The development of palliative care for people with progressive neurological disease

David Oliver BSc, MB BS, FRCP, FRCGP, FEAN

Honorary Professor

Tizard Centre

University of Kent

Submission

March 2020

Thesis submitted in partial fulfilment for the degree of

Doctor of Philosophy Community Care – by Published Works

Tizard Centre

University of Kent

Abstract

The role of palliative care for people with neurological disease has been developing for over 50 years, and was described from the early days of the modern hospice movement. This thesis considers my papers and studies which have helped in establishing the need for palliative care, the involvement of specialist palliative care services, the effectiveness of palliative care for neurological patients, the importance of complex decision making for this patient group and the development of guidelines, to enable care to be more widely established for patients and families.

These papers have developed from the evidence from earlier research and the experience of hospices and specialist palliative care teams and helped to encourage further research. They have been important in providing an evidence-base for neurological palliative care and supported a wider recognition of the role of palliative care for people with neurological disease. The research reported here demonstrates how the increasing collaboration between specialist palliative care services and neurology can result in improved care of patients with neurological disease, together with their families.

(173 words)

Dedication

This thesis is dedicated to the memory of my parents

Professor Ray Oliver (1921-1976)

Lucy Oliver (1920-2015)

Declaration

I confirm that this thesis is my own original work except where I have acknowledged the use of other people's ideas or words by referencing the material as outlined in the Regulations for Research Programmes. I have not submitted this dissertation or any part of it for any other academic award. I have read and understood the definition of plagiarism in the Regulations for Research Programmes.

Signature Date 13th March 2020

Acknowledgements

I would like to acknowledge the support and help of all the people who have collaborated on the projects described in this thesis and the other publications – papers, chapters and books – that I have been involved in. I am very grateful to so many for allowing me to work with them with the aim of improving the care of patients and their families.

I would also like to acknowledge the patients and families who have allowed the studies to be undertaken. I thank them for their involvement, enthusiasm and energy.

In addition, I would like to thank my supervisors – Professor Rachel Forrester-Jones and Professor John Baldock, Professor Peter McGill and Professor Christina Faull – for their support and advice in completing this thesis.

Lastly, I acknowledge Siobhan Malone, my partner, for her forbearance while I have been writing this thesis and her support for all I do.

Table of Contents

1 Introduction

The aim of this commentary is to show how the research which I have undertaken, and the papers resulting from this, have helped in the development of palliative care for neurological disease, and in particular motor neurone disease (MND). The research has contributed to an increased awareness of the palliative care needs of people with neurological disease, in particular consideration of the symptoms of advanced neurological disease, the role and effectiveness of palliative care for this patient group, the difficult ethical decisions that arise and the development of guidelines to provide support for the improvement of care.

This first chapter will introduce the concept of palliative care and how this relates to people with neurological disease, and the development of this concept over the last 50 years. There will also be discussion of the ethical and cultural aspects of care.

1.1. Palliative care

Palliative care is defined by the World Health Organisation as: “An approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering, early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”(WHO 2002).

Palliative care therefore aims to provide a holistic approach for patients and their families and in the UK, this may be within an inpatient hospice, at home, in a day hospice, care home or in hospital. This is a multidisciplinary approach including medical, nursing and other professionals, often together with volunteers.

Although these principles underpin all palliative care there are differences in how the terminology is understood, both within the UK and in other countries. “Hospice care” may be used interchangeably with palliative care but this is not always so. For instance, in Germany a palliative care unit within a hospital aims at intervention in crisis and the management of symptoms, whereas inpatient hospice care is mainly at the end of life (Radbruch et al 2009). There is a similar differentiation in the USA, particularly as to have funding for hospice care the patient should be within the last 6 months of life and have stopped any other curative intervention (Boersma et al 2014).

There has also been discussion of the levels of palliative care and the European Association for Palliative Care (EAPC) White Paper on palliative care suggested three levels of provision:

- Palliative care approach, which should be part of all patient care, ensuring good communication with patient and family, shared decision making and goal setting and symptom management. All services should provide this basic care.
- General palliative care would be provided by primary care professionals and specialist services caring for patients with life threatening illness. Palliative care may not be the entire focus of their role but they should have additional expertise, acquired from special education and training.
- Specialist palliative care provided for patients with more complex issues, which may not be covered by other services. The team would have this as their main activity and have received specialist training and continuing education (Radbruch et al 2009).

There is often confusion as to what level of care is provided, and by whom. This can lead to further confusion in the development of services. Palliative care is important for the care of patients and families and may be as a palliative care approach, by all professionals, general palliative care, from neurology, rehabilitation and primary care services, and by specialist palliative care for more complex issues. At all times there will be a need for close collaboration between all the professionals involved. There is also a move to use a public health approach, with a more unified approach. This would include patients, families, professionals, communities, governments and society, working together to improve care, particularly at the end of life, for all people with needs, regardless of diagnosis. (Abel and Kellehear 2016)

1.2 Historical perspective of the provision of palliative care for people with neurological disease

Although the traditional view has been that hospices care for people with cancer, palliative care has been provided for people with neurological disease by specialist palliative care / hospices for some time. In 1967 St Christopher's Hospice was opened in Sydenham, London, by Cicely Saunders as a new institution dedicated to the care of the dying, with the new dimensions of the facilitation of teaching and research. Although the emphasis was on the care of patients with cancer, patients with motor neurone disease (MND) and multiple sclerosis (MS) were admitted to St Christopher's Hospice from soon after the start and Dame Cicely Saunders wrote of this to Dr Mary Toms in 1990 – "we have been caring for patients in the terminal stages of Motor Neurone Disease, as we call it, since our first patient was admitted in 1967" (Clark 2002). One of the first

publications on palliative care of people with MND was published in 1981 from the experience at St Christopher's Hospice (Saunders et al 1981.)

1.3 Palliative care provision for patients with neurological disease

In the UK there are over 220 hospices caring annually for 200,000 people and 83% of this care is in the community – at home or care home (Hospice UK 2015). However, over 95% of people receiving hospice care have cancer. 88% of all cancer patients receive palliative care at some time during the progression of their disease (NCPC 2010), whereas only 1.2% of surveyed neurological patients had contact with a palliative care team (Neurological Alliance 2015). There is greater involvement with people with non-cancer diagnoses, including neurological disease, within specialist palliative care hospital teams and day hospices, where they contribute 25% of referrals. Compared to cancer fewer patients with neurological disease die at home or in a hospice – for neurological patients 5% of deaths are in a hospice and 18% at home, compared to 16% of cancer patient deaths in a hospice and 29% at home. Moreover, this had not increased substantially over the 13-year period up until 2015 (National Neurological Intelligence Network 2015).

1.4 Evidence of need for neurological palliative care

Within the UK the numbers of patients with progressive neurological disease are large – the estimates of prevalence in England are MND 3750, Huntington's disease (HD) 6580, MS 84,000, Parkinson's disease (PD) 106,680, multiple systems atrophy (MSA) 2520, progressive supranuclear palsy (PSP) 5880 and dementia 665,070 (Neurological Alliance 2014). All these patients face deterioration, although the timescale varies, with MND having average prognosis of 2 to 3 years, whereas PD patients have an average prognosis of 15 years.

Many surveys of patients with progressive neurological disease have shown there is a high symptom burden and poor quality of life. A survey of patients across Australia showed all patient groups rated their quality of life below average, had multiple symptoms, often were shown to have depression, and were often dissatisfied with the care they received (Kristjanson et al 2006). Although the response rate was only 25% and it is likely that the more able patients were more likely to respond, the figures do show that there are considerable issues, even in the earlier stages of disease progression. Other studies have shown high levels of symptom burden and palliative care need for PD (Ng 2018), MND (O'Brien et al 1992), MSA and PSP (Wiblin et al 2017), MS (Edmonds et al 2010) and dementia (van der Steen et al 2014).

A cross-sectional study using the large Canadian Longitudinal Study on Aging of 50,000 people showed that neurological disease was associated with a higher somatic and psychiatric morbidity and increased use of medical services, including hospitalization (Wolfson et al 2018). This study was limited inasmuch as the conditions were self-reported by the participants and its cross-sectional design prevents causal conclusions. In the Czech Republic a study using in-depth interviews with patients with MS and PD and their families showed many unmet needs, in particular relating to coping with the disease and securing professional help (Buzgova et al 2019). Although the study was small, with 11 patients, there was saturation of the themes that were identified.

1.5 Care services for neurological patients

The care of patients with progressive neurological disease varies greatly and involves neurology, rehabilitation and palliative care services. The need for collaboration and involvement of palliative care has been emphasized for many years. The National Service Framework for Long-term Conditions (Department of Health 2005) recommended palliative care for people "in the advanced stages of long-term neurological conditions" and a Quality Requirement for comprehensive palliative care services was recommended, which may be provided "over an extended period of time" (Department of Health 2005).

In 2010 the National End of Life Care Programme commissioned a report "End of life care in long term neurological conditions: a framework for implementation" (End of Life 2010). I chaired this group and was influential in the writing of the report, which recommended palliative care should be considered at any stage of the disease progression and suggested the assessment for end of life care, including the consideration of triggers to identify this last 6 to 12 months of life, advance care planning, the careful management of symptoms and care for family and all carers (End of Life Care Programme 2010). The triggers have been further investigated and have been shown to be valid for patients with neurological disease with an increasing number of triggers being seen as death approaches, and particularly in the last 6 months of life (Hussain et al 2014; Hussain et al 2018).

Although involvement with people with neurological disease has been suggested palliative care services have often been reluctant to provide support and care for these patients. Concerns have been expressed about the lack of experience in the care of neurological disease, the need for more training and a lack of sufficient resources (Turner-Stokes et al 2007), the potential large

numbers of patients, the pressure on resources, the variable trajectory of disease progression and prognosis– from months to years, with varying caring needs over these periods of times - the difficulty in identifying a dying phase, the complexity of assessment and care, and the difficulties in accessing community services and equipment (Wilson et al 2011; Gofton et al 2018). More recently, as part of the research project OPTCARE-NEURO (OPTCARE-NEURO 2019), investigating the effectiveness of a short-term palliative care intervention in neurological disease, a mapping exercise was undertaken of the neurology centres that were to be involved in the research. This showed a heterogeneity in the service provision and level of integration, but with greater integration for MND compared to other disease groups (van Vliet et al 2016). An online survey of neurologists and palliative care professionals within these centres reported that 36% of neurology and 58% of palliative care professionals felt that collaboration was excellent or good and 45% of neurology professionals rated the current collaboration as poor or none (Hepgul et al 2018).

Thus, the care provided for patients with neurological conditions varies across the country and there is evidence of poor collaboration between services caring for patients with neurological disease.

1.6 Research in palliative care

Research in palliative care is often complex as patients have progressive disease, multiple symptoms and comorbidities and may deteriorate and die within a short period of time. These issues are heightened in neurological care and these issues will be discussed further in Chapter 7. The particular issues for the studies I have undertaken will be considered for each study.

1.7 Ethical and cultural aspects

The care of patients with progressive neurological disease will involve complex consideration and discussion of ethical issues:

- Withdrawal and withholding of treatment. Increasingly interventions are undertaken that may affect survival and quality of life, such as the use of gastrostomy for maintaining nutrition and hydration, and ventilatory support when there is respiratory failure, particularly in MND. These interventions need to be considered very carefully as the benefits and risks may be finely balanced. The withdrawal of non-invasive ventilation of MND patients at the end of life is an example of such an ethical situation. The research on these ethical aspects within my work are discussed in Chapter 5.

- Cognitive change is common as neurological disease progresses and affects the ability of the person to make clear decisions, as capacity is lost. There are ethical considerations in enabling patients to make their wishes known earlier – advance care planning – as many people are resistant to looking ahead and considering their deterioration, even though discussion at these earlier stages may be the only opportunity they have to make their views known clearly.
- Therapeutic or palliative sedation is the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers (Cherny et al 2009). This may be considered at the end of life, but may lead to ethical discussion and disagreement within the multidisciplinary team. There may be confusion when morphine and other medication for symptom management at the end of life are used, with possible sedative effects, and this has been an important issue in the discussion of end of life care.
- Hastened death may be discussed by people with progressive neurological disease, including euthanasia and physician assisted suicide. There is evidence that neurological disease is over represented within the people receiving a hastened death in the areas where this is permitted. In the Netherlands in 2010 1.8% of all deaths were a result of euthanasia or physician-assisted suicide but 22% of MND patients received an assisted death, compared to 5% of cancer patients and 0.5% of people with heart failure (Maessen et al 2010).

The papers presented in this thesis expose both ethical and cultural issues, particularly in the care of people at the end of life. The care of patients with neurological disease may vary greatly from country to country, depending on the culture and attitudes within each country. This is seen particularly in the care of MND where, as has been shown above, in the Netherlands many with MND receive euthanasia or physician assisted suicide (Maessen et al 2014), whereas in Japan 15-20% have life extending treatment with a tracheostomy and invasive ventilation and may survive 10 to 20 years, but often becoming “locked in” with no way of communication (Vienelloa and Concas 2014). The aim should be to respond to each particular patient, within their own family and cultural context, and within the norms and possibilities of treatment of the society (Lambert 2014). This will be discussed in Chapter 5 when considering complex decision making.

1.10 Conclusions

This Introduction has aimed to provide an overview of the context of palliative care for people with progressive neurological disease. In the following chapters I will discuss how my work has influenced neurological palliative care:

- Establishing the need for palliative care for neurological patients – Chapter 2 Texts 1,2 and 3
- Establishing the involvement of palliative care with neurological disease, in particular MND – Chapter 3 text 4
- Demonstrating the effectiveness of palliative care for people with neurological disease Chapter 4 Texts 1,2,5 and 6
- Discussing the ethical and complex issues in neurological care Chapter 5 Texts 7,8,9 and 10
- Influencing care through the development of guidelines to facilitate the further development of care and the education of professionals, patients, families and society. Chapter 6 Texts 11 and 12.

The next chapter will consider studies showing the needs of people with progressive neurological disease and their families.

2. Establishing the need for palliative care for neurological patients

2.1 Introduction

This chapter aims to consider three papers which have investigated the palliative care needs of patients with neurological disease. Studies evidencing these needs were limited before my work. Two surveys for St Christopher's Hospice had shown that symptoms and other psychosocial needs were common for people with MND. The first study described the symptoms found in their retrospective survey of 100 patients at the hospice before 1980, with dyspnoea in 60%, dysphagia in 41% and pain in over 40% (Saunders et al 1981). A later survey, considering 124 deaths between 1980 and 1990 described pain in 71%, dyspnoea in 58% and drooling in 47% (O'Brien et al 1992). These were both retrospective surveys from the notes kept at the hospice, which may not have recorded symptoms accurately and would have involved many different clinicians in the completion of these records.

I have been closely involved with three studies looking at the needs of both MND patients and a mixed group of neurological diseases.

2.2 Experience of the Wisdom Hospice – a Case review - Text 1 Oliver 1996

2.2.1 Research study

A retrospective review from the patient notes was undertaken at the Wisdom Hospice of 52 patients with MND who had died under our care between 1985 and 1995, the majority of whom I had seen from soon after diagnosis until death (Text 1 Oliver 1996). At every recorded contact the symptoms and other issues were noted, medication was recorded in a specific chart for patients at home, and at every out-patient clinic appointment this was updated. The medication charts were available if the patient had been admitted to the hospice. Although from a single service, these patients were demographically similar to other studies on MND, with 38% female, average age of 63 years for women and 68 years for men, and an average duration of the disease of 26 months.

2.2.2 Findings

The retrospective case note review, showed that symptoms were very common – for patients dying at home the common symptoms that were recorded at any time from first contact until death were weakness 96%, dysphagia 88%, dyspnoea 88%, pain 76%, dysarthria 60%, constipation 56%.

The symptoms and issues were recorded at all clinic appointments, admissions to the hospice and other contacts in the notes, but not using a specific tool. These were similar symptoms to the earlier St Christopher's Hospice studies but the frequency of symptoms was higher. This may have been seen as the patients were under my care for a long period of time, as referral was made soon after diagnosis and I was involved until death and as the records were primarily made by myself, with close colleagues on occasions, they would be more likely to be accurate and complete.

The review also showed that patients were often able to remain, and die at home, with 48% of the group dying at home. Overall 82% of the care of all the patients was at home, and admission to the hospice was often for a short period only before death. No patients were admitted to hospital. The medication used was also described and this will be considered in Chapter 4.

A larger proportion of the patients who were admitted to the hospice were found to be female, those living alone, unmarried or divorced and with bulbar symptoms, whereas those who died at home were more commonly male and supported by a partner, who was able to provide care at home.

2.2.3 Strengths and limitations

There are concerns that a case note review may not always provide accurate information and may be of a selected group (Hess 2004) but in this retrospective case review the medical notes can be assumed to be both accurate and available as I had been closely involved in the care of the patients, the assessment of symptoms and the prescription of medication. However, this may have introduced bias, as the assessment may have not been impartial.

Although the series was a single cohort, with no control group, the accuracy of the records was good and selection bias was unlikely as all patients known to the hospice were included, and at that time most patients known to any neurological or rehabilitation service or to the MND Association were referred to the hospice.

2.2.4 Contribution

This paper has added to the evidence that patients with MND have many symptoms and despite these symptoms, patients were able to die at home. This has been important, as will be discussed again when considering Text 2 - section 2.3.3

2.3 Experience in Rochester and Munich Text 2 Neudert et al 2001

2.3.1 Research Study

Following the initial case note review described above a further review of the later stages of life of MND patients seen at the Wisdom Hospice between 1991 and 1999 was undertaken and reviewed in collaboration with a team in Munich, who reviewed their patients with MND who were on the database of the Motor Neuron Outpatient Clinic, who were cared for at home and died between 1995 and 1999 (Text 2 - Neudert et al 2001). This was a comparative two site study. There was some overlap with the previous group which had considered patients dying between 1985 and 1995, as patients who had died between 1991 and 1995 were included in both studies.

The review at both centres was again retrospective using the clinical notes of 50 patients, using an identical procedure. In Munich the case note review of 121 patients was combined, where possible, with a telephone interview of the caregivers or nurses who had been present at the time of death. The two groups were similar in the patient characteristics – in Munich 59% male, mean age 63 years, duration of the disease 36 months, 31% bulbar onset; at the Wisdom Hospice 56% male, mean age 66 years and duration 32 months, and bulbar onset 36%.

2.3.2 Findings

The symptoms that were recorded in the last 24 hours of life were broadly similar: dyspnoea 20% in Munich, 30% Wisdom, restlessness 8% and 6%, choking on saliva 7% and 0%, coughing 4% and 20% and pain 2% and 1%. The study showed that the assessment of death, from the comments of carers or from the records in the notes, was that it had been peaceful for vast majority of patients– 88% in Germany and 98% at the Wisdom Hospice. Six patients in Munich had died after a resuscitation attempt, which had highlighted the need for earlier discussion as all six relatives considered, in retrospect, that this attempt had been a mistake. The findings concerning the medications used to manage symptoms will be considered in Chapter 4.

2.3.3 Strengths and limitations

This paper is again following a retrospective review of case notes, although in the Munich arm of the study this was combined with telephone conversations with the carers, either family or professional. There could be selection bias in the telephone results as only two thirds of the families could be contacted. There is the possibility of recollection bias in the memories of those contacted,

although as the comments could be compared to the case note records this was unlikely. The assessment of the death as peaceful could have been influenced by the bias of the researchers. Moreover, it was less likely that distress would be recorded in the notes and families and carers may have been less willing to talk of distress in the interview. The two groups were very similar, with no significant differences found in the sex ratio, age, mean duration of the disease, sites on onset and presence of carers, so that the comparability of the data would appear to be acceptable.

2.3.4 Contribution

This paper has been widely quoted in other literature. The results have shown that dying with MND is usually peaceful, when the patient and family have received palliative care and has been very important in refuting the assertions that a death from MND is distressing - for instance in the section about Diane Pretty on the Dying in Dignity website where there is discussion of "the fear of dying by choking or suffocation" (https://www.dignityindying.org.uk/story/diane-pretty/ Accessed June 2020). This will be discussed further in Section 4.3.4.

2.4 Qualitative study in Turin Text 3 Veronese et al 2015

2.4.1 Research study

To inform the development of a Randomised Controlled Trial of palliative care for neurological patients– see Chapter 4– a qualitative exploration of the needs of patients and families was undertaken. This was part of the study by Simone Veronese for his PhD studies. I was his supervisor for this study and closely involved in the design of the study, the analysis of the results and the later writing of the paper (Text 3 Veronese et al 2015).

Simone Veronese interviewed 22 patients in Turin with MND, MS, PD and MSA, who were considered to be in the later stages of disease progression and might die in the next 6 months, were able to communicate themselves or with a communication aid, could give informed consent, and were resident in Turin. Their caregivers (n=21) were included if the patient consented, and they were able to do so and agreed. Focus groups were also held with health and social care professionals seeking their views of the needs of patients and families.

2.4.2 Findings

The study showed that patients with progressive neurological disease have many distressing symptoms:

- Physical - including movement issues (100%), swallowing and speech (95%), pain (82%), breathing issues (82%), bowel problems (73%) and sleep issues (64%)
- Psychological – feelings of being abandoned (96% of patients and 64% of carers), mood instability, anxiety and depression (mentioned 25 times), difficulties in coping with continual loss (19 mentions) and feeling overwhelmed (17 mentions)
- Social – of isolation (13 mentions), family problems (13), transport issues (14), issues with a paid carer (16) and difficulty obtaining benefits (12)
- Spiritual – loss of hope (5 mentions) and meaning of life as they approach death (11), rage, loss of control (7)

Comments from both patients and carers supported these findings, and provided a depth of understanding the issues and the impact on all involved. Many unmet needs were identified.

The professional carers were aware of the high burden of symptoms and issues and some recognised that they lacked expertise in managing some of these issues. They did accept that there was a need for psychological, social and spiritual support to help the patients and families, and to improve their quality of life. They also felt that they were unable to care for these patients when they were no longer able to attend a clinic at the hospital and they could see the need for palliative care (Text 3 Veronese et al 2015).

2.4.3 Strengths and limitations

There are limitations within this study. This was a small sample and the group was neurologically heterogeneous. The heterogeneity may have reduced the sensitivity of the study in elucidating the issues for specific diseases, although the careful interviewing of each participant would have allowed the issues to be discussed for each individual. However, the involvement of the different diseases did provide clear evidence that there was a commonalty of the issues faced by patients with progressive neurological disease.

The interviews of patients, often with family members present, provided a rich source of data about the needs and concerns of the patients. Simone Veronese undertook these interviews, sometimes using communication aids as the patients could not communicate verbally. He had not been involved in the care of these patients before, and this limited the possible effect of the patient feeling pressurised to take part in the interview. As he was involved in the provision of care and support to the participants this could have influenced them to be more positive about the

care provided. Patients asked for their family to be present and they were often able to help in clarifying what the patient wished to say, if communication was difficult. In this way bias was reduced, although there were concerns that patients and families may have felt pressurised to take part, as they wanted the possibility of extra care and support, and may have over or under emphasised their problems. The family members may also have affected the responses of the participants, as the patient may have not wanted to distress the family in their response.

The focus groups of professionals were held at their hospitals and they were encouraged to talk about the needs of patients with progressive disease, using a prepared schedule. There are limitations that within the group there may be dominance by certain participants and others may feel inhibited to speak. This was minimised by careful explanation of the role of the focus group and facilitation of the group itself, encouraging all to be involved.

The strength of this study was in the single interviewer using a similar approach for all participants and leading all the focus groups. This allowed for consistency in the interviews and focus groups and an iterative approach could be taken, with the earlier interviews and groups informing the later discussions. This, however, may also be a limitation as there is the possibility of bias as the same person was providing and assessing the intervention. More severely affected patients with communication issues were not excluded, as the interview was able to continue with a communication aid. Patients were affected by a heterogeneous group of neurological conditions, which allowed a greater understanding of the many differing issues faced by patients and their families.

2.4.4 Contribution

These results showed that there were many unmet needs experienced by this patient group, and their carers. This can be seen in the number of issues raised by patients and their caregivers and the qualitative approach allowed a richer depth of understanding into these issues, with the use of comments from patients in the paper. Although these were often recognised by the professionals involved in their care, they often felt unable to offer support, particularly as the patients become more disabled and unable to attend for out-patient clinics. The support for patients at home was limited, depending on the interest and expertise of their general practitioner, who provides day to day care. The results again identify the needs of patients, and in this study from a wider group of progressive neurological disease.

Within the literature on MND the two papers (Text 1 Oliver 1996; Text 2 Neudert et al 2001) have been influential in showing that dying with MND can be peaceful, with good palliative care and symptom management, and have been used in the discussions about dying with MND, particularly in the arguments about assisted dying- this will be further discussed in Section 4.3.4. The paper from Turin (Text 3 Veronese et al 2015) is one of the only papers looking at a group of neurological disease in the advanced stages and showing the unmet needs in all aspects of assessment.

2.6 Conclusion

These papers have provided new evidence about the needs of people with progressive neurological disease and they have been reinforced by later studies (Ng 2018; Wiblin et al 2017); Edmonds et al 2010; van der Steen et al 2014).

Building on these studies which demonstrated the needs that patients have for palliative care the next chapter will consider the evidence that specialist palliative care involvement makes a difference for these patients and families.

3. The involvement of specialist palliative care in neurological disease

3.1 Introduction

Other than two studies from St Christopher's Hospice (Saunders et al 1981; O'Brien et al 1992) there was little information when I commenced my work about the involvement of specialist palliative care services in the care of people with progressive neurological disease.
I collaborated on a paper in 2000 looking at the involvement of hospices in the care of people with MND.

3.2 Survey of hospices Text 4 Oliver and Webb 2000

3.2.1 Research study

In 2000 Dr Sandi Webb and I undertook a questionnaire survey of specialist palliative care services in the UK to ascertain their involvement in the care of people with MND. 229 hospices were contacted by post and asked to complete a short questionnaire.

3.2.2 Findings

170 hospices responded (77%). Their involvement with people with MND varied greatly - only 17% were involved from soon after diagnosis and 48% only saw patients in the terminal stages of the disease. Care was provided primarily in the inpatient hospice and only 61% provided care at home. The commonest areas of care provided were symptom management (92%), respite care (91%) and care at the end of life (84%).

There did seem to be involvement of the wider multidisciplinary team within many of the hospices, although speech and language therapy was only involved in less than 25% of the hospices and dietitian in only 21% of the home care services. The study also showed that collaboration with other local services was limited, with only 14% collaborating with disability services, 23% with neurology and 36% with the MND Association.

3.2.3 Strengths and limitations

This study does have limitations. The use of the postal questionnaire allowed information to be gathered easily from a large number of hospices, whose details were obtained from the Hospice

Directory. The data was then anonymised and analysed together. Although the response rate was 77% there could be bias, as those who responded may have been more involved in MND care than the non-responders. With the use of a questionnaire there is the risk that there could be misunderstanding or misinterpretation of the questions, leading to inappropriate and incomplete responses. This was minimised by a careful assessment of the questions and a pilot questionnaire being used at the authors' hospices. Despite these misgivings useful data was generated and could be analysed.

3.2.4 Contribution

This paper was published in Palliative Medicine, the official journal of the EAPC, and has helped to raise awareness of the role of specialist palliative care for MND patients and shown the role of earlier involvement and close collaboration across the multidisciplinary team and with other teams. The results were presented as a poster at the MND/ALS symposium and have been used in my presentations on the role of palliative care for people with MND.

3.3 Conclusions

There is very little evidence of the involvement of palliative care in the care of people with neurological disease. There has been increasing awareness for the need for collaboration between neurology and palliative care (End of Life Care programme 2010; Turner-Stokes et al 2007). A study in 2013 considered the place of death, obtained from the Mortality Statistics in England from 1993 to 2010 and found the proportion of deaths in hospices was 0.6% for PD, 2.5% for MS and 11.2% for MND (Sleeman et al 2013). Thus, MND would still appear to be the most common neurological disease receiving palliative care.

In New Zealand a survey of hospices showed that of the 35 services that replied – 85% of the 41 contacted - all cared for MND, although some did state that this would only be in the terminal stages. There were concerns about the resources needed for this care, the complexity of the multidisciplinary approach, the knowledge needed and the uncertainty of prognosis (McKenna and MacLeod 2005). The paper shared examples of good practice where there was shared care between the rehabilitation team and palliative care. Text 4 Oliver and Webb 2000 was quoted within the paper in the discussion of the need for earlier referral to palliative care, rather than only in the terminal stages.

The level of collaboration between palliative care and neurology has been studied as part of the OPTCARE-NEURO research project to investigate short term palliative care input for neurological disease patients (0PTCARE NEURO 2019). This showed a wide variation in collaboration but with a more integrated approach to MND, a less integrated approach for PD and related diseases and the least collaboration for MS (van Vliet et al 2016). In Germany an online survey of neurological consultants found that they felt 10% of patients with progressive neurological disease would benefit from hospice care (Golla et al 2016). Moreover, the level of collaboration varied from 50% to 78% and only 12% had received any training in palliative care.

Following the involvement of palliative care, the next chapter will consider the effectiveness of palliative care for patients with progressive neurological disease.

4. Effectiveness of palliative care

4.1 Introduction

The evidence base for the effectiveness of palliative care is limited for all disease groups. Thus, there is a need to develop the evidence for the use of palliative care for people with progressive neurological disease so that the care provided can improve, and quality of life for patient and family maintained at as good a level as possible.

The papers described here consider the assessment of effectiveness of palliative care for neurological patients, in particular the management of symptoms, the maintenance of quality of life and the care at the end of life, in particular the aim for death at home and peaceful death.

4.2. Experience from the Wisdom Hospice Case Review – Text 1 Oliver 1992

4.2.1 Research Study

This study was a retrospective review of the notes of patients dying at the Wisdom Hospice and has been discussed in Sections 2.2.1 to 2.2.4.

4.2.2 Results

As discussed in 2.2.2 the study showed that despite many symptoms patients often died at home (48%). The study also considered the use of opioid medication in the management of symptoms and of the patients dying in the hospice, where accurate records of medication were available, 85% received oral morphine, 70% injection of diamorphine and 59% a continuous subcutaneous infusion of diamorphine via a syringe driver. Moreover, the doses of morphine were not large – the mean dose at home was 90mg oral morphine equivalent / 24 hours and the mean duration of use was 240 days. This shows that morphine had often been administered over a period of several weeks and months.

4.2.3 Strengths and limitations

The limitations of a retrospective review have been discussed in 2.1.3. The lack of a control or comparison group limits the study but the findings do suggest that care can be provided and medication can be given, without necessarily leading to premature death.

4.2.4. Contribution

This study has been cited widely and has added to the evidence for the involvement of palliative care in the care of people with MND and opioid medication can be used safely, with limited evidence of it effectiveness in symptom management, for people with MND.

4.3 Experience in UK and Germany – Text 2 Neudert et al 2001

4.3.1 Research study

This was a retrospective case review of people dying of MND at the Wisdom Hospice (50 patients) and Munich, Germany (121 patients) and was described in 2.3.1.

4.3.2 Results

The study showed that people with MND were able to die peacefully – as recorded in the notes or from discussion with family or carer after death – with 88% of patients in Germany reported as dying peacefully and 98% under the care of the Wisdom Hospice. Moreover, 52% of the patients in the UK and 55% of the patients in Germany died at home.

The study also looked at the use of opioids and showed that many people received morphine – 27% in Germany and 82% in the UK. The difference may reflect that hospice care is significantly less available in Germany, with only 6.4 hospice beds/million population compared to 54 beds/million in the UK. The majority of patients in Munich were cared for at home and attended on a regular basis for out-patient clinics, but were less likely to receive ongoing care at home. The primary care services may be less aware of the use of morphine for this patient group, whereas in the UK there was regular contact from specialist nurses at home, working in collaboration and supporting primary care. The doses were not high with a mean dose of 90mg oral morphine equivalent/24 hours in Germany and 115mg oral morphine equivalent/24 hours in the UK. The duration of use was only available in Germany, with a mean duration of use of 6 days, with a range from one to 52 days. 91% of the carers, in Germany, reported that the use of morphine was beneficial.

4.3.3 Strengths and limitations

The limitations of a retrospective review have been discussed in 2.2.3. Although the results show that death was peaceful in the group studied, this was not compared to a control group. Further studies would be needed to confirm these findings.

4.3.4 Contribution

This paper has provided data showing that people with MND are able to die at home, may receive morphine in the later stages of life at a moderate dose which was beneficial and death was felt to be peaceful in over 85% of patients - comparable to or higher than for other patient groups (Cagle et al 2015). This paper has been widely cited and has been used to show that people may die peacefully with MND, if they have received palliative care, including symptom management and support of the patient and carers. This has been used to repudiate the claims of some pro-euthanasia organisations, when MND is described in very negative terms and death from MND is described as distressing and to be feared, as discussed in 2.3.3.

The MND Association has a booklet "A professionals guide to end of life care in MND", for which I provided advice, has a section stating "Death in the majority of cases is very peaceful, following lengthening periods of sleepiness, gradually resulting in a coma" supported by a reference to Text 2 Neudert et al 2001 (MND Association 2019). A review article in Lancet Neurology entitled "End of life management in patients with amyotrophic lateral sclerosis" discusses patients fears of choking to death and uses the results from Text 4 to state "patients with ALS die peacefully" (Connolly et al 2015).

4.4 Opioid use in MND – Text 5 Oliver 1998

4.4.1 Research study

A retrospective case note review of 32 patients dying at the Wisdom Hospice between 1985 and 1996 was undertaken looking at the use of opioid medication. As these patients had died at the hospice the full medication chart and medical and nursing notes allowed the indication, dose, duration of use and effectiveness of opioids could be assessed.

4.4.2 Results

Of the 32 patients 75% received oral morphine, 94% received parenteral opioids and 72% received both oral and parenteral opioids. The mean dose of oral morphine was 96mg/ 24 hours, the median dose 60 mg/24hours and the range was from 15 to 720mg/24hours. The mean duration of use was 95 days, with a range of 2 to 970 days. This was lower than the group in Text 1 Oliver 1992, although in the earlier study both patients dying in the hospice and at home were included, and this may reflect that patients who are able to remain at home may take morphine for a longer duration of time (Text 1 - Oliver 1992). The main indications for morphine were pain 50%, dyspnoea and /or cough 34%, insomnia 6% and in the final stages of life only for 10%. The effectiveness was assessed from the notes, by myself, as "good" or "fair" for all patients and differed according to indication – the assessment was good for 69% for pain relief, 54% for dyspnoea / cough and 100% for terminal distress.

4.4.3 Strengths and limitations

The limitations of a retrospective case note review have been discussed in 2.2.3. As the patients died at the hospice the information on the dose and duration of use was accurate but the assessment of indication or effectiveness was subjective and obtained from reading the notes. These could be subject to bias, as I was both prescriber and assessor. I had aimed to be objective as possible in this assessment.

4.4.4 Contribution

This paper, together with Text 2 and O'Brien et al 1992 and Saunders et al 1981, are the only references quoted in the Cochrane Systematic Review "Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease" in the section on opioids (Brettschneider et al 2013).

A review of pain in MND (Stephens et al 2016) reviews their experience and three papers on pain in MND. In Italy opioids were given to 14% of 91 assessed patients (Chio et al 2012); in the UK 29% of patients attending a specialist MND clinic with pain received opioids (Wallace et al 2014); 13% of MND patients attending a specialised outpatient clinic in Germany received opioids (Hanisch et al 2015); and in the US series 22% received opioids (Stephens et al 2016).These studies were all a survey of a group of MND patients at a specific time point, whereas the Wisdom Hospice series includes the use of opioids by patients over the course of their care, often from soon after diagnosis until death.

Thus, this paper has shown that opioids may be given over extended periods of time and has provided evidence for the safe use of opioids in MND and has contributed to the Cochrane Review.

4.5 Randomised controlled trial – Text 6 Veronese et al 2017

4.5.1 Research Study

This study was a randomised controlled trial investigating the effectiveness of a specialist palliative care approach over 4 months. The study was part of the PhD project of Simone Veronese from Turin, Italy. I was his PhD supervisor and was closely involved in the design of the study, the analysis of the results and the writing of the paper – Text 6 – Veronese et al 2015.

A phase 2 pilot randomised controlled trial was undertaken. The Phase 2 study is defined in the MRC Framework as an "exploratory trial", which would "describe the constant and variable components of a replicable intervention and a feasible protocol for comparing the intervention with an appropriate alternative" (Campbell et al 2000). The intervention was the involvement of a multidisciplinary specialist palliative care service in Turin (FARO) using a waiting list methodology, with a fast track (FT) versus standard track (ST) approach. 50 patients with advanced neurological disease, defined from the specific criteria for MS, MND and PD and associated diseases, were randomised either to FT, with the involvement of the team from the time of recruitment, or to the ST, where the team was only involved after 16 weeks.

The Primary outcomes were the effects of 16 weeks provision of specialist palliative care on individual quality of life – measured using the SEIQol-DW – and the caregivers' burden of care using the Caregiver Burden Inventory. Physical symptoms, psychological issues, social issues and spiritual issues were assessed using Numerical Rating Scales, anxiety and depression using Hospital Anxiety and Depression Scale (HADS) and the disability was assessed using specific disease related scales.

4.5.2 Results

Of the 50 patients enrolled 60% were male and the mean age was 61 years. The diagnosis was MND for 32%, MS for 36% and PD for 32%. 45 carers were included in the study. At baseline there

were no statistical differences in the groups. Only 2 patients dropped out, in the FT group, for personal reasons. There were two deaths in both the FT and ST groups.

Statistically and clinically significant changes were seen in the FT group for quality of life, and physical symptoms – pain control, breathlessness, sleep disorder and bowel symptoms – compared to the ST group. There were no differences in caregiver burden. There were positive trends for improvement in other physical symptoms, service satisfaction and help in finding a meaning in the experience of the disease and social isolation. Psychological issues appeared to have a trend to worsening of symptoms, which may have been partly due to the increased discussion of these issues and confronting the concepts of death and dying.

4.5.3 Strengths and limitations

This approach was chosen as it is considered to be the "gold standard" of evidence on the effectiveness of an intervention, compared to a placebo or an alternative intervention. The randomisation into the intervention and control group at baseline ensures an equivalence of the groups being compared, and this was tested and confirmed statistically in the study (Text 6 Veronese et al 2017). However, there is a risk of a selection bias in the recruitment of participants for inclusion in the study (Higginson et al 2013). The recruitment was from a specialised hospital clinic in Turin by professionals, including neurologists, rehabilitation clinics and respiratory services. There could have been selection bias in recruitment, as these professionals may have tended to include patients who were less disabled, and patients who attended other general neurological clinics or were too ill to attend the specialised clinic may have been excluded. The referred patients were shown to have severe disease at the baseline and there were no statistical differences between the groups – the Expanded Disability Status Scale (EDSS) scores of patients with MS were a mean of 8.5, where over 8 presents patients restricted to bed or chair, ALS Functional Rating Scale - Respiratory (ALSFRS-R) scores for MND patients showed a mean of 10.2, out of a full score of 48 showing severe disease and disability and a Hoehn and Yahr score for PD patients of 4.2 which is described as "severely debilitating" (Veronese et al 2017).

The MRC Framework for a Phase II "Exploratory Trial" was used to investigate this complex intervention, which involves multiple interacting components with variability in content, context and mode of delivery, and often unpredictability of the overall effect (Hepgul et al 2018). A Phase II study has been suggested, when the intervention is complex and is still being developed and the trial will help to assess recruitment, drop out, mortality and feasibility (Campbell et al 2000). This approach had been further supported by the National Institute for Health Research when it established the Methods of

Researching End of Life Care (MORECare) collaboration (Higginson et al 2013). There had been a similar Phase II trial for patients with MS (Higginson et al 2008).

As the trial involved people with advanced progressive neurological disease, it would be very difficult to provide a blinded intervention – with a "Placebo intervention" from a multidisciplinary team. A waiting list RCT was undertaken, with the participants randomised to the intervention of palliative care immediately or to a control group who only received the intervention after 16 weeks (Higginson et al 2006). In this way all patients would receive the intervention, and although all patients would have progressive disease, the likely prognosis was usually in terms of months to years and the delay would not adversely disadvantage patients who were randomised to the standard best practice arm - the disadvantage was time-limited, as although they would not receive the intervention immediately they would all receive the intervention after 16 weeks. As this was part of a limited PhD project it was not possible to have blinded assessment, as the investigator undertook all assessments, which could lead to bias.

There were limitations in this approach, as due to the feasibility of undertaking the study the numbers of patients were limited to 50 overall and there was a mix of patients, with different progressive neurological diseases.

4.5.4 Contribution

There are few studies looking at the effectiveness of palliative care interventions and these have usually been in the care of cancer. This is the first study looking at three advanced neurological diseases and using a full multidisciplinary specialist team approach. This may partly explain the positive results whereas the other studies have limited results – for instance a short-term intervention for people with MS.

Studies in London for patients with MS showed that there was an improvement in symptoms in the group receiving palliative care, whereas there was deterioration in the control group (Edmonds et al 2010). Moreover, there was an improvement of caregiver burden (Edmonds et al 2010) and this care was shown to be cost effective (Higginson et al 2009). A more recent study in Italy showed that the short-term involvement of specialist nurses, who had received extra training in palliative care and support, did lead to a reduced symptom burden but had no effect on quality of life or other outcomes (Solari et al 2017). This study – Text 6 Veronese et al 2015 – did show more positive results. This may be partly due to the involvement of a wider multidisciplinary team

and specialist palliative care team with regular visits throughout the study period, whereas the other studies involved short term, limited input and did not have a full multidisciplinary specialist palliative care approach.

The evidence for the effectiveness of palliative care for cancer patients, has been limited. A trial in 2010 showed that early palliative care for patients with non-small cell lung cancer improved not only quality of life and mood, but led to a longer survival (Temel et al 2010). More recently, a study with newly diagnosed patients with lung and gastro-intestinal cancers involved 350 people, with a monthly consultation with palliative care, showed that there was an improvement of quality of life after 24 weeks and the lung cancer patients showed an improvement in quality of life and depression at 12 and 24 weeks, whereas the control group deteriorated (Temel et al 2017). A recent trial in Denmark showed no evidence for the effectiveness of palliative care for cancer patients, apart from in the management of nausea and vomiting (Groenvold et al 2017).

Thus, this study has provided clear evidence for the effectiveness of palliative care on both quality of life and symptom burden in neurological disease and may reflect the need for a wider multidisciplinary team approach for this patient group, to assess and manage all aspects of care. This may be supported by studies that have shown that a multidisciplinary team approach for people with MND, with a specific MND team, with palliative care involvement and collaboration, showed an improvement in length of life (Aridegbe et al 2013; Rooney et al 2015). There may be aspects of multidisciplinary care that are important and studies are needed to elucidate the most important aspects of this approach to care.

The study has been widely cited, including within the EAN/EAPC Consensus paper (Text11- Oliver et al 2016) and the other studies on neurological palliative care – in OPTCARE-NEURO (Hepgul et al 2018) and PENSAMI (Solari 2017).

4.6 Conclusions

There is limited evidence for the effectiveness of palliative care. A Cochrane Library Systematic Review considered 23 studies, with 37,561 participants and 4042 family caregivers, to evaluate the effect of home palliative care services for patients with advanced illness (Gomes et al 2016). The meta-analysis showed that there was evidence that patients were more likely to die at home and evidence of the reduction in symptom burden in four studies, showing small, but statistically significant, effects. There was no evidence of an effect on caregiver grief and no conclusive evidence

of cost effectiveness. A similar Cochrane Review on palliative care interventions for people with MS showed no evidence for an effect on quality of life, serious adverse events or hospital admission (Latorraca et al 2019). Other studies have shown that palliative care is helpful in MS (Solari et al 2017) and as part of a wider multidisciplinary care in MND (Aridegbe et al 2013; Rooney et al 2015).

These studies have all provided increasing evidence for the effectiveness of palliative care for people with neurological disease and added to the literature on this area.

The next chapter will consider the complexity of palliative care for neurological disease, when there are complex decisions to be made, with ethical and practical implications for all involved.

5. Complex decision making with neurological patients

5.1 Introduction

Within the care of people with neurological disease there has been the increasing use of intervention and new treatments. These often aim to improve quality of life, but there may be an extension of life as well. However, ethical dilemmas may be raised as a result of the discussion, and commencement, of these interventions, for although there may be an initial improvement in the patient's condition and wellbeing the disease will continue to progress and they face increasing issues, such as restricted mobility, deterioration in communication, swallowing and breathing and cognition. These issues have been considered in the papers presented below.

5.2 Difficult decision making – Text 7 -Oliver and Turner 2010

5.2.1 Background

This paper was developed after a discussion between the authors when it was apparent that there were serious issues facing all involved in the care of people with ALS/MND as more was known about the disease and new interventions were developed. It was agreed to write this review paper to help stimulate further discussion in neurology and palliative care.

5.2.2 Review

A discussion paper was drafted looking at the difficult decisions that were faced by professionals, and patients and families, including the telling of the diagnosis, the use of gastrostomy, the use of assisted ventilation, end of life planning and requests for assisted dying. This was not a systematic literature review but was a review of the issues with supporting evidence, where possible, and a discussion of the issues.

5.2.3 Review findings

The paper aimed to encourage the readers to consider the way difficult decisions were approached, in particular the communication about the diagnosis of ALS/MND and the possible interventions, to allow patients to be as autonomous as possible.

In the discussion of these areas of care the importance of careful and considered communication was stressed, as patients may have their own particular concerns of interventions – such as feelings that death may be close if interventions are necessary or loss of control or feeling that they are "giving in". The need to explain the benefits and risks of procedures was stressed, together with earlier discussion so that time can be taken over decision making, rather than in an emergency situation.

For patients and families to make informed decision about the end of life there is a need for earlier discussion and consideration of place of care and death, the use of interventions, such as cardiopulmonary resuscitation, and advance care planning. These issues may also come to the form in requests for a hastened death, euthanasia or physician assisted suicide (PAS), and the need to explore the request was highlighted.

5.2.4 Strengths and Limitations

This was a review paper, using the literature, but was not a systematic review. The views were from the discussions between the authors and are subject to bias. However, the paper was developed from the knowledge and experience of two experts, with different experiences – neurologist and palliative medicine- which allowed a broad view of the issues.

5.2.5 Contribution

This paper has been widely quoted and cited 59 times and has been important in the developing discussion on the management of difficult issues in MND – particularly the communication and ethical issues. In a recent systematic review on NIV the paper was clearly quoted: "Oliver and Turner highlighted that the use or non-use of NIV was one of the many decisions to be faced by an individual ALS patient on their journey of care" (Baxter et al 2019). The paper has also been quoted in a study considering the decision making for the use of tracheostomy (Ceriana et al 2017).

Within the discussion of the use of gastrostomy the ethical and decision-making aspects are usually stressed. An analysis of a large cohort of people with MND quoted the paper in their assessment and discussion of the intervention (Bond et al 2019). A review article on the ethical aspects of decision making in the management of MND uses the paper in their discussion of attempts to have earlier discussions with patients, even when this may be difficult for patients to consider their future

deterioration (Eisen and Krieger 2013). Foley and Hynes (2018) have also quoted the paper in their review of the issues in decision making in MND.

Within the discussion on end of life care the paper has been quoted within a review in Lancet Neurology, in particular stressing that the discussion of end of life issues may not be easy and are often not straightforward (Connolly et al 2015). Although there is increased awareness of the need to discuss potential issues earlier in the disease progression, before communication and cognition may be compromised there is still reluctance to do so (Rietjens et al 2017). Advance care planning is increasing - so the person discusses the care they would wish in the future, if they are unable to make the decisions themselves and this is recorded or a proxy is appointed to make the decision on their behalf (Rietjens et al 2017).

There is increasing discussion internationally about hastened death and euthanasia is now available in several countries – Netherlands, Belgium, Canada, Luxembourg, Colombia- and PAS is available in many states in the USA and Victoria in Australia and assisted suicide is available in Switzerland. The issues of these discussions have been discussed within this paper.

Thus, this paper has been able to stimulate further discussion on these difficult issues and has been widely read.

5.3 Issues surrounding withdrawal of non-invasive ventilation – Text 8 Faull et al 2014

5.3.1 Research Study

Palliative medicine professionals have been involved in the withdrawal of NIV in MND. NIV is an intervention that may be used if the patient develops increasing respiratory muscle weakness causing respiratory failure. Initially NIV may be used only at night, as symptoms are more pronounced on lying down, but as the disease progresses NIV may be used more often, even to 24-hour use. At the same time the disease will progress with increasing weakness and other issues. Some people receiving NIV may then ask for its withdrawal, but this may lead to death within a short time and cause distress, unless medication is given to prevent this. This request is not very common, but it had been identified as a difficult area of care.

An online questionnaire was sent to all 993 members of the Association for Palliative Medicine of Great Britain and Ireland (APM), asking them for their experiences of the withdrawal of NIV, and how they felt challenged practically, emotionally and ethically on a scale of 0 to 10, with 10 being very challenging. There was also the opportunity for free text responses.

5.3.2 Results

134 professionals, including 130 doctors, responded to the questionnaire. It is difficult to calculate a response rate as it is not known how many doctors would have been directly involved in the withdrawal of NIV in a patient with MND. However, 76 of the respondents had been involved and the responses were often profound and showed that these individuals had found the issues very difficult. The challenges they perceived were often great. Of those doctors with direct experience of NIV withdrawal the ratings were at a score of 7 or greater for 42% of the respondents for practical challenge, 33% for ethical challenge and 37% for emotional challenge.

In free text they discussed the time that was taken in planning the procedure, with multiple discussions across the MDT and coping with conflicts in the discussion with patients, families and other MDT members. Although they realised that the withdrawal of a treatment at the patient's request was ethically sound, it felt as if they were causing the patient's death and thus it felt different to the withdrawal of other treatment, particularly when death followed withdrawal within a short time. The emotional burden was great and 20% of respondents scored this challenge at 9 or 10 and the main areas were felt to be management of the emotions of all involved in the discussion and process, the support of others, resolving conflict and the issues for themselves in coping with the withdrawal process and the ensuing death.

5.3.3 Strengths and limitations

There are limitations of an on-line questionnaire as the respondents may be more likely to have strong views than those who did not respond. The response rate was difficult to estimate as the number of people who had been involved in the withdrawal of treatment is unknown. However, the response rate from within the APM was probably less than 15% of the whole membership, but this is found widely in on-line surveys (Atkin et al 2017; Smallwood et al 2017). It is not possible to assess how valid these results would be in a larger group but other on-line questionnaires have been found to have good validity and reliability (Plaete et al 2016). However, this initial questionnaire aimed to start the debate on these issues and this approach, where information could be given anonymously

may have allowed issues to be more openly discussed by the respondents than in focus groups or interviews. Although this may have biased the result, as people with more definite views may have responded, the views expressed were very clear and showed that there were many unresolved issues for these participants.

5.3.4 Contribution

This paper was an initial scoping study to ascertain if there were issues for palliative medicine doctors when they were confronted with the withdrawal of NIV in MND. The results did clearly show that were many issues, particularly in the support and conflicts within the MDT. This has led onto further studies – Text 9 Phelps et al 2015 – and the development of the national guidance document "Withdrawal of ventilation at the request of a patient with motor neurone disease: guidance for professionals" (APM 2015). This document has provided clear guidance on the discussions, procedure, medication that may be used and the ethical issues. It has been endorsed by the General Medical Council and the Coroners' Society of England and published by the APM and is available on their website and also on the MND Association website. Further discussion on the document is presented as Text 10 Faull and Oliver 2016.

5.4 Ethical and legal issues of withdrawal of ventilation – Text 9 Phelps et al 2015

5.4.1 Research study

This study followed from the on-line study in Text 8. A retrospective qualitative interview approach was taken, interviewing doctors who had withdrawn assisted ventilation from a person with MND in the past 5 years. The doctors were contacted from the last study – if they had given their contact details – and doctors were also approached in the APM Neurological Special Interest Forum and from MND care Centres and specialist respiratory teams. 24 doctors were interviewed. The interviews were analysed thematically and coded. I was involved in the design of the study, helping in recruitment, interpreting the findings and the themes that were developed and in writing the paper, in collaboration with Dr Phelps and Professor Faull.

5.4.2 Results

Five main themes were found: ethical and legal aspects, all participants agreed that patients had a right to refuse treatment and ask for it to be withdrawn and they talked of the need for careful, and

often lengthy, discussions; discussions with the family were important and could be complex; discussions with colleagues were often complex and some colleagues opposed withdrawal of NIV and further lengthy discussion was needed and the support of peers was felt to be important; legal advice was experienced as very variable and, on occasions, inaccurate, increasing the stress on the doctors; there were ethical complexities as the doctors talked of the difficulty of removing the NIV, which led to death within a short time, and that this felt as if they were causing the death and this was even more difficult as the patient was usually conscious and may have planned the time of withdrawal.

5.4.3 Strengths and limitations

The use of a qualitative approach was necessary for this study as the aim was to look in detail at the experiences, perceptions and attitudes of the participants (Atieno 2009). The use of interviews allowed the lived experience of the participants to be discussed and then analysed carefully, looking for common themes. The data was able to lead to further exploration of the issues, as the researcher was able to adjust the interviews according to the particular participant, and using the experience from the previous interviews to help in the discussion.

There are limitations to the qualitative approach as the data found can depend on the experience of the interviewer in gaining trust and openness of the participants (Atieno 2000). There was purposive sampling, using the doctors who had been involved in the earlier study, who had offered to provide further information, and then contacting others through MND centres and clinics, and by a snowballing process, with those interviewed suggesting further contacts. Although this could be seen to be limiting the range of people involved, the method did allow the involvement of those who were interested and involved in the care of people with MND and had been involved in the withdrawal of NIV. The interviews were undertaken by an experienced interviewer and were either face to face or by telephone, and consent was taken beforehand.

The transcripts of the interviews were coded using a grounded theory approach to identify themes. The analysis can also be biased by the researcher, although in these studies there were opportunities for other members of the research team, of which I was part, to check and validate the analysis of the themes. The replicability of a qualitative study and the transferability to other groups may be questioned but the aim in these studies was to obtain a greater, in-depth understanding of the issues for this smaller group of participants. As recruitment continued until there was data saturation, it is likely that the results may be transferable to the wider UK population, but they may not be transferable to other countries / cultures.

5.4.4 Contribution

This paper, in conjunction with Text 8- Faull et al 2014 has contributed to the knowledge about the issues in the withdrawal of assisted ventilation. This has led to the APM Guidance, described in 5.3.4. This Guidance is now available for any professional involved in the withdrawal of ventilatory support in MND and has been widely used and overwhelmingly welcomed.

5.5 Withdrawal of NIV – an editorial Text 10 Faull and Oliver 2016

5.5.1 Editorial

This was an invited editorial to the British Medical Journal Supportive and Palliative Care journal. It is a review of the issues involved in the withdrawal of ventilation at the request of the patient with MND and a description of the APM guidance.

5.5.2 Guidance

The Editorial provides background information on the withdrawal of NIV and summarises the APM Guidance. This suggests five standards: Standard 1: that patients are aware that they may stop NIV and that this is a legal option; Standard 2: a senior clinician should validate the patient's request and lead on the procedure; Standard 3: withdrawal should be undertaken within a reasonable timeframe after the request; Standard 4: symptoms should be anticipated and managed effectively; Standard 5: after the death family members should be able to discuss the events. These standards could be audited and it is suggested that after every procedure a data set is submitted and learning shared. The Guidance also supports doctors in asking for mentoring from doctors who have experience in the area, and the APM would provide details of doctors willing to support others.

5.5.3 Strengths and Limitations

This is a review publication, highlighting an evidence- based document, and so may be considered to be biased. However, the aim was to stimulate further thought and discussion in this difficult area.

5.5.4 Contribution

This Editorial has added to the literature on the withdrawal of ventilatory support at the request of a patent with MND. Together with Text 8 and Text 9 it is now available to provide an evidence base and information for professionals when faced with this issue.

5.7 Conclusion

These papers have related to the difficult areas of care of people with neurological disease, and in particular MND. These themes have been developed in the literature, with increased awareness of the need for advance care planning (Foley et al 2018), the need to discuss end of life issues (Connolly et al 2015) and earlier discussion of end of life issues in the disease progression (Eisen et al 2013; NICE 2016). The guidance document to help professionals provide care in the specific situation of NIV withdrawal in MND has also been produced (APM 2016).

In the next chapter the provision of guidelines for neurological palliative care and for MND will be considered.

6. Improvement of care – guidelines and future developments

6.1 Introduction

The previous chapters have considered the identification of the need and then the evidence for palliative care in neurological disease. To enable this evidence to become established within routine day to day care it is important to enable all involved in care to be aware of the best management. The development and use of guidelines can help in this process, with the aim of ensuring care is evidence based and the quality of care can improve for patients and families. These two papers are based on this approach.

6.2 Consensus review of palliative care for progressive neurological disease – Text 11 Oliver et al 2016.

6.2.1 Consensus review

A systematic literature review was undertaken under the auspices of the European Association for Palliative Care (EAPC) Taskforce on Neurology and the European Academy of Neurology (EAN) Specialty Group on Palliative Care. 68 studies were reviewed and Professor Raymond Voltz and I assessed the papers and produced a draft list with possible recommendations. This list was considered by the wider group and in an iterative process the recommendations were made. The initial review was undertaken under the auspices of the European Federation of Neurological Societies (EFNS) and their grading system was used (Brainin et al 2004). This classified the studies Class I to Class IV and the recommendations from Level A (established as effective), Level B (probably effective), and Level C (possibly effective).

6.2.2 Results

Seven main areas were developed with recommendations:

- Early integration of palliative care – which should be considered early in the disease trajectory, depending on the diagnosis
- Multidisciplinary team approach – of at least three professionals with MDT assessment and access to specialist palliative care
- Communication – open communication with patients and families and early advance care planning

- Symptom management – thorough diagnosis, management and review of symptoms, using the principles within palliative care and proactive assessment of physical and psychosocial issues
- Carer support – regular assessment of carers, support of carers before and after death. Professionals should receive education, support and supervision
- End of life care – continued and repeated discussion of end of life issues, encouragement of open discussion, including wishes to restrict treatment and wish for hastened death, recognition of end of life and the dying phase
- Education and training – training of both specialities with palliative care education for neurologists and education in the understanding and management of neurological symptoms for palliative care professionals.

6.2.3 Strengths and limitations

The aim of the EAPC/EAN collaboration was to perform a systematic literature review and develop a clear evidence-based guideline. However, there were limited studies and the quality of the studies was poor. The aim to use randomised controlled trials (RCT) was limited but non-randomised trials and observational studies could be considered if there are no relevant RCTs. This may increase the problems and in particular imprecision may be unclear (Thornton et al 2013). It has also been suggested that the final recommendations may vary with the composition and dynamics within the group assessing the studies, and Raine et al found that there was agreement with the research evidence for only 51% of 192 scenarios she presented to a group of professionals (Raine et al 2004). There appeared to be particular concerns that the results from a specific RCT, with a possible selected population of participants, may not always be extrapolated to the general population, which may be more heterogeneous and be influenced by multiple other factors (Raine et al 2004). These issues were minimised by the involvement of a small group of experts, who were able to collaborate, discuss the evidence and come to clear and agreed recommendations.

There are also concerns that Clinical Guidelines may not always be applied within health services. This may be because the guideline has been “science driven” and not “customer driven” and thus seen as less relevant. There is a need to develop a programme for implementation to ensure the guideline is understood and then used (Grol and Buchan 2006). There is a challenge to ensure Clinical Guidelines do become embedded within routine clinical care, which may be encouraged and facilitated by the use of regular audit.

It has been suggested that guidelines may be inaccessible, may have taken a long time in development and may be superseded by more recent research, be based on RCTs which may not be so relevant in day to day practice and lack user involvement (Chong 2018). A delay did occur, to some extent, as the initial development was under the auspices of the EFNS, which was then amalgamated with the European Neurological Society (ENS) in 2014. The draft paper was ready in 2013 but this could not be considered by the EFNS at this time and was only considered by the EAN when this was fully functional in 2015. Thus, there was the possibility that new studies may have been published during this period, but could not be added.

6.2.4 Contribution

This paper has been cited 87 times in 3 years and has been presented at the congresses of both the EAN and EAPC. It Is available at the EAN website and EAPC and following its publication a Memorandum of Understanding was signed by the Presidents of the EAN and EAPC. This has established collaboration between the two organisations, with educational sessions at each other's congresses. There is very little literature with a clear assessment of the evidence base and this Consensus paper is obviously being read and used in the literature.

6.3 NICE Guideline on MND – Text 12 Oliver et al 2017

6.3.1 Guideline development

This paper was published following the National Institute for Health and Care Excellence (NICE) Guidance on MND. The review questions were developed using the PICO framework – considering the patient population, intervention, comparison group and outcome. These were clearly stated so that the clinical literature search can then be undertaken systematically. The study types are clearly defined – the aim was to use randomised controlled trials but non-randomised trials and observational studies were considered when there were no relevant RCTs. The data were then synthesised and assessed for its quality using the GRADE criteria – the "Grading of Recommendations Assessment, Development and Evaluation" (Guyatt et al 2008). This assessment aimed to consider the risk of bias, indirectness (differences in study population, intervention, comparators and outcomes), inconsistency (unexplained heterogeneity), imprecision (studies with small numbers of participants), publication bias (underestimation or overestimation of the effect with a selective publication of studies). In this way the quality of the evidence was graded from High to Very low.

I was Chair of the Guideline Development Group and closely involved in the development of the questions, PICOs, analysis of the data and the development of the recommendations. The GDG was multidisciplinary and there were patient and carer representatives. Many of the questions had little evidence and a consensus recommendation was made following discussion.

6.3.2 Guideline

The various areas of care that were assessed, and for which recommendations were made were:

- recognition of symptoms and referral to neurology
- information and support at diagnosis- by a Neurologist who is knowledgeable and manages MND
- organization of care – multidisciplinary team approach
- social care – integrating care at home and ensuring care is constant and co-ordinated
- provision of equipment to aid activities of daily living – provided appropriately and speedily
- nutrition – assessment of nutritional needs and coping with swallowing issues
- communication – enabling communication face to face and by web-based systems
- muscle problems – enabling mobility and reducing stiffness
- saliva management – reducing and coping with drooling of saliva
- cough effectiveness – enabling people to cough if necessary
- respiratory function – assessment, commencement and monitoring of respiratory function and the use of NIV
- cognitive assessment- to recognize frontal lobe changes and fronto-temporal dementia
- prognostic factors – specific factors that are related to poor prognosis
- planning for end of life care – facilitating palliative care and advance care planning, supporting patients and families at the end of life and in bereavement.

(NICE 2016).

6.3.3 Strengths and limitations

The use of the GRADE system did allow the evidence to be assessed effectively. The separation of the quality of the evidence and the strength of the recommendation was clear and there is a very explicit and transparent system for evaluation (Guyatt et al 2008). This evidence could then be interpreted by the Guideline Development Group (GDG) and recommendations developed.

There may be problems in developing guidelines. Although the GRADE system was developed by a widely representative group and is explicit and transparent, certain areas may be misunderstood (Guyatt et al 2008). In particular imprecision may be unclear (Thornton et al 2013). It has also been suggested that the final recommendations may vary with the composition and dynamics within the GDG, and as has been discussed in 6.2.3 Raine et al found that there was agreement with the research evidence for only 51% of 192 scenarios she presented to a group of professionals (Raine et al 2004). There are also concerns that the results from a specific RCT, with a possible selected population of participants, may not always be extrapolated to the general population, which may be more heterogeneous and be influenced by multiple other factors (Raine et al 2004). This was minimised by the involvement and discussion at the GDG, coming to clear recommendations, which were acceptable to all.

There are also concerns that Clinical guidelines may not always be applied within health services, as discussed in 6.2.3. There was wide involvement of patients and carer representatives in the GDG, a process of consultation before publication the Guideline was completed within a period of two years and issued within a few weeks of the final deliberations. There is a challenge to ensure Clinical Guidelines do become embedded within routine clinical care. The MND Association in England and Wales has developed an audit process to encourage and facilitate implementation (https://www.mndassociation.org/forprofessionals/transforming-mnd-care/).

6.3.4 Contribution

This NICE Guideline has been developed and has been promulgated by the MND Association (https://static.mndassociation.org/app/uploads/2017/05/19135522/01A-About-the-NICE-guideline-on-MND.pdf). The paper has helped to make the Guideline more available internationally.

The Guideline has been used to develop NICE Quality Standards (NICE 2016) and these have been adapted to allow an audit of the care for people with MND (as above). All areas are encouraged by the MND Association to undertake this audit, with the aim of showing areas of good practice and areas where there is need for improvement.

The Guideline has been widely disseminated, including New Zealand (https://mnd.org.nz/for-professionals/), Scotland (https://www.care-mnd.org.uk/clinical-professionals/), and Marie Curie Foundation (https://www.mariecurie.org.uk/professionals/palliative-care-knowledge-zone/condition-specific-short-guides/motor-neurone-disease). It has also been used by the British Thoracic

Society and the Intensive Care society in their own guidelines on ventilatory management (Davidson et al 2016).

The Guideline is widely referenced on many health websites, including Guideline Central (https://www.guidelinecentral.com/summaries/motor-neurone-disease-assessment-and-management/), Patient info (https://patient.info/doctor/motor-neurone-disease-pro) and the European Reference Network EURO-NMD (https://ern-euro-nmd.eu/publication/motor-neurone-disease-assessment-and-management-2/).

The Guideline has also been used within the NHS England Right Care Progressive Neurological Conditions Toolkit (https://www.england.nhs.uk/rightcare/wpcontent/uploads/ sites/40/2019/08/progressive-neuro-toolkit.pdf) . This has considered MND, MS, MSA and PD and aims to provide advice and guidance on how commissioners and providers can address the key challenges in commissioning and providing services for people with progressive neurological disease.

6.4 Conclusion

These two papers have aimed to increase awareness of the care of people with neurological disease and provide information, from a clear evidence base, to improve the care of patients and their families. They may be considered within a wider literature of evidence-based guidelines which have continued to be developed (Andersen et al 2012; Solari et al 2019; Miller et al 2009; Bede et al 2011).

7. Methodology

7.1 Research in palliative care

There is a need for research in palliative care, as at present many of the interventions and medications used have very limited evidence, at a time when there is an increased move to ensure evidence-based care. The complexity of palliative care with very ill patients, often with a short prognosis, raises challenges for research, but these need to be addressed to enable the field to develop and for the science to be more widely accepted.

In earlier chapters there has been discussion of the methodology used in each of the papers submitted as part of this thesis, including an assessment of their strengths and limitations. In this chapter wider issues of research within palliative care will be considered.

7.2 Issues in undertaking research in palliative care populations

The needs of patients, and carers, within palliative care are complex and very varied. Physical issues, such as the management of pain and other symptoms, are prominent but psychological, social and spiritual issues also arise, often with implications both for the care provided and the methodology to conduct related research. Moreover, there are complexities in undertaking research as patients have progressive disease, may be frail, present multiple rapidly changing symptoms and conditions, and may deteriorate, and die, over short periods of time. There are also issues of recruitment into research studies, as healthcare professionals may act as "gatekeepers" and be reluctant to involve very ill patients in research, even though the latter may see such involvement as a useful contribution they can make to the development of treatment and the understanding of future patients, even if not for themselves.

7.3 Ethical issues

Many ethical issues are raised in palliative care research because of the particular vulnerabilities of potential participants (Raus and Sterckx 2018). Consent may become difficult when a participant has cognitive loss, with dementia or reduced consciousness near the end of life. Participants may also come under undue influence (Cassarrett 2015). They may be influenced to participate inappropriately by any

indication (even a “glimmer of hope”) that an experimental treatment could extend their lives or alter the disease progression (Armon 2018). Their dependence on the caring team may lead to them feeling unable to refuse, lest this affects their overall management. To avoid such issues patients within palliative care have sometimes been excluded from studies (Raus and Sterckx 2018; Cassarett 2015). Instead, there is a need for careful consideration of the steps needed to enable patients to be involved, without them experiencing undue pressure, so that research can proceed in an ethical way.

7.4 Research philosophies and approaches

The study of knowledge, epistemology, stresses the importance of considering not only **what** is known but **how** it comes to be known. Research methods stressing the importance of gathering “data” on an objective reality would be described as “positivist” and are characterised by the use of empirical, quantitative methods. Methods stressing the perceptions of those involved and the subjective meanings they ascribe to events would be described as “constructivist” and would typically depend more on qualitative approaches (Darlaston-Jones 2007).

Both approaches are likely to be necessary in gaining a holistic understanding of issues in palliative care, given the complex interactions between patients’ more objective symptoms and conditions, their broader psychosocial contexts and the subjective meaning of their experiences. A constructivist approach may be more helpful in understanding some phenomena, such as the psychosocial and spiritual aspects of palliative care, where meaning and emotion are likely to be central to participant experience. A positivist approach may enable the objective evaluation of the impact of medication on symptoms, although even here there may be underlying subjective aspects – for instance the assessment of pain may be influenced by emotional reactions, previous experiences and other issues affecting each person uniquely. The use of mixed research methods – quantitative and qualitative - may allow both objective knowledge and the information on the underlying experiences to be ascertained, allowing inferences to be drawn from the integration of the knowledge arising from both approaches (Walshe 2018).

7.5 Research methodologies

Thus, there are implications for the design of research in palliative care

7.5.1 Recruitment

Consideration of more effective "advertising" of studies and allowing recruitment to be part of the routine practice and care within palliative care units have been shown to increase patient involvement in research. It is also important that the culture of an institution allows clinical and research staff time so that research is not seen as a burden (Boland et al 2016).

7.5.2 Consent

A novel approach to consent may also have to be considered, as many patients will not be able to consent to participation in a trial at the end of life, due to loss of communication, extreme weakness or drowsiness or incapacity. For instance, in the CARiAD study of subcutaneous medication for breakthrough symptoms at home patients the inclusion criteria are of an adult in the last weeks of life who is likely to lose the oral route for medication and who has expressed a preference to die at home, together with the carer who is willing to give subcutaneous medication (Poolman et al 2019). The patients and family carers will be identified by the professionals and approached with more information and the researcher will seek advance consent for both patient and carer, so that all are aware of the views on participation in the trial. If the patient loses capacity to consent later, the assent of a Personal Consultee will be sought – usually a family member – or a Nominated Consultee – another health care professional – will be asked to give their assent. In this way very ill patients can be fully included in the consent process and involved in the trial (Pollman et al 2019).

7.5.3 Methodology

The "gold standard" for medical research is generally regarded to be the Randomised Controlled Trial (RCT) since this allows the evaluation of the effects of an intervention – benefits and harms - in an unbiased manner, with experimental and control groups equally matched at the beginning and all parties being blind to whether the participant is having the experimental or the placebo / standard care. It is important to ensure that there is clinical equipoise, with a genuine uncertainty of the effectiveness of the intervention, so that there is an initial null hypothesis, that there is no difference between the intervention and the control (Freedman 1987). This null hypothesis can then be tested within the trial.

However, a RCT may lack external validity and generalization of the findings may be limited and the planning of a study may take so long that alternative treatment options may be available (Drazen et al 2017). There are clearly many difficulties in implementing such a design in a palliative care setting, where the prognosis is poor and participants are frail and less able to withstand periods of investigation.

Notwithstanding these difficulties, and accepting that RCTs will not always be appropriate to the research question, it remains possible to design studies in such a way that these issues can be addressed to a considerable extent.

Other methodologies may be appropriate in the provision of evidence, including observational studies, the use of disease registries and practice-based evidence, from the analysis of policies and campaigns (Drazen et al 2017).

The Medical Research Council Framework allows the assessment of a complex intervention in a four-phase process using qualitative and quantitative methodology – as has been described in Section 4.4.3 and is shown in Table 1 (Campbell et al 2000; Craig et al 2008). This was found to be effective in the study in Turin – Text 3 Veronese et al 2016 reported on the qualitative study to ascertain the issues for patients and Text 6 Veronese et al 2017 was then a pilot evaluation - see sections 2.4.3 and 4.5.3.

Case reviews allow an assessment of the issues facing patients - as in Text 1 Oliver 1996. There are limitations as the group considered may be biased but the information found in such a study can be used to help develop further research – Section 2.2.3. When combined with a qualitative assessment of care – as in Text 2 Neudert et al 2001 – there is the opportunity to test the effectiveness of an intervention to some extent – Section 2.3.3.

Qualitative research, often as part of a mixed methods approach, together with quantitative methods, does allow the more complex aspects of care to be evaluated, such as psychosocial or spiritual aspects of care. This has been described above in Text 3 Veronese et al 2016 and Text 9 Phelps et al 2015. This approach may provide an indepth approach to the concerns of the participants – whether patients, families or professionals.

Single patient (n-of-1) trials have been used – a multicycle, double-blind, controlled crossover trial when a patient receives treatment and intervention in a randomised way and only after the trial is the order revealed and the participant's responses found. Participants all receive the treatment and can assess the efficacy for themselves, when the order is revealed (Nikles et al 2011). It is possible to aggregate studies to derive population estimates of effectiveness of the treatment, and the number of patients involved will be smaller than in a randomised controlled trial.

Other studies have used a wedge cluster randomised controlled trial approach for the implementation of a guideline. After an initial control period the intervention is introduced to several services in a

randomised sequence. There is incomplete blinding (because of the nature of the intervention) but care is taken to reduce bias by standardisation of data collection. This approach also allows a qualitative element to be introduced (Luckett et al 2018).

7.5.4 Different methodological approaches

The advantages and limitations of research methods are shown in Table 1. As can be seen there are strengths and limitations for all and the complexity of research in palliative care may require a complex methodology.

Thus, there is a need within palliative care to look at new ways of undertaking research, ensuring patients and families are involved, collaborating between centres and looking at innovative ways of undertaking mixed methods research. RCTs may be possible and a collaborative approach may be necessary. The PACE study evaluating a palliative care programme in nursing homes was able to collect large numbers of questionnaires from the staff in the homes in 78 clusters across Europe in 7 countries in a multi-facility cluster-randomised trial (Van den Block et al 2019).

There are different methodologies to be considered in undertaking research with in palliative care. The method used will depend on the question being asked, and a qualitative, quantitative or mixed methods approach design may be appropriate.

7.6 Patient participation

There is increasing involvement of patients within the development of research projects – Patient and Public Involvement (PPI) (Noble et al 2015). This is seen as essential to ensure that the patients, families and public are all involved in the development of research, which will not only be important to enable funding from society but to ensure research is relevant to all concerned. However, there are similar concerns to the issues of recruitment of participants in palliative care, as there may be barriers to patient participation, because of illness, weakness or remote location, the discussion may be difficult for patients and families facing the issues of deterioration and dying and death, and there may be risk of tokenism (Chambers et al 2019). The effective involvement of patients and public is worthwhile as this may increase the relevance and quality of research and is often positive for patients - giving meaning to life, reassurance, confidence and rewarding (Chamber et al 2019). There may be other methods of undertaking PPI, including research panels (Collins et al 2015) or online systems facilitating discussion (Brighton et al 2018).

7.7 Conclusion

The complexity of palliative care, looking at physical, psycho-social and spiritual aspects of care with very ill patients, often with a short prognosis, is a challenge for research. Innovative ways of undertaking research, and then ensuring the results and innovations that are found becomes part of an evidence-based approach to care, are essential for the development of the specialty, and the care of patients and families (Visser et al 2015).

Table 1

Methodology	Strengths	Limitations
Randomised control trial	Gold standard Effectively compares intervention between a control and treatment group Ideally blinded – so no influence on management Randomisation to remove bias Stratification can be used to ensure groups have similar prognostic factors	Selection bias possible Blinding of observers and participants may be impossible or difficult Study group may not reflect wider population and results may not be generalisable Power and size may be insufficient Statistical effectiveness may not reflect clinical effectiveness
Medical Research Council Framework	Phase I Defines the components of the study Phase II – defines the trial and design – acceptability/ feasibility/ defining control intervention / outcomes Phase III Main trial – assessing methodology – sample size, inclusion and exclusion criteria, randomisation, challenges of complex intervention Phase IV – Implementation – rate of uptake, stability of intervention, broadening of subject groups, adverse effects Allows complex intervention to be evaluated	Selection bias in recruitment Intervention may not be blinded and subject to bias Commitment to groups may vary, with higher drop out in control group Control may not be possible – but waiting list study used with possible bias in selection / maintenance of groups Recruitment may be difficult – if delay in receiving intervention
Systematic literature review	Rigorous and prospectively defined objective and purpose Transparent Reproducible protocol	Bias in the publications – as non-positive results / unfunded / multicentre studies may never be published Grey literature may be missed Lack of RCTs may reduce the range of literature assessed

Case note review	Notes readily available Can be used to assess an initial hypothesis, which can then be tested	Selection bias in notes used – not all available / not all patients in the group seen Uncontrolled Notes not always accurate
Online survey	Anonymous Easy for participants to complete Less expensive	Bias in responses – people with stronger views may respond more often Small response rate May not be representative of larger group
Focus group	Views of wider group of people ascertained Group members may allow greater discussion and greater depth Clear areas discussed with a clearly prepared schedule	Influence of some participants on others – dominance Inhibition of some participants to join in the discussion Coding may be subjective and can vary Influence of leader – altering the responses
Interview study	Opportunity for participants to voice their concerns and issues Privacy of the response Anonymous use of the comments, allowing participants to be more open	Influences on participants – of family if present, or of interviewer Communication / cognition may be affected reducing participants' responses Coding of themes may be subjective Participants may be inhibited from responding or respond in the way they think they should
Survey	Relatively easy data collection Standardised data collection Anonymous	Questions may be misunderstood or misinterpreted Data may not be uniform due to misunderstanding
N-of-1 study	Double blind for some interventions Controlled	Data may not be collected in a standardised way and may not be comparable

	Randomised Crossover Smaller numbers of patients needed to show effectiveness of an intervention	
Wedge cluster randomised study	Randomised Controlled Blinded	Data may be acquired differently and not comparable
Ethnographic research	Study looking at the social interaction within an environment Shadowing of team interactions Allows team interactions to be observed and studied	Longer term study Presence of the investigator may alter the interactions Higher cost

8. Discussion and Conclusions

8.1 Introduction

The thesis has drawn on a range of my published work over a considerable period of time and has been presented within context of the wider literature. The papers have all been important in the development of palliative care for people with neurological disease. The contribution of each paper has been discussed separately and this chapter will aim to summarise the overall contribution and the development of the area of care.

8.2 Contribution of the research

The role of the papers in the development of neurological palliative care is shown in Figure 1. The other relevant literature is shown in the lower section of the Figure. The research presented has aimed to develop the concepts of care – from assessing the needs of patients and families, considering the care provided, including the effectiveness of the interventions, the role in the complex decision making, the establishment of clear guidelines and the overall development of the concepts of palliative care for people with neurological disease.

8.3 The contribution to the development of neurological palliative care

Over the last 25 years the role of palliative care in neurology has developed greatly. The papers presented in this thesis have been important in showing that people with neurological disease have many symptoms and issues, many of which are unmet – sections 2.2.4, 2.3.3, 2.4.4 – and this has been shown in many different diseases- section 1.4 (Ng 2018; O'Brien et al 1992; Wiblin et al; Edmonds et al 2010; van der Steen et al 2014).

There is increased involvement of palliative care services for neurological patients, building on the evidence from the MND survey in 2000 (Text 4 Oliver and Webb 2000). In Germany an online survey of neurologists showed 90% reported collaboration with palliative care for patient with ALS, MSA and cerebral tumours, although only 12% had received training in palliative care (Golla et al 2016). A online survey of neurologists and palliative care specialists, organized under the auspices of the EAPC and EAN showed widespread collaboration for ALS and cerebral tumours (84% strong or moderate and 87% respectively) but less collaboration with other disease groups (Oliver 2019).

These online studies may be subject to bias, as completion is more likely by neurologists who have involvement or a special interest in palliative care. However, they do provide an insight into the issues, which may then be followed up by more comprehensive studies.

The Ne-PAL RCT (Text 6 Veronese et al 2016) was able to show clearly that quality of life and symptoms could be improved with palliative care involvement, without an increase in mortality. There have been other studies looking at effectiveness of palliative care, although these have primarily focused on short term intervention (Edmonds et al 2010; Hepgul et al 2018) or increasing the expertise of specialist nurses (Solari et al 2018). In the study we undertook (Text 6 Veronese et al 2016) a specialist palliative care team was involved and there was clearer evidence of change and this approach may have had a greater impact on the patient and family. Further research is needed to consider the most effective model of care – see Section 8.4 below.

Palliative care services are often involved in the complexity of advanced disease. The papers on the ethical issues of the withdrawal of NIV in MND have been very important in raising these complex ethical discussions and issues. The papers (Text 8 Faull et al 2014; Text 9 Phelps et al 2015) have shown the pressures and conflicts faced by the professionals involved in the withdrawal of treatment and the importance of clear guidelines and the provision of support for those involved. This led to the production of the Guidance (APM 2015), which was widely endorsed and was discussed and summarised in Text 10 Faull and Oliver 2016.

Decision making is often complex for people with neurological disease, who may face loss of communication and cognition (Text 7 Oliver and Turner 2010). This has been shown in studies, with a retrospective case series showing that within an inpatient setting the commonest reasons for consultation with palliative care were eliciting goals of care (82% of contact) and that this led to an increase in the completion of advance directives (63% to 92%) (Liu et al 2016). A large study, considering over 70,000 consultations within 78 services in the USA showed that consultation was less often for symptom management, compared to cancer patients, but more often for assistance with transition of care at the end of life, and in particular the withdrawal of treatment (Taylor et al 2019). A review of the care of people with advanced neurological disease also emphasized the complexity of patient care, and particular the challenges in decision making and ethical issues (Sreenivasan et al 2018).

The role of palliative care for neurological disease has been emphasised in many guidelines, and since 2016 these have referenced the EAN/EAPC Consensus paper (Text 11 Oliver at al 2016). Guidelines recommending palliative care involvement include those for ALS (Andersen et al 2012; Miller et al 2009; Karam et al 2016; NICE 2016), PD (NICE 2017), glioma (Pace et al 2017) and dementia (van der Steen et al 2014).

8.4 Models of palliative care provision

Thus, the role of palliative care is more accepted, both with neurology and palliative care. There are several models of care provision:

- The MDT approach, with palliative care as a member of this wider MDT. This has been shown to improve length of survival in MND (Aridegbe et al 2013; Rooney et al 2015) but there is little research in the care of other diseases.
- Specialist palliative care involvement from early in the disease progression, with increased involvement when there are specific issues, such as symptoms or psychosocial distress or complex decision making, collaborating with the specialist MDT which provides ongoing care (Bede et al 2011; Oliver 2014)
- Closer collaboration between neurology and palliative care with increased understanding of the roles of both services. This has been shown to be increasing in Germany and across Europe (Golla et al 2016; Oliver 2019). Creutzfeldt et al (2016) emphasized the role of the neurologists as the “primary palliative care provider”, emphasizing the need for further education.
- In the USA there has been the development of a sub-specialty of Neuro-palliative care. Neurologists are able to undertake further training in palliative medicine and provide specialist care (Robinson et al 2017). Within the field there has been a move to develop both services and research targets for the benefit of patients and families (Creutzfeldt et al 2018). The training in palliative medicine is limited, and may be only 6 to 12 months, but this approach does increase the awareness and expertise within neurological services and facilitate the development of a multidisciplinary approach.

The use of specific models will depend on the patient group, the cultural aspects within the society, the experience and skills of the health and social care services and organisational and financial aspects, within health provision in different countries. For instance, in the USA the funding system within Medicare restricts “hospice” to the last 6 months of life, and as a result, patients receive care late in the disease progression and near to the end of life – less than 50% of dying patients

access hospice and the median hospice involvement is 18 days, with a mean of 86 days (Zuckerman et al 2016). The Neuro-palliative care approach allows palliative care provision earlier in the disease progression, but with appropriate funding. The collaborative approach to care will also depend on the experience of all involved, and if primary care providers have limited experience and skills in palliative care, patients may require specialist services earlier, than if primary care provides a wider multidisciplinary approach (Oliver 2018). Cultural issues, both within health and social care and wider society, may also influence how palliative care and end of life care are provided, as in cultures where the discussion of these issues is avoided, patients may be more dependent on palliative care from other services, such as neurology and primary care (Clark and Phillips 2010).

Overall, there is an increased awareness of the need of patients with progressive neurological disease, with palliative care provision earlier in the disease progression, consideration of psychosocial issues, preparation for deterioration and dying and caregiver support (Oliver et al 2016; Oliver 2019). The system that provides this care may vary from country to country.

8.5 Further research

There are several areas which would benefit from further research, in order to establish a clear evidence base and thus encourage further development of the area:

8.5.1 Symptom management

There is a very limited evidence base for the interventions and medications used in the management of symptoms. It is necessary for assessment of the medication that is routinely used at present to test its effectiveness. A RCT approach would allow an assessment that is less open to bias. A N of 1 approach could be used initially to assess the effectiveness of treatments see section 7.5 and Table 1.

8.5.2 Education of neurologists and palliative care specialists

Many of the papers in the field discuss the need for education of neurologists in the techniques and principles of palliative care and of palliative cares specialists in neurology. However, there is very little literature on the most effective way of undertaking this education which would lead to a positive effect on the management and support of patients and families. Different approaches need to be assessed, including on-line training, small group interactive education, mentoring and

shadowing and classroom teaching, to elucidate the most effective way of improving patient and family care.

8.5.3 Assessment of the multidisciplinary team

There is weak evidence that an MDT approach increases quality of life and length of life for people with MND, although these studies have used a historical cohort as the control group and there were differences between the groups in the use of interventions and site of onset (Aridegbe et al 2013). This needs to be studied in other areas, comparing the MDT approach in a RCT or with a historical cohort. The RCT approach would be the ideal approach, but several centres would be needed to recruit the numbers of patients needed and the study may need to continue over a longer period of time – for MND 1 to 2 years and for other disease, with a longer prognosis, this may need to longer. The comparison with a historical cohort may allow a smaller population to be studied, but with the risk of increased bias.

An ethnographic approach could be taken to investigate the interactions within the MDT and to look at how these interactions between team members affect the care provided. A disease specific MDT could be compared to a team where there are no regular meetings, but various disciplines are involved in the care of patients in a relatively unco-ordinated way

8.5.4 The effectiveness of palliative care for neurology

There is a need for further trials of the best way for the provision of palliative care for people with differing neurological diseases. A RCT may be seen as the ideal method to show the effectiveness of an intervention, and for this patient group a Waiting list design may be useful, as discussed in 4.5.3, 7.3 and Table 1.

The exact nature of the intervention should be clear – with options being a specialist palliative care multidisciplinary approach as needed throughout the disease progression, a short-term specialist approach, for assessment when there are specific issues, or the palliative care approach within neurology services. These different approaches may affect the effectiveness of the intervention as at present there is no clear evidence of the most appropriate and effective model of care.

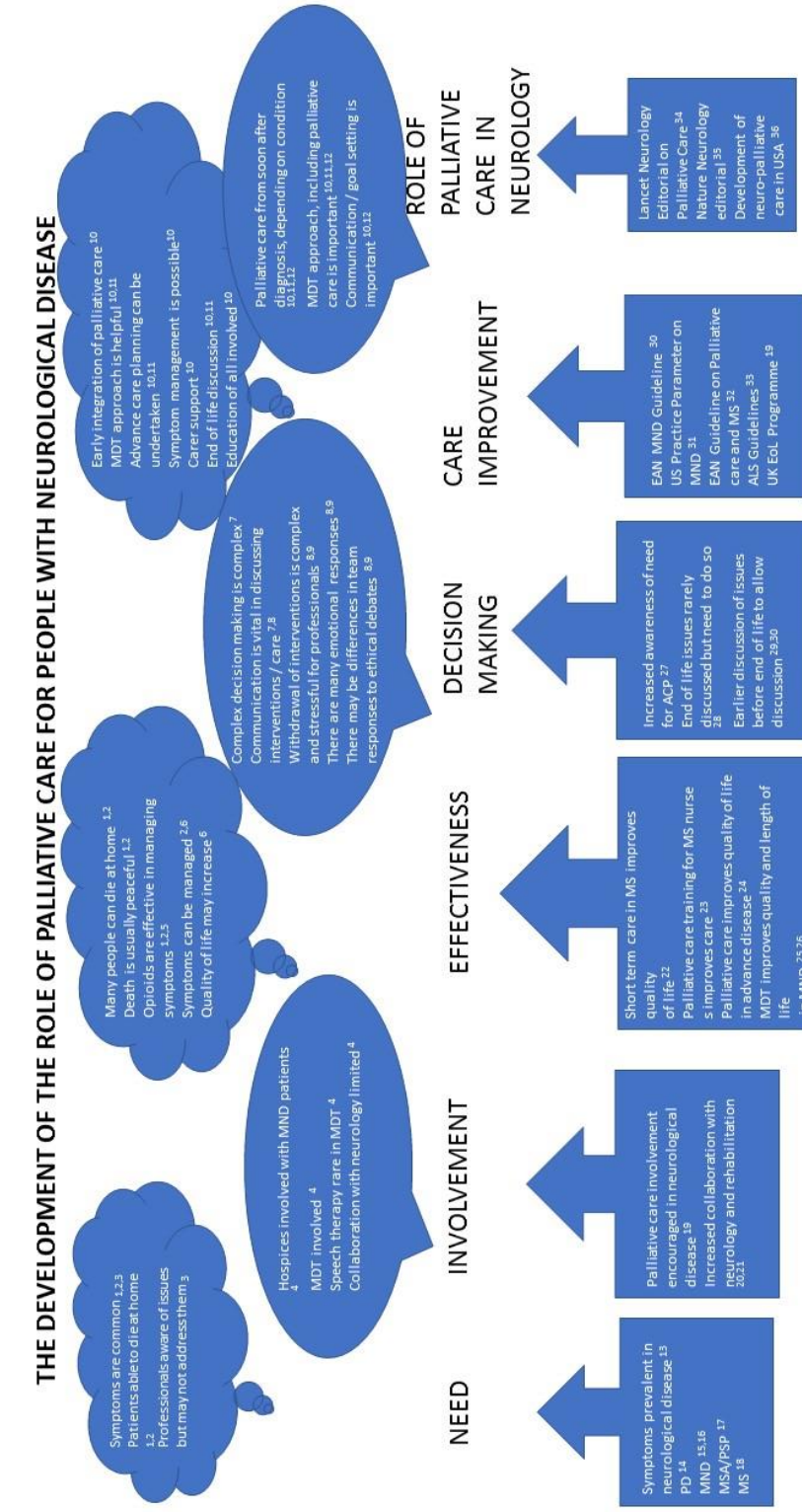
8.5.5 Patient and public involvement

As has been discussed in 7.7 it is important to ensure that there is PPI in the development of future studies. This may enable research to be as relevant as possible for the patients and families, ensuring improved recruitment and ensuring research leads to more effective and evidence-based management and care for neurological patients.

8.6 Conclusions

The papers presented in this thesis all relate to the many differing issues in the care of people with neurological disease. This is now more widely acknowledged (Lancet Neurology 2017; Borasio 2013). My papers have been important in the development of the concepts of neurological palliative care and have contributed to the continuing debate on the future development of the care for people with neurological disease.

Figure 1


THE DEVELOPMENT OF THE ROLE OF PALLIATIVE CARE FOR PEOPLE WITH NEUROLOGICAL DISEASE
NEED
INVOLVEMENT
EFFECTIVENESS
DECISION MAKING
CARE IMPROVEMENT
ROLE OF PALLIATIVE CARE IN NEUROLOGY
Symptoms are common 1,2,3
Patients able to die at home 1,2
Professionals aware of issues but may not address them 3
Hospices involved with MND patients 4
MDT involved 4
Speech therapy rare in MDT 4
Collaboration with neurology limited 4
Many people can die at home 1,2
Death is usually peaceful 1,2
Opioids are effective in managing symptoms 1,2,5
Symptoms can be managed 2,6
Quality of life may increase 6
Complex decision making is complex 7
Communication is vital in discussing interventions / care 7,8
Withdrawal of interventions is complex and stressful for professionals 8,9
There are many emotional responses 8,9
There may be differences in team responses to ethical debates 8,9
Early integration of palliative care 10
MDT approach is helpful 10,11
Advance care planning can be undertaken 10,11
Symptom management is possible 10
Carer support 10
End of life discussion 10,11
Education of all involved 10
Palliative care from soon after diagnosis, depending on condition 10,11,12
MDT approach, including palliative care is important 10,11,12
Communication / goal setting is important 10,12
Symptoms prevalent in neurological disease 13
PD 14
MND 15,16
MSA/PSP 17
MS 18
Palliative care involvement encouraged in neurological disease 19
Increased collaboration with neurology and rehabilitation 20,21
Short term care in MS improves quality of life 22
Palliative care training for MS nurse s improves care 23
Palliative care improves quality of life in advance disease 24
MDT improves quality and length of life in MND 25,26
Increased awareness of need for ACP 27
End of life issues rarely discussed but need to do so 28
Earlier discussion of issues before end of life to allow discussion 29,30
EAN MND Guideline 30
US Practice Parameter on MND 31
EAN Guideline on Palliative care and MS 32
ALS Guidelines 33
UK EoL Programme 19
Lancet Neurology Editorial on Palliative Care 34
Nature Neurology editorial 35
Development of neuro-palliative care in USA 36

The development of the role of palliative care for people with neurological disease

References for Figure 1

1. Oliver D J. The quality and care of symptom control - the effects on the terminal phase of ALS/MND. Journal of Neurological Sciences 1996; 139 (suppl): 134-6.
2. Neudert C, Oliver D, Wasner M, Borasio GD. The course of the terminal phase in patients with amyotrophic lateral sclerosis. Journal of Neurology 2001; 248: 612-616.
3. Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, Oliver DJ. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342
4. Oliver D. Webb S. The involvement of specialist palliative care in the care of people with motor neurone disease. Palliative Medicine 2000; 14: 47-8.
5. Oliver D**.** Opioid medication in the palliative care of motor neurone disease. Palliative Medicine 1998; 12: 113-115
6. Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, Oliver DJ. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172. Oliver DJ,
7. Turner MR. Some difficult decisions in ALS/MND. Amyotrophic Lateral Sclerosis 2010; 11: 339-343.
8. Faull C, Rowe Haynes C, Oliver D. issues for palliative medicine doctors surrounding the withdrawal of non-invasive ventilation at the request of a patient with motor neurone disease: a scoping study. BMJ Supp Pall Care 2014; 4:43-49.
9. Phelps K, Regen E, Oliver D, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.
10. Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38. doi:10.1111/ene.12889
11. Oliver D, Radunovic A, Allen A, Mcdermott C. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1–11. DOI:10.1080/21678421.2017.1304558.
12. Oliver D Palliative care for people with progressive neurological disease: what is the role? Journal of Palliative Care 2014; 30: 298-301.
13. Kristjanson LJ, Aoun SM, Oldham L. Palliative care and the support for people with neurodegenerative conditions and their carers. Int J Palliat Nurs 2005; 12: 368-377.Ng JSC. Palliative care for Parkinson's disease. Ann Pall Med 2018; 7: 296-303.
14. O'Brien, T., M. Kelly, and C. Saunders, Motor neurone disease: a hospice perspective. Br Med J, 1992. 304(6825): 471-3.
15. Saunders C, Walsh TD, Smith M. Hospice care in motor neurone disease. In Saunders E, Summers DH, TellerN (eds) Hospice: the living idea. 1981. London. Edward Arnold pp126-155.
16. Wiblin L, Lee M, Burn D. Palliative care and its emerging role in Multiple Systems Atrophy and Progressive Supranuclear Palsy. Parkinsonism Relat Disorders 2017; 34: 7-14.
17. Edmonds P, Hart S, Gao W, Vivat B, Burman R, Silber E, Higginson I. Palliative care for people severely affected by multiple sclerosis: evaluation of a novel palliative care service. Mult Scler 2010; 16: 627-36.
18. Higginson IJ, Hart S, Burman R, et al. Randomised controlled trial of a new palliative care service: compliance, recruitment and completeness of follow-up. BMC Palliat Care 2008;7:7. doi:10.1186/1472-684X-7-7
19. End of life care in long term neurological conditions: a framework for implementation. National End of Life Care Programme 2010.
20. Turner-Stokes L, Sykes N, Silber E, Khatri A, Sutton L, Young E. From diagnosis to death: exploring the interface between neurology, rehabilitation and palliative care in managing people with long-term neurological conditions. Clin Med, 2007. 7: 129-136.

21. Van Vliet LM, Gao W, DiFrancesco D, Crosby V, Wilcock A, Byrne A et al. How integrated are neurology and palliative care services? Results of a multicentre mapping exercise. BMC Neurology 2016; 16:63 DOI: org/10.1186/s12883-016-0583-6
22. Latorraca COC, Martimbianco ALC, Pachito DV, et al. Palliative care interventions for people with multiple sclerosis. Cochrane Database of systematic Reviews 2019 (10): Art. No. CD012936. Doi: 10.1002/14651858.CD012936.pub2
23. Solari A, Giordano G, Patti F, Grasso G, Confalonieri P et al. Randomised controlled trial of a home based palliative approach for people with severe muliple sclerosis. Multiple Sclerosis Journal 2017; 24: 663-674.
24. Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev 2013; (6):CD0077760. Published 29013 Jun 6. Doi: 10.1002/14651858.CD007760.pub2
25. Aridegbe T, Kandler R, Walters SJ et al. The natural history of motor neuron disease: Assessing the impact of specialist care. Amytroph Lat Scler 2013; 14:13-19.
26. Rooney J, Byrne S, Heverin M et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry 2015; 86: 496-503.
27. Foley G, Hynes G. Decision making among patients and their families in ALS care: a review. ALS FTD 2018; 19: 173-193.
28. Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurology 2015; 14: 435-42.
29. Eisen A, Krieger C. Ethical considerations in the management of amyotrophic lateral sclerosis. Progress in Neurobiology 2013; 110: 45-53.
30. Anderson PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, Hardiman O, and the members of the EFNS Task Force. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis: revised report of an EFNS task force. Eur J Neurol 2012; 19: 360-375.
31. Miller RG, Jackson CE, Kasarkis EJ, England JD, Forshew D, Johnston W. et al. Practice Parameter update. The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/ behavioural impairment (an evidence-based review). Neurology 2009; 73: 1227-1233.
32. Solari A, Giordano A, Sastre-Garriga J et al. EAN Guideline on Palliative Care of People with Severe Multiple Sclerosis. European Academy of Neurology 2019
33. Bede P, Oliver D, Stodart J, van den Berg L, Simmons Z, O'Brannagain D, Borasio GD, Hardiman O. Palliative care in amyotrophic lateral sclerosis: a review of current internationalguidelines and initiatives. J Neurol Neurosurg Psychiatry 2011; 82: 413-418.
34. Lancet Neurology Editorial. Integrating palliative care into neurological practice. The Lancet Neurology 2017; 16:489.
35. Borasio GD. The role of palliative care in patients with neurological diseases. Nature Neurology 2013; 9: 292-295.
36. Creutzfeldt CJ, Kluger B, Kelly AG et al. Neuropalliative care. Priorities to move the field forward. Neurology 2018; 91: 217-226.

References

Abel J, Kellehear A. Palliative care reimagined: a needed shift. BMJ Supp Pall Care 2016; 6: 21-26.

Anderson PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, Hardiman O, and the members of the EFNS Task Force. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis: revised report of an EFNS task force. Eur J Neurol 2012; 19: 360-375.

Aridegbe T, Kandler R, Walters SJ et al. The natural history of motor neuron disease: Assessing the impact of specialist care. Amytroph Lat Scler 2013; 14:13-19.

Armon C. Ethics of clinical research in patients with ALS: is there a risk of exploitation? Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2018; 19: 161-166.

Association for Palliative Medicine. Withdrawal of assisted ventilation at the request of a patient with motor neurone disease: guidance for professionals. Association for Palliative Medicine of Great Britain and Ireland. 2015.

Atkin N, Vickerstaff V, Candy B. "Worried to death": the assessment and management of anxiety in patients with advanced life-limiting disease, a national survey of palliative medicine physicians. BMC Palliative Care 2017; 16:69. Doi 10.1186/s12904-017-0245-5.

Atieno OP. An analysis of the strengths and limitation of qualitative and quantitative research paradigms. Problems of Education in the 21st Century. 2009; 13: 13-18.

Baxter SK, Johnson M, Clowes M et al. Optimizing the noninvasive ventilation pathway for patients with amyotrophic lateral sclerosis/motor neuron disease: a systematic review. ALS FTD 2019; 20: 461-472.

Bede P, Oliver D, Stodart J, van den Berg L, Simmons Z, O'Brannagain D, Borasio GD, Hardiman O. Palliative care in amyotrophic lateral sclerosis: a review of current international guidelines and initiatives. J Neurol Neurosurg Psychiatry 2011; 82: 413-418.

Boersma I, Miyasaki J, Kutner J, Kluger B. Palliative care and neurology. Time for a paradigm shift. Neurology 2014; 83: 561- 567.

Boland J, Currow DC, Wilcock A et al. A systematic review of strategies used to increase recruitment of people with cancer or organ failure into clinical trials: implications for palliative care research. J Pain Symptom Manage 2015; 49: 762-772.

Bond L, Ganguly P, Khamankar N et al. A comprehensive examination of percutaneous endoscopic gastrostomy and its association with amyotrophic lateral sclerosis patient outcomes. Brain Sciences 2019; 9: 223; doi: 10.3390/brainsci9090223.

Borasio GD. The role of palliative care in patients with neurological diseases. Nature Neurology 2013; 9: 292-295.

Brainin M, Barnes M, Baron J-C et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol 2004; 11: 577-581.

Brettschneider J, Kurent J, Ludolph A. Drug therapy for pain in amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database of Systematic reviews 05 June 2013.

Brighton LJ, Pask S, Benalia H et al. Taking patient and public involvement online: qualitative evaluation of an online forum for palliative care and rehabilitation research. Research Involvement and Engagement 2018; 4:14. Doi: 10.1186/s40900-018-0097-z

Buzgova R, Kozakova R, Jurickova L. The unmet needs of patients with progressive neurological disease in the Czech Republic: a qualitative study. J Pall Care 2019; 34: 38-46.

Cagle JG, Pek J, Clifford M et al. Correlates of a good death and the impact of hospice involvement: Findings form the National Survey of Households affected by cancer. Support Care cancer 2015; 23: 809-818.

Campbell M, Fitzpatrick R, Haines A, Kinmouth AL, Sandercock P, Spiegelhalter D, Tyrer P. Framework for design and evaluation of complex interventions to improve health. BMJ 2000; 321: 694-696.

Cassarett D. Ethical issues in palliative care research. In: Cherny NI, Fallon MT, Kaasa S, Portenoy RK, Currow DC (eds) Oxford Teaxtbook of Palliative Medicine 5th edition. 2015. Oxford. Oxford University Press.pp1194-1197.

Ceriana P, Surbone S, Segagni D, Schreiber A, Carlucci A. Decision-making for tracheostomy in amyotophic lateral sclerosis (ALS): a retrospective study. ALSFTD 2017; 18: 492-497.

Chambers E, Gardiner C, Thompson J, Seymour J. Patient and carer involvement in palliative care research: An integrative qualitative evidence synthesis review. Pall Med 2019; 33: 969-984.

Cherny NI, Radbruch L et al European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med. 2009; 23: 581-93.

Chio A, Canosa A, Gallo S et al. Pain in amyotrophic lateral sclerosis: a population-based controlled study. Eur J Neurol 2012; 19: 551-555.

Chong CCN. Pros and cons of clinical practice based on guidelines. Hong Kong Med J 2018; 24: 440-441

Clark, D. Cicely Saunders. Founder of the Hospice Movement. Selected Letters 1959-1999. 2002. Oxford: Oxford University Press. p 322.

Clark K, Phillips J. End of life care: the importance of culture and ethnicity. Australian Family physician 2010; 39: 210-213.

Collins K, Boote J, Ardron D et al. Making patient and public involvement in cancer and palliative research a reality: academic support is vital for success. BMJ Supprt Palliat Care 2015; 5: 203-6.

Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. Lancet Neurology 2015; 14: 435-42.

Craig P, Dieppe P, Macintyre S et al. Developing and evaluating complex interventions: the new Medical research Council guidance. Br Med J 2008; 337:a1665.

Creutzfeldt CJ, Robinson MT, Holloway RG. Neurologists as palliative care providers. Communication and practice approaches. Neurology. 2016; 6: 40-48.

Creutzfeldt CJ, Kluger B, Kelly AG et al. Neuropalliative care. Priorities to move the field forward. Neurology 2018; 91: 217-226.

Darlaston-Jones D. Making connections: the relationship between epistemology and research methods. The Australian Community Psychologist. 207; 19: 19-27.

Davidson C, Banham S, Elliott M et al. BTS/ICS Guidelines for the Ventilatory Management of Acute Hypercapnic Respiratory Failure in Adults. Thorax 2016; 71 (Suppl2): ii1-ii35.

Department of Health. The National Service Framework for Long-term Conditions. London Department of Health 2005.

Drazen JM, Harrington DP, McMurray JVJ et al. Evidence for health decision making – beyond randomized, controlled trials. MN Eng J Med 2017; 377: 465-475.

Edmonds P, Hart S, Gao W, Vivat B, Burman R, Silber E, Higginson I. Palliative care for people severely affected by multiple sclerosis: evaluation of a novel palliative care service. Mult Scler 2010; 16: 627-36.

Eisen A, Krieger C. Ethical considerations in the management of amyotrophic lateral sclerosis. Progress in Neurobiology 2013; 110: 45-53.

End of life care in long term neurological conditions: a framework for implementation.
National End of Life Care Programme 2010.

Faull C, Rowe Haynes C, **Oliver D.** issues for palliative medicine doctors surrounding the withdrawal of non-invasive ventilation at the request of a patient with motor neurone disease: a scoping study. BMJ Supp Pall Care 2014; 4:43-49.

Foley G, Hynes G. Decision making among patients and their families in ALS care: a review. ALS FTD 2018; 19: 173-193.

Freedman B. Equipoise and the ethics of clinical research. N Eng J Med 1987; 317: 141-145.

Gofton TE, Chum M, Schultz V et al. Challenges facing palliative neurology practice: A qualitative analysis. J Neurol Sci 2018; 385: 225-231.

Golla H, Ebke M, Rolke R, Lorenzl S et al. Integration of palliative and hospice care structures in the care of neurological patients; opinion of chief consultant neurologists in Germany (In German). Fortschr Neurol psychiatry 2016; 84: 733-738.

Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. Cochrane Database Syst Rev 2013; (6):CD0077760. Published 29013 Jun 6.
Doi: 10.1002/14651858.CD007760.pub2

Groenvold M, Petersen MA, Damkier A et al. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. Pall Med 2017; 31: 814-824.

Grol R, Buchan H. Clinical guidelines: what can we do to increase their use? MJA 2006; 185: 301-302.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P. et al GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J 2008; 336: 924-926.

Hanisch F, Skudlarek A, Berndt J, Kornhuber ME. Characteristics of pain in amyotrophic lateral sclerosis. Brain and Behaviour 2015; 5(3): e00296. doi: 10.1002/brb3.296.

Hepgul N, Gao W, Evans CJ, Jackson D, van Vliet LM, Byrne A et al Integrating palliative care into neurology services: what do the professionals say. BMJ Supp Palliat Care 2018; 8: 41-44.

Higginson IJ, Vivat B, Silber E et al. Study protocol:delayed intervention randomised controlled trial within Medical Research Council (MRC) Framework to assess the effectiveness of a new palliative care service. BMC Palliat Care 2006; 5:7. DOI: 10.1186/1472-684X-5-7.

Higginson IJ, Hart S, Burman R, et al. Randomised controlled trial of a new palliative care service: compliance, recruitment and completeness of follow-up. BMC Palliat Care 2008; 7:7. doi:10.1186/1472-684X-7-7

Higginson IJ, McCrone P, Hart S et al. Is short-term palliative care cost-effective in multiple sclerosis? A randomized phase II trial. J Pain Symptom Manage 2009; 38: 816-826.

Higginson I, Evand CJ, Gande G et al. Evaluating complex interventions in end of life care: the MORECare Statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. BMC Medicine 2013; 11:111. Doi: www.biomedvcentral.com/1741-7015/11/111.

Hospice UK www.hospiceuk.org/media-centre/facts-and-figures. 2015

Hussain J, Adams D, Allgar V, Campbell C. Triggers in advanced neurological conditions: prediction and management of the terminal phase. BMJ Supp Palliat Care 2014; 4: 30-37.

Hussain J, Allgar V, Oliver D. Palliative care triggers in progressive neurological conditions: An evaluation using a multi-centre retrospective case record review and principal component analysis. Pall Med 2018; 32: 716-725.

Karam CY, Paganoni S, Joyce N et al. Palliative care issues in amyotrophic lateral sclerosis: an evidenced-based review. Am J Hosp Palliat Car 2017; 33: 84-92.

Kristjanson LJ, Aoun SM, Yates P. Are supportive services meeting the needs of Australians with neurodegenerative conditions and their families. J Pall Care 2006; 3: 151-157.

Lambert R. Spiritual care. In Oliver D, Borasio GD, Johnston W (eds). Palliative care in amyotrophic lateral sclerosis- from diagnosis to bereavement. 3rd edition. 2014. Oxford. Oxford University Press. Pp 171-186.

Lancet Neurology Editorial. Integrating palliative care into neurological practice. The Lancet Neurology 2017; 16:489.

Latorraca COC, Martimbianco ALC, Pachito DV, et al. Palliative care interventions for people with multiple sclerosis. Cochrane Database of systematic Reviews 2019 (10): Art. No. CD012936. Doi: 10.1002/14651858.CD012936.pub2.

Luckett T, Phillips J, Agar M et al. Protocol for a phase III pragmatic stepped wedge cluster randomised controlled trial comparing the effectiveness and cost-effectiveness of screening and guidelines with, versus without, implementation strategies for improving pain in adults with cancer attending outpatient oncology and palliative care services: the Stop Cancer PAIN trial. BMC Health Services Research 2018; 18:558. Doi: 10.1186/s12913-018-3318-0.

Liu Y, Kline D, Aerts et al. Inpatient palliative care for neurological disorders: lessons from a large retrospective series. J Pall Med 2017; 20: 59-64.

Maessen M, Veldink JH, van den Berg LH et al. Requests for euthanasia: origin of suffering in ALS, heart failure and cancer patients. J Neurol 2010; 1192-1198.

Maessen M, Veldink JH, Onwuteaka-Philipsen BD et al. Euthanasia and physician-assisted suicide in amyotrophic lateral sclerosis: a prospective study. J Neurol 2014; 261: 1894-1901.

McKenna C, MacLeod R. Access to palliative care for people with motor neurone disease in New Zealand. N Z Med J 2005; 118: 17-24.

Miller RG, Jackson CE, Kasarkis EJ, England JD, Forshew D, Johnston W. et al. Practice Parameter update. The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/ behavioural impairment (an evidence-based review). Neurology 2009*;* 73: 1227-1233.

Motor Neurone Disease Association. A professionals' guide to end of life care in motor neurone disease. Motor Neurone Disease Association. Northampton. 2019. https://static.mndassociation.org/app/uploads/2012/04/19135713/px012-a-professional-guide-to-end-of-life-care-in-mnd-v1-0-jan16-web.pdf.

National Institute for Health and Care Excellence. NICE Guidance on Motor Neurone Disease. 2016. NICE. www.nice.org.uk/NG42.

National Institute for Health and Care Excellence. Motor Neurone Disease- Quality standard [QS126]. 2016. NICE. https://www.nice.org.uk/guidance/qs126

National Institute for Health and Care Excellence Parkinson's disease in adults. 2017.Nice.org.uk/guidance/ng71

National Neurology Intelligence Network. Deaths associated with neurological conditions in England 2001 to 2014. Public Health England 2015.

Neudert C, **Oliver D**, Wasner M, Borasio GD. The course of the terminal phase in patients with amyotrophic lateral sclerosis. Journal of Neurology 2001; 248: 612-616.

Neurological Alliance. Neuro Numbers. Neurological Alliance 2014. www.neural.org.uk/assets/pdfs/2014-04-neuro-numbers-2014.pdf

Neurological Alliance. The Invisible Patients: Revealing the state of neurology services. Neurological Alliance 2015. www.neural.org.uk/store/assets/files/495/original/Invisible_patients_-_revealing_the_state_of_neurology_services_final_14_January_2015_.pdf

Ng JSC. Palliative care for Parkinson's disease. Ann Pall Med 2018; 7: 296-303.

Nikles J, Mitchell GK, Schulter P et al. Aggregating single patient (n-of-1) trial in populations where recruitment and retention was difficult: The case for palliative care. J Clinical Epidemiology 2011; 64: 471-480.

Noble B, Buckle P, Gadd B. Service user and patient and public involvement in palliative and supportive care research. BMJ Support Palliat Care 2015; 5: 459-460.

O'Brien, T., M. Kelly, and C. Saunders, Motor neurone disease: a hospice perspective. Br Med J, 1992. 304(6825): 471-3.

Oliver D J. The quality and care of symptom control - the effects on the terminal phase of ALS/MND. Journal of Neurological Sciences 1996; 139 (suppl): 134-6.

Oliver D. Opioid medication in the palliative care of motor neurone disease. Palliative Medicine 1998; 12: 113-115

Oliver D Palliative care for people with progressive neurological disease: what is the role? Journal of Palliative Care 2014; 30: 298-301.

Oliver D. Improving patient outcomes through palliative care integration in other specialized health services: what we have learned so far and how can we improve? Ann Palliat Med 2018; 7 (Suppl 3): S219-230.

Oliver D, Hepgul N, Borasio GD et al. Collaboration between neurology and palliative care; a European survey. Poster at the 5th European Academy of Neurology Congress, Oslo. June 2019.

Oliver DJ. Palliative care in motor neurone disease: where are we now? Palliative Care: Research and Treatment. 2019 doi.org/10.1177/1178224218813914

Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38. doi:10.1111/ene.12889

Oliver D, Radunovic A, Allen A, Mcdermott C. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1–11. DOI:10.1080/21678421.2017.1304558.

Oliver DJ, Turner MR. Some difficult decisions in ALS/MND. Amyotrophic Lateral Sclerosis 2010; 11: 339-343.

Oliver D. Webb S. The involvement of specialist palliative care in the care of people with motor neurone disease. Palliative Medicine 2000; 14: 47-8

OPTCARE-NEURO. https://www.kcl.ac.uk/nursing/departments/cicelysaunders/research/studies/optcare-neuro/index.aspx. 2019

Pace A, Dirven L, Koekkoek JAF et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. The Lancet Oncology 2017; 18: e330-340.

Phelps K, Regen E, **Oliver D**, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.

Plaete J, De Bourdeaudhuij I, Steenhuyzen S, et al. The reliability and validity of short on-line quetionnaires to measure fruit and vegetable intake in adults: The Fruit Test and Vegetable Test. PLOS One. 2016; https://doi.org/10.1371/journal.pone.0159834.

Poolman M, Roberts J, Byrne A et al. CARer-ADministartion of as-needed subcutaneous medication for breakthrough symptoms in homebased dying patients (CARiAD): study protocol for a UK-based open randomised trial. Trials 2019; 20:105. Doi.org/10.1186/s13063-019-3179-9

Radbruch L, Payne S et al. White Paper on standards and norms for hospice and palliative care in Europe: part 1. Eur J Palliat Care 2009; 16: 278-289.

Raine R, Sanderson C, Hutchings et al. An experimental study of the determinants of group judgements in clinical guideline development. Lancet 2004; 364: 429-437.

Raus K, Sterckx S. Ethics in palliative care research. In MacLeod RD, Van den Block (eds) Textbook of Palliative Care. Switzerland. Springer International 2018. 10.1007/978-3-319-31738-0_109-1

Rietjens JAC, Sudore RL, Connolly M, van Delden JJ, Drickamer MA, Droger M, et al. Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *The Lancet Oncology*. 2017;18(9):e543-e51.

Robinson MT, Holloway RG. Palliative care in neurology. Mayo Clin Proc 2017; 92: 1592-1601.

Rooney J, Byrne S, Heverin M et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. J Neurol Neurosurg Psychiatry 2015; 86: 496-503.

Saunders C, Walsh TD, Smith M. Hospice care in motor neurone disease. In Saunders E, Summers DH, TellerN (eds) Hospice: the living idea. 1981. London. Edward Arnold pp126-155.

Sleeman KE, Ho YK, Verne J et al Place of death, and its relation with underlying cause of death in Parkinson's disease, motor neurone disease, and multiple sclerosis: A population-based study. Pall Med 2013; 27: 840-846.

Smallwood N, Currow D, Booth S et al. Differing approaches to managing chronic breathlessness syndrome in advanced COPD: A Multi-National Survey of specialists. J Chronic Obstruct Pulmon Dis 2018; 15: 294-302.

Smets T, Deliens L. Health services research in palliative and end-of-life care. In Cherny NI, Fallon MT, Kaasa S, Portenoy RK, Currow DC (eds) Oxford Textbook of Palliative Medicine 5th Edition. 2015. Oxford. Oxford University Press. pp 1210-1214.

Solari A, Giordano G, Patti F, Grasso G, Confalonieri P et al. Randomised controlled trial of a home based palliative approach for people with severe muliple sclerosis. Multiple Sclerosis Journal 2017; 24: 663-674.

Sreenivasen V, Nobleza CO. Challenges and ethical issues in the course of palliative care management of advanced neurological diseases. Ann Palliat Med 2018; 7: 304-319.

Stephens HE, Lehman E, Raheja D et al. Pain in amyotrophic lateral sclerosis: Patient and physician perspectives and practices. LAS FTD 2016; 17: 21-29.

Taylor BL, O'Riordan DL, Pantilat SZ, Creutzfeldt CJ. Inpatients with neurologic disease referred for palliative care consultation. Neurology 2019; e1975-1981.

Temel JS, Greer JA, Muzikansky et al . Early palliative care for patients with metastatic non-small-cell lung cancer. N Eng J Med 2010; 19: 733-742.

Temel JS, Greer JA, El-Jawarhi A et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomised trial. J Clin Oncol 2017; 35: 834-841.

Thornton J, Alderson P, Tan T et al. Introducing GRADE across the NICE clinical guideline program. J Clinical Epidemiol 2013; 66: 124-131.

Turner-Stokes L, Sykes N, Silber E, Khatri A, Sutton L, Young E. From diagnosis to death: exploring the interface between neurology, rehabilitation and palliative care in managing people with long-term neurological conditions. Clin Med, 2007. 7: 129-136.

Van den Block L, Honinx E, Pivodic L et al. Evaluation of a palliative care program for nursing homes in 7 coutries. The PACE cluster-randomised clinical trial. JAMA Intern Med 2019; doi: 10.1001/jamainternmed.2019.5349.

Van der Steen JT, Radbruch L, Hertogh MPM et al White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. Pall Med 2014; 28: 197-209.

Van Vliet LM, Gao W, DiFrancesco D, Crosby V, Wilcock A, Byrne A et al. How integrated are neurology and palliative care services? Results of a multicentre mapping exercise. BMC Neurology 2016; 16:63 DOI: org/10.1186/s12883-016-0583-6

Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, **Oliver DJ**. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342

Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, **Oliver DJ**. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: NePAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.

Vianello A, Concas A. Tracheostomy ventilation in ALS: A Japanese bias. J Neurol Sci 2014; 344: 3-4.

Vishnevetsky A, del Mar CZ, Cam JL, Cornejo-Olivas M, Creutzfeldt CJ. Palliative care: perceptions, experiences and attitudes in a Peruvian neurologic hospital. J Pall Med 2018; doi.org/10.1089/jpm.2018.0196.

Visser C, Hadley G, Wee B. Reality of evidence-based practice in palliative care. Cancer Biol Med 2015; 12: 193-200.

Wallace VCJ, Ellis CM, Burman R et al. The evaluation of pain in amyotrophic lateral sclerosis: A case controlled observational study. ALSFTD 2014; 15: 520-527.

Walshe C. Mixed methods research in palliative care. In MacLeod RD, Van den Block (eds) Textbook of Palliative Care. Switzerland. Springer International 2018. 10.1007/978-3-319-31738-0_109-1

Wiblin L, Lee M, Burn D. Palliative care and its emerging role in Multiple Systems Atrophy and Progressive Supranuclear Palsy. Parkinsonism Relat Disorders 2017; 34: 7-14.

Wilson E, Seymour J, Aubeeluck A. Perspectives of staff providing care at the end of life for people with progressive long-term neurological conditions. Pall Sup Care 2011; 9: 377-385.

Wolfson C, Fereshtehnjad SM, Pasquet R et al. High burden of neurological disease in the older general population: results from the Canadian Longitudinal Study on Aging. Eur J Neurol 2018; 26: 356-362.

World Health Organization. (2002). *Palliative care* www.who.int/cancer/palliative/definition/en/

Zuckerman RB, Stearns SC, Sheingold SH. Hospice use, hospitilaztion, and Medicare spending at the end of life. J Gerontol B Psychol Sci Soc Sci 2016; 71: 569-580.

Appendix 1 – Details of the literature used in this thesis

Text no.	Publication	Responsibility	Approach and methodology	Citations
1	Oliver D J. The quality and care of symptom control - the effects on the terminal phase of ALS/MND. J NeurologSci 139 (suppll): 134-6. 1996	Sole Author	A retrospective survey of patients under the care of the Wisdom Hospice looking at their symptoms, management and the events around their end of life phase and death.	108
2	Neudert C, Oliver D, Wasner M, Borasio GD. (2001) The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol 248: 612-616.	Joint author	A retrospective survey in Rochester and Munich. Patient records were assessed and details collated. I provided all the data from Rochester and was involved in the amalgamation of the data and writing the paper.	230
3	Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, Oliver DJ. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342	Joint author	The initial qualitative study of patients, who were then included within a randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.	14
4	Oliver D. Webb S. The involvement of specialist palliative care in the care of people with motor neurone disease. Palliative Medicine 2000; 14: 47-8	Joint author	A questionnaire study of hospices across the UK, ascertaining their involvement and experience in caring for people with motor neurone disease developments.	33
5	Oliver D. Opioid medication in the palliative care of motor neurone disease Pall Med1998; 12: 113-115	Sole Author	A retrospective survey of the use of opioids at the Wisdom Hospice, for patients with MND.	38
6	Veronese S, Gallo G, Valle A, Cungo C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, Oliver DJ. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.	Joint Author	A randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper	38
7	Oliver D.J., Turner M.R.Some difficult decisions in MND. Amyotrophic Lateral Sclerosis 2010; 11: 339-343		A review paper on decision making in the care of people with MND. I was the main author and wrote the paper, in collaboration with Dr Turner.	59
8	Faull C, Rowe Haynes C, Oliver D. issues for palliative medicine doctors surrounding the withdrawal of non-invasive ventilation at the request of a patient with motor neurone disease: a scoping study. BMJ Supp Pall Care 2014; 4:43-49.	Joint author	A survey of palliative medicine doctors was undertaken using and online survey, of members of the Association for Palliative Medicine. I was involved in data collection, analysis and writing of the paper.	16

9	Phelps K, Regen E, Oliver D, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.	Joint Author	Interviews were undertaken with doctors involved in the withdrawal of NIV. I was involved in the planning of the project, data analysis and writing the paper.	6
10	Faull C, Oliver D. Withdrawal of ventilation at the request of a patient with motor neurone disease: guidance for professionals. BMJ Supp Pall care 2016; 6: 144-146.	Joint author	An editorial for the British Medical Journal Supportive and Palliative care. I co-wrote the piece, based on previous research that I had been involved in.	1
11	Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38	Joint author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper	87
12	Oliver D, Radunovic A, Allen A, McDermott C. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1–11. DOI:10.1080/21678421.2017.1304558	Joint author	A review paper of the NICE Guidance. I wrote the paper, which was commented on by the co-authors.	1

Appendix 2

Supporting statements from co-authors

Dr Alex Allen

Professor Gian Domenico Borasio

Professor Augusto Caraceni

Professor Adriano Chio

Ms Claudia Cugno

Professor Marianne de Visser

Professor Christina Faull

Dr Gloria Gallo

Professor Wolfgang Grisold

Professor Stefan Lorenzl

Professor Christopher McDermott

Dr Kay Phelps

Dr AleksanderRadunovic

Dr Emma Regen

Professor Martin Turner

Dr Alessandro Valle

Dr Simone Veronese

Professor Raymond Voltz

Professor Maria Wasner

It was not possible to contact Dr Sandi Webb

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date: 7th November 2017

Re:

15	Oliver D, Radunovlc A, Allen A, Mcdermott**C.**The development of the UK National Institute of Health and Care Excellence evidence-based cllnlcal guidelines on motor neuronedisease. Amyotrophlc Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1-11. DOI:10.1080/21678421.2D17. **1304558**	Joint author	A review paper of the NICE Guidance. I wrote the paper, which was commented on by the co-authors.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above

Name: Alex Allen

Title/ position: Senior research fellow: National Guideline Centre Address

NationalGuidelineCentre:RoyalCollegeofPhysicians,11StAndrewsPlace,Regent'sPark,London, NW14LE.

Signature

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Lausanne, January 15, 2018

Re:

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.
8	Neudert C, **Oliver D**, Wasner M, Borasio GD. (2001) The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol 248: 612-616.	Joint author	A retrospective survey in Rochester and Munich. Patient records were assessed and details collated. I provided all the data from Rochester and was involved in the amalgamation of the data and writing the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above. Both papers would have not been possible without his input.

Name: Prof. Gian DomenicoBorasio

Title / position: Full professor of palliative medicine

Address: CHUV, University of Lausanne,

CH-1011 Switzerland Signature

To
Professor David Oliver
Tizard Centre
University of Kent
Cornwallis North East
University of Kent
Canterbury
Kent CT2 7NF

Milan, 17/01/2018

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

I confirm that Prof. David Oliver contributed to this paper in a substantial way as outlined above.

Augusto Caraceni MD

Director Palliative Care, Pain Therapy and Rehabilitation
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Venezian 1 , 20133 Milan

Professor of Palliative Medicine
Norwegian University of Science and Technology
Trondheim

Vicepresident European Association for Palliative Care Research Network

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date 7th November 2017

Re:

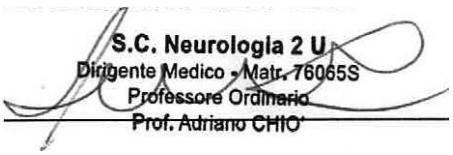
3	Veronese S, Gallo G, Valle A, Cugno C, ChioA, Calvo A, RiveiroC, **Oliver DJ.** The palliative care needs of people severely affected by neurodegenerative disorders: a qualitativestudy. Prag Pall care 2015;6:331-342	Join t author	The initial qualitative study of patients, who were then included within a randomized controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.
4	Veronese S,Gallo G, Valle A, CungoC, Chio A, Calvo A, CavallaP,Zibetti**M,**RiveiroC, **OliverDJ.**Specialistpalliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlledstudy.BMJSupp Pallcare 2017; 7: 164-172.	Joint Author	A randomized controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 16 weeks. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above

Name AdrianoChio

Title/ position Professor of Neurology

Address Turin ALS centre {CRESLA), Department of Neuroscience, University of Turin, Via Chera co 15 10126 Torino, Italy



Signature

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date 7th November 2017

Re:

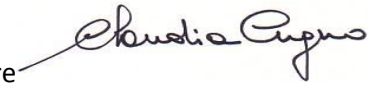
3	Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, **Oliver DJ**. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342	Joint author	The initial qualitative study of patients, who were then included within a randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.
4	Veronese S, Gallo G, Valle A, Cungo C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, **Oliver DJ**. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.	Joint Author	A randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name Claudia Cugno

Title / position Nurse Manager Fondazione F.A.R.O. Onlus Turin

Address Via Morgari21 10125 Turin italy

Signature 

Academisch Medisch Centrum
Universiteit van Amsterdam

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury
United Kingdom

E-mail address: m.devisser@amc.uva.nl

Date November 17, 2017

Re:

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name Marianne de Visser, MD, PhD

Title / position Professor of Neuromuscular Diseases / Neurologist

Address Academic Medical Centre, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

Signature

Meibergdreef 9 Postbus 22660 1100 DD Amsterdam T 020 5669111 F 020 5664440 www.amc.nl

To:
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date 16.1 18

Re:

9	Faull C, Rowe Haynes C, Oliver D. issues for palliative medicine doctors surrounding the withdrawal of non-invasive ventilation at the request of a patient with motor neurone disease: a scoping study. BMJ Supp Pall Care 2014; 4:43-49.	Joint author	A survey of palliative medicine doctors was undertaken using and online survey, of members of the Association for Palliative Medicine. I was involved in data collection, analysis and writing of the paper.
11	Phelps K, Regen E, **Oliver D**, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.	Joint author	Interviews were undertaken with doctors involved in the withdrawal of NIV. I was involved in the planning of the project, data analysis and writing the paper.
12	Faull C, Oliver D. Withdrawal of ventilation at the request of a patient with motor neurone disease: guidance for professionals. BMJ Supp Pall care 2016; 6: 144-146.	Joint author	An editorial for the British Medical Journal Supportive and Palliative care. I co-wrote the piece, based on previous research that I had been involved in.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name Christina Faull

Title / position Consultant in Palliative Medicine

Address LOROS Hospice, Groby Road, Leicester LE3 9QE

Signature 16th January 2018

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date, 6th November 2017

Re:

3	Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, **Oliver DJ**. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342	Joint author	The initial qualitative study of patients, who were then included within a randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.
4	Veronese S, Gallo G, Valle A, Cungo C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, **Oliver DJ**. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.	Joint Author	A randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

If you feel able please feel free to add further details of my individual contribution to this paper below:

Name: Gloria Gallo

Title / position: Palliative physician working at FAROonlus Foundation, Turin, Italy

Address: Via OddinoMorgari 12, 10125 Turin, Italy

Signature: *Gloria Gallo*

To

Professor David Oliver

Tizard Centre

University of Kent

Canterbury

Date: 16/1/2018

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palia2ve care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name : Dr Wolfgang Grisold ; Title / posi2on: MD, Prof., Consultant

Address (Ludwig Boltzmann Ins2tute for Experimental und Clinical Traumatology

Donaueschingenstraße 13

A-1200 Wien above) : Private: Valen2ngasse 19, 1230 Vienna, Austria

Signature: Dr Wolfgang Grisold..

To

Professor David Oliver

Tizard Centre

University of Kent

Canterbury

Salzburg, November 6th, 2017

Re:

5	**Oliver DJ,** Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzi S, Vero- neseS, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease .EurJ Neurol2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative Care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

I hereby confirm that David Oliver contributed to this paper in a substantial way as outlined above. Dr. Oliver has been substantially involved in the paper search and writing of the review. He collected almost all the papers and has compiled the opinions of the co-authors to formulate the research questions. He was the main writer of this paper.

Dr. Stefan Lorenzl, Dipl. Pall. Med. (Univ.

Univ.-P f.

Cardiff)

Paracelsus Medical Uni-
versity Salzburg
Institute of Nursing sci-
ence and - practice
Strubergasse16

A-5020 Salzburg

Tel. +43(0)662 2420 - 80300

email: stefan.lorenzl@pmu.ac.at

The University Of Sheffield.

SITraN
Sheffield Institute for Translational Neuroscience

Department of Neuroscience
Faculty of Medicine, Dentistry & Health

Professor Christopher McDermott PhD FRCP
Professor of Translational Neurology
Sheffield Institute for Translational Neuroscience
University of Sheffield
385aGlossop Road
Sheffield
S10 2HQ

Telephone: +44 (0)114 2222236
Fax: +44 (0)114 2222290
E-mail: c.j.mcdermott@sheffield.ac.uk

Professor David Oliver
Tizard Centre
University of Kent
Canterbury
CT2 7NZ

07 November 2017

Dear Professor Oliver

Re:

11	Phelps K, Regen E, **Oliver D**, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.	Joint author	Interviews were undertaken with doctors involved in the withdrawal of NIV. I was involved in the planning of the project, data analysis and writing the paper.
15	Oliver D, Radunovic A, Allen A, McDermott C. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1–11. DOI:10.1080/21678421.2017.1304558	Joint author	A review paper of the NICE Guidance. I wrote the paper, which was commented on by the co-authors.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Yours sincerely

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date: 09.11.17

Re:

11	Phelps K, Regen E, **Oliver D**, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.	Joint author	Interviews were undertaken with doctors involved in the withdrawal of NIV. I was involved in the planning of the project, data analysis and writing the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above, and do not believe that the paper would have been completed for publication without his contribution.

Name: Kay Phelps

Title / position: Research Fellow

Address: Department of Health Sciences, College of Life Sciences*
University of Leicester, Centre for Medicine, University Road, Leicester, LE1 7RH, UK

Signature: 

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

16th January 2018

Re:

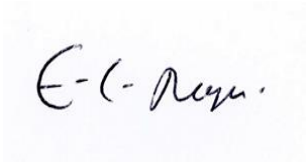
11	Phelps K, Regen E, **Oliver D**, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supp Pall Care 2015; doi: 10.1136/bmjspcare-2014-000826.	Joint author	Interviews were undertaken with doctors involved in the withdrawal of NIV. I was involved in the planning of the project, data analysis and writing the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name: Emma Regen

Title / position: Research Fellow

Address: College of Life Sciences,University of Leicester, George Davies Centre, University Road, Leicester LE1 7RH, UK



Emma Regen

Barts Health NHS
NHS Trust

Dr Aleksandar Radunovic PhD FRCP
MND CLINIC
Neurosciences CAU
The Royal London Hospital
2nd Floor, North Tower
Whitechapel
London E1 1BB

Gitana Zvikaite, MND Coordinator
Ext 41883
Mobile: 07825 935187
Gitana.Zvikaite@bartshealth.nhs.uk
MNDClinic@barts@bartshealth.nhs.uk

Main switchboard: 020 7377 7000
www.bartshealth.nhs.uk

Professor David Oliver
Tizard Centre
University of Kent
Canterbury

6 November 2017

To whom it may concern

Re:

15	Oliver D, Radunovic A, Allen A, Mcdermott C. The development of the UK National Institute of Health and Care Excellence evidence-based clinical guidelines on motor neurone disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 1–11. DOI:10.1080/21678421.2017.1304558	Joint author	A review paper of the NICE Guidance. I wrote the paper, which was commented on by the co-authors.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Yours Sincerely

Dr Aleksandar Radunovic
Consultant Neurologist and Director of Barts MND Centre

NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES

UNIVERSITY OF
OXFORD

Martin R. Turner MA (Cantab.) MBBS PhD FRCP (Lond.)
Professor of Clinical Neurology & Neuroscience
West Wing, Level 6
John Radcliffe Hospital, Oxford, OX3 9DU
Tel: +44(0)1865 223380 (Academic PA), (0)1865 231893 (NHS secretary)
martin.turner@ndcn.ox.ac.uk

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date: 6th November 2017

14	Oliver D.J., Turner M.R. Some difficult decisions in MND. Amyotrophic Lateral Sclerosis 2010; 11: 339-343.		A review paper on decision making in the care of people with MND. I was the main author and wrote the paper, in collaboration with Dr Turner.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

After our initial discussions around the concepts, David drafted the manuscript to which I then contributed. He provided overall editorship of the final version.

M. R. Turner

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Date 06/11/2017

Re:

3	Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, **Oliver DJ**. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342	Joint author	The initial qualitative study of patients, who were then included within a randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.
4	Veronese S, Gallo G, Valle A, Cungo C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, **Oliver DJ**. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.	Joint Author	A randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the design, continued trial and writing of the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

If you feel able please feel free to add further details of my individual contribution to this paper below:

Name ALESSANDRO VALLE

Title / position MEDICAL DIRECTOR
FONDAZIONE FARO

Address V. MORGARI 12 - 10125 TORINO (ITALIA)

Signature

Dr. Alessandro Valle
Responsabile Sanitario
Fondazione F.A.R.O. Onlus

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury
Date 5th November 2017

3	Veronese S, Gallo G, Valle A, Cugno C, Chio A, Calvo A, Rivoiro C, **Oliver DJ**. The palliative care needs of people severely affected by neurodegenerative disorders: a qualitative study. Prog Pall care 2015; 6:331-342	Joint author	The initial qualitative assessment of palliative care unmet needs of patients, who were then included within a randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the conceptual framework, study design, data analysis continued trial and writing of the paper.
4	Veronese S, Gallo G, Valle A, Cungo C, Chio A, Calvo A, Cavalla P, Zibetti M, Rivoiro C, **Oliver DJ**. Specialist palliative care improves the quality of life in advanced neurodegenerative disorders: Ne-PAL, a pilot randomized controlled study. BMJ Supp Pall Care 2017; 7: 164-172.	Joint Author	A randomised controlled trial of palliative care for people with neurological disease, using a waiting list approach, where one group receive the care initially and are compared to a group receiving care after 6 months. This was part of a PhD thesis, which I was sole supervisor for and closely involved in the conceptual framework, study design, data analysis continued trial and writing of the paper.

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

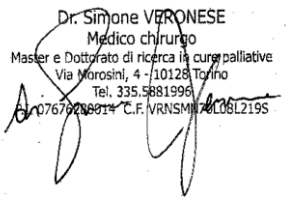
I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Name: Simone Veronese

Title / position: MD, PhD. Head of Research, Faro Foundation

Address: via Morgari 12, 10125 Turin, Italy

Signature:



UNIKLINIK KÖLN | Zentrum für Palliativmedizin

Direktor:
Univ.-Prof. Dr. Raymond Voltz

Oberärzte:
OÄ PD Dr. Heidrun Golla
OA Dr. Klaus Maria Perrar
OA PD Dr. Steffen Simon

Pflegeteamleitung:
Johannes-Christoph König

Uniklinik Köln | Zentrum für Palliativmedizin |
Im Dr. Mildred Scheel Haus · Kerpener Straße 62 · 50924 Köln

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

Köln, 8th November 2017

Deutschlands
erste Palliativstation
Gegründet 1983

Re:

5	**Oliver DJ**, Borasio GD, Caraceni A, de Visser M, Grisold W, Lorenzl S, Veronese S, Voltz R. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol 2016;23: 30-38.	Joint Author	A systematic literature review of neurological palliative care undertaken by a taskforce of the European Association for Palliative Care and the European Academy of Neurology. I was chair of the taskforce and one of the two authors involved in the review and main contributor to the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.
With the best wishes.

Prof. Dr. med. R. Voltz
Director
Department of Palliative Medicine

Kerpener Straße 62 · 50937 Köln
Im Dr. Mildred Scheel Haus
Telefon: +49 221 478-3361
Telefax: +49 221 478-89300
info-palliativzentrum@uk-koeln.de
http://palliativzentrum.uk-koeln.de

Klinikum der Universität zu Köln (AöR)
Vorstandsvorsitzender: Prof. Dr. Edgar Schömig
Bank für Sozialwirtschaft Köln · BLZ: 370 205 00 · Konto: 815 0000
IBAN: DE04 3702 0500 0008 1500 00 · BIC: BFSWDE33XXX
Steuernummer: 223/5911/1092 · Ust-IdNr.: DE 215 420 431
ÖPNV: Linie 9: Lindenburg, Linie 13: Gleueler Str./Gürtel, Linie 146: Leiblplatz

Spendenkonto:
Bank für Sozialwirtschaft Köln
Konto 815 00 00
BLZ 370 205 00
Verwendungszweck:
Palliativzentrum

To
Professor David Oliver
Tizard Centre
University of Kent
Canterbury

14 Nov 2017

Re:

8	Neudert C, **Oliver D**, Wasner M, Borasio GD. (2001) The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol248: 612-616.	Joint author	A retrospective survey in Rochester and Munich. Patient records were assessed and details collated. I provided all the data from Rochester and I was involved in the amalgamation of the data and writing the paper.

I confirm that David Oliver contributed to this paper in a substantial way as outlined above.

Prof.Dr. Maria Wasner
Professor for social work in palliative care
University of Applied Sciences
Preysingstr. 83
81667 Munich
Germany

Appendix 3

Literature used – Texts 1- 12

Available on Kent Academic Repository