prescribing CNS drugs could reasonably be expected to result in more SE and more YC reports. As expected CNS drugs were also linked to severe effects followed by infections and CVS.

A pattern of SE outcomes was identified as follows: incapacity was reported for CNS and CVS drugs; hospitalisation was linked to GI, CVS and CNS drugs; while life threatening events were reported for CNS drugs. An interesting finding was that reported severity levels were not influenced by the number of drugs cited. The overall profile of effects in YC reports was also indicative of certainty in the association - nearly half of reports concerned only one or two effects and were linked to one drug. The most common effects were physical – pain, abdominal discomfort, headache and fatigue. These findings are broadly supported by previous YC research which identified the top five drugs in 270 patient reports as CNS, CVS and skin system drugs. The most frequently reported reactions were also physical – nausea, headache and dizziness. (Avery et al., 2011). A pattern of high frequency and complex impacts was identified amongst GI and CNS drugs respectively. Over 70% of physical impact was reported for GI drugs – this may be related to the variety of drugs within this class which are used in multiple treatments and different conditions. A combination of physical, psychological and social impacts were found to be linked to CNS drugs (30%). Again these findings are not unexpected as there is significant diversity within the CNS class in terms of the type of drugs. Overall GI and CNS drugs can be used to treat numerous diseases which would reflect the findings of common and complicated impacts for these specific BNF classes.

Value of free text comments

This study indicated that many of the free text comments provided vivid and rich descriptions of patients' experiences. An interesting finding was the

comprehensive information, frequently rich in detail, which was supplied by reporters. This information reflected the range and complexity of SE. Many of the illness beliefs/perceptions identified encompass Leventhal's dimensions of illness representations. Over 90% of reports contained descriptions of physical symptoms, highlighting the importance of somatic sensations in YC reports. Drug details and reasons for taking the drug were supplied by over half of reporters - 33% and 21% respectively. These findings are supported by previous YC research which found that patient reports included symptom and history information (Avery et al., 2011). Previous ADR research has also found that patient reports frequently relate descriptions of physical effects (De Smedt et al.,2012; Gandhi et al., 2003; McLernon et al., 2010). Focus on physical sensations as displayed in the YC reports is a key element of the CSM of Self-Regulation (Hagger & Orbell, 2003; Leventhal et al., 2011).

Impact and severity of SE

Regardless of reporter type, elaborate narratives were frequently provided on the severity and impact of SE on patients' lives. Overall 61% of reports related a range of effects; mild (13%), moderate (24%) and severe (25%). A combination of explicit and implicit impacts was described in 95% of reports; physical (93%), psychological (24%) and social (34%). These findings illustrate the serious disruption to many aspects of patients' lives - emotional, social and occupational – which can be a feature of SE (Asseray et al., 2013). A striking finding was the prolonged consequences of effects for just under 20% of YC patients. These included persistent negative physical (9%), psychological (3%), social (2%) and life changing (3%) effects. Previous YC research found similar patterns of impaired emotional (34%) and social (27%) functioning in patients (Avery et al., 2011).

Another important finding was the subjective experience of SE, over half of reports described effects as 'severe' which included effects commonly labelled as mild such as rash, muscle pain. These results can be explained by research which has identified the role of individual perceptions and attentional biases in health behaviours (Lee et al., 1997). Patients with heighted health anxiety have negative perceptions about their symptoms and illness in general. These beliefs can lead to vigilance to symptoms and increased somatosensory perceptions. Attentional biases are therefore associated with increased pain reports and elevated perceptions of severity (Chapman, 2011). Overall the information on SE impact

highlight the value of YC free text comments and highlight their potential to contribute knowledge to health research.

Identification of SE

This study found that 30% of reports provided details on how individuals identified experiences as suspected side effects. The most commonly reported method was related to the timing of effects – 13% - followed by differential diagnoses in 5% of reports. These findings are supported by previous research which also identified the use of timing relationships by patients to assess SE (Chaipichit et al., 2014; Krska et al., 2011). However, these levels are below those observed by Avery et al., (2011) who found over 60% of patients reported temporal associations. In terms of information sources an interesting pattern emerged with the use of multiple sources by many reporters. Surprisingly low proportions - just 6% - confirmed effects with HCPs while just 1% used the Internet and 2% reported they used PILs. Previous research of reporters to the YCS found similarly low proportions of HCP use (9%); but higher proportions of Internet use (5%) and use of PILs (16%) (Krska et al., 2011). A possible explanation for the findings of this study might be that that Internet or PILs were used by the YC reporters but not specifically reported. However this result could also link to an evolving pattern of information use in YC reporters and thus indicate a focus for future research. Survey data from Phase One of this study found a contrasting pattern of information use with over 60% of survey respondents using GPs or PILs to confirm their SE. These findings will be compared and fully discussed in the following chapter – Chapter 8.

Behaviours and outcomes

Over 40% of reports described a variety of patient behaviours such as HCP consultation (30%); non-adherence (16%) and counteracting SE symptoms with medicines (8%). These findings contrast with previous research which identified coping behaviours in patients with heart failure (De Smedt et al., 2012). A higher proportion of these patients consulted HCPs (49%) and used additional medicines to alleviate the SE (14%) when compared to YC reports. In contrast to the findings from this study non-adherence was reported in just 7% of heart failure patients. However it is not unexpected that patients with a chronic condition such as heart failure would display different patterns of health behaviours to those of general YC reporters. The former have different health concerns and would be expected to consult with their HCPs, adhere to their medicines or take alleviating

medicines. There has been extensive research into non-adherence which has identified its risk factors (Martin et al., 2005; Van Dulmen, 2007). Non-adherence studies have found that patients with concerns about their medicines who receive conflicting similar information are more likely to be non-adherent. In addition, patients who sought information from non-HCPs were more likely to be non-adherent (Carter et al.,2013; Nunes et al., 2009). These findings contrast with this study which found that over half of those who consulted with HCPs engaged in non-adherent behaviours. The levels for non-adherence were higher in this study than those of the Omnibus survey (2009) which found just 5% of respondents stopped their medicine.

It is noteworthy that just 1% of YC reports described recording the suspected effects in medical records. This indicates some cognitive dissonance amongst reporters who report to the YCS yet did not make contact with their HCP to get their medical records updated. These findings may be explained by issues of accessibility or time constraints with HCPs. It may also be related to dismissive attitudes among HCPs towards SE.

YC reporters and reports

This study found that patients had specific issues including concerns about HCPs. Just under 10% reported negative experiences with HCPs with 4% disagreeing with the diagnosis and/or treatment. Previous YC research supports these findings – 8% of reporters to the YCS described dismissive attitudes to ADRs amongst HCPs with 4% of patients stating a HCP had refused to make a report when requested (Avery et al., 2011). These negative HCP interactions are an important finding as 33% of reports described interactions across a range of HCPs: GPs (17%); pharmacists (4%); hospital admissions (4%) and multiple HCP contacts (14%). Engaging with HCPs is a key component for many patients who experience SE. Therefore, this may be a useful result in indicating a focus for future research.

Previous YC research identified that many patients reported their ADRs for altruistic reasons (Avery et al., 2011). Research in the Netherlands found that over 90% of patient reporters expressed altruistic motives for reporting – to share their experience, prevent harm to others and benefit research (Van Hunsel et al., 2010). A later review of the factors which influence patient reporting in the UK, Australia and the Netherlands found that altruism was identified as the primary motivation to report in 21 studies (Al Dweik et al.,2016). This research study

found that the altruistic motivations which underlined reporting to the YCS were described in 4% of reports. These findings support previous research - that in common with other patient reporters YC reporters also wish to share their experiences and prevent others from suffering similar reactions (Al Dweik et al., 2016).

A characteristic identified by this study were the reports which included supporting evidence in the form of medical documents, letters, photos (1%). Advice was requested by 2% of reports and was frequently linked to severe effects. Research has illustrated the advantages that accrue in adaptive health behaviours when effective feedback is provided to patients (Morrison et al., 2014; Pu et al., 2015). This indicates the importance of developing appropriate feedback channels for YC reporters – further research is required to identify the benefits of such tailored feedback which was found to be desired in the evaluation of patient reporting (Avery et al 2011).

Individual free text narratives

A novel finding of this study was the results of the template analysis undertaken of selected narratives. The focus was to explore and conceptualise the relationship between YC reporters and the multidimensional impact of SE. Five major themes were identified: reconstruction; impact of SE; coping; attitudinal change and meaning seeking.

Reconstruction of SE event

Research has proposed that memory retrieval is a process of reconstruction greatly influenced by cognitive schema. These schemas affect both memory encoding and retrieval processes (Bower et al., as cited in Chan et al, 2009). An interesting finding was the subthemes of description and evaluation that occurred as part of the reconstruction of SE. Reporters frequently used their cognitive schema to evaluate their effects as they retrieved the SE event from their stored memory. This raises the issue that this process of reconstruction may be strongly influenced by mental representations such as illness beliefs/attitudinal changes. This suggests that reporters' accounts should be considered as the filtered output of memory retrieval which may not accurately reflect the actual SE event. However, it can also be argued that these additional schemas are essential for comprehensive reconstruction of the SE event and can result in informative and comprehensive narratives.

Multidimensional impact of SE

As expected there was a sense amongst reporters that SE could negatively impact on many aspects of patients' lives. Examples of adverse physical, psychological, social and economic effects were related. Previous research supports these findings with patients describing physical, psychological and social effects as distressing and persistent in nature (Avery et al., 2011; Judd et al., 2014). These findings are also consistent with the Interview findings in Phase Two of this study. Interviewees described the significant and debilitating impact of SE on their lives. An interesting finding was the emphasis that was placed on the negative effects on family life. This focus was apparent for all reporters and may be characteristic of severe reports in general. It suggests possible avenues for future research as impact on family life may be a key component in assessments of severity.

Coping with SE

As expected effective coping strategies amongst YC reporters are primarily composed of both cognitive and behavioural responses. These strategies included information seeking, social support seeking and non-adherent behaviours. Previous research supports this pattern of coping with social support seeking and information seeking being common coping strategies (de Smedt et al., 2009; de Smedt et al., 2012).

Seeking meaning

An interesting finding from these narratives was the process of seeking meaning and understanding SE. Reporters identified essential components such as clarifying/making sense of their SE event, re-establishing control and accessing feedback. This desire to re-establish control is supported by previous research. The health locus of control is an important element in theories of health behaviours. Its three dimensions are internal locus, external (others) and external (chance) loci (Levenson, 1974; Wallston et al., 1978). Research has established that a strong internal locus is related to positive health behaviours, while the chance locus is related to maladaptive health behaviours (Grotz et al., 2011; Sarafino, 2002). Some YC reporters indicated their desire for feedback stipulating that this desire had motivated them to report. The narratives also illustrated that reporters who did receive feedback via the YCS found it beneficial and often expressed gratitude for the contact. As mentioned effective feedback has been found to contribute to positive health behaviours (Morrison et al., 2014; Pu et al.,

2015). The importance attached to sense making processes across reporter types suggest an area for future research.

Attitudinal change

Reporters frequently indicated that their health beliefs and perceptions were affected by their SE experience. Changes occurred in their attitudes towards their medication, their confidence in ability to manage side effects and their perceptions about their general health. The narratives suggest that these changes might be a cconsequence of negative interactions with HCPs. These findings of attitudinal change are supported by the interview findings from Phase Two of this study. As mentioned the findings from earlier phases will be compared to the YC findings in the following chapter.

4.6 Strengths and Limitations

Overall the objectives for this phase of the study were largely met:

- The free-text comments of YC reports were investigated.
- When the information was available within the YC reports, analysis identified the different sources of information used by YC reporters and their assessment of the value of these sources.
- When the information was available within the YC reports, analysis identified the impact of ADRs on peoples' daily lives and the consequences of ADRs on medicines use in a large sample of YC reporters.

A considerable strength was the use of a previously untapped resource, the free text comments from YC reports. These findings proved that the comments were valuable sources of information that contribute novel findings to the body of health research. Another advantage of this research is that it has highlighted numerous areas which merit future research – such as the role of feedback; positive HCP interactions and non-adherence. The large number of reports ensured a large sample size which contributed to the statistical power of the findings. The main limitation of this phase was time constraints which impacted negatively on the scope of the analysis. Data were available on the reaction outcomes, the duration of the reaction the method of administration, where the patient obtained the drug and in some cases details of the patient's medical history. Analysis could have been conducted to identify associations between specific drugs and reaction outcomes, reaction duration and drug administration. Future research could be undertaken which could investigate potential relationships between medical history and reaction outcomes and reported severity of SE. In addition the free text comments are a

rich data source which could be subjected to future analysis. This might include creating narrative profiles for specific drug types; reaction outcomes and reaction types. The application to access YC data and the demands of working with the large dataset all contributed to these time pressures. A large component of this phase involved qualitative analysis which may have been subject to researcher bias. However, attempts were made to address this possible limitation through techniques such as inter-rater coding.

4.7 Summary

YC reports were examined to gather information on how YC reporters identify and manage their SE. In addition to quantitative analysis of the reports, this phase of the study focused on the novel use of free text in YCs to examine SE experiences.

- Quantitative analysis of the 2285 reports was divided into description of YC reports; causative drugs; identification of SE; impact and SE behaviours and outcomes. Some key findings are as follows: most YC reports for females; patient reports; commonly one drug with one/two effects; linked to CNS drugs. Severity levels do not increase with number of drugs; not linked to unresolved outcomes; linked to CNS drugs.
- The in-depth qualitative analysis of free text comments illustrated their value as sources of information about the SE experience. Thirteen hierarchical categories were identified with the main categories being identification of SE, management, impact and consequences of SE
- Individual narratives provided details on the multidimensional impact of SE. Five themes were identified; reconstruction, impact, coping, attitudinal change and seeking meaning/sense making.

CHAPTER 8: DISCUSSION

8.1 Introduction

The primary purposes of this PhD study were to explore how people identify and manage SE from their medicines and examine the impact and consequences these SE have in their lives. An explanatory mixed method design was used to address the range of research questions in varied ways. This approach was chosen so that data could be generated from different sources and subjected to different analysis.

Phase One of the study involved the development of a questionnaire to gather general information on peoples' experiences of SE and recruit potential interviewees for Phase Two. For Phase Two a phenomenological approach was selected to explore the opinions and experiences of people who had recently experienced a SE, through in-depth interviews. Phase One and Phase Two of the study overlapped and analysis of the interviews from Phase Two informed the following phase – Phase Three. For Phase Three a novel assessment tool for the general public to use to assess suspected side effects was developed, the Side Effects Patient Assessment Tool (SE-PAST). This assessment tool was validated amongst members of the general public known to have experienced side effect(s) and in a larger online population. Finally, in Phase Four data was elicited from a large sample of YC reports - submitted to the YCS by patients, parents and carers. This phase provided further insight into peoples' experiences of SE and examined the potential value of data within YC reports from non-HCPs. It also facilitated comparison of YC reporters and the wider general public.

Health research has slowly come to recognise the potential of a patient-centred approach which moves past the clinical aspects of SE. There is genuine value to be gained by exploring the alternative viewpoint that patients can provide to SE reporting. As part of this thesis, a literature review was conducted which examined current research on patients' identification and management of SE. This review avoided repeat of the literature and identified a lack of knowledge surrounding how people cope with and manage SE. This study attempted to address these deficits. A mixed methods study, which used data from multiple sources, was employed to explore the following key areas: how patients' experience SE and the perspectives of patient reports; how SE impact on patients' lives; how patients' cope with SE; what information sources are used by patients to identify SE; and finally, the value of a causality assessment tool for patients' use. This study used a combination of survey, interview, YC data and in-depth analysis of YC free text comments to investigate patients' experiences of SE. This chapter discusses the main findings,

comparing noteworthy results from the four phases of the study, and describes how they answer the research questions.

8.2 Primary findings

The principal findings of this study relate to the complexity of SE and the need to conceive of SE as distinctly subjective experiences. The thesis provided a unique and insightful perspective on patients' personal experiences of SE. It found that SE can frequently have overwhelming impacts on many aspects of patients' lives. Descriptions of adverse physical, psychological, social and economic effects were provided across all phases of the research.

This study also provided information on the strategies employed by patients to manage SE. These strategies varied greatly and included both cognitive and behavioural responses such as non-adherence; HCP consultation; seeking information from a range of sources and seeking social support. Decisions made by patients were influenced by a range of factors including established health beliefs; previous SE experiences; cognitive biases; perceived severity of SE; individuals' coping styles and HCP interactions.

As expected the study data showed that females and older patients were more likely to have experienced SE and also more likely to report them as severe. These findings are consistent with previous research and indicate some of the healthcare challenges faced by policy makers. The UK population continues to age with 18% aged 65 years and older (Office for National Statistics, 2016). Aspects of this ageing population are the corresponding increases in multimorbidity and polypharmacy which in turn leads to increased risks of SE in older patients. The implications of these findings are discussed further in Section 8.6. Research into gender differences have indicated that females frequently use data more comprehensively than males. In stressful situations – such as experiencing SE – females engage in more extensive cognition than males who tend to rely more on heuristics when assessing stimuli/cues (Meyers-Levy & Loken, 2015). These studies have also found that females are more likely to express anxiety/fear and also report more physical symptoms and psychological distress than males (McLean & Anderson, 2009; Meyers-Levy & Loken, 2015). Electrophysiological research into gender differences in attentional processing suggests that gender could be an important factor in regulating attentional biases. Females showed greater engagement with and more elaborate processing of threat-related stimuli (Pintzinger et al., 2017). These findings are supported by the study data as female respondents were more likely than males to have experienced SE and also more likely to report them as severe. It is suggested that gender differences in

SE experience could be influenced by the different cognitive resources which females allocate to processing their SE (Thompson et al., 2016). Research has also identified gender differences in relation to pain with pain-related health conditions and symptoms more frequent in females than males (Fillingim et al., 2009; Vambheim & Flaten, 2017). A pattern of medicine use was evident in YC reports and users of the SE-PAST. The majority of YC reports were for one drug regardless of gender or age, with most reports being linked to CNS, infections and CV systems. SE-PAST respondents most commonly reported causative medicines linked to CN and CV systems as well as Infection drugs. These findings have implications for prescribers and are discussed in Section 8.6
There were also several key findings related to the type of information sources patients used to identify SE and their assessment of these sources. GPs and PILs were identified as the most commonly used sources in general, irrespective of coping styles. GPs were assessed as the most trustworthy and PILs as the most accessible sources respectively. This study indicated that a hierarchy of source characteristics could exist, where individual components such as accessibility, trustworthiness, ease of understanding and relevance are ranked in importance by patients seeking health information. The data also suggested that predominantly positive assessments of pharmacists were not reflected in their actual use as information sources. Just 28% of survey respondents used pharmacists to find out about the SE. These findings on information sources present opportunities for future research and are discussed in Section 8.8.

8.3 Addressing the research questions

The central research question of this study was:

How do people identify and manage ADRs from their medicines and what impact and consequences do these ADRs have in their lives?

This was developed into four sub-questions:

1. What are the personal experiences of people in managing ADRs?
    a. What are the impact(s) and consequences of their ADR experiences?
    b. What coping strategies do people use when they experience ADRs?
2. What types of information sources do people use to find out about ADRs?
    a. What are the factors contributing to the use of these different information sources?
3. What would be the essential characteristics of a reliable assessment tool for patients to use to assess ADRs?

a. Would patients consider such an assessment tool to be valuable and useful to them?

4. What is the value of patient reports within pharmacovigilance?
    a. Are there differences between people who report ADRs and the general public in terms of impact of ADRs and information sources used?

What are the personal experiences of people in managing ADRs?

There were important findings about the SE experience across the phases of this study. A pattern of multiple medicine use was evident in both survey and SE-PAST respondents. Overall medicine use increased with age among survey respondents – over 30% of those aged 61-70 used five-eight medicines, increasing to over 40% of those aged 71-80 years and 50% of those over 80. Survey data indicated that the majority – over 70% - who had experienced one or more SE used more than one medicine, while 65% of SE-PAST respondents used more than one medicine. Analysis of YC reports added to this information and indicated that reports linked to CVS drugs increased for older age categories. This finding is not unexpected as CVS drugs are the most commonly prescribed medicines for older patients. Similar proportions of CNS drugs were evident across age categories - indicating widespread use for a variety of conditions.

The data collected from SE-PAST respondents and YC reports also indicated a pattern of causative drugs. The most commonly reported causative drugs by online respondents to SE-PAST were CNS, cardiovascular system and infection medicines. Similarly, most YC reports were linked to CNS, infections and CV systems. There were important findings concerning knowledge about causality – linking confidence in causality to use of information sources and medicine use. Analysis of survey data indicated that using multiple information sources could increase confidence in causality assessment. YC reports linked certainty about causality to number of drugs, with nearly half of reports describing one/two effects which were linked to one drug. In addition, the finding that 95% of YC reports overall cited only one drug suggests a degree of certainty in identifying a causative drug among this population, regardless of the number of symptoms reported. Data from SE-PAST respondents confirmed this link, displaying decreased causality knowledge with increased medicine use.

An overall profile of effects was found across the study phases which indicated that the most common effects were physical. Over 80% of survey and SE-PAST respondents described the physical effects of SE, while over 90% of YC reports described physical

effects. The most frequently reported effects in both survey responses and YC reports were pain, abdominal discomfort, headache and fatigue.

In terms of severity, data from survey, SE-PAST respondents and YC reports suggested that severe SE were most commonly reported for females and older patients. These findings supported previous research but also provided additional information on the association between SE severity and coping style. Analysis of the survey data demonstrated that more Monitors – over 50% - reported their SE as 'unpleasant' than either of the other two coping styles.

The impact of nocebo and placebo susceptibility amongst survey, SE-PAST respondents and YC reports should also be considered. Nocebo and placebo effects are generally defined as a worsening or improvement in clinical symptoms in response to the administration of an inert substance. However nocebo and placebo effects are also used to describe unexpected reactions to active medicine/treatments which are not linked to the pharmacological action of the medicine/treatment (Dodd et al., 2017). These effects occur within a physiological and psychological context - psychological mechanisms include expectancy and classical conditioning. (Belcher et al., 2017). Respondents susceptible to these effects might experience an unexpected reaction/nocebo response to their medicine. These responses could be the result of expectations created by their pre-existing health beliefs or direct information they received prior to taking their medicine/reporting their SE (Dodd et al., 2017). Placebo and nocebo research has suggested that medication information from PILs, could influence patients' expectations and cause the nocebo effect (Schmitz et al., 2017; Tan et al., 2014; Verdu & Costello, 2004). Nocebo effects can also occur when patients experience an association between their medicine and previous negative experiences (Dodd et al., 2017). Adverse effects such as SE which are purely symptomatic can therefore be difficult to verify at an individual level in patients, as they may be nocebo effects (Chavarria et al., 2017).

What are the impact and consequences of their ADR experiences?

Data from all phases of this study add considerably to research findings concerning the impact of SE. Analysis of survey and SE-PAST data showed that females were more likely to describe the impact on QDL as 'serious'/'severe'. A majority of survey respondents focused primarily on the physical impact of SE – over 80%. Psychological and social effects were less frequently described, by

12% and 10% respectively. These findings from the general public can be compared with YC reports, many of which provide more detail of the SE experience. A majority of YC reporters also described physical impacts, but higher proportions of reports described both psychological (24%) and social impacts (34%). In particular, a combination of physical, psychological and social impacts was reported by many carers (just under 30%). This finding suggests that carers could provide a comprehensive insight into the complexity of SE. It also provides support for the potential benefits of carer engagement in reporting SE. Most of the physical effects in YC reports were linked to GI drugs, while the combination of physical, psychological and social impacts was most common in relation to CNS drugs. This is supported by SE-PAST data which linked severe/moderate impacts to CNS and CVS medicines.
When interview data and YC reports are compared, similar examples of adverse and debilitating physical, psychological, social and economic effects are found.

Data from interviewees and YC reports suggest that a wide range of SE had both explicit and implicit impact on their lives. For interviewees, the explicit impact was primarily related to physical symptomology such as stiffness, headaches, or rashes. They also linked their SE to explicit economic impacts. The implicit impact of SE was linked to psychological effects which were described as less obvious but significant in impact. A combination of explicit and implicit impacts was also described in the majority of YC reports – over 90%. These included physical, psychological and social effects which could result in serious disruption to many aspects of patients' lives. A striking finding was the additional detail supplied by YC reports on the prolonged consequences of effects for patients (just under 20%). These included persistent negative physical, psychological, social and life changing effects.

Both the survey and YC reports also provided consistent findings on the consequences of SE. Analysis of survey and YC data showed that females and older respondents were more likely to experience negative consequences. Survey respondents with monitoring coping styles were also more likely to require a GP visit/hospitalisation. Data from YC reports indicated that severe SE resulted in negative consequences such as incapacity, hospitalisation and life threatening outcomes. YC reports indicated that CNS and CVS drugs were those most likely to result in incapacity.

What coping strategies do people use when they experience ADRs?

A pattern of coping styles was identified in survey respondents and YC reports. Data were obtained from survey respondents about predicted coping strategies such as information seeking, social support seeking and non-adherent behaviours, from the amended SECope scale. The findings suggest that the most frequent predicted behaviours were based on positive information seeking strategies in around 70% of respondents, but also negative adherence strategies in almost 40%. Moreover, a majority of respondents who predicted non-adherence engaged in actual non-adherence behaviours. Those with monitoring coping styles were more likely to engage in non-adherent behaviours than those with other coping styles. These findings contrast with YC reports - coping strategies were described by just over 40% of YC reporters. Just under 10% of YC reports described information seeking behaviours across a range of sources which included HCPs, family/friends and the Internet. Non-adherent behaviours – stopping/reducing medicines - were described in just under 20% of reports. This difference can be explained since the survey specifically sought information about coping strategies, while there is no requirement to provide information on YC reports. It is thus possible that coping strategies such as seeking information/social support were used by the YC reporters but not specifically reported. However these findings could also indicate a difference in coping strategies between people who report ADRs and the general public, with more YC reporters engaging in non-adherence behaviours.

The Miller's Monitoring and blunting model of coping is based on categorisation of coping behaviours (Miller, 1989). The MBSS was used to categorise survey respondents into those with monitoring, blunting and neutral coping styles and blunting coping styles. However there are disadvantages to taking this approach as coping styles can frequently exist along a continuum rather than an 'all-or-none' phenomenon with distinct parameters (Rossler, 2013). It should also be acknowledged that coping styles are not stable across situations and an individual's coping style can change over time and particularily with context. The MBSS measures coping with scenarios that differ in their predictability and perceived controllability. Research has found that situations with a combination of high predictability and high controllability promote monitoring behaviours while those with low predictability and controllability promote blunting behaviours (Van Zuuren et al., 1996 as

cited in Bijttebier et al., 2001). A conceptualisation of coping styles as a continuum of behaviours may address the disadvantages associated with a categorial approach to coping. Qualitative analysis does suggest that there could be a pattern of coping strategies specific to YC reporters. In order to find meaning and understand the SE experience so they could report it, it was necessary for reporters to engage in appraisal and coping processes. Reporters described factors such as clarifying/making sense of their SE event, re-establishing control and accessing feedback. These cognitive and behavioural factors suggest a link to Lazarus and Folkman's theory of Stress and Coping (Lazarus & Folkman, 1984). This theory identifies coping as a response to stress - stress-related problems lead to coping strategies which are influenced by personal and environmental factors. Within this theoretical framework stressful events trigger appraisal and coping processes which can vary greatly across patient groups. The coping process is composed of problem focused actions and emotion focused actions. These findings have implication for HCPs and are discussed further in Section 8.6.

What types of information sources do people use to find out about ADRs?

Phases One, Two, Three and Four elicited important findings on the information sources that patients use and the factors that contribute to their use. Analysis of survey and interview data show that factors such as the timing of the side effect, eliminatory thinking, previous health experiences and knowledge (from a range of sources) were used to identify SE. A similar use of timing relationships is evident in YC data - the most common method of identifying SE was related to the timing of effects. These findings reflect previous research which established that patients use temporal associations to link the medicine to SE.

Acquisition of knowledge through a variety of information sources was investigated amongst survey respondents, interviewees and YC reporters. This resulted in novel findings with regard to information sources, as it can be acknowledged that differences exist between people who report ADRs and the general public.

Survey and interview data found that HCPs or PILs were most commonly used to confirm SE. This contrasts with surprisingly low use of HCPs or PILs by YC reporters, although these were the most commonly cited methods. Again, one possible explanation might be that these sources were used but not reported. An interesting finding was that multiple sources were reported as being used by YC reporters, which was also noted in survey

respondents, 52% of whom used multiple sources to confirm causality. From analysis of the survey data a picture of predicted use and actual use of information sources was created. The majority of survey respondents maintained their predictions and actually used GPs and PILs. This reflected the respondents' assessment of GPs as the most trustworthy, and easy to understand information sources; with PILs as the most accessible source. Both survey respondents and interviewees had reservations about the Internet and considered it the least trustworthy source, although it was used by a high proportion of respondents in practice, probably due to its accessibility. Interview data added depth to this pattern of Internet use and showed that specific sites – such as NHS Choices (http://www.nhs.uk/pages/home.aspx)- were deemed high in quality and therefore trustworthy sources. Interestingly, a low proportion of YC reporters (7%) cited using the Internet to confirm their SE. High proportions of survey respondents assessed pharmacists as trustworthy and easy to understand. These findings are supported by previous research - however, an important finding was that the positive assessments of pharmacists across the four source characteristics did not correspond with actual use (under 30%). This indicates that perceptions of information sources can be very influential factors in source selection. These perceptions may in turn be mediated by a hierarchical order of characteristics. Pharmacists were not used - despite positive assessments - however, PILs which received mixed assessments were actually used by a majority of survey respondents. These findings have implications for future research and are discussed further in Section 8.7.

What would be the essential characteristics of a reliable assessment tool for patients to use to assess ADRs?

This study developed and validated a novel assessment tool – the SE-PAST - for the general public to use to assess suspected SE. A theoretical framework is provided by the Self-Regulation Model/CSM. It is based on survey and interview data with additional criteria data from the Thai questionnaire (Jarernsiripornkul et al., 2015) and the gold standard Naranjo algorithm (Naranjo et al., 1981). As outlined in Chapter Two there are some existing assessment tools for patients to use to assess SE causality. A patient-reported adverse drug event (ADE) questionnaire intended for postmarketing studies and clinical trials was developed by researchers in the Netherlands (De Vries et al., 2013). A questionnaire for patient self-assessment of ADRs was later developed and validated in Thailand (Jarernsiripornkul et al., 2015).

Structure of assessment tools

These three instruments were based on previous research and existing questionnaires. In addition all were developed with iterative processes and patient input. Both the ADE questionnaire and the Thai ADR questionnaire used expert opinion to assess the instruments.

The ADE questionnaire was composed of four sections:

Section 1 - questions about general patient characteristics.

Section 2 – questions about drug use in the past 4 weeks, details of diseases for which drugs were used and any other diseases.

Section 3 – checklists for ADEs experienced in the past 4 weeks.

Section 4 - describe the ADE in the patient's own words and questions about nature and causality of ADE. ADEs coded according to body categories.

This structure led to some problems – the main one was over reporting of ADEs. The checklists created confusion in respondents as there was no distinction between related and unrelated ADEs. In addition the recall period for ADEs – set at four weeks – was identified as too short and insufficient to capture ADEs that vary over time.

The Thai ADR questionnaire was composed of two sections as follows:

Section 1 - Questions to obtain demographic data on gender, age, education level, career and income, plus an additional question to obtain information on underlying chronic diseases.

Section 2 - Details of ADR experiences were sought and a checklist of information sources used to confirm suspected ADR. Open and closed questions were used to obtain details of timing, symptoms, causative medicines, severity and confidence in causality. Drugs were classified according to anatomical therapeutic chemical classification system (ATC) and ADRs were classified by system organ class (SOC) according to MedDRA terminology.

The majority of respondents were able to complete the questionnaire without assistance. The instrument had some of the characteristics essential for an effective tool. Its structure ensured it was clear, consistent and easy for patients to use. A large amount of detailed information was gathered on ADR experiences, use of information sources and causative drugs. However no weightings were given to the causality assessment tool, in contrast to standard methods, such as the Naranjo method, on which it was based.

As described in Chapter Six the SE-PAST was composed of two sections:

Section A – questions to obtain background information including demographic information, description of SE, timing, impact, medicine use, causative medicine, medical conditions/allergies.

Section B – the Assessment Tool (ten item scale), Scoring Box, which used weightings for key items, and SE Probability Key. Additional information about the four causality levels was provided, accompanied by advice for respondents.

This structure ensured the instrument was simple, easy to use and helped achieve study objectives. It assisted respondents to fully recall a particular event - their SE - before they assessed it using the AT. A majority of respondents found the SE-PAST useful, but also indicated that it was potentially helpful – it would encourage them to report their side effect or talk to a HCP about it.

Validation of assessment tools

These three instruments were validated using different methods. Cognitive debriefing interviews of twenty-eight patients were used to test the content validity of the ADE questionnaire. Tests of feasibility and reliability were also conducted – however problems with low kappa values arose as a result of an unbalanced sample. A clearer analytical picture was gained by reporting of the proportions of positive agreement. The researchers concluded that the ADE questionnaire was not a reliable instrument. It was suggested that improving the questionnaire could increase reliability.

The Thai ADR questionnaire was validated by HCP experts with experience of ADRs identification and reporting. Index of consistency (IOC) scores were generated by these raters to assess content validity. The IOC scores were considered acceptable and an overall indication of good content validity.

Initial and online validation of the SE-PAST involving people with ADR experiences indicated good face and content validity. Exploratory factor analysis was conducted to investigate the factor structure of the instrument and correlations between its variables. PCA and parallel analysis identified the number of factors/components and which variables were linked to these factors/components. The PCA was deemed effective as the criterion of 5-10 respondents per statement was met. A low Cronbach's alpha - below 0.7 – was obtained suggesting poor construct validity. However the SE-PAST assessed the probability of SE for respondents. It gathered information on SE – a defined construct - and was not measuring an underlying theoretical trait/construct. This suggests that there was no requirement for construct validity for this instrument.

When the three instruments are critically reviewed it can be argued that more robust validation methods were used to assess the Thai ADR questionnaire and the SE-PAST. Comparison of the techniques indicate that the assessment of the ADE questionnaire for reliability and validity was compromised by its unbalanced sample. Reliability analysis and expert raters were employed to validate the Thai ADR questionnaire. This analysis was

sufficient to identify the reliable psychometric properties of the instrument. Validation of the SE-PAST also included common measures of internal reliability and validity. However additional factor analysis further investigated the instrument's structure and increased the robustness of the analysis. Overall the Thai ADR questionnaire and the SE-PAST display some of the essential characteristics of a reliable assessment tool. The SE-PAST is shorter and is available online with automatically calculated weightings which may be less onerous for patients/the public and thus increase its uptake and usability. Unlike the Thai ADR questionnaire, it does not contain questions about additional medicines used or medical conditions, which could be used by an assessor to help assess causality, but are not essential for supporting patients to self-assess.

What is the value of patient reports within pharmacovigilance?

This study found that YC reports provide a unique and significant perspective on SE. In particular the free text comments are valuable sources of information providing vivid and rich descriptions of patients' experiences. Comprehensive information is provided which reflects the range and complexity of SE. A pattern of significant disruption to many aspects of patients' lives has been established. These problems can include prolonged consequences of SE with persistent negative physical, psychological, social and life changing effects. Another important finding was the subjective experience of SE - many reports described severe effects commonly labelled by HCPs as mild. Such findings could indicate a disconnect between the perceptions of patients and HCPs in relation to SE severity. Analysis of the YC reports suggest they are valuable data sources that can contribute to PV and more widely to health research.

8.4 Strengths and limitations

Health research can produce controversial scientific evidence however the great benefit of such evidence is that it can be both checked and challenged. A fundamental strength of this study is that it provides information on side effects from medicines which can be examined and assessed for reliability. It is perhaps inevitable that this study was influenced by the researcher's personal characteristics, previous experiences and knowledge. Attempts were made to minimise this researcher bias by a basic strategy of systematic study design. Study records and documentation of the analytical processes were carefully maintained throughout the research. In addition, collaboration with supervisors throughout

this study ensured rigour and lessened bias. The studies within this body of work have several limitations, but also many strengths, which are described within Chapters Four to Seven. A significant strength of the overall thesis was its explanatory mixed method design that combined the strengths of both qualitative and quantitative research. This design also enabled the triangulation and confirmation of results across the different phases of the study. Overall this study contributes to the knowledge surrounding how people cope with and manage SE. There are no published studies which have explored this topic through thematic analysis of free text comments from YC reports. This PhD study also developed a reliable assessment tool for assessing SE, specifically designed for patient use. The most significant limitation of this study was the problem of self-selecting bias. The respondents who chose to participate in Phases One, Two and Three, may have been particularly interested in SE. Their high levels of interest in the research topic may not have represented the opinions and experiences of the wider general population and contributed to a high proportion of survey respondents being categorised as Monitors. In addition the opinions and experiences of HCPs in relation to SE were not sought which could have resulted in a limited/skewed perspective. In Phase One of this study (Chapter Four) the survey was distributed in numerous small to medium sized pharmacies. The use of these multiple distribution sites across several geographical regions facilitated diversity in the data collection. This diversity may have helped to correct self-selection distortions and thus generate representative data. In Phase Two (Chapter Five) the interviews relied on participants who believed they had experienced significant SE. They may have wished to portray their SE as uncommon and their interpretations of questions may have been highly subjective. However, the IPA approach to the interviews acknowledged and allowed interpretation of participants' subjective experience of SE. The interviews led to interesting results which provided insight into how people identify and manage their SE. In Phase Three (Chapter Six) a novel causality scale was developed and validated for use by the general public to assess suspected SE. Respondents from this phase confirmed the value of a simple, useful assessment tool which could motivate people to report and/or discuss their SE with a HCP. In Phase Four (Chapter Seven) a current picture of the experiences of SE amongst YC reporters was established. The findings are limited to YC reports but developed previous YC research by focusing on in-depth analysis of free text comments. This analysis was strengthened by using a

specifically developed coding frame which revealed the multidimensional impact of SE. A wide range of physical, psychological, social and economic issues related to SE were identified. This research had incremental value and developed previous YC studies. The key strength of the research was the value in including patients' experiences and perspectives in SE research.

8.5 Novel findings

A review of the literature surrounding patients' experience of SE identified deficits in knowledge and understanding of the subject. A central aim of this thesis was to contribute to current knowledge by providing a more comprehensive picture of the side effects experience for patients. The research resulted in several novel findings:

- information on the impact of coping styles on the overall SE experience of patients (Phase One)
- the identification of a pattern of information use across coping styles in patients with SE (Phase One)
- the novel finding on the concept of body awareness in those who have experienced SE (Phase Two)
- the development and validation of a novel causality assessment tool for patient use (Phase Three)
- the novel findings that arose from analysis of the free-text responses in a large unselected sample of YC reports (Phase Four)

Coping styles

The survey phase gathered information on the impact of coping styles on the experience of SE. This was facilitated by the use of a gold standard psychological scale – the MBSS – in a novel population. The results were original findings as the MBSS had not been previously used in SE research. It was found that respondents with monitoring coping styles perceived greater risks from their SE while blunting coping styles were associated with non-adherence to medicines. Another important novel finding was that PILs and GPs are influential information sources which are commonly used across different coping styles. These findings could have implications for effective communication of health information and suggest further research is required.

Body Awareness

The interviews identified body awareness as a key process in patients' experience of SE. This is a novel research finding as the concept of body awareness had not been previously identified as a significant aspect of ADR research. Interviewees who had experienced SE indicated that attending to body signals was an essential element of positive self-care health behaviours. This phase of the study found that body awareness and an appreciation of how the body reacts in differing circumstances is important in the context of SE from medicines. These findings suggest that further research should be undertaken to investigate the role of body awareness in the SE experience.

SE-PAST (Side Effects – Patient ASsessment Tool)

A review of ADR research was conducted as part of this research and indicated the limited numbers of assessment tools for assessing causality available for patients. It was suggested that a standardised assessment method could have multiple benefits and facilitate improved reporting of SE by patients. A novel assessment tool was developed for use by the general public to assess suspected SE. This tool underwent two processes of validation – by people known to have experienced SE and further validation in a larger online population. The SE-PAST is a novel research instrument which addressed current deficits within patient causality tools and had some promising findings for practice. A majority of respondents considered it a useful tool which could empower them to discuss their experiences of suspected SE with health professionals.

In-depth qualitative analysis of free text comments

The in-depth qualitative analysis of free text comments provided novel and interesting findings covering identification, impact and consequences of SEs in a large UK-wide sample. In general, this study illustrated the value of YC free text as sources of information about the SE experience. The findings reflect the range and complexity of SE and contribute novel findings to the body of health research.

8.6 Implications for practice and policy

There are a variety of key stakeholders interested in side effects from medicines – these include policy makers; government agencies; national and international

organisations; healthcare professionals; pharmaceutical industry; academic researchers and patients who use medicines. These stakeholders have distinct perspectives and health research can thus present different implications for them.

Policy makers and agencies/organisations

Policy makers focus on improving policy making, by identifying effective practice. Agencies and organisations, both national and international - such as the MHRA, the Commission on Human Medicines (CHM), the European Medicines Agency (EMA) and the WHO - attempt to improve standards and ensure good practice. A recent report from the Academy of Medical Sciences has explored how to improve the generation, trustworthiness and communication of scientific evidence to strengthen its role in decisions by patients about the benefits and harms of medicines (Tooke et al., 2017). The concept of patient-centred care has been established within the NHS. The Department of Health in England has stated that patients should be positively involved in their care – with access to the information they need, greater choice and control over their care and shared decision making at the centre of NHS services:

"The system will focus on personalised care that reflects individuals' health and care needs, supports carers and encourages strong joint arrangements and local partnerships."

(Department of Health, 2010).

This research study has explored patients' personal experiences of SE and provided a picture on the impact and consequences these SE have in their lives. It has demonstrated the complexity of SE and highlighted the overwhelming impacts SE can have on many aspects of patients' lives. As part of the 'information revolution' advocated by the NHS this research has implications for agencies which want to plan and improve quality dialogue with patients and HCPs.

Patient Information Leaflets (PILs)

PILs are highly regulated by the EU and the MHRA approves all packaging and labelling information for medicinal products sold in the UK (Directive 2001/83/EC). A review of PILs was conducted in 2014 which made a number of recommendations to increase their clarity and readability (Van Dijk et al., 2014). These included better guidelines and sharing of best practice, increased involvement of patients in developing PILs and an increased role for electronic media. It highlighted the improvements in practice made by the MHRA

in making good PILs examples - which had been tested by users - available to the pharmaceutical industry (Van Dijk et al., 2014). The present research study found that PILs are commonly used information sources which were assessed by 80% of survey respondents as accessible. However just over 50% of respondents considered that PILs were easy to understand and under 50% considered PILs to be relevant to them. These findings indicate a significant problem with patients' understanding and perceptions of PILs. It supports the previous review which also found that patients had reservations about the overall quality of PILs and changes could be made to improve patients' understanding of PILs (Van Dijk et al., 2014). Perhaps more importantly, only 60% of respondents considered PILs to be trustworthy, which suggests more work is required to ensure that the information they provide is focused on patients' needs.

The Internet

The study also found that websites such as NHS Choices which were identified as quality trustworthy sources were frequently used by survey respondents and interviewees. This study found that many respondents perceived the Internet as untrustworthy and were cautious in accessing healthcare information online. However more respondents used the Internet to find out about SE than used pharmacists. This may be related to patients' perceptions that the internet is an accessible and relevant information source. These findings indicate that clear risk communication could be facilitated by an increased focus on high quality trusted sites. A recent report recommended that NHS Choices should be used as a central repository of clear up-to-date, evidence-based information on the potential benefits and harms of medicines. In addition reputable online information sources could facilitate informed health decisions by describing and providing links to useful/evidence based decision tools for patients' use (Tooke et al., 2017). The SE-PAST was identified in this study as a useful assessment tool which can facilitate engagement with HCPs and is available in an online format. This finding could help to progress these recommendations, prove beneficial to patients and assist their active involvement in their healthcare.

Healthcare Professionals (HCPs)

There are a number of findings in this study that are relevant to HCPs. A recent report by the Royal College of General Practitioners highlighted GPs' concerns about the challenges associated with an ageing UK population. Patients' with numerous long-term conditions can have complicated treatment regimens with multiple medicines. This polypharmacy can

in turn lead to increased risks of SE (Royal College of General Practitioners, 2016). This research study found that GPs were widely used by the general public but infrequently cited by YC reporters as information sources. There were 9% of YC reports which described negative interactions with HCPs, including some relating to GPs. The YCS provides the opportunity for patients to report their experiences without interpretation by a health professional, hence this could be a factor contributing to the low use of HCPs as information sources. In contrast, survey respondents assessed both GPs and pharmacists as trusted information sources which were easy to understand, although pharmacists were used less frequently than GPs to confirm SE

These findings highlight the important role that HCPs can play in providing accurate, consistent and useful health information. A recent report recommended training HCPs to ensure they can clearly communicate the potential benefits and risks of medicines to patients (Tooke et al., 2017) a need which is borne out by the negative experiences described by some YC reporters. The survey also found that using GPs as information sources could mediate the influence of coping styles. In general this study suggests that comprehensive information for medicine users should include both the risks and potential impact of SE from medicines. Although prescribers and dispensers of medicine do have a good understanding of adverse effects from medicines, perhaps more in-depth training is needed in how to communicate risks more effectively to their patients. Research indicates that information about medicines and SE influence how people take their medicines. It is essential therefore that the information provided is both accurate and easy to understand. Complex health information is more effectively communicated through effective use of language – using simple language and terms (Sawant et al., 2016). Verbal descriptors have been identified as a manageable and appealing format for communicating risks from medicines to patients. (Berry et al., 2003; Carrigan et al., 2008; Dickinson et al., 2016; Knapp et al., 2009). However patients can frequently overestimate the risk of SE by misinterpretation of verbal and numerical descriptors (Carrigan et al., 2008; Knapp et al., 2010). Using frequencies to communicate risks to patients could increase the accuracy and effectiveness of SE risk information (Knapp et al., 2009; Knapp et al., 2010). Improvements in education and training in patient counselling could therefore address the challenges associated with communicating SE risk. The consequences of experiencing some ADRs which could have a significant impact on an individual may be more difficult to convey, perhaps needing a personalised approach and awareness of an individual's life situation. Health services increasingly advocate patient-centred approaches to care, which could include information tailored to the individual. Communication training for HCPs

which focuses on providing such tailored information would be an evidence based intervention with beneficial outcomes for patient-centred healthcare.

Prescribers

The pattern of medicine use which was evident in YC reports and SE-PAST respondents was unsurprising. The most commonly reported drugs were linked to CNS, infections and CV systems. These reports reflect a pattern of prescribing in England - NHS statistics indicate that the top three system drugs prescribed in the English community in 2015 were for drugs in infections; followed by CVS and CNS drugs (NHS, 2016). NHS statistics also show that the greatest recent increase in prescribing was for antidepressant drugs. These included increased use of amitriptyline, mirtazapine and citalopram. There were also significant increases in prescribing antisecretory drugs and mucosal protectants - with increased use of omeprazole and lansoprazole. An increased volume of prescribing was evident for drugs used in diabetes, with increased use of metformin hydrochloride, gliclazide and sitagliptin. Lipid regulating drugs, were also increasingly prescribed with increased use of atorvastatin (NHS, 2016). It is reasonable to assume that increased prescribing results in more SE and therefore more patient reports. Data from SE-PAST respondents and YC reporters suggest that this is indeed the case - the most commonly reported drugs included citalopram, omeprazole, atorvastatin and metformin.

The aging UK population - with its complex prescribing needs - ensure that rational prescribing by HCPs is an area of interest in healthcare (Royal College of General Practitioners 2016). Research has indicated that GPs must keep up to date on current prescribing practice as well as displaying an awareness of their prescribing profile (Vægter et al.,2012). These findings indicate that even though drugs are commonly prescribed, their impact can be significant – as was shown in this study. Patient experiences of SE should therefore not be dismissed by HCPs. HCPs need to ensure they are aware of potential SE and the consequences these may have for their patients, therefore the findings could contribute to the education of GPs.

Pharmacists

The findings of this study also suggest that patients who experience SE do not use pharmacists as information sources as consistently as GPs. NHS policy – the Five Year Forward View – has identified a “health and well-being role” for community pharmacies in patient-centred healthcare. Progression has been made with a series of practical steps such as increasing numbers of clinical pharmacists in GP surgeries, increased use of Medicines Use Reviews and Prescription Intervention Services (Twigg et al., 2017). A role has been

identified for pharmacists in responding to patients with multimorbidity and complicated medical needs. This requires them to be 'translators' of complex health information and conduct medication reviews in collaboration with GPs (Royal College of General Practitioners 2016). However, it is noteworthy from this study that the positive perceptions about pharmacists which patients exhibited did not result in actual use. In light of the central role which community pharmacies have been assigned in NHS policy this is of potential concern to the pharmacy profession and suggests a need for greater publicity about how they can support medicines use.

Academic researchers

This study is also of potential interest to researchers in the areas of pharmacovigilance and medicines information. Unlike many studies, it employed a flexible mixed methods approach that combined the strengths of both qualitative and quantitative research to create a fuller picture of patients' SE experiences and also involved both YC reporters and the wider population of medicine users. This approach resulted in some significant findings and identified several areas which require further investigation. It can be hoped that this research study will help to increase awareness among health researchers of the multidimensional impact of SE; the variation in SE experience for patients and the unique perspective that can be gained from patient reports.

Patients who use medicines

From the beginning this study sought to place patients and their SE experience at its centre. As a result of this patient-centred approach its findings have implications for patients who use medicines. Research has identified the beneficial health outcomes that result from patient engagement in decisions related to their health (Tooke et al., 2017). A recent study made recommendations to support shared decision making about medicine use between HCPs and patients (Tooke et al., 2017). These included the development of decision tools/aids to assist in the decision making process. This study developed and validated a side effects assessment tool for patients' use (SE-PAST). Most on-line users of the SE-PAST agreed it was a useful instrument and would encourage them to report their side effect or talk to a healthcare professional about it. These findings suggest that the SE-PAST could play a valuable role in helping patients to clarify their concerns and priorities in relation to their medicines. It could empower patients in their HCP consultations and facilitate genuine shared decision making about their

health. It is also noteworthy from this study that the YCS makes a valuable contribution to patient wellbeing when they experience SE. This scheme provides patients with an opportunity to describe their SE experiences. Research has suggested that adaptive coping behaviours can be facilitated/influenced by outlets such as the YCS which assist patients in understanding their SE experience (Lazarus, 1993;1999).

8.7 Implications for future research

The findings of this study indicate that further research may be warranted in several areas. These include investigation of information source characteristics; coping styles; body awareness; SE-PAST; a review of SE impact according to established SE profiles and the sense making processes of the SE experience.

Future research on source characteristics is recommended. Phase One of this study indicated that perceptions of information sources can be a key factor in their use. The survey data suggested that source characteristics of accessibility and relevance can be significant predictors of information use. It was found that perceptions of information sources may be influenced by a hierarchical order of source characteristics. Further research is required to examine the important characteristics of information sources in information seeking behaviours. Such research could identify if a hierarchy of source characteristics exists which may mediate perceptions. In addition, research is needed to determine how to increase the understandability and trustworthiness of PILs from the patient perspective.

The results of this study indicated that PILs and GPs are information sources which are commonly used across different coping styles. Previous research has found that providing information to patients which is consistent with their coping style can have beneficial outcomes. These findings could therefore have implications for effective communication of health information and suggest further research is required. In particular, more research involving those with Blunting coping styles is required.

Another focus for future research is body awareness/sensitivity in the context of SE. Previous research has identified adaptive body awareness as a response to immediate sensations/effects which occurs in combination with non-judgemental attention to such effects. The novel interview findings indicate that body

awareness is a key process in the SE experience, which merits continued investigation. SE could be mediated by adopting a self-focus that directs attention to the effects in a mindful, non-judgmental manner. Research therefore could examine if mindfulness training in patients who are most likely to experience SE could be beneficial.

The SE-PAST also offers an avenue for further research and development. A recent study identified the importance of shared decision making about medicine use between HCPs and patients (Tooke et al., 2017). Organisations such as Age UK are developing tool-kits for older patients to use in HCP consultations, with the intention of facilitating effective decision-making processes. The SE-PAST was validated in this thesis as a useful tool which motivated patients to discuss their SE with HCPs. It may be a valuable addition to a tool-kit that supports shared decision making, contributing to patient knowledge and self-confidence.

Findings from YC reports indicated that a review of the impact of SE according to SE profile could be warranted. Psychological impact was reported for drugs which did not specifically describe psychological effects in their SE profiles. These reported psychological effects are therefore unexpected and may simply be a consequence of illness. Future research could investigate these discrepancies between reported effects for drugs and the known safety profiles for these drugs. The potential for using material from patient YC reports to contribute to HCP education is also worthy of consideration.

The results of this study found that SE can be a predominantly subjective experience, with potential to impact future decisions about using medicines. An interesting finding related to the sense making processes which patients engage in to facilitate their understanding of the SE experience. This is an important area for future research. Further investigation could assist in developing a model of these processes and confirm the role of influential components such as re-establishing control and beneficial feedback in the SE experience.

8.8 Conclusion

ADRs are a significant public health problem worldwide, which affect patient outcomes and future behaviours. This thesis focused on patients' perspectives in identifying and managing side effects from medicines and its findings have implications for both HCPs

and government organisations. The studies which comprise the thesis have provided a comprehensive picture of how patients identify, seek to understand and engage in a variety of strategies to manage their effects. It has also demonstrated the noteworthy impact which SE can have on patients' lives often with prolonged consequences. Health professionals, particularly GPs, PILs and the Internet are frequently used sources of information about medicine SE, but sometimes fall short of patients' expectations. This thesis found that GPs and PILs were widely used by the public but less regularly by YC reporters as information sources. This frequent use of PILs by the public was notwithstanding their assessment of PILs as not relevant or easy to understand sources. These findings indicate that the information provided by PILs do not appear to fully address patients' needs. It suggests that changes to PILs may be required to increase the comprehension and relevance of PILs. It is also noteworthy that negative interactions with HCPs were described by just under 10% of YC reporters. Patient engagement in heath decisions requires reliable, clear information about the benefits and harms of medicines. The use of a self-assessment tool, such as the SE-PAST, could empower patients to have more effective communication with HCPs about their SE experiences. Improved communication between patients and HCPs could reduce uncertainty and lead to informed choices/decisions by patients. Further research is required to establish how best information on SE can be tailored to patients' needs and communicated in a clear, consistent, reliable and useful manner and how a patient causality assessment tool, such as the SE-PAST, could best be used in practice.

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APPENDICES

APPENDIX 1: Literature searches, search terms and paper selection

Key search terms and appropriate Medical Subject Headings (MeSH) terms were identified by searching relevant ADR research literature. The following words were used as search terms: adverse drug reactions; side effects; pharmacovigilance; patients; reporting/patient reporting; information sources; causality assessment and patient experience. The MeSH terms 'consumer participation' and 'ADR reporting systems' were also used. Multiple databases were searched: Cochrane *Database of Systematic Reviews (CDSR);* EBSCO Host database (MEDLINE, PsychARTICLES, PsychINFO) PubMed, SAGE Journals online and ScienceDirect.

Search 1

#	Searches	Results
1	Adverse drug reactions	79,494
2	Side effects	10,630
3	1 AND 2	1,038
4	Pharmacovigilance	5850
5	Patient reporting	1328
6	4 AND 5	116
7	3 AND 6	60
8	Kept by title	38
9	Kept by abstract	4
10	Included in review	42

Search 2

#	Searches	Results
1	Adverse drug reactions	79,494
2	Side effects	10,630
3	1 AND 2	1,038
4	Pharmacovigilance	5850
5	Patient reporting	1328
6	4 AND 5	116
7	3 AND 6	60
8	Information sources	218,512
9	Causality assessment	720
10	3 AND 6 AND 7	3
11	Kept by title	3
12	Kept by abstract	3
13	Included in review	3

Search 3

#	Searches	Results
1	Adverse drug reactions	79,494
2	Side effects	10,630
3	1 AND 2	1,038
4	Pharmacovigilance	5850
5	Patients	4,877,499
6	4 AND 5	2622
7	Causality assessment	720
8	3 AND 6	44
9	Kept by title	28
10	Kept by abstract	28
11	Included in review	28

Search 4

#	Searches	Results
1	Adverse drug reactions	79,494
2	Side effects	10,630
3	1 AND 2	1,038
4	Patient Experience	78,340
5	3 AND 4	393
6	Kept by title	65
7	Kept by abstract	65
8	Included in review	65

APPENDIX 2: Side Effects Assessment Tool (SE-PAST)

Assessment Tool for Suspected Side Effects

- Please focus on one side effect/symptom or one group of side effects/symptoms when answering the following questions.
- There are two parts to this assessment tool to be completed. Section A is seeking general information about you, your suspected side effect(s) and your use of medicines. Section B is a standard assessment tool for suspected side effects.

Instructions for Section A:

- For questions that ask you to write something, please write in the space provided.
- For questions with tick-boxes ☐ please put a tick (√) in the box that is closest to your chosen answer.

Instructions for Section B:

- There are ten statements relating to side effects experiences. Each statement has four possible responses 'Yes' 'No' 'Don't Know' or 'Not applicable'.

Think about the time that you experienced the suspected side effect(s).

- For all ten statements, select the response that most clearly represents what happened in your experience of the suspected side effect(s). You must answer all ten statements.
- Then use the Scoring box as follows - fill in the scores which correspond to each of your selected responses in this box, then add these scores up to get your total score.
- Use the tool's probability key to understand what your score means.

Section A: Background information (personal information will be treated with strictest confidence)

1) Please describe the suspected side effect(s) you experienced in detail, including any information that you think may be relevant.

2) When did you experience the suspected side effect(s)?

☐ In the past month ☐ In the past 3 months ☐ In the past 6 months ☐ One year/longer

3) How would you describe the level of impact the suspected side effect(s) had on your daily activities?

☐ Severe impact ☐ Moderate impact ☐ Mild impact ☐ No impact

4) What medicine or medicines were you taking at the time that you experienced the suspected side effect(s)? Please list them below, as far as you are able to, including prescription, over the counter and/or herbal medicines.

5) Which of these medicines do you think caused the side effect(s)?

6) Do you have any existing medical condition(s) or allergies?

☐ Yes ☐ No ☐ Don't know

If yes please list the medical conditions/allergies below

7) Are you? ☐ Male ☐ Female

8) What age group are you in?

☐ Below 40 ☐ 41-50 ☐51-60 ☐ 61 to 70 ☐ 71-80 ☐Over 80

9) What is the highest level of education you have obtained/reached?

☐ Left school at 16 years /younger ☐ Further education ☐ Left school at 17/18 years ☐ University

Section B: Assessment Tool

Statement	Yes	No	Do not know	Not Applicable
1. I experienced this effect(s) for the first time after taking this medicine.				
2. I have experienced similar effect(s) from this medicine or a related medicine in the past.				
3. When I stopped taking the medicine the effect(s) decreased in severity or disappeared altogether.				
4. When I took the medicine again the effect(s) reappeared.				
5. When I increased the dose the effect(s) became more severe.				
6. When I decreased the dose the effect(s) became less severe.				
7. I confirmed the effect(s) with some or all of the following information sources – doctors, pharmacists, information leaflets with your medicine, the internet or medicine books.				
8. I think that something else apart from the medicine could have caused the effect(s).				
9. I think an existing medical condition or conditions could have led to the effect(s).				
10. I think that other medicine(s) that I was using at the time could have caused the effect(s).				

Scoring Box:

Statements	Yes	No	Do not Know	Not applicable	Score
1.	+2	-1	0	0	
2.	+1	0	0	0	
3.	+1	0	0	0	
4.	+2	-1	0	0	
5.	+1	0	0	0	
6.	+1	0	0	0	
7.	+1	0	0	0	
8.	-1	+1	0	0	
9.	-1	+1	0	0	
10.	-1	+1	0	0	
				Total Score	

Side Effect(s) Probability Key

Score	Interpretation of scores
Total Score **8 or higher**	**Highly probable:** Highly probably that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **4-7**	**Probable/Likely:** Probable that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **1-3**	**Possible:** Possible that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **0 or a negative number**	**Unlikely:** Unlikely that effect is related to your medicine(s) but may be caused by other factors.

Version L1.0, 26/01/16

APPENDIX 3: Ethical approval letters from NHS REC, MSoP and ISAC

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1

Jarrow REC Centre
Room 002
Jarrow Business Centre
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 428 3565

27 June 2014

Ms Bernadine O' Donovan
Pharmacy Practice Research Office
Medway School of Pharmacy
Anson Building
Universities of Greenwich & Kent
Central Avenue, Chatham Maritime
Kent ME4 4TB

Dear Ms O' Donovan

Study title:	**Investigation of how coping mechanisms influence the use of information sources and experiences of people who have recently undergone an Adverse Drug Reaction (ADR) to medication**
REC reference:	**14/NE/1053**
IRAS project ID:	**157130**

The Proportionate Review Sub-committee of the NRES Committee North East - Newcastle & North Tyneside 1 reviewed the above application on 25 June 2014.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Ms Gillian Mayer, nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net.

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.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be

made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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 within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

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 contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

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

Social or scientific value; scientific design and conduct of the study

The Committee requested clarification regarding the number of participants called for interview and how realistic it may be to obtain a high number, considering aspects such as the length of time taken to hand out questionnaires, which seem quite lengthy considering

the anticipated number of respondents. It was also noted that pre-paid envelopes for return of the questionnaires will be expensive.

You clarified that there will be a maximum number of 50 interview participants called for interview. These interviewees will be asked to discuss a wide and diverse range of issues including the cognitive processes they employ to help them identify potential side effects. It is anticipated that the complexity of these issues will require a large number of interviewees to achieve data saturation. It was decided that assigning a high maximum value of 50 interview participants is necessary in order to ensure this complexity is covered. It was acknowledged that recruiting up to a maximum of 50 interview participants for a research project would be difficult. However it was noted that this is a maximum number aimed at ensuring that there is sufficient flexibility to achieve data saturation. (Once this point has been reached the interviews will not continue).The costs of the study are fully supported by the Medway School of Pharmacy (including travel and questionnaire return costs). It is proposed to distribute questionnaires over a three month period which may seem an extended distribution period, however the pharmacies selected as distribution venues fall within a wide geographical area - Kent and the West Midlands. The allocation of three months will therefore afford the researcher the time needed to travel to and from these areas, to make contact with the pharmacies and distribute the questionnaires.

The Committee noted that there is a very short recruitment period for this intensive process and the large sample size seems ambitious. Further justification was requested for the sample size as the study includes only those participants who did experience side effects and the explanation for the sample size relates to the prevalence of side effects.

You clarified that survey recruitment is not solely limited to participants who have experienced side effects. The questionnaire phase of this project seeks to determine what people do in relation to sources of information about the side effects of medicines either in the event that they have experienced side effects or if they were to experience side effects. With regard to the power calculations and survey sample size, questionnaires will be distributed amongst the general population. General population parameters therefore suggest an assumption of normal distribution with a mean of 100 and variance of 100 under the null hypothesis. Under the null hypothesis the mean to be greater than 105 or less than 95 and at a significance level at 95%. It is proposed that the study will require a sample size of 900 completed questionnaires. A previous study in the Kent area utilising similar methodology found a response rate of 36% among the general public using community pharmacies. Therefore based on this rate, a total of 2500 questionnaires will be distributed.

With regard to power calculations for the interview sample size, with a large sample size of 2500 questionnaires a response rate of approximately 20% can be selected. This is an appropriate estimation of response rates for survey research. Based on the estimation that 900 questionnaires will be completed and returned and that 30% of the respondents will have experienced side effect, it is estimated that 270 participants who have experienced side effects could be eligible for interview. Of these it is anticipated that approximately 20% (58) may be willing to consent to interview, therefore up to 50 interview participants will be recruited from this pool to ensure flexibility and achieve data saturation.

Recruitment arrangements and access to health information, and fair participant selection

The Committee requested clarification why recruitment will be limited to those taking prescribed medicines as it was noted that it may be beneficial to include any medication users. Medications that can be purchased without prescription can cause side effects which are more difficult to manage and there is less knowledge about these unlike prescribed medicines, they are not closely monitored.

You explained that you had initially considered the option of approaching any customer using a pharmacy, but since you aim to engage those who use medicines of any source, it was considered that the likelihood of people using prescribed medicines engaging with this study would be higher. You stated that you will revise the recruitment selection so it is not limited to those presenting prescriptions only in the pilot phase and assess the extent to which responses are obtained from those not using prescribed medications. You informed that you had amended the inclusion criteria to include pharmacy customers who have used prescription medicines or non-prescribed medicines in the past six months.

Informed consent process and the adequacy and completeness of participant information

The Committee noted that the participant information sheet should include an estimated time for completion of the questionnaires. It was queried if you will wait for pilot data regarding this – the IRAS form indicates 30 minutes for completion of the questionnaire.

You stated that the time for completion of the questionnaire is currently estimated as no more than 30 minutes. Once the questionnaire is piloted this completion time will be amended in the participant information sheet if it is found to be shorter than 30 minutes.

The consent form should include the standard paragraph, as appropriate for this study – 'I understand that the relevant section of my medical notes and data collected during the study may be looked at by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records'. Also the version number and date of the current participant information sheet should be included.

You provided a revised participant information sheet and consent form accordingly.

Suitability of supporting information

The Committee noted that the lay out of the questionnaire would be more logical if section B appeared first.

You explained that the structure of the questionnaire is determined by the research objectives. It is organised to gather a maximum amount of data from a maximum range of people. The questions move from the general to the specific. It initially gathers general information in Section A - from a range of people who may or may not have experienced side effects. This develops into a specific set of questions dealing with peoples' personal experiences of side effects in Section B. Section A therefore sets out a hypothetical scenario and asks how people would use information sources about side effects if they experienced side effects. Placing Section A at the beginning of the questionnaire ensures that even respondents who have no personal experience of a recent side effect can contribute useful data regarding their potential use of information sources in the event that they experienced side effects and their perceptions of the attributes of selected information sources.

Other general comments

The Committee requested further information regarding the potential risk to researchers as the interviews may be undertaken in the participants' homes and if a lone worker policy will be adhered to.

You informed that potential risks to the researcher have been considered and are described in the REC application form). The guidelines set out in the University of Kent's Policy for identifying and controlling the lone working risks to staff have been consulted and will be adhered to. A Risk Assessment has been conducted to comply with these guidelines to reduce the risks to the researcher. As a result of this assessment, precautionary measures

have been put in place, e.g. a system of notification via text which alerts selected contacts when the researcher (a) arrives at interview, (b) leaves interview and (c) reaches home. In addition, the researcher will also strictly adhere to the guidelines laid down by the Medway School of Pharmacy, University of Kent, for Conducting Research in Participants Homes (Potentially Vulnerable Situations).

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UoK liabilities]	1.0	09 June 2014
IRAS Checklist XML [Checklist_19062014]		19 June 2014
Letters of invitation to participant [Invitation letter Version 1.0]	Version 1.0	09 June 2014
Non-validated questionnaire [Questionnaire]	1.0	09 June 2014
Other [Pharmacist Information Sheet Version 1.0]	Version 1.0	09 June 2014
Other [MSoP Policy doc]	1.0	09 June 2014
Other: Response to issues raised		24 June 2014
Participant consent form [Consent form]	1.1	24 June 2014
Participant information sheet (PIS) [Participant Information]	1.1	24 June 2014
REC Application Form [REC_Form_19062014]		19 June 2014
Research protocol or project proposal [project protocol Version 1.0]	Version 1.0	09 June 2014
Summary CV for Chief Investigator (CI) [CV (CI)]	1.0	09 June 2014
Summary CV for student [CV (CI)]	1.0	09 June 2014
Summary CV for supervisor (student research) [CV doc (S)]	Version 1.0	09 June 2014
Validated questionnaire [SECope questionnaire]	1.0	09 June 2014
Validated questionnaire [MBSS abbreviated (SE)]	1.0	09 June 2014

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
- 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.

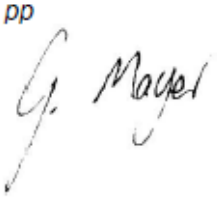
Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service 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/
We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

14/NE/1053	**Please quote this number on all correspondence**

Yours sincerely
pp



Dr Mike Bone
Vice Chair

Email: nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

'After ethical review – guidance for researchers'

Copy to: *Ms Nicole Palmer – R&D Office, University of Kent*

Dr Peter Dodds - RM&G Consortium for Kent and Medway

medway school of pharmacy

28th January 2016

Dear Bernadine

Your application for ethical approval for the project entitled *Validation and testing of an assessment tool for use by the general public in identifying suspected side effects from their medicines* (REF 0116/2) *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 will be approved, subject to the following minor amendments;

- A number of the documents show the Birmingham logo, however there is no reference to the collaboration with Birmingham within the text of the documents. Please include information of the connection
- The committee felt that destroying the consent forms after one month was too soon. Please scan the consent forms on to an encrypted memory stick and keep for 12 months
- Please explain reason for collating postcode data on the information leaflet or the questionnaire

Please resubmit your documents with track changes to J.Mowbray@kent.ac.uk

I must also 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

MHRA 151 Buckingham Palace Road Victoria London SW1W 9SZ United Kingdom **www.mhra.gov.uk**

Bernadine O' Donovan
Sent via email:
bo77@kent.ac.uk
Date 14th December 2015
Ref: GENQ-00097958

Dear Bernadine O'Donavan,

Application: ACYD042

The Independent Scientific Advisory Committee for MHRA database research (ISAC) considered the above application by electronic review. The Committee considered that your application was an appropriate use of Yellow Card data and that the proposed methodology is appropriate for the objectives of the study. The Committee advised that the application should be granted provided you comply with the following conditions:
• It is our understanding that the three comment boxes referred to in section D2 are the narrative, reporter comment and free text medical history boxes.

• In addition, as your proposal will involve the release of Category II data, I should remind you of the undertakings you agreed to when you completed the application form. These are included at Annex A.

• You must abide by the *Guidelines for Safe Disposal of Electronic Yellow Card Data for External Users* included at Annex B.

• Please note the enclosed information at Annex C on the National Research Register (NRR). We strongly recommend that you register with the NRR.

The MHRA has accepted the advice of the ISAC. If you are willing to accept the above conditions, please let me know as soon as possible and no later than 28 days after the date of service of this letter.
Yours sincerely,
Yours sincerely,

Rebecca Owen
Signal Management Co-ordinatior / Yellow Card Secretary to the ISAC
Vigilance and Risk Management of Medicines

APPENDIX 4: IRAS application

Full Set of Project Data IRAS Version 3.5

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
How people identify and manage side effects from medicines 1.0

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
(●) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

[x] England
[ ] Scotland
[ ] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (●) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which review bodies are you applying to?

- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] National Information Governance Board for Health and Social Care (NIGB)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

( ) Yes (●) No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

( ) Yes (●) No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

( ) Yes (●) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

( ) Yes (●) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
The project is undertaken as part of a PhD and the student will be the Chief Investigator.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
How people identify and manage side effects from medicines 1.0

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Investigation of how coping mechanisms influence the use of information sources and experiences of people who have recently undergone an Adverse Drug Reaction (ADR) to medication

A2-1. Educational projects

Name and contact details of student(s):

Student 1

Title	Forename/Initials	Surname
Ms	Bernadine	O' Donovan

Address	Pharmacy Practice Research Office, Medway School of Pharmacy, Anson Building,Universities of Greenwich & Kent, Central Avenue, Chatham Maritime, Kent.
Post Code	ME4 4TB
E-mail	bo77@kent.ac.uk
Telephone	01634202920
Fax	

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
PhD in Pharmacy

Name of educational establishment:
Universities of Greenwich & Kent

Name and contact details of academic supervisor(s):

Academic supervisor 1

Title	Forename/Initials	Surname
Professor	Janet	Krska

Address	Room Anson 111, Anson Building, The Universities of Greenwich and Kent at Medway, Central Avenue, Chatham Maritime, Kent.
Post Code	ME4 4TB
E-mail	j.krska@kent.ac.uk
Telephone	01634 (20)2950
Fax	

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Ms Bernadine O' Donovan	☑ Professor Janet Krska

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- ◉ Student
- ○ Academic supervisor
- ○ Other

A3-1. Chief Investigator:

Title	Forename/Initials	Surname
Ms	Bernadine	O' Donovan

Post	PhD student
Qualifications	MSc Cognitive Neuropsychology MSc Neuropharmacology BA (Psychology)
Employer	University of Kent
Work Address	Pharmacy Practice Research Office, Medway School of Pharmacy, Anson Building, Universities of Greenwich & Kent, Central Avenue, Chatham Maritime, Kent.
Post Code	ME4 4TB
Work E-mail	bo77@kent.ac.uk
* Personal E-mail	
Work Telephone	01634202920
* Personal Telephone/Mobile	
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

to complete them at their leisure. Questionnaires will include an invitation to participate further in the study through interviews with the researcher. People selected to be interviewed will have experienced a side effect from medicines in the last 6 months. The interviews will last for an hour and people will be asked to discuss their experience of side effects. Overall this study will collect information through questionnaires and interviews over a period of approx 12 months. This information will then be used to develop an assessment tool for the public to use to help them identify side effects to medicines.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

Purpose and design
The aim of this project is to build on this research and investigate how people identify ADRs. It will also explore peoples' experiences of ADRs. Questionnaires will be distributed in independent and small to medium sized multiple pharmacies within the following geographical areas - Kent and West Midlands urban centres.
Recruitment
Initial emphasis will be on recruitment from independent and small to medium sized multiple pharmacies. This strategy for pharmacy inclusion is based on practical considerations such as ease of access to premises, utilisation of collaborators' contacts within the sector and reduced need for internal company governance. (However if the inclusion of the large chain multiple pharmacies is proved necessary during the course of this project then the researcher will go through the requisite in-house governance procedures.) The researcher has developed an initial approach to pharmacists that clearly describes the purpose and structure of the study. Care has been taken to ensure the Invitation Letter to Pharmacists has useful study information and is free of coercion or unreasonable claims.
Consent
The study is designed to ensure that valid consent is obtained from the participants. All potential participants will be provided with adequate information on the purpose and nature of the study. These details will facilitate the potential participant to reach a fully informed decision. Each envelope which will be distributed by the researcher will therefore include consent forms and Participant Information Sheets. The Participant Information Sheet will describe the purpose of the study in general as well as the specific details of what is involved for participants. It will avoid coercion of potential participants and will not make unreasonable claims of merit for the study. This focus on obtaining valid consent also extends to the interviews. Written consent will be obtained prior to interviews. Participants will also be verbally informed prior to any interviews that they do not have to answer any question they do not wish to, and that they may terminate the interview at any time. Verbal permission to record the interview will also be sought prior to the interview process.
Risks, burdens & benefits
The researcher has consulted with experienced researchers (the study collaborators) to identify and assess potential risks to participants. Efforts have been made to limit risk and protect all participants. This study involves completing a questionnaire so any risks to respondents are considered minimal. There may be ethical concerns that the initial approach by the researcher would place pressure on potential survey participants to make a hurried and unconsidered decision to take part in the research. However the researcher will invite potential participants to complete the questionnaire at their leisure. This will ensure that there will be no unnecessary pressure or time constraints on the potential participants.
However potential risks exist for all those participants who agree to the interview process. The interviews with the researcher involve participants recollecting a negative event (an ADR). Sensitive issues could potentially arise and participants could become distressed. This minimal risk to participants during the interview process has been addressed as follows. Suitable locations for interview will be agreed between researcher and interviewee. By selecting locations that are agreeable to participants they will feel secure and/or comfortable and either prevent or reduce potential distress. If a particular question makes the interviewee uncomfortable the researcher will remind the interviewee that their participation is voluntary and they may skip the question if they wish. If an interviewee becomes distressed during the interview the researcher will immediately suspend the interview. The researcher will offer to terminate the interview and recommend that the participant contact their G.P.or pharmacist or the Patient Advice and Liaison Service (PALS) if necessary for advice and support.
This study has potential benefits for interview participants as shopping vouchers to the value of £20 will be offered to all those who attend for interview.
The researcher has also considered possible risks to the researcher. The interviews will be conducted off-campus so there may be some issues concerning personal safety. Precautionary measures have been put in place which reduce the risk for the researcher. These include a system of notification via text which alerts a selected contact when researcher (a) arrives at interview (b) leaves interview and (c) reaches home. The researcher will strictly adhere to the guidelines laid down by the Medway School of Pharmacy, University of Kent, for Conducting Research in Participants

Homes. (Potentially Vulnerable Situations) - See Supporting Documentation. These guidelines have been written to help identify and minimise potential risks.
Confidentiality
Ethical considerations regarding confidentiality have also been considered while designing this study. All participating pharmacies as well as questionnaire respondents and interviewees will remain anonymous. All participants will be informed that the project is being undertaken by a researcher and is confidential. Interviewees will be informed in writing prior to the interview. Lists of the pharmacies will be generated with unique identifying numbers. The researcher will also allocate a unique identifying number to interviewees. These lists will be written on paper and locked in a secure filing cabinet. These will be the only copies and no computer records of these lists will be generated. Access to these lists will be limited to named members of the research team for the following purposes - to arrange interviews according to protocol and to disseminate the research findings. At the end of this study these lists will be held for a period of one month and subsequently destroyed by shredding. All consent forms will be locked in a secure filing cabinet, separate from questionnaire responses. These forms will be held for one year after the completion of the project and then shredded. The project data will be identifiable only by unique study numbers. This will ensure anonymity as they will contain no personal identifiable information. All data collected will be stored on password protected files on computers which are also password protected. This data will be fully anonymised. These digital records will be destroyed five years after the final report has been written.
Survey respondents will be asked to provide details of their post codes. Post codes will be used to assign deprivation levels to the data sets. This detail is required by the researcher for social research purposes only. It will not be used to contact respondents and will not be passed along to third parties.
Conflict of interest
No conflicts of interest have been identified amongst the research team. Consideration has also been given to providing feedback after the study has ended. Summaries of the study results will be sent to interviewees who indicate their interest by ticking the appropriate box in the Contact Details (Section D) of the questionnaire.

A6-3. Proportionate review of REC application *The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether you wish to apply through the proportionate review service or, taking into account your answer to A6-2, you consider there are ethical issues that require consideration at a full REC meeting.*

(●) Yes - proportionate review ( ) No - review by full REC meeting

Further comments (optional):

Note: This question only applies to the REC application.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply.*

- [ ] Case series/ case note review
- [ ] Case control
- [ ] Cohort observation
- [ ] Controlled trial without randomisation
- [ ] Cross-sectional study
- [ ] Database analysis
- [ ] Epidemiology
- [ ] Feasibility/ pilot study
- [ ] Laboratory study
- [ ] Metanalysis
- [x] Qualitative research
- [x] Questionnaire, interview or observation study
- [ ] Randomised controlled trial
- [ ] Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The principal aims of this project are to investigate how people use information sources to help them identify ADRs to medicines and to explore peoples' experiences of ADRs.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

Additional objectivies involve
1) identifying the perceived value of different sources of information about ADRs.
2) assessing if there is a link between peoples' coping strategies and their experiences of ADRs.
3) determining the patterns of ADR experiences among pharmacy customers.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Justification of research
Many people take medication - both items prescribed by doctors or items bought at their local pharmacy/shop. They may experience negative side effects - adverse drug reactions (ADRs). Research into these reactions to medicines has found that ADRs can have considerable impact on an individual's quality of life. There are also economic costs to the National Health Service (NHS) in the UK - estimated in 2004 at over £450 million annually. In 2005 direct patient reporting of ADRs in the UK by patients - via the Yellow Card Scheme - became possible. Subsequent research identified patient reports as an effective resource in increasing knowledge and understanding of drug effects. These reports can provide information on causality, provide more detail in general and frequently report different types of drugs and types of reactions than healthcare professional reports.
Research objective
The aim of this project is to build on this research by focusing on ADR experiences from the perspective of the public. It will investigate how people use information sources in helping to identify ADRs and also explore peoples' experiences of ADRs. This research will help to form a more comprehensive picture of how individuals' identify and manage ADRs, which may help in developing a tool to support patient identification of ADRs.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Study design & methodology
This project will recruit approx. 2500 members of the public through distribution of questionnaires in independent and small to medium sized multiple pharmacies. Limiting recruitment to pharmacies of this size will reduce the necessity of applying for internal company governance. Selected pharmacies in Kent and the West Midlands will receive an invitation to participate via letter. This strategy is intended to optimise study collaborators' contacts within the sector. Pharmacies who agree to participate will be visited by the researcher. Pre-prepared envelopes will be distributed to the general public by the researcher. Each envelope will contain the following - participant information sheet, consent form, assessment instruments and prepaid envelope (to return the questionnaires to the researcher). People who have presented NHS prescriptions in the pharmacy will be approached by the researcher. The researcher will outline the study, invite participation by completing the questionnaires within this envelope at their leisure and ask questions to determine if they can be included in the study -"Are you 18 or over?", "Are you resident in the UK?" "Do you take prescription medicine?" and "Are you able to complete the questionnaire as it is only available in English?"
Justification for methodology
This methodology was choosen to gain access to a cohort who have used prescription medication and may have experienced an ADR. It was also designed to ensure there is no interference in the day-to-day running of the particpating pharmacy.
Interviews
The questionnaires will include an invitation to participate further in the study through interviews with the researcher (Section D). The interviewees will be asked to discuss how their experience of ADRs. To ensure the ADR has occurred in the recent past and facilitate optimum recall by participants a time parameter of an ADR within the last 6 months will be applied. of the ADR. Potential interviewees will be contacted by phone/email to arrange an interview time and location. Suitable locations for interview will be agreed between researcher and interviewee and these may include public settings such as cafes and/or rooms in private dwellings. In depth interviews will be conducted by the researcher with up to a maximum of 50 participants who have provided their consent. Interviewees will receive a consent sheet to sign before the interview and verbal permission to record the interview will be obtained.
Research Stages
It is proposed that recruitment of pharmacies will take place over a period of 2 months (approx). Distribution of questionnaires is proposed to take place over a 3 month period (approx). Analysis of the questionnaire data will be conducted over a period of 3 months (approx). Interviews will take place over a 4 month period (approx). Analysis of the

interview data and write-up of the findings will take place over a period of 5 months (approx).
Instruments
This project will use the following questionnaires
- project questionnaire will be used to gather general information about side effects
- the Side Effect Coping Questionnaire (SECope) will be used to assess coping strategies/behaviours
The abbreviated version of the Miller Behavioural Style Scale (MBSS) will also be used. This psychological scale will assess if coping strategies influence whether and how people access information sources. This scale will be used to identify the coping styles of potential interviewees.
Analysis
The quantitative data from the questionnaires and the abbreviated MBSS will be analysed through SPSS software. Descriptive statistics, with ANOVAs and multiple regressions will be generated. The demographic details will be used to determine patterns of ADR experiences among respondents. The instruments will also identify the patterns of resources people use to identify ADRs.
Content analysis will be used to code the responses to the open-ended questionnaire questions. The reponses will be coded - using the data management program NVivo - according to their thematic content and then assigned to categories. Independent evaluators will be used during this analysis to control for researcher bias and ensure reliability in the coding process.
The analytical approach to the interviews will be confirmed once the questionnaire data is analysed. However the research literature suggests that an interpretative phenomenological analysis (IPA) will be used.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [ ] Design of the research
- [ ] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [ ] Dissemination of findings
- [x] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The instrument developed for this project will be piloted among members of the public but there was no direct involvement by the public in its design. However it is based on previous patient instruments which have been validated in previous studies. The research can be seen as a response to recommendations contained in a previous review of the UK Yellow Card Scheme. This identifies the research as being of incremental value despite the lack of public involvement in its design.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [x] Generic Health Relevance

- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Skin
- ☐ Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Inclusion criteria for pharmacies
- Independent and small to medium sized multiple pharmacies within the following geographical areas - Kent and West Midlands urban centres.

Inclusion criteria for survey participants
- Adults aged 18 or over.
- Resident in the UK.
- Able to complete questionnaire, which will be available only in English.
- People who used prescription medicines recently.

Inclusion criteria for interview participants
- Participants who are willing to be interviewed by researcher will have experienced an ADR within the last 6 months.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Exclusion criteria for pharmacies
- Large chain multiple pharmacies

Exclusion criteria for participants
- Under 18 years
- Vulnerable groups
- Unable to communicate in English
- Do not use prescribed medicines

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Questionnaires	1		30 mins	Self administered by participants At their convenience.
Interviews	1		1 hour	Bernadine O' Donovan Chief Investigator Locations - public settings or participant's home

A21. How long do you expect each participant to be in the study in total?

Questionnaires are completed at participants' leisure - estimated time to complete is 30 mins approx (to be confirmed by piloting).
Respondents that indicate willingness to being interviewed will participate in the study for approximately 1 hour and 30 mins in total. (This involves 30 mins to complete questionnaire and a 1 hour interview).

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The researcher has considered the ethical issues of possible risks and burdens for study participants. Consultation with the study collaborators - who are experienced researchers - has helped to identify and assess potential risks and burdens for participants. Efforts have been made to both limit risk and protect participants. This study initially involves completing a questionnaire so any risks to participants during this phase are considered minimal. However potential risks exist for participants during the interview process. The interviews with the researcher involve participants recollecting a negative event (an ADR). Sensitive issues could potentially arise and participants could become distressed. This minimal risk to participants during the interview process has been addressed as follows. Suitable locations for interview will be agreed between researcher and interviewee. By selecting locations that are agreeable to participants they will feel secure and/or comfortable and either prevent or reduce potential distress. If a particular question makes the interviewee uncomfortable the researcher will remind the interviewee that their participation is voluntary and they may skip the question if they wish. If an interviewee becomes distressed during the interview the researcher will immediately suspend the interview. The researcher will offer to terminate the interview and recommend that the participant contact their G.P.or pharmacist or the Patient Advice and Liaison Service (PALS). Potential risks for participants have therefore been identified and addressed.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

(●) Yes ( ) No

If Yes, please give details of procedures in place to deal with these issues:

These interviews involve participants recollecting a negative event. Sensitive issues could potentially arise and participants could become distressed. Suitable locations for interview will be agreed between researcher and interviewee and these may include public settings such as cafes and/or rooms in private dwellings. By selecting locations that are agreeable to participants they will feel secure and/or comfortable and either prevent or reduce potential distress. If a particular question makes the interviewee uncomfortable the researcher will remind the interviewee that their participation is voluntary and they may skip the question if they wish. If an interviewee becomes distressed during the interview the researcher will immediately suspend the interview. The researcher will offer to terminate the interview and recommend that the participant contact their G.P. /pharmacist or the Patient Advice and Liaison Service (PALS) .

A24. What is the potential for benefit to research participants?

This study has potential benefits for interview participants as vouchers to the value of £20 will be offered to all those who attend for interview.
There may also be limited therapeutic benefit for interviewees which can arise from describing their negative experience during the interview.

A26. What are the potential risks for the researchers themselves? *(if any)*

The researcher will be conducting interviews off-campus so there may be some risks to personal safety. Precautionary measures have been put in place which reduce the risk for the researcher. These include a system of notification via text which alerts a selected contact when researcher (a) arrives at interview (b) leaves interview and (c) reaches home. The researcher will strictly adhere to the guidelines laid down by the Medway School of Pharmacy, University of Kent, for Conducting Research in Participants Homes. (Potentially Vulnerable Situations) - See Supporting Documentation. These guidelines have been written to help identify and minimise potential risks. If a difficult situation arises during an interview this policy document advocates the following actions -
1.In a difficult situation, let it be known that a colleague is expecting you to contact them regarding your safety. If possible phone supervisor with pre-arranged code word to alert them of the situation.
2.Get out as soon as you can
3.If you are under attack or feel immediately threatened use your personal alarm. Even if there is no-one else in the house, the alarms are very loud and may confuse or annoy the client, giving you an opportunity to get out.
4.Try to defuse or de-escalate a situation as soon as you can. The following suggestions might help:
• Allow the client to say why they are angry
• Show concern and understanding of their feelings
• Tell them that you want to help them/ ask how you could help them. Do not promise anything that you cannot deliver. But you may be able to say that you could arrange something for the person, if they let you go back to/ contact your office for authorisation. Emphasise that you are a relatively junior staff member (even if this is not true) and that you need to check it out first.
• Make a token concession e.g., "I see you do have a point, we may well have made a mistake there"
• Make a deliberately friendly gesture e.g. "would you like me to try and sort that out for you?"
• Avoid provocative phrases e.g. "I think you're really over-reacting there"
5.Leave as soon as you can. Don't go back under the same circumstances.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the responsible care organisation(s).*

Contacts amongst the research team (study collaborators) will be used to facilitate the identification of potential pharmacies. Information will be compiled from the NHS Choices website.
Potential participants who present with NHS prescriptions in the selected pharmacies and satisfy the inclusion criteria will be identified by the researcher.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

Potential pharmacies will be identified by the research team as likely to be willing to participate in research. A letter of invitation to participate in the study will be sent to the independent and small to medium sized multiple pharmacies known to staff members at both universities. The envelope will include a pharmacist information sheet explaining the study, a consent form and a copy of the assessment tools. The initial postal contact will be followed a week later by a telephone call to each pharmacy. The researcher will ask the pharmacies for permission to access their premises to

distribute questionnaires to the general public. If permission is granted suitable dates and times for the researcher to distribute the questionnaire will be decided.
Survey participants will be identified by the researcher as people who present NHS prescriptions in the pharmacy. The researcher will arrive at the pharmacy premises with prepared envelopes to distribute to the general public. Each envelope will contain the following; participant information sheet,consent form, assessment instruments and a pre-paid envelope to return the questionnaires. The researcher will approach potential participants and outline the study, invite participation by completing the questionnaires within this envelope at their leisure and ask questions to determine if they can be included in the study. Care will be taken by the researcher to ensure there is no interference in the day-to-day running of the business premises e.g. waiting until transactions are completed, not interrupting public interactions with the staff, not blocking entry/exit points etc.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Implied consent will be obtained from survey participants as the questionnaire will include a statement which will gain consent through completion and return of the questionnaire. Informed consent will be obtained from interview participants. Written consent will be obtained from participants prior to interviews. Interviewees will receive a consent sheet to sign before the interview begins. Verbal permission to record the interview will be obtained. Participants will also be verbally informed prior to any interviews that they do not have to answer any question they do not wish to, and that they may terminate the interview at any time.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Survey participants may complete the questionnaire at their leisure.
Interview participants have 2/3 weeks before they are contacted by the researcher to arrange interview.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Questionnaires are available only in English so participants must satisfy this inclusion criteria i.e. competency in English language.
Resource constraints preclude the translation of the research materials into other languages.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

○ The participant would continue to be included in the study.

○ Not applicable – informed consent will not be sought from any participants in this research.

◉ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☑ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☑ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☐ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:
Personal contact details will be stored seperately from research information in a secure filing cabinet.
Research data will be fully anoymised and stored securely in locked filing cabinets.
Research data stored digitally will be stored in password protected files on password protected University computers.
Direct quotations from respondents will be fully anonymised.
Access to confidential research information (paper or digital) will be limited to named members of the research team for the following purposes - to arrange interviews according to protocol and to disseminate the research findings.

Paper and other manual files should be appropriately filed and stored securely.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal data in paper format will be locked in a secure filing cabinet. Study data collected will be stored in password protected file on computers which are also password protected. This data will be fully anonymised.
All contact details forms will be seperated from completed questionnaires and locked in a seperate secure filing

cabinet.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All research data will remain anonymous. Unique identifying numbers will be allocated to the data sets by the researcher. The project data will be identifiable only by these unique study numbers. These lists will be safely secured with access limited to members of the research team. All data collected will be stored on computers and memory sticks which are password protected until the report is published. Study data will be retained for a period of up to 5 years after the final report has been written and subsequently destroyed.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Access to personal data will be limited to named members of the research team (the CI and collaborators) for the following purposes - to arrange interviews according to protocol and to disseminate the research findings.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Study data will be analysed by the researcher and the study collaborators on University of Kent staff computers. These files will be password protected and the computers are also password protected.

A42. Who will have control of and act as the custodian for the data generated by the study?

Title	Forename/Initials	Surname
Ms	Bernadine	O' Donovan

Post	PhD student
Qualifications	MSc Cognitive Neuropsychology MSc Neuropharmacology BA (Psychology)
Work Address	Pharmacy Practice Research Office, Medway School of Pharmacy, Anson Building,Universities of Greenwich & Kent, Central Avenue, Chatham Maritime, Kent.
Post Code	ME4 4TB
Work Email	bo77@kent.ac.uk
Work Telephone	01634202920
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 5
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Research data will be stored on University of Kent premises in locked filing cabinets and password protected computers. Access to this data will be limited to named members of the research team. At the end of this study data will be held for a period of up to 5 years after the final report has been written. Paper records will then be destroyed by shredding and digital records (including audio recordings) will be destroyed.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

(●) Yes ( ) No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined.
If the interviewee is required to travel to selected interview locations then interviewees will be reimbursed for their travel expenses.
Interviewees will also be offered shopping vouchers - value of £20 - as an incentive to attend the interviews.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (●) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (●) No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

( ) Yes (●) No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

( ) Yes (●) No

Please give details, or justify if not registering the research.

Registration of research studies is encouraged wherever possible.
You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have

entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [ ] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [ ] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [x] Other (please specify)

PhD thesis

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

This study will ensure that respondent anonymity will be maintained during publishing of results. Reported data will not identify individuals and participant characteristics wil be published as aggregated information and not linked to specific respondents.

A53. Will you inform participants of the results?

(•) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
A summary of the study results will be sent to interviewees who have supplied their email address and indicated their interest in receiving a summary of the findings. This interest is indicated by ticking the appropriate box in Section D of the questionnaire.

5. Scientific and Statistical Review

A54-1. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [ ] Independent external review
- [ ] Review within a company
- [ ] Review within a multi−centre research group
- [ ] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [x] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
Reviewed by academic supervisors/key collaborators from the University of Kent and University of Birmingham.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☐ Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☐ Review by a statistician within the research team or multi–centre group

☑ Review by educational supervisor

☐ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Janet	Krska
Department	Medway School of Pharmacy		
Institution	Universities of Greenwich & Kent		
Work Address	Anson Building, Universities of Greenwich & Kent,		
	Central Avenue, Chatham Maritime,		
	Kent.		
Post Code	ME4 4TB		
Telephone	01634202950		
Fax			
Mobile			
E-mail	j.krska@kent.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Information sources - types & characteristics
ADRs - frequency & severity

A58. What are the secondary outcome measures? *(if any)*

Coping strategies

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 2500

Total international sample size (including UK):

Total in European Economic Area:

Further details:
Based on a prevalence rate of ADRs in the general UK population of 1-5%.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

UK population estimated at 63 million approx with an ADR prevalence rate of 1-5%. Accuracy set to 50%.
Random sample of the general population at a confidence level of 95%.

Confidence Interval ± 1.96.
Power equation applied as follows

$$Ss = \frac{Zsq \times (p) \times (1-p)}{Csq}$$

(Ss = sample size; Z = 1.96 (95% CL); p = % accuracy expressed in decimals; C = CI expressed in decimals = 0.02)

$$Ss = \frac{(1.96)(1.96) \times (0.5) \times (1-0.5)}{(0.02)(0.02)}$$

$$Ss = \frac{3.8 \times 0.5 \times 0.5}{0.0004}$$

$$Ss = \frac{0.95}{0.0004}$$

Ss = 2375
Therefore the study will utilise a sample size of 2500 approx.

A61-1. Will participants be allocated to groups at random?

○ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The quantitative data from the questionnaires will be analysed through SPSS software to generate descriptive statistics, using appropriate statistical tests such as ANOVAs and multiple regressions. Content analysis will be used to code the responses to the open-ended questionnaire questions and identify points of commonality. A coding frame will be generated that describes the thematic content of the responses. These responses will then be grouped into similar categories. This assigning of codes will be generated by the researcher and independent evaluators ensuring there is reliability in the coding process. Once quantified in this manner the responses will be represented graphically in a frequency chart according to the frequency of responses per category. The data management program NVivo will be used.
The analytical approach to the interviews will be confirmed once the questionnaire data is analysed. However the research literature suggests that an interpretative phenomenological analysis (IPA) will be used.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co–applicants, protocol co–authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Professor	Janet	Krska
Post	Professor of Clinical & Professional Practice		
Qualifications	PG Certificate (Health economics) PG Certificate (Tertiary level teaching) PhD (pharmacology) BSc (pharmacy)		
Employer	Universities of Greenwich & Kent		
Work Address	Medway School of Pharmacy		

	Universities of Greenwich & Kent, Central Avenue,
	Chatham Maritime, Kent.
Post Code	ME1 1TB
Telephone	01634202950
Fax	
Mobile	
Work Email	j.krska@kent.ac.uk

Title	Forename/Initials	Surname
Dr	Stuart	Gill-Banham

Post	Clinical Lecturer Clinical Lecturer - Applied Therapeutics (Mental Health & Neuropharmacology)
Qualifications	PhD Post Graduate Certificate in Higher Education (PGCHE) Post Graduate Certificate in Managing Health and Social Care Post Graduate Diploma Psychiatric Pharmacy Bsc(Hons) Pharmacy
Employer	Universities of Greenwich & Kent
Work Address	Medway School of Pharmacy
	Universities of Kent, Central Avenue,
	Chatham Maritime, Kent.
Post Code	ME1 1TB
Telephone	01634 (20)2949
Fax	
Mobile	
Work Email	s.gill-banham@kent.ac.uk

Title	Forename/Initials	Surname
Dr	Anthony	Cox

Post	Lecturer in Clinical Pharmacy, Joint Academic Programme Lead MPharm.
Qualifications	BSc PhD MRPharmS C Clin Dip Pharm
Employer	University of Birmingham
Work Address	School of Clinical and Experimental Medicine
	The Medical School, Vincent Drive,
	University of Birmingham, Birmingham.
Post Code	B15 2TT
Telephone	0121 4146926
Fax	
Mobile	
Work Email	a.r.cox@bham.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status: ◯ NHS or HSC care organisation Commercial status:

- (●) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Other

If Other, please specify:

Contact person

Name of organisation	University of Kent
Given name	Nicole
Family name	Palmer
Address	Room Reg 152, Registry, University of Kent
Town/city	Canterbury, Kent.
Post code	CT2 7NZ
Country	UNITED KINGDOM
Telephone	01227 (82)4797
Fax	
E-mail	N.R.Palmer@kent.ac.uk

Is the sponsor based outside the UK?

( ) Yes (●) No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

- [ ] Funding secured from one or more funders
- [ ] External funding application to one or more funders in progress
- [x] No application for external funding will be made

What type of research project is this?

- ( ) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- (●) Other

Other – please state:
PhD project

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (●) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another

country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Dr	Peter	Dodds
Organisation	RM&G Consortium for Kent and Medway,		
Address	No. 6 The Courtyard, Campus Way,		
	Gillingham Business Park,		
	Gillingham, kENT.		
Post Code	ME8 0NZ		
Work Email	pdodds2@nhs.net		
Telephone	01634 350403		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/08/2014
Planned end date: 31/05/2015
Total duration:
Years: 0 Months: 10 Days:

A71-1. Is this study?

○ Single centre
◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

☑ England
☐ Scotland
☐ Wales
☐ Northern Ireland
☐ Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	5
☐ NHS organisations in Wales	
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent (private or voluntary sector) organisations	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	5

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Research carried out at University of Kent is covered by University of Kent Code of Practice for Quality Assurance for Research Programmes of Study.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:* in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland**

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

Research carried out at University of Kent is covered automatically by existing policies.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as*

applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

Research carried out at University of Kent is covered automatically by existing policies.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☐ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Research carried out at University of Kent is covered automatically by existing policies.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

◉ Yes ○ No ○ Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Research site		Investigator/ Collaborator/ Contact	
Institution name	Primary Care Trust	Title	Ms
Department name	Eastern & Coastal Kent PCT	First name/ Initials	Bernadine
Street address	6 The Courtyard, Campus Way, Gillingham Business Park	Surname	O' Donovan
Town/city	Gillingham, Kent.		
Post Code	ME8 0NZ		
Institution name	Primary Care Trust	Title	Ms
Department name	Medway PCT	First name/ Initials	Bernadine
Street address	6 The Courtyard, Campus Way, Gillingham Business Park	Surname	O' Donovan
Town/city	Gillingham, Kent.		
Post Code	ME8 0NZ		

Institution name	Primary Care Trust	Title	Ms
Department name	Former West Kent PCT	First name/ Initials	Bernadine
Street address	6 The Courtyard, Campus Way, Gillingham Business Park	Surname	O' Donovan
Town/city	Gillingham, Kent.		
Post Code	ME8 0NZ		

Institution name	CCG (former PCT)	Title	Ms
Department name	Sandwell and West Birmingham CCG	First name/ Initials	Bernadine
Street address	Kingston House, 438-450 High Street	Surname	O' Donovan
Town/city	West Bromwich		
Post Code	B70 9LD		

Institution name	CCG (former PCT)	Title	Ms
Department name	Birmingham CrossCity	First name/ Initials	
Street address	Bartholomew House,142 Hagley Road	Surname	
Town/city	Edgbaston, Birmingham.		
Post Code	B16 9PA		

Institution name	CCG (former PCT)	Title	Ms
Department name	Birmingham South Central	First name/ Initials	Bernadine
Street address	Ground floor, Bartholomew House,142 Hagley Road,	Surname	O' Donovan
Town/city	Birmingham		
Post Code	B16 9PA		

Institution name		Title	
Department name		First name/ Initials	
Street address		Surname	
Town/city			
Post Code			

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

(•) Chief Investigator

( ) Sponsor

- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☑ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name: BERNADINE O' DONOVAN

Date: 06/06/2014 *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co–sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Signature: .....

Print Name: NICOLE PALMER

Post: Research Ethics & Governance Officer

Organisation: university of Kent

Date: *(dd/mm/yyyy)*

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

Signature:	.....
Print Name:	JANET KRSKA
Post:	Professor of Clinical & Professional Practice
Organisation:	Universities of Greenwich & Kent
Date:	06/06/2014 *(dd/mm/yyyy)*

APPENDIX 5: R&D emails

km rmgconsortium (MAIDSTONE AND TUNBRIDGE WELLS NHS TRUST)
<rmgconsortium.km@nhs.net> Fri 05/12/2014 10:02

Dear Bernadine

The last thing that we will need before you can start on your research project is for us to issue you with a Letter Of Access. In order for us to so this please can you let us have a Research Passport (with DBA and Occupational health checks). Your university HR department will be familiar with the Research Passport process & will be able to help you with this.

As we will probably be the first site to review you Research Passport please can you supply original copies of all the documents.
Many thanks

Richard Collins
RM&G Manager
RM&G Consortium for Kent and Medway
No 6 The Courtyard
Campus Way
Gillingham Business Park
Kent ME8 0NZ

km rmgconsortium (MAIDSTONE AND TUNBRIDGE WELLS NHS TRUST)
<rmgconsortium.km@nhs.net> Wed 25/02/2015 09:15

Dear Bernadine

I have looked into this a little more & because of the abolition of the PCT's I am sorry but we are no longer able to issue Letters Of Access in primary care & you will have to ask the pharmacies on an individual basis to do this. I would hope that as you are carrying out a very low risk activity that this should be straightforward.
Regards

Richard Collins
RM&G Manager
RM&G Consortium for Kent and Medway
No 6 The Courtyard
Campus Way
Gillingham Business Park
Kent ME8 0NZ

APPENDIX 6: Survey – Side effects from medicines: your views and experiences

Side effects from medicines: your views and experiences

This questionnaire asks about your opinions of, and experiences of, identifying and managing side effects from medicines.

Please complete the questionnaire and return it to the Medway School of Pharmacy, Universities of Kent and Greenwich.

A prepaid envelope is provided so there is no need to put a stamp on the envelope.

Please note that all the information that you will provide will be treated in confidence and in accordance with the Data Protection Act.

Thank you for agreeing to fill in this questionnaire survey.

Researcher contact details:

Bernadine O' Donovan

Medway School of Pharmacy

Chatham Maritime

Kent ME4 4TB

Phone 0163420 Ext 2920

Email bo77@kent.ac.uk

- Please try to answer all the questions truthfully, but if you do not want to answer any question, then please ignore it.
- For questions with tick-boxes □ please put a tick (√) in the box that is closest to your chosen answer.
- For questions that ask you to write something, please write in the space provided.

Section A: About how you might use information on medicines

1) **If** you experienced side effect(s) from a medicine that you have been taking, which of the following would you use to find out about the side effect(s)? *(you may tick more than one box)*

Healthcare professionals

☐ GPs

☐ Hospital doctors

☐ Pharmacists

☐ Nurses

Formal sources of information

☐ Leaflets found with your medicine - Patient Information Leaflets (PILs)

☐ Print & Broadcast Media (e.g. newspapers, magazines, radio, television)

☐ Medicine books/guides

Informal sources of information

☐ Relatives and/or friends

☐ The Internet

☐ Other

If other, please specify .....

2) There are many possible reasons why you might use sources of information e.g. because they are ***easy to access,*** they are ***trustworthy***, they are ***easy to understand*** or they are ***relevant to you***. Please consider **each** of the following information sources and indicate – by ticking the appropriate box – if you think they are easy to access, trustworthy, easy to understand or relevant to you.

For example, if you think GPs are *Trustworthy*, *Easy to understand* and *Relevant to me*, but not *Easy to Access*, then tick the boxes as shown below:

	Easy to access	*Trustworthy*	*Easy to understand*	*Relevant to me*
GPs	☐	✓	✓	✓

	Easy to access	*Trustworthy*	*Easy to understand*	*Relevant to me*
Healthcare professionals				
GPs	☐	☐	☐	☐
Hospital doctors	☐	☐	☐	☐
Pharmacists	☐	☐	☐	☐
Nurses	☐	☐	☐	☐

	Easy to access	*Trustworthy*	*Easy to understand*	*Relevant to me*
Formal Sources of information				
Patient Information Leaflets	☐	☐	☐	☐
Print & Broadcast Media	☐	☐	☐	☐
Medicine books/guides	☐	☐	☐	☐

	Easy to access	*Trustworthy*	*Easy to understand*	*Relevant to me*
Informal sources of information				
Relatives and/or friends	☐	☐	☐	☐
The Internet	☐	☐	☐	☐
Other	☐	☐	☐	☐

Section B: About suspected side effects from medicines

3) Do you think that you have ever experienced side effect(s) from a medicine?

(please tick one)

☐ Yes, once

☐ More than once

☐ No, never ***(Please go to Section C)***

4) When did you last experience side effect(s) from a medicine?

☐ In the past month

☐ In the past 3 months

☐ In the past 6 months

☐ One year or longer

5) Did you see a doctor because of the side effect(s)?

☐ Yes ☐ No

6) Were you admitted to hospital because of the side effect(s)?

☐ Yes ☐ No

7) In your opinion how serious was this side effect(s)?

☐ Very serious, caused very serious illness

☐ Serious enough to affect everyday activities

☐ Unpleasant, but did not affect daily activities

☐ Mild

8) How would you describe the level of impact the side effect(s) had on the quality of your daily life?

☐ Severe impact

☐ Moderate impact

☐ Mild impact

☐ No impact

9) Please describe in your own words how the side effect(s) affected your daily life.

10) How confident were you that the side effect(s) was due to your medication?

(please tick one)

☐ Very confident

☐ Fairly confident

☐ Not very confident

☐ Not at all confident

11) What made you think that the medicine had caused the side effect(s)?

12) Did you use any of the following sources of information to confirm your view that the medicine had caused the side effect(s)? *(you may tick more than one box)*

Healthcare professionals

☐ GPs

☐ Hospital doctors

☐ Pharmacists

☐ Nurses

Formal Sources of information

☐ Patient Information Leaflets (PILs)

☐ Print & Broadcast Media

☐ Medicine books/guides

Informal sources of information

☐ Relatives and/or friends

☐ The Internet

☐ Other

13) Did you stop taking the medicine because of the side effect(s)?

☐ Yes ***(Go to Question 14)*** ☐ No ***(Go to Section C)***

14) Were you advised to stop taking the medicine by any of the following? (please tick one)

☐ Yes –relatives and/or friends

☐ Yes - Healthcare Professionals (e.g. GPs, hospital doctors, pharmacists and/or nurses)

☐ No - It was my own decision to stop

Section C: How you cope with side effects in general

15) There are many things that people do in order to deal with problems such as side effects from medicines. Please look at the following list and indicate - by ticking the box – how closely each statement corresponds with **what you would do when you experience side effects.**
Use the following scale and tick the box that most closely describes how you would cope with side effects: **Never; Rarely; Sometimes; Often;** and **Always**

When you experience side effects would you:	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Decide that the benefit from the medication is not worth the side effect and stop taking it?					
Get support from other people?					
Talk to your doctor or health care professional about the problem?					
Try to get more information about the medication or side effect?					
Reduce the dose of the medication that is causing the side effect?					
Talk to family, friends, loved ones about the problem?					
Take another medication to deal with the side effect?					
Accept the side effect and take the medication as prescribed?					
Request a medication from your doctor to help the side effect?					
Ask your doctor to prescribe a different medication?					

Section D: How you cope with stressful situations in general

I would like to find out some more information concerning your experience of side effects. I would like to assess, if the way you respond to stressful situations, affects your experiences of a suspected side effect from a medicine. This questionnaire will provide information on styles of coping in times of stress. It outlines two possible scenarios and eight possible ways to react to each situation. Please try to put yourself in each situation and indicate if the proposed reactions describe what you would do or think if you were personally involved in the situation. There is no right or wrong answer.

16) Vividly imagine that you are afraid of the dentist and have to get some dental work done.

Which of the following would you do? *Tick all of the statements that might apply to you.*

- ☐ I would ask the dentist exactly what he or she was going to do
- ☐ I would take a tranquillizer or have a drink before going
- ☐ I would try to think about pleasant memories
- ☐ I would want the dentist to tell me when I would feel pain
- ☐ I would try to sleep
- ☐ I would watch all the dentist's movements and listen for the sound of the drill
- ☐ I would watch the flow of water from my mouth to see if it contained blood
- ☐ I would do mental puzzles in my mind

17) Vividly imagine that, due to a large drop in sales, it is rumoured that several people in your department at work will be laid off. Your supervisor has turned in an evaluation of your work for the past year. The decision about lay-offs has been made and will be announced in several days. *Tick all of the statements that might apply to you.*

- ☐ I would talk to my fellow workers to see if they knew anything about the supervisor's evaluation of me.
- ☐ I would review the list of duties for my present job and try to figure out if I had fulfilled them all
- ☐ I would go to the cinema to take my mind off things
- ☐ I would try to remember any arguments or disagreements I might have had with the supervisor that would have lowered his or her opinion of me
- ☐ I would push all thoughts of being laid off out of my mind
- ☐ I would tell my family and close friends that I'd rather not discuss my chances of being laid off
- ☐ I would try to think which employees in my department might be thought by the supervisor to have done the worst job
- ☐ I would continue doing my work as if nothing special was happening

Section E: About you
(the personal information you supply will be treated with strictest confidence)

18) How many medicines, prescribed for you, do you use regularly?

☐ None ☐ One ☐ Two to Four ☐ Five to Eight ☐ More than Eight.

19) Are you? ☐ Male ☐ Female

20) What age group are you in?

☐ Below 40 ☐ 41-50 ☐ 51-60 ☐ 61 to 70 ☐ 71-80 ☐ Over 80

21) What is your current employment status? (please tick one)

☐ Full time employment ☐ Part time employment

☐ Retired ☐ Unemployed

☐ Student ☐ Other (please specify) .....

22) What is the highest level of education you have obtained/reached?

☐ Left school at 16 years or younger ☐ Further education

☐ Left school at 17 or 18 years ☐ University

23) What is your ethnicity? *(please tick one)*

☐ White ☐ Mixed/Multiple ethnic groups

☐ Asian/Asian British ☐ Other ethnic group

☐ Black/African/Caribbean/Black British

24) Please provide us with your full postcode, we will **NOT** contact you or pass your details on to anyone else.

☐☐☐☐ ☐☐☐

Thank you for taking the time to complete this survey.

Should you have any questions or concerns about this survey please contact Bernadine O' Donovan whose contact details are shown below.

Researcher contact details:

Bernadine O' Donovan

Medway School of Pharmacy

Chatham Maritime

Kent ME4 4TB

Phone 0163420 Ext 2920

Email bo77@kent.ac.uk

Please return your completed questionnaire to the Medway School of Pharmacy, Universities of Kent and Greenwich, in the prepaid envelope that is provided.

Section F: Learning more about your experience

If you have experienced a side effect(s) in the last 6 months would you be willing to talk to a researcher about your experience?

I would like to interview some of the people who have completed this questionnaire. If you would be willing to participate further and be interviewed, please give your details below. This Contact Details form will be detached from the questionnaire and kept separately. The details will only be used so I can contact you about taking part in an interview. This will be in two to three weeks. The Contact Details form will be destroyed once the interview has taken place or if you decide when contacted that you have changed your mind and do not want to be interviewed. Not everyone who completes the Contact Details form will be contacted by the researcher. If I contact you I will ask if you are still willing to be interviewed – you can say no at that stage. If you change your mind later you can contact the research team directly and say you have changed your mind. The contact details for the research team are in the Participant Information Sheet.

1) **Your Contact details**

Name: ……

What is your preferred method of contact?: *(you may tick more than one box)*

☐ Telephone/mobile number

Please provide telephone/mobile number ……

☐ Email address

Please provide email address ……

2) **Preferred time for contacting you (in two/three weeks' time):**

☐ Morning ☐ Afternoon ☐ Early Evening

3) **Preferred day for contacting you:**

☐ Weekday ☐ Saturday ☐ Sunday

4) **Would you like a summary of the study results to be sent to you?**

☐ Yes ☐ No

If Yes, please make sure you provide an email address……

Version 1.1 13/11/14

APPENDIX 7: Permissions to use MBSS & SECope instruments

MBSS AGREEMENT FORM

Please fill in the requested information, sign, and mail, fax, or email a scanned copy to John Scarpato, Project Manager. (Address: Psychosocial and Biobehavioral Medicine Program, Division of Cancer Prevention and Control, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111; Fax: (215) 728-2707; john.scarpato@fccc.edu)

Name: **Bernadine O' Donovan**
Affiliation/Institution: **University of Kent**
Address: **Pharmacy Practice Research Office,** **Medway School of Pharmacy, University of Kent,** **Central Avenue, Chatham Maritime,** **Kent, England.** **ME4 4TB.**
Phone: **0163420 Ext 2920**
Fax:
Email: **bo77@kent.ac.uk**
Please briefly describe the research in which you will be employing the MBSS and how the MBSS will be used in this research: The aim of this project is to investigate how people identify adverse drug reactions (ADRs) and also explore peoples' experiences of ADRs. It will also assess relationships between peoples' coping strategies and their experiences of ADRs. This project will recruit approx. 2500 members of the public through distribution of questionnaires in independent and small to medium sized multiple pharmacies. Interviews with up to 50 selected participants will be conducted to discuss how they identified their experience as an ADR from a medicine. It is proposed to use the MBSS to gather additional information on coping styles and as part of the sampling strategy used to select potential interviewees for future interviews ie. a mix of Monitors and Blunters.

I, B O' Donovan, **agree to the following terms and conditions:**

1) The MBSS will be used solely for research purposes.
2) No part of the MBSS will be published without the additional written consent of Suzanne M. Miller, Ph.D.
3) All research findings and publications produced with use of the MBSS will be shared with Suzanne M. Miller, Ph.D.

BERNADINE O' DONOVAN — **Print Name**

16/06/14 — **Date**

B O'Donovan — **Signature**

From: Denig, P (med) [p.denig01@umcg.nl]
Sent: 28 May 2014 20:42
To: B.O'Donovan
Subject: RE: Request to use MBSS in PhD project (UK)

Dear Bernadine O'Donovan,

First, my apologies for not reacting sooner. I have asked within our organisation whether there would be any restriction regarding the use of our revised version of the SECope questionnaire. As far as I understand, there is no restriction. This implies that you are free to use our revised version as presented in Table 2 of our publication, using the following reference: Coping with adverse drug events in patients with heart failure: Exploring the role of medication beliefs and perceptions.
De Smedt RH, Jaarsma T, Ranchor AV, van der Meer K, Groenier KH, Haaijer-Ruskamp FM, Denig P.
Psychol Health. 2012;27(5):570-87.

I would, however, be interested in the results from using our revised SECope questionnaire in another population. Maybe we could conduct some additional (construct) validity testing together, using the data you are going to collect?

Kind regards
Petra Denig

APPENDIX 8: Participant Information Sheet & Feedback form

PARTICIPANT INFORMATION SHEET

Title of Project: A study exploring how people identify and manage side effects from medicines.

Name of Researcher (s): Bernadine O' Donovan, Dr R. Rodgers, Dr A Cox and Professor J Krska.

You are being invited to take part in a study. It is being carried out by the Medway School of Pharmacy, University of Kent and the University of Birmingham. You have been chosen because you have experienced side effect(s) from your medicine. 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 designed to explore peoples' experiences of identifying side effects from medicines and an assessment tool has been developed to help people do this. This study seeks to confirm the validity of this assessment tool.

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 legal rights 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 via email to provide feedback on the assessment tool. If you decide you would like to do so, you will be sent a copy of the assessment tool by post with a consent form and a prepaid envelope. If you agree to take part, you will be asked to sign a consent form and return it to the Medway School of Pharmacy in the prepaid envelope. I will contact you and arrange a telephone interview at a time and date that suits you. The interview will take no more than 30 minutes and you can change your mind and end the interview at any time. During this interview I will ask you to review and comment on the assessment tool. I will also ask you for any suggestions you may have for its possible improvement.

Are there any risks if I take part?
The telephone interview will be conducted at a date and time which is convenient for you and it will take no more than 30 minutes. There are no risks to taking part in the study.

Are there any benefits if I take part?
If you are interviewed you will be offered a shopping voucher to the value of £10.

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?
If you decide to take part in the interview, the information you provide will be treated in the strictest confidence in accordance with the Data Protection Act 1998 and used only for the purpose of arranging the interview. Consent forms will be scanned on an encrypted memory stick and will be held for no longer than 12 months after the completion of the project. Research data will be securely stored in a secure filing cabinet and on password protected computers. All the data collected will be fully anonymised and digital records will be destroyed five years after the final report has been written.
This project forms part of a larger PhD project, which will be published as a PhD thesis. A copy of this project's report will be produced and disseminated to the Medway School of Pharmacy. The findings will also be disseminated through conferences, and in the writing of research papers.
If you wish to be provided with information about the findings please provide your contact details to Bernadine O' Donovan and you will be sent a copy of the findings in two/three months

Who is Organising and Funding the study?
This study is being carried out by students and staff at Medway School of Pharmacy. It is being funded by the Medway School of Pharmacy, University of Kent.

Who should I contact if I want to know more about the study?
Bernadine O' Donovan
Medway School of Pharmacy
Chatham Maritime
Kent ME4 4TB
Phone 0163420 Ext 2920
Email bo77@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 Chair of the MSoP Research Ethics Committee on S.A.Corlett@kent.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
Version 4.0, 02/02/16

Feedback Form

I found this Assessment tool easy to read.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this Assessment tool easy to understand.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this Assessment tool was clearly laid out.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this Assessment tool had a logical structure.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this Assessment tool easy to complete.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

How long (approx.) did it take you to complete this Assessment tool?

Do you think this Assessment tool was too long?

This Assessment tool asks you about your past experiences of side effects. Did you find it difficult to recall details of this experience?

Are there any suggestions you can make on how to improve this questionnaire?

Any additional comments:

APPENDIX 9: Invitation letter to pharmacists

Date

Dear pharmacist

PhD project: Exploring how people identify and manage side effects from medicines.

My name is Bernadine O' Donovan and I am a PhD student at the Medway School of Pharmacy. I am investigating peoples' experiences of symptoms they perceive to be medicine side effects and how they have identified these as potential adverse drug reactions, for example using information in PILs, the internet or from health professionals.

I am writing to ask if you would kindly support this study in a small way. I have developed a questionnaire which I would like to give out to as many people as possible, not just those who are collecting prescriptions from pharmacies. A copy of this questionnaire is enclosed and an information sheet with more details. Please take time to read this and decide if you wish to take part. If you agree, this will involve you:

● Allowing me to distribute questionnaires to a sample of your customers.

● I will only visit your premises at mutually agreed times, for a maximum of four hours in total.

I **will not**:

- Interfere in the day-day running of your pharmacy
- Coerce any customer to take a questionnaire
- Access any confidential medical information of any pharmacy customer.

I have many years of customer service experience within pharmacies and will adhere to established research ethical and confidentiality guidelines.

I will call you within the next week to see whether you are willing to participate. Thank you for reading this letter.

Yours sincerely Version 1.0 16/06/14

APPENDIX 10: Pharmacist Information Sheet

PHARMACIST INFORMATION SHEET

Title of Project: Exploring how people identify and manage side effects from medicines.

Name of Researcher (s): Bernadine O' Donovan

1. What is the purpose of the study?
This study is aimed at finding out how people identify ADRs and what they do when they experience an ADR. 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?
I have contacted you because you are working in a Boots pharmacy in Kent and I would like your permission to distribute this 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. I will contact you by telephone to ask when you are willing to allow me to conduct this study in your pharmacy.

4. What will happen if I agree?
If you agree, I will visit your pharmacy at an agreed time and distribute questionnaires to a sample of your customers. I 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 me to approach them, but no-one will be pressured into filling in or taking a questionnaire.

5. How long will this take?
I will try to recruit up to 50 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 four hours.

6. Are there any risks / benefits involved?
There are no risks to you or your business in taking part. I am not able to offer 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?

Researcher:
B O' Donovan,
PhD Practice Office,
Medway School of Pharmacy, Universities of Greenwich and Kent, Central Avenue,
Chatham Maritime, Kent ME4 4TB
Tel: 0163420 Ext 2920 email: bo77@kent.ac

Professor Janet Krska
Medway School of Pharmacy, Universities of Greenwich and Kent, Central Avenue,
Chatham Maritime, Kent ME4 4TB
Tel: 01634 202950 e-mail: j.krska@kent.ac.uk

Dr Anthony Cox,
School of Clinical and Experimental Medicine,
University of Birmingham,
Birmingham, B15 2TT
Tel: 0121 414 6926 email: a.r.cox@bham.ac.uk

This project has been looked at and approved by the National Research Ethics Service (NRES) Committee North East – Newcastle & Tyneside 1.

Version 1.1 02/02/15

APPENDIX 11: Topic Guide for interviews

• Introduction – 5 mins

[Cover purpose, confidentiality, format, duration and recording of interview; contact information; any questions from interviewee.]

• Factual account of side effect(s) experience – 5 mins

"So..you recently experienced a side effect..from a medicine that you had been taking...could you tell me what happened? You were.....(raised questioning tone & pause)."

• Cognitive processes involved in identification – 15 mins

- Symptoms
- Timeline
- Sequence
- Aided/unaided decision

"We've been talking in general about your side effect(s) I'd now like to ask you what made you suspect (pause) that the medicine/named drug had caused the side effect(s)."

"So you decided the medicine/named drug had caused the side effect because xxx" (echo)

• Impact of side effect on daily functioning – 10 mins

- Physical elements
- Psychological elements
- Social elements

"Now if I could just ask you (pause) to think back some more to the time that you had this side effect(s)....would you say that the side effect(s) affected your daily life?"

"Could you tell me some more about that?" (probing q)

• Coping strategies – 10 mins

- Behaviours (action)
- Social support

"So we've talked about the impact the side effect(s) had on the quality of your daily life. I'ld like to ask you to think back again to the time that you had this side effect(s).....People who experience a side effect(s)....generally they deal with it in

many different ways.....Could you tell me about what happened in your situation.....how you coped with this side effect(s)?"

• Appraisal of strategies – 10 mins

"So you've told me that when you experienced the side effect(s) you xxx." (echo)

"If I asked you to consider your reaction(s) at that time to the side effect(s)...looking back…what do you think now about your reaction(s)?"

• Close - 5 mins

Version 1.0 13/11/14

APPENDIX 12: MBSS scoring key

Monitor/Blunter Style Scale – Scoring Key

1. Vividly imagine that you are afraid of the dentist and have to get some dental work done. Which of the following would you do? Check all of the statements that might apply to you.

__M__ I would ask the dentist exactly what work was going to be done.

__B__ I would take a tranquilizer or have a drink before going.

__B__ I would try to think about pleasant memories.

__M__ I would want the dentist to tell me when I would feel pain.

__B__ I would try to sleep.

__M__ I would watch all the dentist's movements and listen for the sound of the drill.

__M__ I would watch the flow of water from my mouth to see if it contained blood.

__B__ I would do mental puzzles in my mind.

3. Vividly imagine that, due to a large drop in sales, it is rumored that several people in your department at work will be laid off. Your supervisor has turned in an evaluation of your work for the past year. The decision about lay-offs has been made and will be announced in several days. Check all of the statements that might apply to you.

__M__ I would talk to my fellow workers to see if they knew anything about what the supervisor's evaluation of me said.

__M__ I would review the list of duties for my present job and try to figure out if I had fulfilled them all.

__B__ I would go to the movies to take my mind off things

__M__ I would try to remember any arguments or disagreements I might have had that would have resulted in the supervisor having a lower opinion of me

__B__ I would push all thoughts of being laid off out of my mind.

__B__ I would tell my spouse that I'd rather not discuss my chances of being laid off.

__M__ I would try to think which employees in my department the supervisor might have thought had done the worst job.

__B__ I would continue doing my work as if nothing special was happening.

APPENDIX 13: Consent form for interviews

CONSENT FORM for INTERVIEW

A study exploring how people identify and manage side effects from medicines.

Name of researcher: Bernadine O' Donovan

I have read and understand the information provided for the above study in the Participant Information Sheet Version 1.1 24/06/14. 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 and that this will not affect my legal rights	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 understand that verbatim quotes taken from the recording of our conversation may be used in publications and reports, but that these will be anonymised and not traceable to me	Initial Here
I understand that data collected during the study may be looked at by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I agree to discuss my experiences of adverse drug reactions.	Initial Here

Name of Participant (Print) _____

Signature _____ Date _____

APPENDIX 14: Interview notes

Initial reflections on the interviews:

Int1	Short interview ended at request of interviewee as was tired.
Int2	Interview takes place in quiet apartment. Interviewee recalls SE experience in detail.
Int3	Interview difficult as interviewee focused on her negative experiences with HCPs.
Int4	Interview takes place in noisy surroundings. Interviewee recalls SE clearly and describes their impact on him.
Int5	Interview takes place in quiet sitting room. Interviewee fully engaged throughout.
Int6	Interview takes place in private house. Excellent rapport with interviewee.
Int7	Interview takes place in quiet sitting room. Interviewee experiences chronic pain and talks in detail about his SE.
Int8	Interview takes place in café so background noise throughout. Interviewee speaks in detail about his SE and coping strategies.
Int9	Interviewee engaged with questions and was keen to share his experiences of both mild and severe SE.
Int10	Good rapport established with interviewee.
Int11	Interviewee was elderly with a soft voice.
Int12	Interviewee engaged with questions and was keen to share her SE experiences.
Int13	Interview takes place in quiet kitchen. Good rapport established and SE clearly described.
Int14	Interview conducted in café so background noise on recording fluctuates. Good rapport established with interviewee.
Int15	Interviewee engaged fully and was keen to share her SE experiences. Some background noise on recording from family dog.

APPENDIX 15: Participant Information Sheet, Feedback and Consent Forms for Assessment tool

PARTICIPANT INFORMATION SHEET

Title of Project: A study exploring how people identify and manage side effects from medicines.

Name of Researcher (s): Bernadine O' Donovan, Dr R. Rodgers, Dr A Cox and Professor J Krska.

You are being invited to take part in a study. It is being carried out by the Medway School of Pharmacy, University of Kent and the University of Birmingham. You have been chosen because you have experienced side effect(s) from your medicine. 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 designed to explore peoples' experiences of identifying side effects from medicines and an assessment tool has been developed to help people do this. This study seeks to confirm the validity of this assessment tool.

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 legal rights 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 via email to provide feedback on the assessment tool. If you decide you would like to do so, you will be sent a copy of the assessment tool by post with a consent form and a prepaid envelope. If you agree to take part, you will be asked to sign a consent form and return it to the Medway School of Pharmacy in the prepaid envelope. I will contact you and arrange a telephone interview at a time and date that suits you. The interview will take no more than 30 minutes and you can change your mind and end the interview at any time. During this interview I will ask you to review and comment on the assessment tool. I will also ask you for any suggestions you may have for its possible improvement.

Are there any risks if I take part?
The telephone interview will be conducted at a date and time which is convenient for you and it will take no more than 30 minutes. There are no risks to taking part in the study.

Are there any benefits if I take part?
If you are interviewed you will be offered a shopping voucher to the value of £10.

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?
If you decide to take part in the interview, the information you provide will be treated in the strictest confidence in accordance with the Data Protection Act 1998 and used only for the purpose of arranging the interview. Consent forms will be scanned on an encrypted memory stick and will be held for no longer than 12 months after the completion of the project. Research data will be securely stored in a secure filing cabinet and on password protected computers. All the data collected will be fully anonymised and digital records will be destroyed five years after the final report has been written. This project forms part of a larger PhD project, which will be published as a PhD thesis. A copy of this project's report will be produced and disseminated to the Medway School of Pharmacy. The findings will also be disseminated through conferences, and in the writing of research papers.
If you wish to be provided with information about the findings please provide your contact details to Bernadine O' Donovan and you will be sent a copy of the findings in two/three months

Who is Organising and Funding the study?
This study is being carried out by students and staff at Medway School of Pharmacy. It is being funded by the Medway School of Pharmacy, University of Kent.

Who should I contact if I want to know more about the study?
Bernadine O' Donovan
Medway School of Pharmacy
Chatham Maritime
Kent ME4 4TB
Phone 0163420 Ext 2920
Email bo77@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 Chair of the MSoP Research Ethics Committee on S.A.Corlett@kent.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
Version 4.0, 02/02/16

CONSENT FORM for **TELEPHONE** INTERVIEW

A study exploring how people identify and manage side effects from medicines.

Name of researcher: Bernadine O' Donovan

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 and that this will not affect my legal rights	Initial Here
I understand that any personal information collected during the study will be anonymised and remain confidential	Initial Here
I agree to provide feedback on the assessment tool for suspected side effects	Initial Here

Name of Participant (Print) _____

Signature _____ Date _____

Name of Researcher (Print) _____

Signature _____ Date _____

Version 2.0 07/12/15

FEEDBACK FORM

I found this assessment tool easy to read.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this assessment tool easy to understand.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this assessment tool was clearly laid out.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this assessment tool had a logical structure.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

I found this assessment tool easy to complete.

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

How long (approx.) did it take you to complete this assessment tool?

Did you think this assessment tool was too long?

This assessment tool asks you about your past experience of side effects. Did you find it difficult to recall details of this experience?

Are there any suggestions you can make on how to improve this assessment tool?

Any additional comments:

APPENDIX 16: Online statement for AT

Welcome,
You are invited to take part in a research study which looks at peoples' experiences of identifying side effects from medicines. The research is conducted by the Medway School of Pharmacy and the University of Birmingham**.**

This study will take approximately 15 minutes of your time. You will be asked to participate by completing an on-line survey about your experience of the suspected side effect(s). For questions where you are asked to describe your experience in your own words, the boxes will expand as you type. The survey will include questions which will help you to assess the event you suspect may be a side effect from a medicine (Side Effects - Patient Assessment Tool).

You must be at least 18 years old and a UK resident to take this survey.

The decision to participate in this research is voluntary. You do not have to participate and you may skip any questions you do not wish to answer. If you do not wish to complete this survey just close your browser.

Your part in this study is anonymous to the researcher. However, because it is web based, by completing it you will leave behind an electronic record. Neither the researcher nor anyone else involved with this survey will be capturing this information.

To find out more about the study please read the Participant Information Sheet which can be accessed on the following page.

If you have any questions about this study, please feel free to contact Bernadine O' Donovan, Medway School of Pharmacy, Chatham Maritime, Kent ME4 4TB, Phone 0163420 Ext 2920, Email bo77@kent.ac.uk
The study was approved by the Medway School of Pharmacy Research Ethics Committee. If you have concerns about how this research study has been conducted please contact the Chair of this Committee: S.A.Corlett@kent.ac.uk

By clicking on the Submit button at the end of the page you confirm that you have read and understand this page.

Thank you for your time.

APPENDIX 17: Side Effects Patient Assessment Tool (SE-PAST) leaflet format

Assessment Tool for Suspected Side Effects

- Please focus on <u>one side effect/symptom</u> or <u>one group of side effects/symptoms</u> when answering the following questions.
- There are two parts to this assessment tool to be completed. Section A is seeking general information about you, your suspected side effect(s) and your use of medicines. Section B is a standard assessment tool for suspected side effects.

Instructions for Section A:

- For questions that ask you to write something, please write in the space provided.
- For questions with tick-boxes ☐ please put a tick (√) in the box that is closest to your chosen answer.

Instructions for Section B:

- There are ten statements relating to side effects experiences. Each statement has four possible responses 'Yes' 'No' 'Don't Know' or 'Not applicable'.

<u>Think about the time that you experienced the suspected side effect(s).</u>

- For all ten statements, select the response that most clearly represents what happened in your experience of the suspected side effect(s). You must answer all ten statements.
- Then use the Scoring box as follows - fill in the scores which correspond to each of your selected responses in this box, then add these scores up to get your total score.
- Use the tool's probability key to understand what your score means.

Section A: Background information (personal information will be treated with strictest confidence)

1) Please describe the suspected side effect(s) you experienced in detail, including any information that you think may be relevant.

2) When did you experience the suspected side effect(s)?

☐ In the past month ☐ In the past 3 months ☐ In the past 6 months ☐ One year/longer

3) How would you describe the level of impact the suspected side effect(s) had on your daily activities?

☐ Severe impact ☐ Moderate impact ☐ Mild impact ☐ No impact

4) What medicine or medicines were you taking at the time that you experienced the suspected side effect(s)? Please list them below, as far as you are able to, including prescription, over the counter and/or herbal medicines.

5) Which of these medicines do you think caused the side effect(s)?

6) Do you have any existing medical condition(s) or allergies?

☐ Yes ☐ No ☐ Don't know

If yes please list the medical conditions/allergies below

7) Are you? ☐ Male ☐ Female

8) What age group are you in?

☐ Below 40 ☐ 41-50 ☐51-60 ☐ 61 to 70 ☐ 71-80 ☐Over 80

9) What is the highest level of education you have obtained/reached?

☐ Left school at 16 years /younger ☐ Further education ☐ Left school at 17/18 years ☐ University

Section B: Assessment Tool

Statement	Yes	No	Do not know	Not Applicable
1. I experienced this effect(s) for the first time after taking this medicine.				
2. I have experienced similar effect(s) from this medicine or a related medicine in the past.				
3. When I stopped taking the medicine the effect(s) decreased in severity or disappeared altogether.				
4. When I took the medicine again the effect(s) reappeared.				
5. When I increased the dose the effect(s) became more severe.				
6. When I decreased the dose the effect(s) became less severe.				
7. I confirmed the effect(s) with some or all of the following information sources – doctors, pharmacists, information leaflets with your medicine, the internet or medicine books.				
8. I think that something else apart from the medicine could have caused the effect(s).				
9. I think an existing medical condition or conditions could have led to the effect(s).				
10. I think that other medicine(s) that I was using at the time could have caused the effect(s).				

Scoring Box:

Statements	Yes	No	Do not Know	Not applicable	Score
1.	+2	-1	0	0	
2.	+1	0	0	0	
3.	+1	0	0	0	
4.	+2	-1	0	0	
5.	+1	0	0	0	
6.	+1	0	0	0	
7.	+1	0	0	0	
8.	-1	+1	0	0	
9.	-1	+1	0	0	
10.	-1	+1	0	0	
				Total Score	

Side Effect(s) Probability Key

Score	Interpretation of scores
Total Score **8 or higher**	**Highly probable:** Highly probably that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **4-7**	**Probable/Likely:** Probable that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **1-3**	**Possible:** Possible that effect is due to your medicine(s). A healthcare professional should be consulted and you should also consider reporting the effect.
Total Score **0 or a negative number**	**Unlikely:** Unlikely that effect is related to your medicine(s) but may be caused by other factors.

APPENDIX 18: Naranjo algorithm/scale

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			TOTAL SCORE:	

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

APPENDIX 19: Invitation email to potential assessors

Mr X/Ms X
My name is Bernadine O' Donovan and I am a PhD student at the Medway School of Pharmacy. I have received your details from [Research team member's name] who has been in touch with you to let you know that I would be contacting you regarding our project.

As you are aware we are exploring peoples' experiences of identifying side effects from medicines and an assessment tool has been developed to help people do this. This study seeks to confirm the validity of this assessment tool.

You are being invited to take part in a study, to provide feedback on the assessment tool. You have been chosen because you have experienced side effect(s) from your medicine. Before you decide if you want to take part, you must understand why the study is being done and what it involves. I have attached a Participant Information Sheet which provides this information.

If you decide you would like to provide feedback on the tool, I will send you a copy of the assessment tool by post with a consent form and a prepaid envelope. If you agree to take part, you will be asked to sign a consent form and return it to the Medway School of Pharmacy in the prepaid envelope. I will contact you and arrange a telephone interview at a time and date that suits you. The interview will take no more than 30 minutes and you can change your mind and end the interview at any time.

I will be in touch within the next few days to see whether you can help us.

Thank you for reading this email.

Regards
Bernadine O' Donovan (PhD student)

APPENDIX 20: Invitation email to patient support groups and organisations

Dear Sir/Madam,
My name is Bernadine O' Donovan and I am a postgraduate student at the Medway School of Pharmacy. I would like to invite XX to take part in a research study that is being carried out by the Medway School of Pharmacy, University of Kent and the University of Birmingham.
This research is looking at peoples' experiences of identifying side effects from their medicine(s). We have developed an assessment tool to help people who suspect they may have experienced side effects. This assessment tool has been specially designed based on interviews with people who have had side effects from their medicine(s). At this stage of the research we would very much like to check if people find this assessment tool useful.
I am aware that XX patients can experience problems with generic medication.
Your website has the link to the Yellow Card Scheme, but some of your members may find our assessment tool helpful in clarifying their suspected side effect/effects.
If XX is willing, we would like you to help us distribute a link to our anonymous online assessment tool through your website, for up to three months.
Below is a link to the Side Effects - Patient Assessment Tool (SE - PAST)
https://msp.eu.qualtrics.com/SE/?SID=SV_8Jq61lhD9OoUPT7
I hope that XX will consider posting this link on your website as it would greatly help our research.
If you would like more information about this research you can contact me:
Bernadine O' Donovan,
Medway School of Pharmacy,
Chatham Maritime
Kent ME4 4TB
Phone 0163420 Ext 2920
Email bo77@kent.ac.uk

Regards
B O' Donovan

APPENDIX 21: ISAC approval letter

MHRA
151 Buckingham Palace Road
Victoria
London SW1W 9SZ
United Kingdom

www.mhra.gov.uk

Bernadine O' Donovan

Sent via email:
bo77@kent.ac.uk

Date 14th December 2015

Ref: GENQ-00097958

Dear Bernadine O'Donavan,

Application: ACYD042

The Independent Scientific Advisory Committee for MHRA database research (ISAC) considered the above application by electronic review. The Committee considered that your application was an appropriate use of Yellow Card data and that the proposed methodology is appropriate for the objectives of the study. The Committee advised that the application should be granted provided you comply with the following conditions:

- It is our understanding that the three comment boxes referred to in section D2 are the narrative, reporter comment and free text medical history boxes.
- In addition, as your proposal will involve the release of Category II data, I should remind you of the undertakings you agreed to when you completed the application form. These are included at Annex A.
- You must abide by the *Guidelines for Safe Disposal of Electronic Yellow Card Data for External Users* included at Annex B.
- Please note the enclosed information at Annex C on the National Research Register (NRR). We strongly recommend that you register with the NRR.

The MHRA has accepted the advice of the ISAC. If you are willing to accept the above conditions, please let me know as soon as possible and no later than 28 days after the date of service of this letter.

Yours sincerely,

Yours sincerely,

Rebecca Owen
Signal Management Co-ordinatior / Yellow Card Secretary to the ISAC
Vigilance and Risk Management of Medicines

APPENDIX 22: ISAC application for access to YC data

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ACCESS TO YELLOW CARD DATA
ISAC APPLICATION FORM

Applicants must read the Access to Yellow Card Data Guidance Notes before completing this form. These notes give relevant advice on each individual question in the Access to Yellow Card Data application form, as well as the conditions of use which applicants will be contractually obliged to adhere to when using Yellow Card Data.

Undertakings by the MHRA in relation to information provided by applicants

The information submitted on this form will be considered by the Independent Scientific Advisory Committee on MHRA database research (ISAC) established by the Medicines and Healthcare products Regulatory Agency (MHRA) to advise on applications for access to Yellow Card data. Any personal data provided in an application will be used only for statistical analysis, management, planning and in the provision of services by the MHRA. In accordance with the Data Protection Act 1998, the ISAC and the MHRA will respect the confidentiality of all personal information, but reserve the right to publish in an anonymous and unidentifiable form summary data about applications received (via the internet or in its annual report) for reference and audit purposes.

Yellow Card data requests fall into the following categories:

Category Ia – Anonymised aggregated adverse drug reaction (ADR) data in the format of Drug Analysis Prints (DAPs). Drug Analysis Prints contain complete listings of all suspected adverse drug reactions or side effects, which have been reported to the MHRA via the Yellow Card Scheme. These are freely available from our website at www.mhra.gov.uk/daps

Category Ib – A list of data fields which exclude any information that can identify the patient and reporter and therefore can be released without the need for ISAC

consideration. A list of all the data fields that can be provided is given on the next page. Details of your request should be sent to Pharmacovigilanceservice@mhra.gsi.gov.uk

Category II – If you require more than the Ib data fields then your request will be classed as a category II request (see section D.2 for the list of category II data fields). Applicants should complete this form and then send to isacyellowcarddata@mhra.gsi.gov.uk

Please note there is no requirement to complete this form for Category Ia or Ib data.

Category I releasable data fields (Category Ib data)

Category Ib data case details listed below are releasable under the Freedom of Information Act (FOIA) without consideration by the ISAC. These are known as Category Ib data. Provision of these data will depend on the number of cases held by the Agency. The MHRA will not release any data subset in which there are five or fewer cases per cell. This is necessary to prevent identification of patients and/or reporters. Where there are less than five cases per cell the data will be aggregated with adjacent cells. Any aggregation will be clearly marked on the dataset.

Data fields
Patient age categories
Patient gender
Suspect drug(s)
Dose of suspect drug(s)
Route of administration
Duration of treatment
Suspected adverse drug reaction(s)
Adverse drug reaction outcome(s)
Time to onset
Past medical history
Year of receipt

For ISAC use only: **Protocol Number:** ..... **Date submitted:**	**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** isacyellowcarddata@mhra.gsi.gov.uk

Section A – Personal details

A.1: Principal applicant (full name, job title, organisation, address, e-mail address for correspondence regarding this protocol)

Bernadine O' Donovan, PhD student, Medway School of Pharmacy, Anson Building, Universities of Greenwich & Kent, Central Avenue, Chatham Maritime, Kent ME4 4TB.

bo77@kent.ac.uk

A.2: List of all co-applicants / collaborators (Please list the names, job title, organisation, address and email addresses of all collaborators)

Professor Krska, Professor of Pharmacy Practice, Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham ME4 4TB

j.krska@kent.ac.uk

Dr Rodgers, Senior Clinical Lecturer, Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham ME4 4TB

r.m.rodgers@kent.ac.uk

Dr Cox, Lecturer in Clinical Pharmacy, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham B15 2TT

a.r.cox@bham.ac.uk

Section B – Title and summary of the proposal

B.1: Title of proposal for use of Yellow Card data

Investigation of Yellow Card reports to evaluate reporters' use of information sources, plus other methods of identifying ADRs, and the impact of their experiences

B.2: Name and address of the department / institution / place at which the research / analysis will be conducted

Medway School of Pharmacy, The Universities of Greenwich and Kent, Central Avenue, Chatham ME4 4TB

B.3: Proposed start date 01/01/16 Proposed duration (if known) 30/11/16

Section C – Use of other databases

C.1 Are you intending to use Yellow Card data in combination with another database or other data sources1 (local, national, international or personal data archive).

Yes ☐ No ☒

If yes, please specify

Section D – Details of proposal

D.1: Would your research involve contacting the reporter and/or patient via the MHRA?

Yes ☐ No ☒

If yes, please specify (Note you will need to include with your application any documentation to be provided to reporters/patients regarding the proposed research project (e.g. information sheets, invitations letters, consent forms)

D.2: The main data fields that are usually provided as Category II are listed below. Only tick the fields that you require to meet the needs of the study.

Data fields	**Yes**	**No**	**If yes give further details as necessary**
Patient age	☒	☐	
Patient gender	☒	☐	
Suspect drug(s)	☒	☐	
Dose of suspect drug(s)	☒	☐	
Route of administration	☒	☐	
Drug start / stop dates	☒	☐	
Indication for suspect drug	☐	☐	
Suspected adverse drug reaction(s)	☒	☐	

1 For example GP, hospital, Health board, death, employee records

Reaction outcome	☒	☐	
Reaction start / stop dates	☒	☐	
Reaction details (including description of reaction as provided by the reporter, action taken with the suspect drug as a result of the reaction)	☒	☐	
Test results	☐	☐	
Past medical history	☒	☐	
Previous drug history	☒	☐	
Other – List any other fields you require	Name of the drug(s) Where drug(s) were obtained Severity of the side effect Free text comments from 3 comment boxes		
	Yes	**No**	**If yes, please give details**
D.3: Have you applied for or received ethical approval for your request? Please provide a copy of any ethics committee approval and the reference number.	☐	☒	
D.4: Is the proposal subject to any agreement with any academic, commercial or other organisations?	☐	☒	
D.5: Is the proposal likely to lead to any patentable or commercially exploitable results	☐	☒	
D.6: Do you consider that the consequences of your research may have implications for public health?	☒	☐	This research may have potential benefits for public health as it will offer important and useful insight into what information sources people may use in identifying ADRs as well as information on peoples' experiences of side effects in general.
Section E – Relevant applications and publications			
	Yes	**No**	**If yes, please give details**
E.1: Have you used Yellow Card data previously?	☐	☒	

E.2: Is this application a resubmission of a previous application?	☐	☒	
E.3: Have you previously submitted other applications to the ISAC or its predecessor, the Interim Committee on Yellow Card Data?	☐	☒	

Section F – Security & confidentiality

F.1: Please confirm that you will abide by the principles of the DPA 1998 as detailed in the guidance notes on Applications for Access to Yellow Card Data

Yes ☒ No ☐

F.2: How long do you intend to retain the Yellow Card data? If longer than 12 month, please provide justification.

Retention period of 5 years is proposed. This retention period is in line with University of Kent Research Data Management Policy. The UK Data Archive also supports a method of managing data based on a Research Data Lifecycle (http://www.data-archive.ac.uk/create-manage/life-cycle). This Lifecycle suggests that retaining data for extended periods can provide increased opportunities for future research.

F.3: Please confirm all Yellow Card data provided will be confidentially and securely held on networks/laptops and that data will be appropriately destroyed once the research has been completed. (Please refer back to the guidance notes for further details)

Yes ☒ No ☐

Section G – Publication

G.1: How do you intend to disseminate the findings and results of your proposal? Please specify

In peer reviewed scientific journals, at relevant conferences and published as a PhD thesis. The findings will also submitted to the MHRA Group Manager of the Vigilance Intelligence and Research Group. Study results will uploaded to suitable research data repositories and also uploaded for public access to the Kent Academic Repository. The research will also be voluntarily registered with a suitable registry as epidemiological research which is utilising MHRA databases.

The results of the study will also be disseminated to the public through presentations to the MHRA Patient and Public Engagement Expert Advisory Group (PPEEAG), the Medway School of Pharmacy public engagement group (Public Involvement in Pharmacy Studies Group; PIPS) and to the Patient Safety Congress 2016.

G.2: Please confirm that you will submit any draft abstracts / papers / presentations or publications to the MHRA for necessary regulatory action and review at least four calendar weeks prior submission.

Yes ☒ No ☐

Section H – Relevant research history

H.1: All applicants (principal and co-applicants) who will have access to any Yellow card data must list a brief summary of relevant research history. Any recent experience and/or publications which are of particular relevance to the current application should be highlighted.

Bernadine O' Donovan

Experience in Masters level research involving qualitative and quantitative analysis of survey data (MSc Cognitive Neuropsychology & MSc Neuropharmacology)

See attached CV for additional information

Professor Krska

Member of research team in previous large study evaluating Yellow Card data

See attached CV for additional information

Dr Rodgers

Research into use of information sources

Research into public views on NHS services

See attached CV for additional information

Dr Cox

Member of the Advisory group for UK Yellow Card study

Senior pharmacist at the West Midlands Centre for Adverse Drug Reactions

See attached CV for additional information

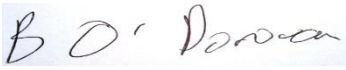
Section I – Supplementary Information

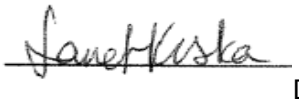
I.1: If you have any comments on this application form please provide feedback:

Section J – Undertakings by the applicant(s) in relation to the application

1. I confirm that I have read, understood and agreed to comply with the Data Protection Statement and the Guidance Notes on Applications for Access to Yellow Card Data (see annex B).
2. I agree to use the data only for the intended purpose for which access was granted.

3. I will submit in writing any change to the proposed research methodology as soon as they are identified or communicated to me, and will await approval by ISAC before proceeding.
4. I will submit in writing any amendment to the principal applicant and/or co-applicants to the MHRA for approval by ISAC.
5. I understand data will only be provided if Yellow Card data is considered feasible for the research being conducted.
6. I will submit any draft articles to the MHRA for approval at least four calendar weeks before submission.
7. I will ensure that any Yellow Card data is maintained securely and confidentially at all times.
8. I will inform the MHRA of any new drug safety issues identified at the time of recognition.
9. I understand that I will be required to sign a contract detailing the terms under which the Yellow Card data is provided (including the conditions of release listed in section 2.2 of the Guidance Notes on Applications for Access to Yellow Card Data) before any data will be released by the MHRA.
10. To the best of my knowledge the information provided in this application is accurate and comprehensive.

Signature of principal applicant:  Date: 02/12/15

Signature of co-applicant:  Date: 02/12/15

Signature of co-applicant:  Date: 02/12/15

Signature of co-applicant:  Date: 02/12/15

Please also complete the following protocol check list on the next page to ensure all the necessary information has been included as part of your application. Then add your protocol below the checklist starting on the following page.

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using Yellow Card data. Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

	Included in protocol?		
Required area	**Yes**	**No**	**If no, reason for omission**
Lay Summary	☒	☐	
Objectives, specific aims and rationale	☒	☐	
Study Type (Descriptive, Hypothesis Generating Hypothesis Testing,)	☒	☐	
Study Design	☒	☐	
Statistical Analysis Plan (including how you will address missing data)	☒	☐	
Selection of any comparison group(s) or controls	☐	☒	No comparison group(s) or controls will be used
Plans for contacting Yellow Card reporters (include information sheets, invitation letters, consent forms, copy of ethics committee approval letter, etc)	☐	☒	No plans for contacting Yellow Card reporters
Patient group involvement	☐	☒	No patient group involvement
Potential limitations of the study	☒	☐	
Plans for disseminating and communicating study results	☒	☐	
Relevant research history	☒	☐	

Voluntary registration of ISAC approved studies

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted

using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

Please add your protocol here (aim for no more than 5 pages)

Investigation of Yellow Card reports to evaluate reporters' use of information sources, plus other methods of identifying ADRs, and the impact of their experiences

Research team: Bernadine O' Donovan, Professor J. Krska, Dr R. Rodgers and Dr A. Cox.

Lay summary

Side effects from medicines can have a significant negative impact on peoples' daily lives. This impact can extend into many areas with physical, economic, social and/or psychological effects. This study is gathering information on how people identify and manage side effects, and is looking at the different types of information sources people may use to find out about side effects (e.g. pharmacists, patient information leaflets (PILs), the internet, family/friends).

Around 2,000 people each year report their experience of a side effect to the Medicines & Healthcare products Regulatory Agency (MHRA), using Yellow Card reports. These Yellow Card reports allow people to describe in detail what happened to them, how it has impacted on their lives and how they managed the side effect. Some earlier work has shown that many people also describe how they came to realise the experience was a side effect and where they found information about it.

The experiences which people who submit Yellow Cards is used by the MHRA in deciding whether a side effect has occurred and its' seriousness. However the MHRA does not conduct any in-depth analysis of the (sometimes lengthy) descriptions of reporters' experiences. We propose to conduct an analysis of all the text written on Yellow Card reports (both paper and electronic reports) sent to the MHRA in the last year, to determine how people who report suspected side

effect have identified and managed them, the impact on their lives and the different types of information sources they have used. We will not have any personal details about the reporters or their doctors, so the text will all be anonymous.

We have already carried out a study with members of the public to learn about how they identify and manage side effects and the impact of these, but we wish to find out whether the experiences of people who report their side effect to the MHRA are different in any way. This is an exploratory study which will also help us to see how much we can learn about peoples' experiences of side effects by using Yellow Card reports.

Background

The large evaluation of patient reporting of adverse drug reactions (ADRs) to the Yellow Card Scheme, which reported in 2011, recommended that future research should "investigate the burden of ADRs in terms of impact on patients' lives, and evaluate the extent to which patients' views and experiences of the seriousness of ADRs concur with those of regulatory bodies, such as the MHRA" (Avery et al., 2011)

As part of a PhD study investigating the personal experiences and opinions of the general public in identifying and managing side effects from medication, I am exploring how people cope with and manage ADRs, the consequences of ADRs, in terms of use of medicines and impact on daily lives. In addition, this study is investigating different types of information sources people use to find out about ADRs (e.g. pharmacists, patient information leaflets (PILs), the internet, family/friends), factors contributing to the use of these different information sources and how they are used by people to inform their experiences of adverse drug reactions (ADRs). An output of this work is the development of a tool for patients to use to assist them in identifying potential ADRs, which could encourage reporting. Other such tools are in development elsewhere (De Vries et al., 2013; Jarernsiripornkul et al., 2015).

It is well known that some ADRs can have considerable negative impact on peoples' daily lives (Anderson et al., 2011; Anson, 2006; Butt et al., 2011; De Langen et al., 2008; Krska et al., 2011;

Shet et al., 2014). However relatively little is known about how people cope with and manage ADRs and the consequences of their experience for their future use of medicines, including the suspected medicine. The present study is using questionnaires distributed to patients using community pharmacies, followed by in-depth interviews with a sub-sample, to explore these questions, in addition to use of information sources on ADRs.

Over 4,000 people, including parents and carers, submit Yellow Card reports to the MHRA annually. Free-text questions on YC reporting forms cover: symptoms and how the event happened; details of the outcome including use of medicines, and other relevant information. Previous work has shown that reporters to the Yellow Card Scheme may include information on their reports about how they identified ADRs, the information sources they use and the impact on their lives (Anderson et al., 2011; Krska et al., 2011). However this study was able to utilise only a small, purposively selected sample of YCs involving only 4.4% of the YCs received during the study period: 148 covered the five drugs most commonly reported by patients and 82 covered 'black triangle' drugs. The free-text data were analysed qualitatively and were found to cover: a description of the problem, the impact of the adverse reaction on the patient, descriptions of the possible association between the drug and adverse effects, the patient's background medical history, actions taken by the patient and involvement of health professionals (Avery et al 2011).

Given the small size and purposive selection of this sample, it is not known how many YC reports overall include information about how reporters identified ADRs or the impact of the ADR within free-text responses. An opportunity thus exists to study the free-text data on a larger, unselected sample of YC reports to determine the frequency with which reporters describe information sources used, the types of information sources, how these contribute to ADR identification and the consequences of ADRs.

The previous study suggested that Yellow Card reports frequently provide explicit detail of the effects of ADRs on the patient's life, family and/or carers, which could be used to create a rich narrative, enabling a comprehensive picture of each individual's experiences of their ADR and

their subsequent use of medicines (Avery et al., 2011). The previous study also showed that both the timing of events and information sources were key factors influencing reporters' suspicions of their ADR. A larger sample, depending on the data contained in the reporting forms, could not only confirm these findings, but also facilitate evaluation of the assessment tool currently in development. In addition, the data may provide more useful learning about reporters' use of information sources in general. A large study of YC data is thus warranted.

Evaluating the free-text and other content of a large sample of YC reports will not only provide an overall picture of the type of data and its potential value, it will also permit a comparison to be made between YC reporters and the wider general public, recruited through the survey currently under way (O' Donovan B et al., unpublished data). The possibility exists that many YC reporters may have a higher educational level than the general population, therefore may differ in how they identify or manage ADRs (McLernon et al., 2011).

Aim:

The aim of this study is to investigate the value of YC reports in determining how people use information sources to help them identify ADRs, and to further explore peoples' experiences of ADRs.

Objectives:

- To determine the different sources of information used by YC reporters in finding out about ADRs and their perceived value for this purpose.
- To assess the impact of ADRs on peoples' daily lives and the consequences of ADRs on medicines use in a large sample of YC reporters.
- To confirm the methods used by a large sample of YC reporters to identify ADRs.
- To compare use of information sources and impact of ADRs among YC reporters and the wider general public.

Study Design:

This study will involve the analysis of both free-text comments and responses to closed questions derived from a large sample of Yellow Card data. It will thus use both qualitative and quantitative analysis. As a study primarily involving analysis of free-text data using qualitative and semi-quantitative methods, it is seeking to generate hypotheses about the information sources reporters use, how they are used and the impact of ADRs on their daily lives. It will seek to determine the extent to which different information is included by YC reporters on reporting forms and the potential usefulness of these data in addressing the objectives.

Methodology:

Yellow Card data

This project will require access to a sample of recent patient reports to the Yellow Card Scheme. It will analyse all patient reports submitted to the scheme over a 6 month period – estimated at a sample size of approx. 2000 reports. MHRA staff will extract and clean the YC data. This data will then be delivered in a passport protected CD format for analysis. Category II data fields are required for this study and a Category II request will be made to the ISAC. All data fields listed in Section D.2 of the ISAC application form except test results are required for this study. Additional details are also required from Sections 1, 2 and 3 of the Yellow Card report, which will include all responses to open questions contained in the Yellow Card form. The required data fields are listed in the following table:

Table 1: Required data fields

Patient age	Reaction outcomes
Patient gender	Reaction start/stop dates
Suspect drug(s)	Reaction details
Dose of suspect drug(s)	Past medical history

Route of administration	Previous drug history
Drug start/stop dates	Other: where drug(s) were obtained Severity of the side effect
Suspected adverse drug reaction(s)	Other: Full free text comments provided in response to questions covering: symptoms and how it happened, more details of the outcome, any other relevant information.

The research methodology will not utilise controls or comparison groups. There are no plans for contacting Yellow Card reporters as part of this research.

Inclusion criteria for Yellow Card data

▪ Yellow Card reports from the general public.

▪ Yellow card reports generated from July – December 2015.

▪ Yellow card data fields as specified above.

Data Analysis

The Yellow Card data will be transferred into SPSS and checked using simple frequencies to assess completeness of all data fields, remove any duplicate cases, detect and remove any errors and inconsistencies and ensure missing data are accounted for. The cleaned data will be subjected to both qualitative and quantitative analysis. Content analysis will be used to code the free-text responses and identify points of commonality, in addition to a semi-quantitative analysis of coded data. For the latter, free-text responses will be analysed using Excel to develop a coding frame as follows: two researchers will initially independently read 100 different responses to identify and agree emergent themes, these will be used to code a further 100 responses, to determine the need for further themes, then the final agreed themes will be used to code the entire dataset, by two researchers independently ensuring there is reliability in the coding process. Any

discrepancies will be discussed and agreed. This method has been used previously for quantitative analysis of free-text responses to questionnaires from YC reporters (Avery et al., 2011).

Secondly, the data management program NVivo will be used to further analyse the free-text responses from individual reporters qualitatively, combining them with responses to closed questions, to create narratives of individual experiences, which can then be subjected to phenomenological analysis.

The quantitative data from responses to closed questions within the YC reports will be analysed using SPSS software. Descriptive statistics will be generated covering suspect drug, indication, whether or not stopped after the ADR, reported seriousness and outcome, in relation to age and gender. It is our intention to also combine the categorised free-text data with these data, depending on the information available within the free-text responses. This will potentially enable an analysis of the information sources used, methods used to identify ADR and its impact in relation to suspect drug, indication, whether stopped, reported seriousness and outcome.

Ethical considerations

We believe that accessing anonymised Yellow Card data can be considered of minimal risk. We will not be seeking any information about the reporter or the reporter's doctor.

The Research Ethics and Governance Officer at the University of Kent has been consulted in relation to ethical approval for this study. Her opinion is that as the data will be anonymised, the study does not require ethical approval. Access to this data will be limited to named members of the research team (the Principal applicant and co-applicants. The Yellow Card data will be safely stored on university computers and memory sticks which are password protected. The Yellow Card data will be extracted and cleaned by MHRA staff and passed to us in passport protected CD format for analysis. These digital records will be retained for five years after the final report has been written and subsequently securely destroyed. The data will be retained for this period of time in keeping with University of Kent Research Data Management Policy. University of Kent policies covering the management of research data support the retention of data for public

consultation and re-use. The Research Data Management Policy supports data archiving principles and therefore it is anticipated that the data will be placed in suitable repositories. DataCite the global registry of research data repositories will provide a list of suitable repositories. In line with University of Kent policy once uploaded to a recommended repository the data will be linked to the Kent Academic Repository.

Potential limitations

As indicated, at present little is known about the overall content of material available in free-text sections of YC reports, other than was reported in a previous, small study, involving only 230, purposively selected reports (Krska et al., 2011). Our analysis plan must therefore be subject to the availability of the data. We propose to use methods similar to those used in previous work, but may need to adapt these, depending on the amount and type of written data obtained. Regardless of the eventual detailed analysis, the study will provide learning about the potential value of free-text data available on patient reporting forms, both for future research and for use by the MHRA in their own analyses.

Dissemination

The results of the study will be reported and disseminated in peer reviewed scientific journals, (such as Drug Safety, Pharmacoepidemiology and Drug Safety) at relevant conferences (such as ISPE) and published within a PhD thesis, available electronically from the University of Kent. Study results will be uploaded to a recommended repository. A list of suitable research data repositories will therefore be generated via DataCite. In line with University of Kent policy once uploaded to a recommended repository the data will also be uploaded for public access to the Kent Academic Repository. The findings will also be submitted to Mick Foy, Group Manager of the Vigilance Intelligence and Research Group at the MHRA. The research will also be voluntarily registered with a suitable registry as epidemiological research which is utilising MHRA databases. The results of the study will also be disseminated to the public through presentations to the MHRA Patient and Public Engagement Expert Advisory Group (PPEEAG), the Medway School of Pharmacy public

engagement group (Public Involvement in Pharmacy Studies Group; PIPS) and to the Patient Safety Congress 2016.

Relevant research experience

I have previous experience at Masters and undergraduate level of conducting research projects.As part of these projects I have distributed screening questionnaires, recruited and debriefed participants as well as conducting in-depth interviews, focus groups and telephone interviews. I have previously worked on research studies which required the analysis of both quantitative and qualitative data. I also have experience of presenting my research to lay audiences in an uncomplicated and understandable manner. My co-applicants have considerable relevant research experience in the general area of ADRs and in particular in direct patient reporting. Prof Krska was part of the team which conducted a large evaluation of patient reporting of ADRs through the UK's Yellow Card Scheme. Dr Anthony Cox was a member of the Advisory group for this large study and is also senior pharmacist at the West Midlands Centre for Adverse Drug Reactions. Both have investigated patient experiences of NHS healthcare services and the impact of ADRs on patients and their views on reporting. Dr Ruth Rodgers has conducted research into public views of NHS services and use of information sources. These histories are outlined in Section H of the ISAC application form and also in supporting documents (see summary CVs for Principal and Co-applicants).

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