THE UNIVERSITY *of* EDINBURGH

Evaluating Participant-Centred Outcomes in Clinical Trials for Motor Neuron Disease

Emily Beswick
S1313329

THE UNIVERSITY *of* EDINBURGH

Doctor of Philosophy

2022

Declarations

This thesis has been submitted in fulfilment of the requirements for a postgraduate degree (e.g. PhD, MPhil, and DClinPsychol) at the University of Edinburgh. Please note the following terms and conditions of use:

Supervisory Team

Lead Supervisor:

Dr Suvankar Pal

Consultant Neurologist & Clinical Senior Lecturer in Neurology

Euan Macdonald Centre for Motor Neuron Disease Research

Centre for Clinical Brain Sciences

Anne Rowling Regenerative Neurology Clinic

University of Edinburgh

Secondary Supervisors:

Professor Sharon Abrahams

Human Cognitive Neuroscience & Psychology, School of Philosophy Psychology & Language Science

Euan Macdonald Centre for Motor Neuron Disease Research

University of Edinburgh

Professor Alan Carson

Consultant Psychiatrist & Honorary Professor of Neuropsychiatry

Centre for Clinical Brain Sciences

Anne Rowling Regenerative Neurology Clinic

University of Edinburgh

Independent Thesis Mentor:

Professor Robert McIntosh

Human Cognitive Neuroscience & Psychology, School of Philosophy Psychology & Language Science

University of Edinburgh

Acknowledgements

Thank you to the participants, and their loved ones, who provided feedback on the studies, completed questionnaires and came to study visits. I am truly grateful for your time.

Thank you to the Euan MacDonald Centre for funding this work, and to the team at the Anne Rowling Regenerative Neurology Clinic for your support.

Thank you to my supervisors, and independent mentor, for their endless patience, feedback and help for the last three years.

Thank you to my supportive family and long-suffering friends; particularly to Sarah, Niall, Indy and Cali for being there every step of the way.

Grandma and Grandad, this is for you, thank you for everything.

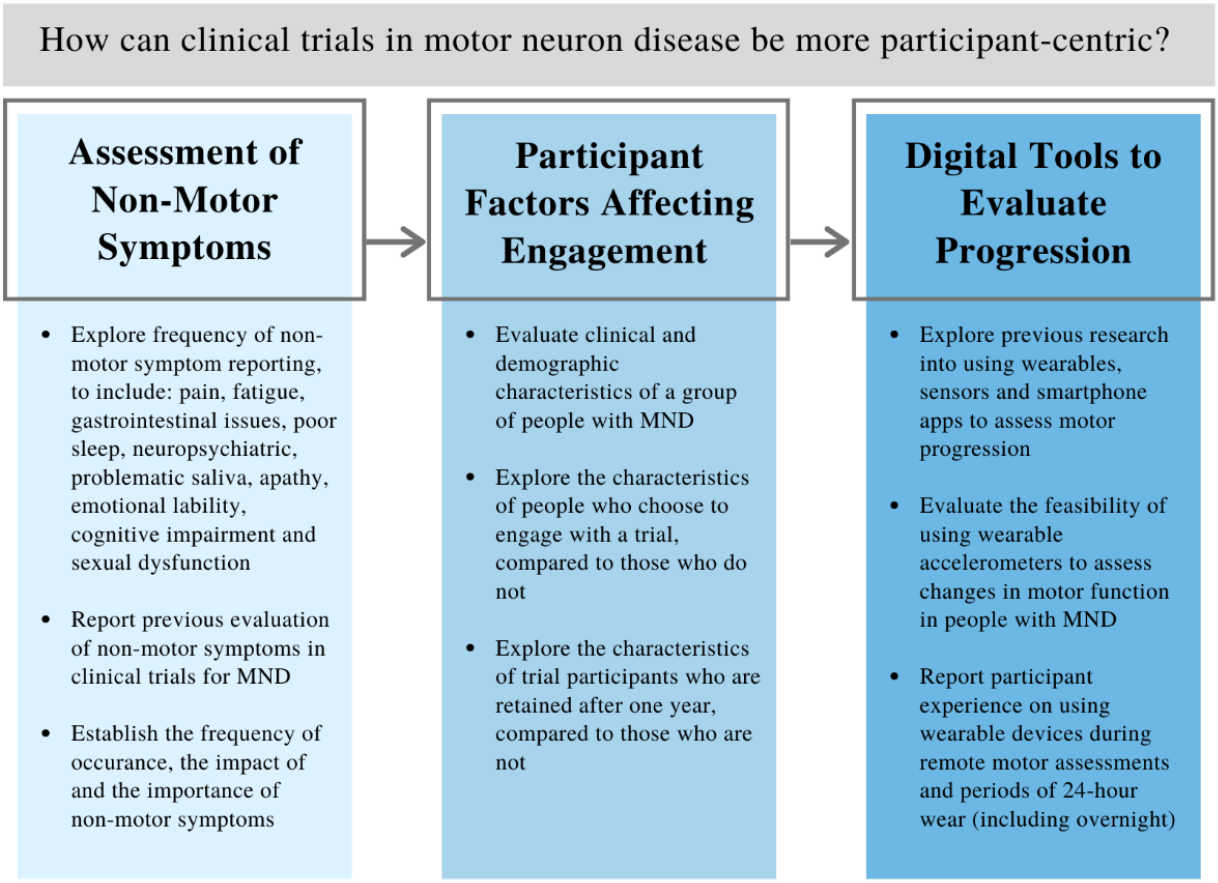
Aims

Overall, this PhD thesis aimed to evaluate holistic assessments that may be of utility in contemporary trials of motor neuron disease (MND), including non-motor outcome measures and digital assessment tools, and explore person-specific reasons that determine participation in an innovative new clinical trial for MND.

In addition this thesis aims to:

1. Establish the frequency of neuropsychiatric, cognitive and behavioural assessments in historical clinical trials in MND, using rigorous unbiased systematic review methodology.
2. Establish the frequency of a broader range of non-motor outcome measures in historical MND trials, using a second rigorous unbiased systematic review.
3. Explore how frequent, severe and impactful non-motor symptoms are to people living with MND.
4. Explore if people with MND support including non-motor symptoms in trial design, how frequently they are assessed in clinical care, and their preferences on assessment method.
5. Evaluate differences in person-specific characteristics, in a cohort of people with MND in Scotland who opt to participate in an innovative new UK multi-site clinical trial for MND, compared with those who do not participate.
6. Evaluate differences in person-specific characteristics, in a cohort of people with MND in Scotland who participate in a clinical trial and remain as participants, compared to characteristics of those who withdrew.
7. Establish the number of studies using digital technologies to evaluate motor function in people with MND and the type of devices used, with a rigorous unbiased systematic literature review.
8. Explore the acceptability of a wrist and ankle-worn accelerometer to a group of people with MND during sleep, 24-hour wear and during motor tasks via videoconferencing.

Figure 1: Overview of Thesis Aims



Thesis Abstract

Background: Motor neuron disease (MND), often referred to by its most common subtype amyotrophic lateral sclerosis (ALS) is a devastating and rapidly progressive neurodegenerative disorder for which there is no cure. Average life expectancy from onset is 30 - 36 months and the majority of individuals experience disabling limb weakness and bulbar symptoms, ultimately succumbing to respiratory failure.

Established in 1989, the Scottish Motor Neuron Disease Register is the first population-based register for MND in the world. In 2015 the register was re-launched as an electronic platform, Clinical Audit Research and Evaluation of MND (CARE-MND) and records all cases of MND in Scotland. This register will be used to support recruitment, and provide additional clinical data for the studies in this thesis.

Despite more than 75 trials being completed in the past decade, only one disease modifying treatment with limited efficacy is licensed in the United Kingdom. However, the trials landscape in MND is rapidly changing. Multi-arm, multi-stage adaptive trials such as MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) encapsulate this new direction. Many of the issues associated with the failure of previous trials are addressed by MND-SMART; a definitive statistical design with large numbers of participants and long duration follow up assessing functioning (ALS-FRS(R) and survival as co-primary outcome measures, an ability to discontinue ineffective drugs at interim analysis points due to futility, an ability to seamlessly add new treatment arms, wide inclusion criteria, remote assessment, liquid medications and a lower chance of being assigned to the placebo arm. With many barriers to participation already acknowledged we have a unique opportunity to prospectively explore the characteristics of individuals who self-select to participate in a trial.

It is also widely understood and accepted that MND does not exclusively affect the motor system, and that non-motor symptoms occur secondary from, or in addition to motor degeneration are part of the disease. These symptoms also require new treatments and should be addressed when evaluating candidate drugs' therapeutic mechanisms. Progression of functionally impairing MND symptoms has been traditionally evaluated, in clinical care and as a primary outcome of trials, using the ALSFRS(R) (ALS Functional Rating Scale Revised), a questionnaire-based assessment, usually administered face to face in clinic, but which has limited sensitivity to detect smaller changes in functional ability. Technology-based outcome measures are increasingly being evaluated across various neurological disorders as an alternative, sensitive and objective assessment of progression, and may offer new directions in MND research.

Aims: To evaluate holistic assessments that may be of utility in contemporary motor neuron disease (MND) trials, including non-motor outcome measures and digital assessment tools, and explore person-specific determinates of participation in an innovative new clinical trial for MND.

Objectives: Through a series of systematic reviews we evaluated the previous use of non-motor outcome measures in MND trials, and an experimental study using a participant-completed questionnaire to provide a participant perspective on the occurrence and importance of these symptoms. To explore person-specific reasons for participation in clinical trials, a second experimental study was conducted involving participant and caregiver questionnaires and clinical data, the responses from which were then evaluated against trial participation data. A final systematic review provided background on the previous use of digital devices to evaluate motor progression in MND, which informed a final experimental study evaluating the acceptability of wearable accelerometers to a group of people with MND.

Hypotheses:

1. Non-motor symptoms have been historically under evaluated in MND trials, but people with MND report them as frequent and consider these symptoms as important to include in future trial design.
2. Person-specific factors, such as neuropsychiatric symptoms, cognitive impairment, demographics, phenotype, quality of life, apathy and physical functioning, are associated with an individual with MND's deciding to engage or not with a clinical trial.
3. The use of technology to evaluate motor progression in MND is in the early stages of development and validation, but new studies are emerging as technology becomes more common in health research.
4. People with MND will find using technology to monitor motor decline an acceptable method of data collection, with wearable sensors offering a feasible alternative to traditional questionnaire-based approach.

Methods: In order to answer the above research questions, the thesis is structured as follows:

1) Systematic Review 1: A rigorous unbiased systematic literature review to establish the frequency of neuropsychiatric, cognitive and behavioural assessments in the last 25 years of MND trials.
2) Systematic Review 2: A rigorous unbiased systematic literature review considering a broader range of non-motor symptoms.
3) Experimental Study 1: A questionnaire-based study evaluating non-motor symptoms and investigating the frequency, severity, impact, and importance of these symptoms to people with MND for inclusion in trials.

4) Experimental Study 2: A standardised questionnaire-based study with associated relevant clinical data to evaluate the characteristics of a cohort of people with MND, followed up at least a year later to establish participation and retention in MND-SMART, an innovative new UK wide clinical trial of MND.
5) Systematic Review 3: A rigorous unbiased systematic review of digital technologies used to evaluate motor progression in MND. The results of this review were used to inform the design of the final study of this PhD thesis:
6) Experimental Study 3: A study to evaluate the acceptability of a wearable accelerometer in remote longitudinal videoconferencing based motor assessments, including 24-hour wear periods, in a cohort of people with MND.

Results: Neuropsychiatric, cognitive, behavioural and other non-motor symptoms have been under evaluated in the last 25 years of MND trial design. In experimental study 1, all but one of the 120 participants experienced at least one non-motor symptom, with pain and fatigue most frequently identified (76%). 80% of participants considered non-motor symptoms to be important to include in trial design, independent of the number of symptoms that they reported themselves. Results from experimental study 2, identified that older age and the presence of apathy were associated with lower likelihood of trial participation and retention. Despite this, the cohort were overall highly motivated to engage with MND-SMART, with 50% of participants being randomised to the trial by the one-year data collection time-point. Systematic review 3 identified 20 studies, involving 1,275 people with MND which used 26 types of digital technologies. All studies showed initial feasibility, but well-powered longitudinal studies were needed. Only 25% of studies in this review evaluated the acceptability of these devices to people with MND. In experimental study 3, 10 participants completed the full 12-week protocol of motor tasks and 24-hour wear periods, with wear-time increasing as the study progressed. 80% found wearing the devices to be a positive experience, and although 30% experienced technical issues all participants remained excited about the potential benefits of using technology to assess MND.

Conclusions: Findings in this thesis should be used to inform the design of future trials; particularly recruitment and retention strategies. Engaging older prospective participants, supporting participants with apathy-related behavioural change and continued exploration of support for people with MND to become involved in a clinical trials if they wish to do so, are essential directions for future research in this area. To deliver participant-centred clinical trials in MND it is important to expand the concept of impairment, and treatment, to include non-motor symptoms. Previous trials have not adequately explored the potential secondary benefits or side effects of investigative medicinal products on the

broad range of symptoms that can affect people with MND. Non-motor symptoms are present, frequent and impactful to people with MND, who are supportive of evaluating the holistic impact of candidate drugs in clinical trials.

Results from this thesis confirm that the way in which trial outcomes are measured is changing. Technologies to monitor health, track progression and evaluate motor symptoms offer promising new directions for MND research. These devices are often more sensitive than traditional questionnaire-based assessments, and their capacity to detect smaller changes in function may mean that they are better suited to evaluate trial outcomes. Further, larger well-powered studies are needed to establish the responsiveness and suitability of different devices, but participants found wrist and ankle worn accelerometers to be an acceptable method to measure motor symptoms remotely over 24-hour wear periods.

Publications derived from this thesis to date

Beswick, Emily, Emily Park, Charis Wong, Arpan R. Mehta, Rachel Dakin, Siddharthan Chandran, Judith Newton, Alan Carson, Sharon Abrahams, and Suvankar Pal. "**A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis."** *Journal of Neurology* 268, no. 12 (2021): 4510-4521.

Beswick, Emily, Deborah Forbes, Zack Hassan, Charis Wong, Judith Newton, Alan Carson, Sharon Abrahams, Siddharthan Chandran, and Suvankar Pal. "**A systematic review of non-motor symptom evaluation in clinical trials for amyotrophic lateral sclerosis**." *Journal of Neurology* (2021): 1-16.

Beswick, Emily, Stella A. Glasmacher, Rachel Dakin, Judith Newton, Alan Carson, Sharon Abrahams, Siddharthan Chandran, and Suvankar Pal. "**Protocol: Prospective observational cohort study of factors influencing trial participation in people with motor neuron disease (FIT-Participation-MND)**" *BMJ Open* 11, no. 3 (2021).

Beswick, Emily, Thomas Fawcett, Zack Hassan, Deborah Forbes, Rachel Dakin, Judith Newton, Sharon Abrahams et al. "**A systematic review of digital technology to evaluate motor function and disease progression in motor neuron disease**." *Journal of Neurology* (2022): 1-15.

Co-author:

Wong, Charis, Maria Stavrou, Elizabeth Elliott, Jenna M. Gregory, Nigel Leigh, Ashwin A. Pinto, Timothy L. Williams et al. "**Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective.**" *Brain communications* 3, no. 4 (2021): fcab242.

Pearson, Iona, Stella A. Glasmacher, Judith Newton, Emily Beswick, Arpan R. Mehta, Richard Davenport, Siddharthan Chandran, and Suvankar Pal. "**The prevalence and management of saliva problems in motor neuron disease: a 4-Year analysis of the Scottish motor neuron disease register.**" *Neurodegenerative Diseases* 20, no. 4 (2020): 147-152.

Presentations derived from this thesis to date

A Systematic Review of Neuropsychiatric and Cognitive Assessments in Clinical Trials of MND

- **Poster:** European Network to Cure ALS, *May 2021*
- **Poster:** Brain Meeting, *March 2021*
- **Poster:** Motor Neuron Disease Association International Symposium, *December 2020*
- ***Poster prize:** Annual Scientific Meeting of NHS Scotland Mental Health Researchers, *November 2020*
- **Poster:** Federation of European Neuroscience Virtual Forum, *July 2020*

A Systematic Review of Non-Motor Symptom Evaluation in Clinical Trials for MND

- **Poster:** Motor Neuron Disease Association International Symposium, *December 2021*
- **Poster:** European Network to Cure ALS, *May 2021*
- **Poster:** British Neuropsychology Meeting, *April 2021*
- **Poster:** Brain Meeting, *March 2021*
- **Poster:** British Neuropsychiatry Association, *March 2021*
- **Poster:** Federation of European Neuroscience Virtual Forum, *July 2020*
- **Poster:** Motor Neuron Disease Association International Symposium, *December 2020*

Holistic Assessment of Non-Motor Symptoms for People with MND (NMS-MND)

- **Poster:** European Network to Cure ALS, *June 2022*
- **Poster:** Neuroprogressive Network Meeting, *December 2021*
- **Oral:** MND-SMART Trial Investigators Meeting, *November 2021*
- **Oral:** European Academy of Neuroscience, *June 2021*

Factors Impacting Trial Participation in People with MND (FIT-P-MND)

- **Poster:** European Network to Cure ALS, *June 2022*
- **Poster:** Neuroprogressive Network Meeting, *December 2021*
- **Poster:** Motor Neuron Disease Association International Symposium, *December 2021*
- **Oral:** MND-SMART Trial Investigators Meeting, *November 2021*
- **Oral:** Euan Macdonald Centre Postgraduate Afternoon, *June 2021*
- **Poster:** Neuroscience Day Centre for Clinical Brain Sciences, *September 2021*
- **Oral & Poster:** British Neuroscience Association, *April 2021*
- **Poster:** British Neuropsychology Meeting, *April 2021*

A Systematic Review of Digital Technology to Evaluate Motor Function and Disease Progression in MND

- **Poster:** European Network to Cure ALS, *June 2022*
- **Poster:** Neuroprogressive Network Meeting, *December 2021*
- **Poster:** Neuroscience Day Centre for Clinical Brain Sciences, *September 2021*

Suitability and Acceptability of Wearable Sensors to Evaluate Disease Progression in People with MND

- **Oral:** European Network to Cure ALS Euan McDonald Supporters Satellite, *June 2022*
- **Poster:** European Network to Cure ALS, *June 2022*
- **Oral:** MND-SMART Trial Investigators Meeting, *November 2021*

Abbreviations

6MWT	Six Minute Walking Test
ACCORD	Academic and Clinical Central Office for Research and Development
ACE	Addenbrooke's Cognitive Examination
ACT-Q	Attitudes Towards Clinical Trial Participation Questionnaire
ADI-12	Amyotrophic Lateral Sclerosis Depression Inventory
ALS	Amyotrophic Lateral Sclerosis
ALSAQ	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALSFRS(R)	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
ALS-CBS	Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen
ALSSQOL-20	Amyotrophic Lateral Sclerosis Quality of Life 20-Item Questionnaire
ARRNC	Anne Rowling Regenerative Neurology Clinic
b-DAS	Brief Dimensional Apathy Questionnaire
BDI	Beck's Depression Inventory
C9ORF72	Chromosome 9 Open Reading Frame
CARE-MND	Clinical Audit Research and Evaluation for Motor Neuron Disease
C-SSRS	Columbia Suicide Severity Rating Scale
CDC-HQOL-4	Centre for Disease Control and Prevention Health-Related Quality of Life
COVID-19	Coronavirus Disease
CTIMP	Clinical Trial of an Investigational Medicinal Product
CNS-BFS	Centre for Neurologic Studies Bulbar Function Scale
CNS-LS	Centre for Neurologic- Lability Scale
DSM	Diagnostic Statistical Manual
KFSS	Krupp Fatigue Severity Scale
ECAS	Edinburgh Cognitive and Behavioural Assessment Screen
EMA	European Medicines Agency
EduraCT	European Union Clinical Trials Register
EQ-5D-5L	EuroQol 5 Domain Assessment
ESAS	Edmonton Symptom Assessment System
FDA	Food and Drug Association
FTD	Frontotemporal Dementia
FBI	Frontal Behavioural inventory
FIT-P-MND	Factors Impacting Trial Participation in MND
GI	Gastro-Intestinal Feeding Tube
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Depression Scale
ICTRP	International Clinical Trials Registry Platform
IMP	Investigative Medicinal Products
IMU	Inertial Measurement Unit
MET	Metabolic Equivalent Task
MoCA	Montreal Cognitive Assessment

MMSE	Mini Mental State Examination
MND	Motor Neuron Disease
MND-CBS	Motor Neuron Disease Cognitive Behavioural Screen
MND-FRS	Motor Neuron Disease Functional Rating Scale
MND-SMART	Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial
MS	Multiple Sclerosis
ND	No data
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIV	Non-Invasive Ventilation
NMS	Non-Motor Symptoms
NPI	Neuropsychiatric Inventory
NS	Norris Scale
ONRI	Ontario Neurodegenerative Research Initiative
PBP	Progressive Bulbar Palsy
PD	Parkinson's Disease
PHQ-9	Patient-Health Questionnaire 9-Item
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSQI	Pittsburgh Sleep Quality Index
QOL	Quality of Life
REC	Research Ethics Committee
SEIQoL	Schedule for the Evaluation of Individual Quality of Life Questionnaire
SFQ	Short Form Patient Questionnaire
SIP	Sickness Impact Profile
SOD1	Superoxide Dismutase
STAI-Y	State-Trait Anxiety Inventory
SSRI	Selective Serotonin Reuptake Inhibitor
SD	Standard Deviation
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation
WAIS	Wechsler Adult Intelligence Scale

Tables and Figures

Contents

1 Chapter 1: Introduction

1.1 Lay Summary of Background

Motor neuron disease (MND) is a group of diseases that affect the nerves (neurons) which control muscles; eventually causing these neurons to stop working and die. It is often referred to as 'amyotrophic lateral sclerosis', the most common type. Over half of people with MND will die within two years of diagnosis. There is currently no cure. The only licensed drug for MND, riluzole, has a limited impact on the condition.

Established in 1989, the Scottish Motor Neuron Disease Register was the first population-based register for MND in the world. In 2015 the register was re-launched as an electronic platform Clinical Audit Research and Evaluation of MND (CARE-MND). This register records all cases of motor neuron disease in Scotland. 180-220 people are diagnosed and registered every year, with approximately 450 people living with MND in Scotland at any point in time. Clinical teams contribute data to CARE-MND and information gathered can be used to improve care and to help understand more about how MND affects people. CARE-MND is also used as a research interest registry; people with MND who are interested in participating in research can be contacted about upcoming projects which they might be eligible for. The projects within this thesis have used CARE-MND to recruit participants and to obtain additional clinical data, reducing the number of questionnaires participants are required to complete.

MND-SMART (Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial) was launched in the United Kingdom in January 2020 and aims to address the limited treatment options currently available. Multi-arm means that, unlike typical clinical trials which test a single treatment, MND-SMART is testing more than one drug at the same time. Trial participants taking the different treatments will be compared with a single group who receive a dummy drug, called a placebo. This means that people in MND-SMART are more likely to receive active treatment when compared to standard clinical trials where typically half of participants receive the placebo and half the active treatment. The trial is also adaptive so that researchers can change the drugs being tested according to emerging results, stopping ineffective treatments, and introducing new drugs. This is a phase 3 trial which means if drugs is shown to be effective, approvals can be sought for prescribing to the wider community without the need for additional trials to confirm the result. The trial will initially test medicines that are already approved as treatments for other diseases, so-called drug repurposing. This also means there is a reduced risk of negative effects in trial participants. Repurposing drugs in this way also avoids some of the lengthy approval process needed for new drugs and could cut years off the time taken for the medications to become more widely available. MND-SMART is a long-term study that will test medications for many years to come.

1.2 Motor Neuron Disease

Motor neuron disease (MND) is a progressive, degenerative condition characterised by loss of motor function. There are a number of subtypes of MND, the most common of which, accounting for 80-90% of which is amyotrophic lateral sclerosis (ALS) [1]. Other subtypes include progressive muscular atrophy (PMA) (%), primary lateral sclerosis (PLS) (%) and progressive bulbar palsy (PBP) %) [2].

MND is a heterogeneous condition with significant variation in age of onset, site of onset, disease trajectory, prognosis, and disease duration. Diagnosis of subtypes varies depending upon the clinical features, onset of symptoms, pattern of deterioration, and investigation results. In MND, the motor neurons that facilitate voluntary movement degenerate, resulting in muscle atrophy and difficulty with motor and respiratory function [3]. Respiratory failure, due to degeneration of muscles of the respiratory system, is the primary cause of death for people with MND [4]. Only 51.3% of people with MND survive more than 12 months after their diagnosis [5].

Understanding of the physical, psychological and social impact of MND continues to develop. Ongoing research into how MND develops and progresses is essential in providing effective care and potential treatment options for those currently affected, and for people who may be affected by MND in the future.

1.2.1 Onset of MND

The prevalence of MND is approximately 5,000 in the UK, with approximately 420 of these individuals resident in Scotland [5]. Based on prevalence data MND is often described as a 'rare' condition. However, considering diagnosis and incidence data, MND is not rare. Approximately 1,321 new cases of MND are diagnoses each year in the UK [6], with a lifetime risk of 1 in 472 (2.1 per 1000) in women and 1 in 350 (2.9 per 1000) in men [7]. In Scotland specifically, the incidence of MND was 3.83/100,000 person-years (95% CI 3.53-4.14) [5].

The male preponderance observed is accounted for by the earlier age onset group, after the age of 70 MND occurs in a ratio of 1:1 for males and females [2]. Mean age of onset is 65.3 years [5]. The median survival time from onset to death ranges from 20 to 48 months with 10–20% of individuals surviving over ten years [3]. People with MND who are older at the time of diagnosis, and those who have the bulbar subtype of MND, are consistently reported to have a worse prognosis [3].

1.2.2 Genetic Associations of MND

5-10% of people with MND have a first degree relative who also has a diagnosis of MND, these cases are considered 'familial' [2]. Familial cases of MND are clinically indistinguishable from 'sporadic', cases without an affected family member, but do tend to have a median age of onset approximately 10 years earlier. All subtypes of MND can be familial or sporadic, and the significant overlap between clinical presentation regardless of heritability, may offer interesting avenues to explore the pathophysiology of motor neuron diseases [1]. Many genes have been causally linked to MND presentation. The genes which account for the majority of genetic cases are C9ORF72 (chromosome 9 open reading frame) and SOD1 (superoxide dismutase) [8]. The C9ORF72 expansion is present in 11% of people with MND, and the SOD1 variant in 4% of MND cases [5]. The same mutations can be found in both apparently sporadic and familial cases, and these mutations are frequently associated with similar phenotypic presentations and disease trajectories. However, presence or absence of genetic mutations alone does not explain the variation in MND occurrence and impact.

1.2.3 Scottish MND Register (CARE-MND)

Established in 1989, the Scottish MND Register was the first population-based register for MND in the world [9]. The register was developed to collate data on the clinical and epidemiological features of MND. In 2015 the register was re-launched as Clinical Audit Research and Evaluation of MND (CARE-MND), after a formal review of the register indicated a need for a synchronised and standardised approach to care for people with MND across Scotland (REC number: 15/SS/0216).

The introduction of this electronic platform has facilitated access to research for people with MND and continuity of harmonised uniform clinical data collection in the Scottish population [10]. The CARE-MND platform is designed to integrate clinical care, audit, research and evaluation to monitor and facilitate care consistency for all people living MND in Scotland, across the multidisciplinary team. The platform has achieved 99% case ascertainment in Scotland [10] with detailed clinical annotation including site and age of onset, disease duration, presence of cognitive symptoms, and El Escorial classification. Approximately 400 people are living with a diagnosis of MND in the Scottish population at any point in time, with almost 70% of these people providing consent to the use of their routinely collected clinical data for research purposes.

The projects within this thesis have used CARE-MND to recruit participants and to derive additional clinical data (through a standardised and peer reviewed application for clinical data), reducing the burden of participation on the people with MND who supported the projects.

1.2.4 Evaluating Progression in MND

Accurate measurement of MND progression is a significant challenge in both clinical care and research design. The current gold standard for evaluating physical symptom severity and disease progression is the ALSFRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale Revised), a questionnaire based assessment, evaluating the presence and resulting disability of physical symptoms commonly affecting people with MND.

However, the ALSFRS(R) is reliant on clinical judgement, subjective reporting and people with MND's recollection of symptoms [11]. An ideal tool must be sensitive enough to detect small changes in a person's function as the disease progresses and particularly useful as a clinical trial outcome measure evaluation change. Tools such as the ALSFRS(R) derive composite scores that may not be sufficient to detect smaller changes in function and therefore necessitate large trial sample sizes and frequent assessments points, potentially increasing the burden of engagement on participants [12].

1.2.5 Therapeutic Options in MND

There is an urgent need for new therapies in MND. Only one disease modifying therapy, riluzole, has been approved for treatment in the UK, with limited impact on median survival [2]. Riluzole was licensed for use in people with MND following modest, but statistically significant prolongation of tracheostomy survival in a 1994 trial [13], and a second, larger multinational follow-up trial in 1996 [14]. Edaravone is now licensed for use in MND in the United States of America (USA) and Japan, following a 2017 randomised controlled clinical trial in a small, highly-stratified, sample [15]. Another drug Masitinib is currently under investigation in the USA for use in MND [16], but neither medication is globally licensed as a disease modifying therapy in MND. Recently, after initially promising results from the CENTAUR trial, AMX0035 (also known as Albrioza or Relyviro) was approved by the Federal Drug Association for people with MND in the USA [17], with later phase trials in the USA and Europe ongoing (NCT05021536). In addition, the antisense oligonucleotide tofersen offered biomarker results to support a reduction in the synthesis of the superoxide dismutase 1 (SOD1) protein [18]. SOD1 protein mutations are associated with a familial form of MND [19]. Results did not meet the pre-specified primary clinical endpoints in the initial study although changes in motor and respiratory function were reported in individuals receiving longer-term treatment. The results of open label extension data are pending.

The heterogeneity of MND provides a significant challenge for the development and exploration of suitable drug therapies. Stratification of participants by disease phenotype, genotype, or both, may lead to limited generalisability of findings. Alternatively, participant samples that do not account for the variation in subtype, presentation and pathology of MND may miss the potential effectiveness of candidate treatments for some people affected by this condition.

1.3 Clinical Trial Delivery

1.3.1 Historical Failures in MND Trials

A recent systematic review identified 125 historical trials, registered between 2008 and 2019, involving 15,647 people with MND, and evaluating 76 investigative medicinal products (IMPs) [20]. Despite a substantial increase in the number of trials for people with MND registered, completed and reported in the last decade, progress towards developing new treatments has been painfully slow [21]. Since its licensing in 1994, riluzole remains the only globally licensed disease modifying treatment, with limited efficacy [22].

It is estimated that fewer than 5% of people with MND in the UK, and 8% in the USA, have participated in a clinical trial, representing just 2.5% of the available population [20]. MND provides a series of disease-specific challenges to investigators that must be addressed in trial design to provide equitable access to prospective participants. Some of these challenges, and the impact that they can have on MND trials, are explored in Table 1.

Table 1: Challenges to MND Trial Recruitment and Retention

Issue	Explanation of Issue	References
Eligibility criteria	• Narrow eligibility criteria employed with the intention of reducing between participant variation • Exclude over 59.5% of people with MND from participating in trials • Overly stringent exclusion criteria could result in the indirect removal of prospective participants with specific drug responsive pathways • Potentially limits the sample representation and affects the ability to draw conclusions on the responsiveness of trial drugs	[23, 24]
Progressive nature of MND	• Contributes in part to the high rates of attrition, with up to 22% of surviving participants withdrawing prior to trial completion • Remote appointments, follow-up through medical records and remaining in the trial even if the person opts to stop taking the IMPs provides more people with the opportunity to remain engaged if they wish	[25, 26]

Difficulty swallowing trial medications	• Amending trial design to include IMPs in liquid form • Ensures participants can remain in the trial if their disease progression results in swallowing difficulties • IMPs are also then suitable for people enteral feeding tubes	[20]
Requirements to travel	• Clinical trials often require participants to attend in-person appointments at their local site • High burden of travel on the participant and their caregiver • As the condition progresses, may no longer be able to travel and have to leave the trial even when they wish to remain involved • Reduce trial engagement opportunities for people with MND who wish to participate	[25, 26]
Probability of being assigned to the placebo condition	• Identified as ways for trialists to 'design retention' • Reducing the likelihood that participants will be assigned to the placebo condition • Increasing the number of IMPs tested, whilst keeping the number of participants in the placebo condition to a minimum improves the likelihood of being assigned to an active arm	[26-28]
Candidate drugs tested	• Repeated testing of compounds across research groups, even with limited early evidence of efficacy • Ten IMPs were tested in three or more trials, despite repeatedly indicating negative results • Recent influential discoveries in basic and translational research, leading to recent advancement in knowledge of the underlying pathogenesis of MND and prospective therapeutic mechanisms • Potential benefit of repurposed drugs is another area of significant progression • Enables trials to reduce drug development costs and widening inclusion criteria due to known safety concerns	[20, 24] [29, 30]

1.3.2 Rethinking Trial Design

The aim of a clinical trial is to answer the research question of a candidate drug's efficacy. The traditional two-arm clinical trial involves the sequential testing of candidate drugs against a placebo arm. This approach has many inefficiencies in terms of time taken, and resources required.

Novel multi-arm, multi-stage trial designs offer a new and more efficient approach to testing new therapeutic drugs or strategies. In a disease such as MND, which is relatively rare and often progresses quickly, a multi-arm, multi-stage, adaptive trial design is particularly efficient as it requires fewer participants and less time. Adaptive designs enable testing of more than one candidate drug in both phases 2 and 3, adding new candidate drugs under the same trial infrastructure. Establishing multiple stages with pre-defined interim analysis also reduces the chance of a participant taking an ineffective drug for longer than necessary, crucial in a condition with such a short life expectancy.

Although historical trials have been limited in their success, the landscape of MND research has shifted dramatically in the last decade; with increased investigation into MND-specific diagnostic and predictive biomarkers [31], improved understanding of the biological basis of the condition and a shift towards translational medicine. An advanced understanding of the mechanisms underlying this disorder has provided a number of potential therapeutic targets to be explored across clinical trial phases.

The 2019 revision of Airlie House consensus guidelines for design and implementation of MND clinical trials encapsulates the new direction of research in this area [32]. These guidelines recommend innovation in trial design to also establish quality of life, cognitive and behavioural outcomes of treatment [32]. Additional outcome measures ensure exploration of a Clinical Trial of an Investigational Medicinal Product (CTIMP) candidate drugs' holistic effect on multiple facets of life impacted by an MND diagnosis.

This sentiment echoed earlier guidance from the European Medical Agency, published in 2015, on the clinical investigation of potential treatments for MND, encouraging global assessment of functionality and cognitive outcomes [33]. The Food and Drug Association guidance for developing drugs to treat MND reiterates the multi-system nature of the condition, with cognitive and behavioural features, but does not explicitly discuss these aspects of MND as potential additional outcome measures [34].

1.3.3 MND-SMART

The Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART) is globally the first multi-arm multi-stage (MAMS) phase III double-blind, placebo-controlled trial

launched for any neurodegenerative disease. The trial is the largest to date for MND in the UK, both in terms of numbers of participants (417 as of October 2022), and sites (17 sites distributed across the UK. MND-SMART complements the aims of the HEALEY platform trial (established in the USA) and is paving the way for trials in other neurodegenerative disorders, through the ACCORD collaboration [35]. MND-SMART is registered on clinicaltrials.gov (NCT04302870) and on the European Clinical Trials Registry (2019-000099-41), with the full trial protocol available [36] and information for prospective participants at https://mnd-smart.org.

The multi-arm trial design facilitates simultaneous evaluation of multiple treatments against a single control group. The adaptive design allows additional arms to be added in what is in effect a 'continuous' trial platform. These features improve efficiency in time, cost and sample size requirements, compared with the pursuit of multiple conventional two-arm studies, each with their own control arm. Recruitment and retention are demonstrably better than in historic trials, owing to innovations at every stage of the trial design and delivery and co-production alongside people with MND [37]. Ineffective arms can be discontinued at interim analysis, while new arms can be added.

MND-SMART's broad potential inclusion criteria allows wider participation and ensures generalisability of results in a clinically heterogeneous condition. MND-SMART will initially assess the efficacy of memantine (arm A) and trazodone (arm B) against a single contemporaneous placebo control arm (arm C), with investigational medicinal products (IMPs) delivered as liquids. Participants are being randomised 1:1:1 to arms A, B and C [38].

Co-primary outcome measures are ALS-FRS(R), and survival, with the aim of providing robust and definitive evidence for licensing if a drug is successful, and for stopping due to futility. ALSFRS(R) comparisons are being conducted in three stages with the opportunity to stop randomisation to arms that do not meet the predefined continuation criteria at the end of Stage 1.

Stage 1 was completed in Spring 2022 when 50 participants per arm (excluding long survivors defined as >8 years since diagnosis at baseline) completed 6 months of treatment. The outcome of preliminary analyses was to continue randomising further participants to both research arms and assess both arms against the control arm again, at the end of Stage 2 analysis.

Stage 2 will be complete when 100 participants per arm (excluding long survivors) have completed 12 months of treatment (anticipated to be in Summer 2023). The primary analysis (Stage 3) will be conducted based on rate of decline of ALSFRS(R) when 150 participants per arm (again excluding long survivors) complete 18 months of treatment. Participants will continue to take their allocated treatment until 113 deaths have been observed in the placebo group, or Stage 3 analysis data is collected - whichever is later, with the primary analysis of survival being performed at this point.

In addition to stopping arms that do not meet continuing criteria at the end of Stages 1 and 2, MND-SMART will introduce new arms by substantial amendment. These arms will be compared with contemporaneous controls, with each comparison following the multi-stage process. Future drug candidates are being selected using an integrated human stem cell-based in vitro and in vivo selection platform, led by international experts.

In addition to the novel statistical design, the trial encompasses key features of design innovation, with have been chosen in co-production with people living with MND. These features include delivery of liquid IMP, IMP couriered to people's homes, e-consenting, and telehealth-based follow up to reduce travel burden.

MND-SMART is an excellent example of inter-disciplinary and collaborative working, bringing together people from a wide range of disciplines, including medical statistics and oncology, people living with MND, and multiple philanthropic funders in partnership with charities and academic institutions. The next steps are to continue opening more sites across every part of the UK, evaluate more drugs, and to maximise reverse translational opportunities. A comprehensive bio resource has been established, which is a powerful vehicle for collaboration and reverse translation. The protocol will evolve to include combinatorial therapies, including different modes and routes of administration, targeting different cells, cellular compartments, and molecular pathways.

1.3.3.1 MND-SMART Trial Design

The multi-arm, multi-stage, adaptive design has been shown to be of particular benefit to enable a reduction of participant numbers and time required to test more than one candidate drug in later stage trials of stroke [39] and cancer [40]. These may be particularly crucial changes in trial delivery for rarer and higher-burden diseases such as MND.

In MND-SMART many of the trial and doctor-specific factors that have previously affected engagement with MND trials have been addressed. MND-SMART utilises inclusive trial participant criteria, remote follow-up appointments to address progressive disability and liquid medication to minimise potential swallowing difficulties.

The recent launch of MND-SMART provides a unique opportunity to explore within this thesis how person-specific factors can also influence trial participation decisions. Although focused on a single trial, we believe these findings will inform future trial design both in MND and other related conditions. The findings from this thesis more broadly will also be used to develop strategies to support staff in recruiting and retaining participants in clinical trials.

1.3.3.2 Patient and Public Involvement

People with MND were involved in every stage of the design process for MND-SMART. Formation of a trial-specific patient and public involvement (PPI) group enabled the research team to collect feedback from potential participants, and their caregivers, on outcome measure selection, trial design and recruitment materials. This feedback enabled the inclusion of adaptations that will in turn have a beneficial effect on recruitment and retention. Feedback from the PPI group informed decisions such as offering wider inclusion criteria, proposing more remote appointments and providing liquid medication to address potential difficulties with swallow as MND progresses.

The utility of this feedback to inform trial design was evident. As MND-SMART is a multi-arm multi-stage adaptive trial, with multiple analysis points, the protocol for the study could be changed based on feedback from participants and their caregivers. To gather this feedback from those directly involved in the trial, a sub-study focusing on the expectations and experiences of participant-caregiver dyads was implemented. The aim of this sub-study continues to be the implementation of participant feedback, and the continuation of PPI engagement that was so crucial in developing a participant-centric trial protocol.

1.3.4 New Directions in MND Trials

MND-SMART represents a wider movement of new directions in MND trial delivery. Novel trial designs, including multi-stage and multi-arm platform trials, are increasingly acknowledged as a key tool in the search for MND therapies [41]. Table 2 explores some of the currently recruiting, or recently completed, trials in MND that represent this new direction in research.

Table 2: Overview of Current New Direction Trials in MND

Trial Name	Trial Identifiers	Trial Collaborators	Investigative Medicinal Products	Trial Details	Progress Status
ATLAS	NCT04856982	Sponsored by Biogen and recruiting at a site in Sheffield in the UK	BIIB067 (Tofersen)	• Phase 3 trial • Focusing on people who have SOD1 gene mutations but have not yet started to show symptoms • Exploring the potential benefit of a candidate drug on people with have a genetic mutation but no clinical signs of MND	Recruiting
CENTAUR	NCT03127514	Completed through Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) at the Healy Centre in collaboration with Amylyx Pharmaceuticals in the USA	AMX0035 (sodium phenylbutyrate and tauroursodeoxycholic acid)	• Multi-stage • Phase 2/3 • Over 6 months in 137 individuals with fast-progressing ALS • Showing initially promising data on slowed progression as measured by the ALSFRS(R)	Completed
CENTAUR-OLE	NCT03488524	Open-label extension trial for participants of CENTAUR	AMX0035	• Survivability and long-term safety will be studied	Completed
CENTAUR Extension	NCT04516096	Additional year of continuation of treatment for CENTAUR participants	AMX0035	• Participants able to continue treatment for an additional year and any emergent adverse events will be accessed	To be completed in 2023
Healey ALS Platform Trial	NCT04297683	Healy Centre with sites across the USA	Current arms: 3rd CNM-Au8 4th Pridopidine 5th SLS-005 Trehalose Prior arms: 1st Zilucoplan 2nd Verdiperstat	• Perpetual multi-centre, multi-regimen clinical trial evaluating the safety and efficacy of different IMPs and drug regimens	Recruiting to newly added arms

MAGNET	2020-000579-19	TRICALS (Treatment Research Initiative to Cure ALS) European network	Lithium Carbonate	• Focusing on participants with the UNC13a mutation • Multi-arm adaptive design to test multiple compounds under a single protocol	Recruiting
ADORE	NCT05178810	TRICALS (Treatment Research Initiative to Cure ALS) European network	Edaravone	• A repurposed drug originally developed to treat acute ischemic stroke • Already licensed in Japan and USA based on small trials with limited efficacy	Recruiting

1.3.5 Recruitment and Retention in MND trials

Recruitment involves the selection of participants who are representative of the wider target population, in numbers sufficient to meet the requirements of trial-specific power calculations. A difficulty in previous MND trials has been the heterogeneity in presentation and progression of the individuals affected.

Formerly, to address this, many trials employed restrictive inclusion criteria in an attempt to stratify a heterogeneous population to detect a potential effect of a candidate drug. However, results from these studies may not be readily generalisable, and raise ethical concerns of restricted opportunities for research participation. The decision to restrict participation may homogenise trial outcomes but at the cost of inclusivity [13]. Limitations on inclusion criteria can also affect the likelihood of the clinical trial meeting enrolment targets, in turn affecting statistical power, the interpretation of findings and increasing the likelihood of a trial being stopped prematurely or failing to provide any meaningful results.

Attrition is defined as the loss of participating individuals to follow-up or as a result of missing data at one or more time-points [42]. Any level of attrition bias results reported as the characteristics of those individuals remaining, versus those lost to follow-up or with significant levels of missing data, may differ. Whilst some level of attrition is inevitable, successful trial retention is an important consideration in trial design to ensure participants remain representative, of sufficient number for analysis and with conclusions from the findings which are applicable to the wider patient population.

Sub-optimal recruitment and retention can affect a study's power and an insufficient number of participants will have a significant impact on the validity of conclusions drawn from the data, increasing the probability of type II error [43]. These methodological issues can lead to trials reporting invalid or inconclusive results, prolonging trial time and potentially result in the trial being terminated prematurely [44, 45]. Trials that do not recruit efficiently, or sufficiently, can have a high social, financial and administrative cost. For researchers, clinicians and people affected by the relevant conditions, effective trial recruitment and retention is essential to definitively answer the research question posed.

1.3.5.1 Considering Recruitment and Retention in MND Trials

The majority of research in this area has been conducted within the context of oncology and dementia trials. Recruitment and retention of individuals who to opt to participate in clinical trials has been problematic in oncology [46] and Alzheimer's disease clinical trials [47]. A review of clinical trials in oncology [48] identified three areas that impact recruitment: patient factors, trial factors and doctor factors. This concept was also reflected in Atassi's 2013 review of factors affecting adherence in MND trials; study population characteristics, trial design and site/staff facilities [25] .

Historically, trials of motor neuron disease have been affected by sub-optimal recruitment and retention figures. In a recent review of historical clinical trials in MND 87% of trials met at least 90% of their target recruitment, meaning a significant number were underpowered based on initial enrolment targets even without considering trials that were halted early due to inability to recruit [49]. 40% of these clinical trials reported attrition rates of more than 20% [49]. The risk of bias is high at attrition rates in this level [50]. Any level of attrition may result in bias in results reported as the characteristics of those individuals remaining, versus those lost to follow-up or with significant levels of missing data, may differ.

Availability of trials to people with MND is an additional concern. While 83% of people with MND indicated they are open to participating in research trials [25] actual enrolment figures of 25% are reported for clinical trials [26].

The factors that influence recruitment and retention in MND have been under-evaluated. Further investigation of factors that may account for variability in recruitment and retention, particularly within MND, is essential to devise strategies to address issues in enrolment and attrition and improve trial delivery. The presence of neuropsychiatric dysfunction, behaviour change and cognitive impairment pose significant challenges for recruitment and can impact a person's ability to give informed consent and maintain protocol adherence [11] [21]. Participants' demographic characteristics [22, 23] and attitudes towards research and health behaviours [24] may be predictive of trial enrolment and attrition.

This thesis will explore how person-specific factors affect the decision to participate in a clinical trial for people with MND, and how engaging with research can be influenced by an individual's characteristics and experience of MND.

1.4 Non-Motor Symptoms

1.4.1 Non-Motor Symptoms in Neurological Conditions

Diagnosis, clinical care and research of many neurological conditions often focuses on the motor symptoms that characterise these disorders, including changes to the way the body moves and a person's physical functioning. Non-motor symptoms incorporate other ways that an individual may be affected by a neurological condition. These may be symptoms directly related to motor changes, such as pain from muscle stiffness, or those which are aspects of a neurological condition not associated with motor dysfunction. Many non-motor features of neurological conditions remain underdiagnosed, undertreated and understudied.

These symptoms differ in frequency, severity and occurrence in many neurological conditions [51]. Most of the previous service evaluation, quality improvement, and research into non-motor symptoms of neurological conditions has focused on Parkinson's disease (PD), which has established these symptoms as a core feature of the condition, preceding the onset of motor symptoms, predictive of disability and negatively affecting prognosis [52, 53].

The Trajectories of Outcomes in Neurological Conditions (TONiC) study [54] is an ongoing, national project which sought to address the conflicting evidence for non-motor symptoms' presence and impact in multiple sclerosis [55]and MND [56]. As a longitudinal and multi-phase exploration of quality of life determinants in MND, the TONiC study reported the prevalence of pain, depression and anxiety, and the resulting negative impact on an individual's quality of life [54].

Despite evidence from the TONiC group that people with MND and their clinical team believe that several of these symptoms can affect quality of life [57], non-motor symptoms are often not reported by patients in clinical consultations, perhaps due to a lack of awareness that they are related to the presenting condition [58]. Improving the understanding of how frequently these aspects of the condition affect people with neurological disease, assessment in clinical care and importance to the individual is critical.

1.4.2 Non-Motor Symptoms in MND

Non-motor symptoms in MND can arise secondary to motor dysfunction, such as inefficient saliva clearance from bulbar motor dysfunction, and pain from inability to regularly move and turn, or be independent. Symptoms may localise elsewhere neuroanatomically [59] potentially broadening our

understanding of the aetiopathogenesis of MND and provide insights into wider neuroanatomical dysfunction [60]. MND is a multisystem disorder with non-motor symptoms that are poorly understood. Their impact upon the individual is not well established.

Non-motor symptoms are often inadequately addressed in clinical management and research in MND, with the focus on breathing, muscle weakness, swallowing and speech. Clinical guidance [61], symptomatic treatment [62] and trial design guidance [32, 63] encourages a broader conceptualisation of MND, with non-motor symptoms as areas that also require effective management and treatment.

Until effective treatments are found the focus on supporting people with MND is symptom management and maintaining optimal quality of life. Non-motor symptoms in people with neurological conditions can be responsive to pharmacological and non-pharmacological interventions [64].

Non-motor symptoms reduce health related quality of life and a person's wellbeing [51]. Significantly poorer quality of life and shorter median survival times are consistently found in people with MND experiencing these type of symptoms [51]; low mood in the early post-diagnostic phase in particular is predictive of poorer survival in the first 6 months [65]. People with MND experiencing distress are at a seven-fold greater risk of mortality than individuals who report positive well-being [66].

Non-motor symptoms can also influence the lives of those caring for and supporting people with MND. Behavioural symptoms in particular are consistently reported as significant predictors of carer burden alongside physical impairment of the people with MND and depressive symptoms in the caregiver [67].

1.4.3 Symptomatic Profile of MND

1.4.3.1 Neuropsychiatric

Comorbid concurrent neuropsychiatric symptoms, particularly depression and anxiety, are common in people with MND. Findings from a recent population based study of multimorbidity in MND in Scotland indicate the presence of neuropsychiatric disorders at 19.7% in people with MND, 70% of which were mood disorders and 31.67% neurotic disorders (inclusive of anxiety, stress-related and somatoform disorders) [68]. The prevalence of these disorders in people with MND is significantly elevated in comparison to rates in the general population, 6.9% of whom fulfil diagnostic thresholds for major depressive disorder and 14% an anxiety disorder [69, 70].

1.4.3.2 Cognition and Behaviour

Cognitive impairment is an additional non-motor feature of motor neuron disease which is prevalent, experienced by 30-50% of people with MND [71] and detrimental to an individual's quality of life and prognosis [3, 72]. Cognitive changes in people with MND are characterised by executive dysfunction, language impairment and affected social cognition [73-75] .

Apathy is the most commonly reported behavioural change [76]. Frontotemporal dementia (FTD) and MND exist on a disease spectrum [77], with 15% of people with MND also reaching diagnostic threshold for FTD [78, 79]. Many individuals who do not reach diagnostic thresholds still exhibit behavioural changes and neuropsychiatric symptoms characteristic of FTD, such as executive dysfunction, perseveration, disinhibition and emotional lability [80].

1.4.3.3 Sleep and Fatigue

Sleep disturbance and poor quality sleep are frequently reported in MND and primarily assessed using the Epworth Sleepiness Scale [81]. Sleep quality, length of sleep and REM duration can be improved in people with MND using non-invasive ventilation [82], suggesting that respiratory weakness due to motor decline might be the primary cause of these difficulties. Sleepiness is a key aspect of fatigue in people with MND, along with reduced alertness, loss of stamina and lack of energy [51]. Fatigue has been previously reported by up to 44% of people with MND, co-occurring with depression in 15% of individuals [83]. Despite its prevalence this non-motor symptom is often under evaluated in clinical care and research design, considered a subset of depression or sleepiness rather than characterised as a distinct aspect of the disease [84].

1.4.3.4 Pain

Pain is an additional non-motor symptom, directly impacted by motor decline, which has a significant impact on the management of MND. 50-85% of people with MND reported severe pain, becoming more problematic over time [85] and when present, having a significant negative impact quality of life [54]. However, pain in MND has been shown to be responsive to physical therapy [86] and pharmacological interventions [87]. Accurate identification of pain and appropriate management may improve the quality of life for people with MND.

1.4.3.5 Gastrointestinal

Gastrointestinal symptoms such as constipation, nausea, vomiting, acid reflux or excessive flatulence may occur for people with MND [88]. Gastrointestinal abnormalities were reported in 16– 83% of people with MND, depending on the symptom considered [89]. These symptoms may occur as a response to interventions (particularly new drug treatments or non-invasive ventilation), secondary to increasingly physical disability or may be indicative of wider nervous system degeneration [89, 90].

1.4.3.6 Problematic Saliva

We have recently reported that problematic saliva production and handling, characterised by thickened saliva and sialorrhea, is experienced by 37.5% of people with MND [91]. Bulbar onset, but not age, sex, time to diagnosis or area of onset have been shown to be associated with the presence of saliva problems [91]. Saliva thickening and excessive drooling can be detrimental to an individual's well-being, increase the risk of respiratory complications and exacerbate dysarthria [92].

1.4.3.7 Sexual Functioning

Although sexual functioning is not directly affected by MND the impact of an MND diagnosis on sexuality, intimacy and libido remain relevant to exploring the holistic impact of the condition on the individual [93]. Despite the significant impact changes in sexual behaviour can have on an individual's quality of life [93], sexuality is often not considered or discussed in routine clinical consultations, and psychosocial support is not available [94]. Interest in sex has been reported to decrease 28% after an MND diagnosis, with the main issues presented as reduced libido, problems with physical weakness and difficulty coping with body image changes due to MND progression [94].

1.4.4 NMS in Clinical Care

To deliver holistic disease management for people with MND it is necessary to expand our conceptualisation of 'treatment' beyond improved physical function and extended survival. Holistic assessment is essential to providing comprehensive health care for people suffering from neurological disorders [59]. Without awareness of which symptoms are prevalent in people with MND, the

delivery of supportive, symptomatic care for these individuals may be compromised. NICE 2016 guidelines recommends that the multidisciplinary team screen for saliva problems, pain, mental health, fatigue, cognitive dysfunction, behavioural change and sleep, and encourage referrals to specialist services where required [61].

Accurate identification and specialist management of non-motor symptoms has shown to significantly improve the lives of people living with other neurological conditions, and their caregivers [95]. Preliminary findings in MND indicated the effectiveness of psychological interventions [96] on quality of life for people with MND and their caregivers. A short-term course of cognitive behavioural therapy demonstrated possible reduction in self-report anxiety and depressive symptoms [97].

1.4.5 Non-Motor Symptoms in Clinical Trial Design

Effective management, or ultimately slowed progression, of non-motor symptoms (NMS) due to pharmacological intervention should be evaluated as part of any novel investigative medicinal products' efficacy in clinical trials [98]. The potential beneficial effect of candidate drugs that successfully manage non-motor features of a debilitating condition may have significant clinical impact, improve quality of life, reduce disability and alleviate disease burden.

An improved understanding of the potential impact of candidate drugs on non-motor symptoms, for trials of prospective therapies for MND, enables a more complete picture of the safety and efficacy. It is important to ensure trials of drugs that focus on improved physical functioning or survival outcomes, also address or consider the potential improvement or worsening of a range of NMS symptoms. Detection of change in these additional symptoms is crucial to assess how severe the effect of an IMP is on the expression and development of added symptoms.

Airlie House [32] and EMA [63] provide guidelines for designing and completing trials in MND. Both encourage researchers and trialists to include additional evaluations of cognitive function, behavioural changes or mood as primary or secondary outcome measures. Physical function and survival remain the primary focus for trials in this condition, but the potential for additional benefit to reduce or reverse the effects of non-motor symptoms is an opportunity to improve the lives of people currently living with MND, their loved ones and those who will be affected in the future.

1.5 Using Technology to Evaluate MND Progression

1.5.1 Background to Wearable Devices

Technology is increasingly used in both diagnosis and management of disease with a focus on earlier identification and disease monitoring [99]. The clinical and research utility of wearable sensors in people with MND, and other neurological conditions, and their potential suitability as trial outcome measures, has steadily gained attention in research. There are a broad range of sensor types available, establishing acceptability and accuracy to monitor motor symptoms is essential to progress this potential alternative to traditional questionnaire-based assessment of deterioration.

Wearable sensors closely align with the new directions of remote, real-time and objective assessment of clinical care and research delivery that characterises neurology. Remote data capture decentralises research, reducing the need for travel to specialist sites, and its associated burdens, the travel, and resulting burden, can also be reduced in clinical care by using wearable technology.

Collecting data outside the clinical environment may result in fewer appointments, requiring less travel and assessment of real-world impairment [100]. Using technology to collect healthcare data directly engages respondents and enables them to collect symptom-focused data in real-time of occurrence and then share this with their care team. These changes to methods of delivery will be significant in the progression of research and clinical care alike and may help the multi-disciplinary care team better shape clinical appointments to the individual's needs, facilitating the delivery of more personalized care [101, 102].

The National Health Service (NHS) Long Term Plan acknowledges that digital technology has the potential to change the face of health and social care delivery [99]. Clinical care and research are closely intertwined for people with neurological conditions, and aligning research objectives with the NHS' healthcare plan for digital data is essential.

1.5.2 Types of Devices Available

There are a broad range of types, and brands, of wearable devices available to clinicians and researchers. When choosing a device there must be a balanced decision made on accessibility, suitability and accuracy of the sensor to evaluate the changes in this population. Studies exploring the acceptability of these devices to patients, and the validity of the assessment of physical change, are necessary to establish guidelines about how to integrate these devices into day-to-day monitoring and clinical care delivery.

Activity monitors evaluate changes in participants' overall capability for engaging in physical activity [103]. These activity monitors explore aspects of physical function such as step count (using a pedometer), periods of inactivity and elevation gain (using an inclinometer). These can be inbuilt within a smartphone, or worn as separate devices.

Smartphones can be used to passively collect activity data (automatically collected by the phone itself) and or actively (entered by participants into specialized apps or web forms) data on function, symptoms and daily activity [104]. This data can then be used by researchers to gain insight into the changing profile of a disease, or inform clinical care decision-making.

Some wearable devices contain an inertial measurement unit (IMU), which can enable clinicians and researchers to establish a picture of an individual's ability to move their affected limbs [105]. An IMU is used to measure velocity, orientation and gravitational force, which in turn can provide detailed information on the participant's movements. Within the IMU are an accelerometer, gyroscope and magnetometer sensor.

Accelerometers measure acceleration from inertia (movement from a resting baseline), gyroscopes measure angular rotation (direction of movement) with the magnetometer improving the accuracy of the gyroscope's determination of direction [106].

Sensors, often integrated within wearable devices, can be worn to evaluate heart rate, blood pressure, oxygen saturation and other measures of physical health. Wearables devices can also be used to evaluate an individual's sleep [107]. Activity trackers and IMUs track movement during sleep, oxygen monitors assess oxygen saturation and heart rate monitors combine to explore different aspects of rest. Time spent asleep, time taken to fall asleep, periods of wakefulness and quality of sleep can be informative to researchers and clinicians for an individual's health.

1.5.3 Wearable Technology for Motor Symptoms

In other progressive motor disorders, such as Parkinson's disease, wearable devices have offered an alternative method of continuous and objective monitoring of motor symptoms in both clinical care and trial delivery [108]. These devices enable continuous monitoring, whilst using the participant as their own baseline. The low patient burden offered by passive data collection can lead to improved adherence, particularly suited to patient groups such as those with dementia or cognitive impairment, who may have difficulty adhering to more involved study protocols [109]. Accelerometers have previously been the most commonly used research tool for people with multiple sclerosis (MS), but as the field of wearable technology continues to develop and expand, more specialised and detailed

measures of physical activity can help us to better understand the nuanced changes in functionality [110].

Initial research into the suitability of these devices for people with MND has found similar promising avenues [111, 112]. Due to the heterogeneity of MND presentation and progression, different individuals may show very different patterns of impairment that are difficult to capture in traditional questionnaire-based evaluation [12, 105]. Wearable devices offer the opportunity to explore limb-specific deterioration [113], changes in gait when walking [114] and general activity levels [103] to provide a more holistic picture of disease progression.

1.5.4 Devices to Evaluate Progressive Speech Deterioration

For many people with MND and other neurological conditions, a disturbance in speech production and intelligibility is a primary presenting complaint and hallmark of disease progression. Dysarthria is particularly prominent in the bulbar-onset sub-type of MND, but up to 85% of people with MND will encounter bulbar dysfunction during the course of their disease, regardless of their initial presentation. Speech disturbance inevitably presents a huge challenge in the management and care provision for people with MND. Changes in speech may also offer a unique, and clinically relevant, measure of disease progression.

Sensors offer more detailed assessment than traditional questionnaire-based measures, with greater objectivity that clinician evaluation. Utilising devices specifically intended to detect acoustic parameters indicative of speech decline provide a unique opportunity in the diagnosis and progression monitoring of people with neurological conditions.

1.5.5 Technology Mediated Patient-Reported Outcome Measures

People with neurological conditions are also able to actively contribute to clinical care and research by completing assessments remotely; using a specialist app or website to record health information. These technological platforms enable delivery of questionnaires, cognitive assessments and symptom-tracking in real-time, directly completed by the patient themselves. Technology can be used to facilitate patient-centric research design and promote engagement with the clinical care team.

Users are encouraged to complete bespoke questionnaires on symptoms, disability and impact, to track their mood and wellbeing, monitor activity and engage with their healthcare. This data can then

be shared with research and clinical care teams to provide a more complete picture of an individual's health.

Apps focusing on disease-specific questionnaire-based assessments and cognitive test games, have reported positive feedback and good rates of engagement from people with MS [115], dementia [116], Parkinson's disease [28] and MND [117]. A pilot study on administering cognitive testing for people with MS using an app indicated positive ratings of usefulness, enjoyment and acceptance, with 84% adherence [115]. Smartphone assisted administration of cognitive testing was also shown to be feasible, through convergent validity, to people at increased risk of dementia [116].

Similar positive feedback was reported in an app for people with PD, with 86% reporting no significant difficulties in using and supportive of using the app once a day to track symptoms [28]. Bespoke MND focused apps have also been shown to be useful and feasible to collect complex speech data, with the majority of participants reporting positive feedback on their experience of being involved in a study with completely remote data collection [117].

Apps, and specialised data collection websites, offer a promising new direction in participant-led data collection. Decentralising research participation, and enabling respondents to share detailed information on disease impact with their clinical team in a structured manner.

1.5.6 Wearable Devices as Trial Outcome Measures

The greater sensitivity of wearable devices to record alternative outcome measures may lead to a significant reduction in sample size requirements for trials, by as much as 30.3% for 12-month trials and 44.6% for 18-month trials [105]. Smaller sample size requirements for detecting effects of novel medicines reduces trial delivery costs, and shortens timelines for trials to answer important research questions on potentially effective therapeutic targets [105].

In addition, using sensors for remote data collection negates the need for frequent, burdensome, clinical appointments for participants. Decentralized trial delivery offers the opportunity for more frequent assessment, in turn reducing sample size requirements further by up to 73% for weekly versus monthly ALSFRS(R) completion [103, 118]. The opportunity for remote data collection also offers trialists the opportunity to reduce the burden of trial participation on people with MND and optimise retention, essential in a condition where individuals often experience rapid deterioration.

The different types of wearable devices offer an opportunity to evaluate the diverse areas functional impairment, whilst enabling each person to act as their own baseline for detecting change and progression [105].

2 Chapter 2: Systematic Review 1 - A Systematic Review of Neuropsychiatric and Cognitive Assessments in Clinical Trials of MND

The substantive body of work in this chapter has been published [119] and the full paper is available in Appendix 1.

Beswick, Emily, Emily Park, Charis Wong, Arpan R. Mehta, Rachel Dakin, Siddharthan Chandran, Judith Newton, Alan Carson, Sharon Abrahams, and Suvankar Pal.
"A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis." *Journal of Neurology*. 268, no. 12 (2021): 4510-4521.

10 citations.

2.1 Abstract

Background: Up to 50% of people with motor neuron disease (MND) experience cognitive dysfunction, whilst depression and anxiety are reported in up to 44% and 33%, respectively. These symptoms impact on quality of life, and are associated with poorer prognosis. Historically, outcomes in clinical trials have focussed on the effect of candidate drugs on physical functioning.

Aim: We aimed to systematically review 25 years of clinical trials in MND, since the licensing of riluzole, to identify if neuropsychiatric symptoms and cognitive impairment were evaluated. If neuropsychiatric symptoms and cognitive impairment were evaluated, we assessed if this was as an exclusion criteria or outcome measure and describe the tools used.

Hypothesis: We hypothesised that neuropsychiatric and cognitive symptoms have been under-evaluated in clinical trials and that when assessed using standardised tools, these are not specifically designed or suitable for assess people with MND.

Methods: We reviewed the last 25 years of clinical trials of investigative medicinal products in people with MND, since the licensing of riluzole, and extracted data on frequency and type of assessment for neuropsychiatric symptoms and cognitive impairment. Trial registry databases including World Health Organisation (WHO) International Trials Registry, European Clinical Trials Register, clinicaltrials.gov, and PubMed were systematically searched for Phase 2, 3 or 4 trials registered, completed or published between 01/01/1994 and 31/10/2019. No language restrictions were applied. Outcome measures, exclusion criteria and assessment tool used were extracted.

Results: 216 trials, investigating 26,326 people with MND were reviewed. 35% assessed neuropsychiatric symptoms, and 22% assessed cognition, as Exclusion Criteria or Outcome Measures. 3% (n = 6) of trials assessed neuropsychiatric symptoms as a Secondary Outcome Measure, and 4% (n = 8) assessed cognition as Outcome Measures; only one trial included assessments for both cognition and neuropsychiatric symptoms as Outcome Measures. Three MND-specific assessments were used in six trials.

Conclusions: Trials for people with MND have neglected the importance of neuropsychiatric symptoms and cognitive impairment. Evaluation of these non-motor features is essential to understand the impact of candidate drugs on all symptoms of MND.

2.2 Lay Summary

Information from 216 trials was included in this study. Only 3% of the trials looked at the impact of the possible new drug on neuropsychiatric symptoms (affecting a person's mood, feelings of anxiety), and 4% considered how participants' cognition, potential changes to how a person thinks and is able to process information, was affected.

Amongst people with the amyotrophic lateral sclerosis (ALS) form of MND, up to 50% of people can experience cognitive and behavioural changes. In 15% of individuals with ALS, the changes can be severe enough to lead to a diagnosis of frontotemporal dementia. Depression and anxiety are also commonly experienced amongst people diagnosed with MND. These symptoms affect people's quality of life, and can be associated with increased disability and shorter life expectancy for those affected. Historically, outcomes in clinical trials have focussed on the effect of drugs on physical functioning and the importance of cognition and mental health has frequently been neglected.

A recommendation from this study is that that trial outcomes should also consider how drugs tested impact on a broader range of MND symptoms, including neuropsychiatric and cognitive.

2.3 Introduction

2.3.1 Neuropsychiatric Symptoms, Cognitive Impairment and Behavioural Change

Motor neuron diseases (MND) have been traditionally characterised by their effect on the motor system [3], however, non-motor symptoms, including neuropsychiatric and cognitive symptoms are now becoming more widely acknowledged as prevalent [120] and debilitating [121] features of this condition which are predictive of disability [65].

Findings from a recent population based study in Scotland reported a prevalence of neuropsychiatric disorders of 19.7% in people with MND, 70% of which were mood disorders and 31.67% neurotic disorders (inclusive of anxiety, stress-related and somatoform disorders) [68]. The prevalence of these disorders in people with MND is higher than the general population, 6.9% a depressive disorder and 14% an anxiety disorder [69, 70]. These differences remain when focusing on a group more representative of the general individual with MND, the older adult population [122].

Cognitive impairment is an additional non-motor feature of MND that is highly prevalent, with some form of cognitive or behavioural symptoms experienced by 30-50% of people with MND [71]. 15% of people with MND meet diagnostic criteria for frontotemporal dementia (FTD) [78, 79]. Cognitive impairment in people with MND is characterised by executive dysfunction, impairments in language and social cognition [73-75] whilst apathy is the most pronounced behavioural change [76].

Individuals with chronic physical illness and comorbid depression or anxiety often experience a higher level of somatic symptom burden that has a impair functioning [123]. Symptoms of depression, anxiety, and apathy reduce quality of life (QoL) for people with MND [84, 124]. Lower psychological well-being generally has been identified as predictive of disability and shorter survival in people with MND [65]. Presence of concomitant neuropsychiatric conditions and cognitive impairment predicts greater carer distress [125-127].

Despite this, neuropsychiatric symptoms are often under-recognised in clinical care. Assessments are often performed using tools which have not been adapted for people with physical disability or communication difficulties. Assessments may also not be specifically addressing the cognitive domains impaired in people with MND, or providing disease-specific thresholds for impairment. Scores may be significantly impacted by the overlap of somatic features of neuropsychiatric conditions and those attributable to the progression of MND. In a group that is predominantly affected by motor impairment, speech and respiratory difficulties, lengthy administration time can also reduce the suitability of a tool.

2.3.2 Assessment in MND Trials

The only globally licensed disease modifying therapy for MND is riluzole [22], with Edaravone (Radicava) and Masitinib emerging as promising treatments licensed in some countries following positive trials in highly stratified cohorts [128]. After initial success in the CENTAUR trial, AMX0035 [17] (also known as Relyviro) has been approved for use in the USA by the Federal Drug Association. All of these currently available disease modifying therapies are intended to target the motor symptoms of MND.

Cognitive assessments have been included in some studies investigating the effects of riluzole as a disease modifying therapy in various other neurodegenerative conditions [129]. To our knowledge, the impact of riluzole on cognition in people with MND has not been investigated in initial licensing trials.

Whilst survival and functioning remain the gold standard outcome measures used in clinical trials, incorporation of measures of neuropsychiatric and cognitive function enable more holistic assessment of the impact of drugs. Awareness of how a candidate drug may affect non-motor features is clinically relevant in disease management and quality of life. Including individuals with neuropsychiatric and cognitive impairments, and using assessments to evaluate these as outcome measures enables the trial team to evaluate the impact of the candidate drug on people with non-motor features of MND.

Candidate drugs may have a selective effect on neuropsychiatric or cognitive symptoms, therefore, measurement of these areas is pertinent investigate the impact of an investigative medicinal product on both motor and non-motor symptoms in MND. The potential impact of candidate drugs is of therapeutic relevance, even if not the primary intended effect, considering the potential for impact on quality of life and disease management of MND.

Despite evolving guidance to include non-motor secondary outcome measures in trial design [32], and significant progress in establishing cognitive assessments within clinical care [61], we hypothesised that neuropsychiatric and cognitive symptoms have been under-evaluated in clinical trials. In addition, we hypothesised that when these aspects of MND were assessed it would be with standardised tools, and that these tools are not specifically designed for people with MND, which may affect their suitability for this population.

2.4 Methods

2.4.1 Search Strategy

We completed a systematic, unbiased, search of trial registries including clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), European Union Clinical Trials Register (EduraCT) and PubMed on 18/11/2019 for Clinical Trials of an Investigational Medicinal Product (CTIMP). Using the search terms “amyotrophic lateral sclerosis” or “motor neuron* disease” we searched clinicaltrials.gov for interventional trials of investigative medicinal products. We searched EduraCT and ICTRP for trials of “amyotrophic lateral sclerosis” with the filters “Phase II”, “Phase III” and “Phase IV” applied. Using the advanced search feature we filtered PubMed with ("amyotrophic lateral sclerosis"[MeSH Terms] OR “motor neuron* disease” [MeSH Terms]).

2.4.2 *Inclusion and Exclusion Criteria*

Phase II, III or IV trials assessing potential disease modifying therapies in subjects with amyotrophic lateral sclerosis that were registered, completed or published between 01/01/1994 to 31/10/2019 were included. No language restrictions were applied. Extension trials, post-hoc analysis papers and trials focused on symptom management were excluded.

2.4.3 *Data Extraction*

The following details of selected trials were extracted “Investigative Medicinal Product (IMP) Assessed”, “Number of Participants”, “Date of Commencement”, “Primary Outcome Measure(s)” and “Secondary Outcome Measure(s)”.

Assessment of neuropsychiatric conditions or cognitive symptoms within each trial was categorised as; “Exclusion Criteria”, “Primary Outcome Measure”, “Secondary Outcome Measure”, “No Data Available for Trial” or “Not Assessed”. We also noted the assessment tool included, if documented, and a brief summary of the trial’s stipulations regarding neuropsychiatric conditions or cognitive symptoms. We also evaluated the use of Quality of Life measures within the trials. We investigated the number of clinical trials that recruited people with frontotemporal dementia (FTD).

We documented the tools used and described the characteristics of tools used to evaluate neuropsychiatric or cognitive symptoms in trials identified in this systematic review. The areas assessed, features of administration and availability of disease-specific scores were recorded.

2.5 Results

A total of 1,312 records were identified (see PRISMA diagram in Figure 2 for details). 296 duplicates were removed, and a further 800 results were removed due to unsuitability defined by inclusion criteria, resulting in 216 clinical trials of investigative medicinal products. 216 trials, proposed to include a total of 26,326 participants with MND, were included in the final review.

Only one trial, the Therapy in Amyotrophic Lateral Sclerosis (TAME) trial evaluating memantine (Barohn et al, currently recruiting, Trial ID: NCT02118727), assessed both neuropsychiatric symptoms and cognitive impairment as Secondary Outcome Measures. A full list of the 13 trials assessing neuropsychiatric symptoms and cognitive impairment as primary or secondary outcome measures is shown in Table 3.

Four trials had results available. In the trial of memantine (NCT00353665) the use of Hamilton depression scale as a planned secondary outcome measure was noted in the trial record on clinicaltrials.gov, however, there was no discussion of use or results of this outcome in the final report of the trial findings [130]. In a trial evaluating lithium carbonate (EduraCT 2008-006891-31), depression worsened and anxiety increased over time in participants, but there was no significant difference between study groups [131].

A trial of omigapil (NCT00072709) reported no change in neurocognitive evaluations, using the Addenbrooke's Cognitive Examination (ACE) [132]. A study of triumeq (NCT02868580) assessed suicidal ideation as a secondary outcome measure using the Columbia Suicide Severity Rating Scale (C-SSRS). Only two participants (5% of total trial participants) reported suicidal ideation and this was deemed unrelated to triumeq [133].

Figure 2: PRISMA Diagram for Record Selection

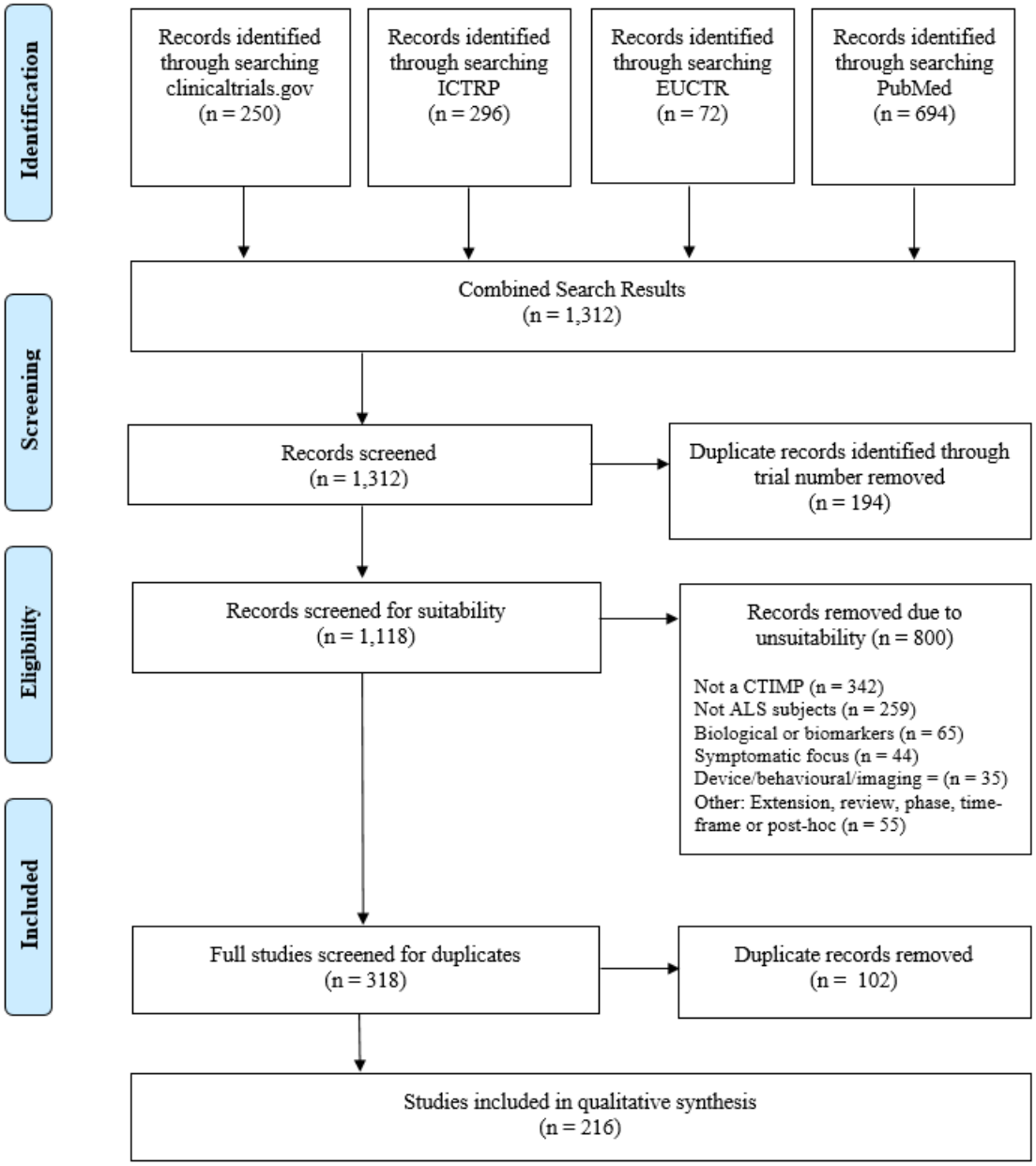


Table 3: Trials Including Neuropsychiatric and Cognitive Outcome Measures

Unique Trial Identifier	Data Source	Start Date	Trial IMP	Neuropsychiatric Assessment Tool	Cognitive Impairment Assessment Tool	Use of Assessment as Outcome Measure	Results Summary
NCT00072709	Clinical Trials.Gov	Sept 2003	Omigapil		Addenbrooke's Cognitive Examination (ACE)	Secondary	No efficacy for IMP or change in neurocognitive measure
NCT00353665	Clinical Trials.Gov	July 2005	Memantine & Riluzole	Hamilton Depression (HAM-D)		Secondary	No efficacy for IMP and no results on HAM-D available
NCT00409721	Clinical Trials.Gov	March 2007	Memantine		Addenbrooke's Cognitive Examination (ACE)	Primary	No results available
2008-006891-31	EudraCT	June 2009	Lithium carbonate	Hospital Anxiety and Depression Scale (HADS)		Secondary	No efficacy for IMP or difference in HADS scores across groups.
NCT02118727	Clinical Trials.Gov	November 2011	Memantine	Neuropsychiatric Inventory (NPI)	ALS Cognitive Behavioral Screen (ALS-CBS)	Secondary	
NCT01935518	Clinical Trials.Gov	Sept 2013	Fasudil		Frontal Behavior Inventory (FBI) & Verbal Fluency	Secondary	

NCT02868580	Clinical Trials.Gov	October 2016	Triumeq	Columbia Suicide Severity Rating Scale (C-SSRS)		Secondary	IMP safe and potential efficiacy. Suicidal ideation in 2 participants, unrelated to IMP.
NCT03508453	Clinical Trials.Gov	August 2018	IC14		Edinburgh Cognitive and Behavioural ALS Screen (ECAS)	Secondary	
NCT03652805	Clinical Trials.Gov	August 2018	IPL344	Hospital Anxiety and Depression Scale (HADS) and ALS-Depression-Inventory (ADI-12)		Secondary	
NCT03293069	Clinical Trials.Gov	January 2019	Deferiprone		Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and Montreal Cognitive Assessment (MoCA)	Secondary	
NCT03690791	Clinical Trials.Gov	January 2019	CBD Oil		Edinburgh Cognitive and Behavioural ALS Screen (ECAS)	Secondary	
KCT0001984	ICTRP	March 2019	Mecasin	Hamilton Depression (HAM-D)		Secondary	No results available
NCT04082832	Clinical Trials.Gov	Sept 2019	Cu(2ii)ATSM		Edinburgh Cognitive and Behavioural ALS Screen (ECAS)	Primary	

2.5.1 *Neuropsychiatric Symptoms*

35% (n = 76/216) of the total 216 trials included in this study assessed neuropsychiatric symptoms. Of these 76 trials, 92% (n = 70/76) assessments were used as an Exclusion Criteria, 3% (n = 2/76) as a Secondary Outcome Measure and 5% (n = 4/76) defined neuropsychiatric symptoms as both a Secondary Outcome Measure and an Exclusion Criterion.

29% (n = 22/76) of the 76 trials that reported assessing neuropsychiatric symptoms used investigator clinical judgment, 32% (n = 24/76) clinical history or medical records, and 11% (n = 8/76) specified a standardized assessment tool.

2.5.2 *Cognitive Symptoms*

21% (n = 46/216) of the 216 trials included assessed cognitive functioning, of these 46 trials assessing cognitive functioning, 83% (n = 38/46) assessments were used as an Exclusion Criteria, 4% (n = 2/46) as a Primary Outcome Measure and 13% (n = 6/46) as a Secondary Outcome Measure.
Of these 46 trials which reported assessing cognitive impairment and provided data on the method of assessment, 23% (n = 11) utilized investigator clinical judgment, 9% (n = 4) clinical history or medical records, and 26% (n = 12) specified a standardized assessment tool.

The ECAS was the only assessment tool used as both a primary and secondary outcome measure, to assess cognitive impairment in people with MND.

2.5.3 *Dementia and Quality of Life*

A comorbid diagnosis of dementia was an Exclusion Criteria in 32% (n = 69) of the 216 trials reviewed. Subjects with dementia were explicitly referenced as able to participate in just 1% of trials (n = 3). 67% (n = 144) did not provide data on whether they accepted participants with a dementia diagnosis.

Quality of life measures were utilized as primary and secondary outcome measures in 1% (n = 3) and 27% (n = 59), respectively, of 216 trials reviewed. Table 4 summarises quality of life measures used, and considers their content as some measures include limited assessments of mood and self-reported psychological health and functioning.

Table 4: Quality of Life Assessments Tools and Areas of Evaluation

Assessment Name	Total Number of Items	Number of Trials Utilising	Domains Addressed	Mood Items
Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 Item (ALSAQ-40)	40	14	Hopelessness, depression and emotional reactivity	10 items with 5-point Likert scale for frequency of mood symptoms
Amyotrophic Lateral Sclerosis Assessment Questionnaire-5 Item (ALSAQ-5)	5	6	Hopelessness	1 item with 5-point Likert scale on frequency of hopelessness
ALS Specific Quality of Life (ALSQOL-R)	50	6	Depression and anxiety	10-point Likert rating scales for level of agreement or frequency of experiences
EuroQol 5 Domain Assessment (EQ-5D-5L)	5	4	Health perception and functional impact	5-point Likert rating scale for severity of anxiety/depression combined
Edmonton Symptom Assessment System (ESAS)	10	1	Pain, depression, anxious and general wellbeing	10-point Likert rating scale for depression and anxiety
McGill Quality of Life-Revised	14	7	Depression, anxiety, mood and hopelessness	10-point Likert scale for severity of mood symptoms in previous 48 hours
Schedule for the Evaluation of Individual Quality of Life Questionnaire (SEIQoL)	3	1	Self-reported areas of concern and effect on function	Identify 5 most important areas in their life and rate importance
Short Form Patient Questionnaire – 12 Item (SF-12)	12	3	Emotional problems	2 items identifying the extent to which emotional problems affected activities
Short Form Patient Questionnaire – 36 Item (SF-36)	36	6	Low mood, lack of energy, anxiety	4 items identifying the extent to which emotional problems affected activities

Sickness Impact Profile – ALS Items (SIP/ALS-19)	19	1	ALS-adapted SIP. Focus on activities of daily living, self-care and activities	No items specifically focused on mood, 1 item on social interaction
Visual Analogue Scale (VAS - 3 health status questions)	3	1	General, physical and mental health self-rating	0-100 scale for overall mental health
Visual Analogue Scale and Patient's Global Impression of Change	2	1	Pain and self-perception of health	7-point and 10-point Likert rating scales for change in emotion and overall quality of life

Table 5 reports the characteristics of the tools used in the trials and studies included in this review.

Table 5: Characteristics of Assessment Tools Identified

	Area Assessed in Trials	***Domains***	***Designed for, or adapted for MND with abnormality cut-offs***	***Administration Time (min)***	***Total Score***	
Beck's Depression Inventory	Depression	Depression	-	5-10	63	**[134]**
Columbia Suicide Severity Score	Suicidality	Suicidality	-	5-30	Binary outcome of 10 categories	**[135]**
Hamilton Depression Scale	Depression	Depression	-	20-30	52	**[136]**
Hospital Anxiety and Depression Scale	Anxiety and Depression	Anxiety and Depression	+	5-10	21 per disorder	**[137, 138]**
Neuropsychiatric Inventory Questionnaire	Depression	Neuro-psychiatric conditions	-	5	100 for 10-item & 144 for 12-item	**[139, 140]**
Amyotrophic Lateral Sclerosis Depression Inventory	Depression	Depression	+	5	48	**[141, 142]**

Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen	Cognition and Behaviour	Executive Functioning and Behaviour	+	5-10	20 for cognitive section	**[143, 144]**
Addenbrooke's Cognitive Examination	Cognition	Attention, memory, verbal fluency, language and visuo-spatial	-	15+	100	**[145]**
Montreal Cognitive Assessment	Cognition	General cognition	-	10-15	30	**[146, 147]**
Edinburgh Cognitive and Behavioural Assessment Screen	Cognition and Behaviour	Executive functioning, language, fluency, memory, visuospatial, social cognition, verbal fluency index and behaviour	+	15-25	136 for cognitive section.	**[148]**
Frontal Behavioural Inventory	Behaviour	Behaviours characteristic of FTD	-	15-30	Severity rating 0-3 on 24 items	**[149, 150]**
Verbal Fluency	Cognition	Language	+	<5	N/A	**[73, 150]**
Mini Mental State Examination	Cognitive	General cognition	-	<5	30	**[151]**

+ Test designed or adapted for ALS and ALS-specific impairment thresholds are available
- Test not designed/adapted for ALS and no ALS-specific impairment thresholds currently available

NB: Time to administer is indicated as a guide only. This will vary depending upon the respondent's functional ability, presence of a communication impairment and use of assistive devices and the researcher's experience in administering the instrument.

The only tool specifically designed and validated for neuropsychiatric assessment in people with MND, the MND Depression Inventory (ADI-12) [141], was used in 1 trial. This tool is validated to screen for depressive symptoms in people with MND, with a sensitivity of 100% and specificity of 82%, meaning all people with a major depressive disorder were identified [141]. However, this tool focuses only on the evaluation of depression and does not account for the range of neuropsychiatric symptoms which may affect people with MND.

The other tools used in the trials included in this review are Beck's Depression Inventory (BDI) [134], Hamilton Depression Inventory (HAM-D) [136], Columbia Suicide Severity Score (C-SSRS) [135], Hospital Anxiety and Depression Scale (HADS) [138] and the Neuropsychiatric Inventory Questionnaire (NPI-Q) [139]. The BDI and HAM-D are extensively validated [152, 153], well-established measures of depressive symptoms. However, their reliance on somatic features of depression mean scores may be confounded by physical decline and no MND-specific impairment thresholds are available. The HADS is designed to reduce the focus on somatic symptoms and MND-specific impairment thresholds have been proposed [137].

The C-SSRS is a considered a useful tool to structure discussions of suicidal ideation and intent [154]. However, the C-SSRS can be lengthy to administer, insufficient to cover the full spectrum of suicidal ideation [155] and responses to questions of end-of-life planning may be influenced by the presence of a terminal diagnosis. The NPI-Q is a validated informant-based questionnaire to evaluate the presence and severity of 12 neuropsychiatric domains [140].The ability of the tool to discriminate effectively between disorders has been queried [156]. Of the 8 trials that did assess cognitive and behaviour change as an outcome measure, 6 used tools where scoring was unaffected by physical or communication impairment and were specifically designed, and validated, to identify domains impaired in people with MND. 1 trial used the MND Cognitive Behavioral Screen (MND-CBS) [144] and 5 trials used the Edinburgh Cognitive and Behavioural MND Screen (ECAS) [148].

The MND-CBS is a brief assessment of executive functions while the ECAS assesses a wider profile of cognitive and behavioural impairment in MND including executive and language functions, fluency and social cognition. Both are designed to be completed by either written or spoken responding to be suitable for MND patients with differing disabilities. Additionally, ECAS scoring is also corrected for differences in motor speed during both speech and writing tasks, to accommodate for a range in disability severity.

Additionally, the Montreal Cognitive Assessment Scale (MoCA) [146], Addenbrooke's Cognitive Examination (ACE-III) [157] and Mini Mental State Examination (MMSE) were used to evaluate

cognition in the trials reviewed. Although widely validated for use in neurological conditions, particularly dementia, these tools were not specifically designed to assess the cognitive profile of people with MND. As a result, no MND-adapted thresholds for impairment were available and scoring on the tools was potentially impacted by motor decline experienced in MND.

Verbal fluency a commonly found deficit in MND and is included as a sub-test on other cognitive assessments identified in this review, and as a standalone test of cognition in one trial. However, it was not clear from the trial record if motor speed was controlled for in the assessment which can affect interpretation of the scores [73].

The Frontal Behavior Inventory (FBI) [150], and the behavioural interview of the ECAS and MND-CBS, were utilised to screen for behavioural symptoms which may be indicative of fronto-temporal dementia. An additional assessment tool used by one trial, to exclude individuals with an intellectual disability, is the Wechsler Adult Intelligence Scale (WAIS) [158]. As the WAIS was intend to screen for lower intelligence quotients rather than specific cognitive impairments we have not included this tool in Table 5 which focuses specifically on tools used to assess neuropsychiatric symptoms and cognitive impairment.

2.6 Discussion

This review of 216 clinical trials from the last 25 years of MND research highlights that assessment of neuropsychiatric and cognitive symptoms has been frequently neglected. Only one trial assessed the impact of the candidate drug on both neuropsychiatric symptoms and cognitive impairment. This is despite overwhelming evidence that these non-motor features are prevalent across, and impactful upon, people with MND.

Whilst the impact on physical functioning and survival justifiably remain the primary objectives for clinical trials of MND, the importance of additional assessments for neuropsychiatric and cognitive functioning needs to be addressed. This will enable future trial design to align with the 2019 revision of Airlie House consensus guidelines, recommendations for the design and implementation of clinical trials in MND.

As the only globally licensed treatment for MND, riluzole use is sometimes an exclusion criteria, or a minimisation criteria at point of randomisation, in many MND trials. The effect of riluzole on cognition in people with MND is not yet established, with study results reporting variable impact [56, 57]. Frequent inclusion in trials in other neurological conditions, and conflicting reports of impact, provides further justification for the inclusion of cognitive measures to evaluate how established medications such as riluzole, and exploratory study drugs, impact upon people with MND.

2.6.1 *Assessment of Neuropsychiatric and Cognitive Symptoms in Trials*

Despite research indicating the presence of neuropsychiatric symptoms and comorbidities as pervasive and pernicious in people with MND, the impact of candidate drugs on neuropsychiatric functioning is under evaluated. Of the 216 trials included in this review, only 8 reported using a formal neuropsychiatric assessment tool. Accuracy of evaluation is additionally hindered by the limited availability of tools specifically designed and validated for neuropsychiatric evaluation of the MND population.

A diagnosis, historical or current, of symptoms of a neuropsychiatric disorder were still explicitly identified as an exclusion criterion for the majority of trials included in this study. Cognitive impairment was also often included as an exclusion criterion, with thresholds for impairment often subjective or not addressed. This could be due to researcher's concerns over capacity to consent, potential issues with adherence, compliance with assessments and medication regimens.

Ultimately, results from studies with strict exclusion criteria, thus reducing the sample representativeness of a heterogeneous patient group, may not be generalisable to the whole MND population. Furthermore, excluding individuals with and neuropsychiatric conditions and cognitive impairment, unless when absolutely necessary, and neglecting to include these dimensions as outcome measures, misses a vital opportunity to explore how candidate drugs may affect people with MND across this diverse condition.

2.6.2 *Assessment of Cognition in Clinical Trials*

The last 15 years of research has highlighted the ubiquity of cognitive and behavioural impairment in people with MND, [148, 159]. Whilst the assessment of these changes has become widely accepted in clinical care for people with MND [160], clinical trials are lagging behind, with only 21% of the 216 trials reviewed in this study assessing cognition.

The inclusion of cognitive assessment in clinical trial design as an additional outcome measure is progressing slightly. In the previous decade of research, 2010 to 2020 inclusive, 7% (n = 6) of 86 trials registered, commenced or published within this time frame assessed cognition as an outcome measure. In comparison, of 101 trials from the decade prior, 2000 to 2010, 2% (n = 2) assessed cognition as an outcome measure.

Cognitive assessment in trial design is also increasing in accuracy, in part due to the availability of MND-specific tools validated specifically to assess the domains impaired in this cohort [144, 161]; particularly the MND Cognitive Behavioral Screen (MND-CBS) and Edinburgh Cognitive and

Behavioural MND Screen (ECAS) in the trials reviewed here. Cognitive assessments used previously may not be suitable for individuals with physical disabilities, due to an over-reliance on motor tasks, and limited focus on cognitive domains impaired in people with MND.

Our review focused on the inclusion of cognitive functioning assessment in trial design, however, assessing evolution in in cognitive functioning during disease trajectory may also be of interest in future trial design. Longitudinal cognitive assessments were evaluated as an outcome measure in the MND Multicentre Cohort Study of Oxidative Stress (MND COSMOS [162]). Baseline data in this study of 247 participants evaluated with the MND-CBS, indicated that cognitive and behavioural impairments were common, 6.5% scoring below cut-offs for frontotemporal dementia [144], 54.2% scoring consistent with mild cognitive impairment and behavioural sub scores outside the normal range in 30.6% of responders [163]. Analysis of longitudinal data did not detect cognitive decline over a 12 month period but did detect an increase in behavioural changes, notably disinhibition, while initial behavioural impairment predicted attrition [164]. Other studies have demonstrated increasing prevalence of cognitive and behavioural impairment in later disease stages [165, 166].

Non-interventional studies which have assessed change in cognition over time have shown mixed results [166, 167]. Attrition of individuals with cognitive and/or behavioural impairments from longitudinal repeated assessments may also bias the sample towards individuals with slower disease progression and more stable cognitive functions.

Only one trial in this review, the Omigapil trial (NCT00072709), reported data on cognitive outcomes. No change in neurocognitive secondary outcome measure was reported, with the Addenbrooke's Cognitive Examination (ACE) [132]. Understanding of cognitive change across the disease course is of prime importance for the interpretation of cognitive data in clinical trials.

2.6.3 *Conclusion*

This review clearly demonstrates that the impact of candidate drugs on neuropsychiatric symptoms and cognition has been under-evaluated in clinical trials, and that when these symptoms have been evaluated, the tools used may not be suitable for people with MND. Accurate identification of neuropsychiatric comorbidity and cognitive impairment is an essential requirement to improve our understanding of how candidate drugs impact the non-motor features of MND.
The evaluation of neuropsychiatric and cognitive symptoms is recommended for inclusion as additional outcome measure in clinical trials of investigative medicinal products. Additionally, when evaluating these areas, using tools which are designed to assess domains affected in MND and are adapted to account for motor decline and communication difficulties is crucial.

2.7 Key Findings

- A systematic review of 216 clinical trials from the previous 25 years of MND research
- Only one trial assessed the impact of the candidate drug on both neuropsychiatric symptoms and cognitive impairment
- 21% (n = 46) of the 216 trials included assessed cognition; 83% as an exclusion criteria and 17% as an outcome measure
- 35% (n = 76) of the 216 trials included assessed neuropsychiatric symptoms; 92% as an exclusion criteria, 3% as an outcome measure and 5% as both
- Quality of life measures were outcomes in 28% of trials

- **These symptoms are important features of MND and the potential impact of candidate drugs on cognition and neuropsychiatric symptoms must be considered**

3 Chapter 3: Systematic Review 2: A Systematic Review of Non-Motor Symptom Evaluation in Clinical Trials for Motor Neuron Disease.

The substantial body of this work has been published [168] and the full paper is available in Appendix 2.

Beswick, Emily, Deborah Forbes, Zack Hassan, Charis Wong, Judith Newton, Alan Carson, Sharon Abrahams, Siddharthan Chandran, and Suvankar Pal. "**A systematic review of non-motor symptom evaluation in clinical trials for amyotrophic lateral sclerosis**." *Journal of Neurology* (2021): 1-16.

To expand upon the findings of the systematic review of neuropsychiatric, behavioural and cognitive assessments in clinical trials, a further systematic review of historical clinical trials and the outcome measures used was pursued, this time broadening search criteria to additional non-motor symptoms. MND is a multi-system disorder, with a wide range of symptoms occurring secondary to, or distinct from, motor degeneration. Symptoms such as cognitive impairment, behavioural change, neuropsychiatric, pain, sleep disturbance, problematic saliva and fatigue can often have a significant impact on quality of life, disability and caregiver burden.

In the first review neuropsychiatric, behavioural and cognitive assessments in clinical trials were found to be underutilised. The aim of this review was to explore the frequency of evaluation and assessment tools used in historical MND trials for a wider range of non-motor symptoms. Exploring the potential additional benefits, and side-effects, of candidate drugs, enables consideration of the impact of these drugs beyond motor function.

3.1 Abstract

Background: Motor neuron disease (MND) is increasingly recognised as a multi-system disorder, presenting with common and impactful non-motor symptoms, such as problematic saliva, neuropsychiatric, cognitive and behavioural changes, pain, disordered sleep and fatigue.

Aim: We aimed to systematically review 25 years of clinical trials data in MND to identify if non-motor features were evaluated, in addition to the traditional measures of motor functioning and survival, and where evaluated to describe the instruments used to assess.

Hypothesis: We hypothesised that assessment of non-motor symptoms has been largely neglected in trial design and not evaluated with MND specific instruments.

Methods: We reviewed clinical trials of investigative medicinal products in MND, since the licensing of riluzole in 1994. Trial registry databases including WHO International Trials Registry, European Clinical Trials Register, clinicaltrials.gov, and PubMed were systematically searched for Phase II, III or IV trials registered, completed or published between 01/01/1994 and 16/09/2020. No language restrictions were applied.

Results: 237 clinical trials, including over 29,222 participants, were investigated for their use of non-motor outcome measures. These trials evaluated neuropsychiatric symptoms (75, 32%), cognitive impairment (16, 6.8%), behavioural change (34, 14%), pain (55, 23%), sleep disturbances (12, 5%) and fatigue (18, 8%). Problematic saliva was assessed as part of composite ALSFRS(R) scores in 184 trials (78%) but with no focus on this as an isolated symptom, 31 (13%) trials including 3,585 participants did not include any assessment of non-motor symptoms.

Conclusions: Non-motor symptoms such as neuropsychiatric, cognitive and behavioural changes, pain, disordered sleep, fatigue, and problematic saliva have not been consistently evaluated in trials for people with MND. Where evaluated, non-symptoms were primarily assessed using instruments and impairment thresholds that are not adapted for people with MND. Future trials should include non-motor symptom assessments to evaluate the additional potential therapeutic benefit of candidate drugs.

3.2 Lay Summary

MND has been traditionally thought of as a 'motor disorder'; affecting the muscles people use to move and breath. In addition to these 'motor symptoms' people with MND can also experience other health problems, related to their disease, which are collectively known as 'non-motor symptoms' as they can occur as well as the motor symptoms.

Non-motor symptoms that are common in MND, and can have a significant impact on people's quality of life include problematic saliva, mental health symptoms, pain, cognitive impairment, and changes in behaviour, fatigue, and disturbed sleep.

In this study data from 237 clinical trials conducted over the last 25 years was reviewed. The study investigated how many of these trials assessed non-motor symptoms and the tools used for these assessments.

Results showed that non-motor symptoms were not consistently assessed in trials. By focusing only on how new drugs affect motor symptoms it may be that trials are missing out on finding out how new drugs could have a positive effect on improving these non-motor symptoms for people with MND. In addition, trials may also be missing how new drugs treatments may make non-motor symptoms worse, which may affect how suitable to prescribe they are for some people with MND.

This study also found that when non-motor symptoms were assessed they were often asked about by single superficial questions found within larger tools that focused on evaluating physical functioning and quality of life.

In future trials it is important to consider how new drugs tested affect non-motor symptoms, and where possible, use assessment tools which are designed for, or adapted to, detect the symptoms and changes people with MND may experience.

3.3 Introduction

3.3.1 Non-Motor Assessment in MND

The focus of assessment and symptom management in MND is traditionally on limb weakness, speech and swallowing difficulties, and respiratory failure. Despite this, a range of other symptoms are repeatedly reported as impactful and poorly evaluated in people with MND including, neuropsychiatric symptoms, cognitive and behavioural changes, pain, disordered sleep, fatigue, and problematic saliva [51]. Clinical management [61] and trial design guidelines for MND [32] have evolved to incorporate evaluation and treatment of non-motor symptoms as part of holistic assessment of MND [62].

The work in Chapter 2 has reported how neuropsychiatric, cognitive and behavioural assessments have been employed as outcome measures and exclusion criteria in MND trials [119]. This identified that these aspects were under-evaluated in trial design, and often using measures unsuitable, or not adapted for, people with progressive disability. This study broadens scope to include other non-motor symptoms important in MND: neuropsychiatric symptoms, cognitive and behavioural change, pain, sleep disturbance, fatigue, and problematic saliva. In addition the assessment tools used as outcome measures are evaluated in greater detail, alongside neuropsychiatric and cognitive assessments to provide a more complete picture of non-motor evaluation.

3.3.2 Clinical Care and Trial Design

The focus on motor symptoms in clinical and research contexts is likely driven by the limited availability of disease modifying drugs available to people with MND. To deliver holistic disease management for people with MND it is necessary to expand conceptualisation of 'treatment' beyond improved physical function and extended survival. Effective management, or ultimately slowed progression, of non-motor symptoms due to pharmacological intervention should be evaluated as part of any novel investigative medicinal products' efficacy in clinical trials [98]. Inclusion of alternative outcome measures to evaluate potential impact of candidate drugs on non-motor impairment is recommended as a potential area of consideration for trial design in the current Airlie House guidelines, which focus on MND-specific trial development recommendations [32]. The potential beneficial effect of candidate drugs which successfully manage non-motor features of a debilitating condition may have significant clinical impact, improving quality of life, reducing disability and disease burden.

The method of assessment is also of particular relevance in trials of people with MND. Due to progressive disability, overlap with somatic symptoms, disease-specific impairments and speech decline, traditional measures may not be as effective in detecting change in symptoms, directly reducing their suitability to evaluate people with MND [51]. This can be mediated through using tools which are validated specifically for this cohort [141, 161], or tools with revised impairment thresholds [169] which account for the specific profile of impairment characterised by MND. In this systematic review of non-motor outcome measures in MND trials, the types of assessment tools used and their suitability to evaluate non-motor presentations in this population are considered.

3.4 Methods

We completed a systematic, unbiased, search of trial registries including clinicaltrials.gov, World Health Organisation's (WHO) International Clinical Trials Registry Platform (ICTRP), European Union Clinical Trials Register (EduraCT) and PubMed on 16/09/2020 for Clinical Trials of an Investigational Medicinal Product (CTIMP). Using the search terms "amyotrophic lateral sclerosis" or "motor neuron* disease" we searched clinicaltrials.gov for interventional trials of investigative medicinal products. We searched European Union Clinical Trials Register (EduraCT) and WHO International Clinical Trials Registry Platform (ICTRP) for trials of "amyotrophic lateral sclerosis" with the filters "Phase II", "Phase III" and "Phase IV" applied. Using the advanced search feature we filtered PubMed with ("amyotrophic lateral sclerosis"[MeSH Terms] OR "motor neuron* disease" [MeSH Terms]). We then applied the 'Clinical Trial' filter for Article Type, Human trials only and Publication Date within the criteria defined above.

Phase II, III or IV trials assessing potential disease modifying therapies in subjects with any form of motor neuron disease that were registered, completed or published between 01/01/1994 to 16/09/2020 were included. No language restrictions were applied. Extension trials, post-hoc analysis papers, stem cell therapies, imaging studies, medical device studies, non-MND subjects and trials focused on symptom management were excluded.

3.4.1 Data Extraction

The following details of selected trials were extracted "Investigational Medicinal Product (IMP) Assessed", "Number of Participants", "Date of Commencement", "Primary Outcome Measure(s)" and "Secondary Outcome Measure(s)". We reviewed each assessment tool used as an exclusion criteria or outcome measure in the included trials to explore whether they evaluated non-motor symptoms;

defined in this study as neuropsychiatric, cognitive impairment, behavioural changes, pain, disordered sleep, fatigue, and problematic saliva. Each assessment tool was categorised as MND-specific, symptom-specific, both MND and symptom specific or generic in content focus. We then reviewed each trial included in this review for their use of each assessment tool and subsequent evaluation of each non-motor symptom. Each assessment tool was reviewed and data extracted on the intended focus of assessment, administrator (clinician or self-report), if the scoring is affected by the presence of motor disability or speech impairment and the time to administer. We also explored the availability of disease specific impairment thresholds where applicable, and the availability of non-English translations.

3.5 Results

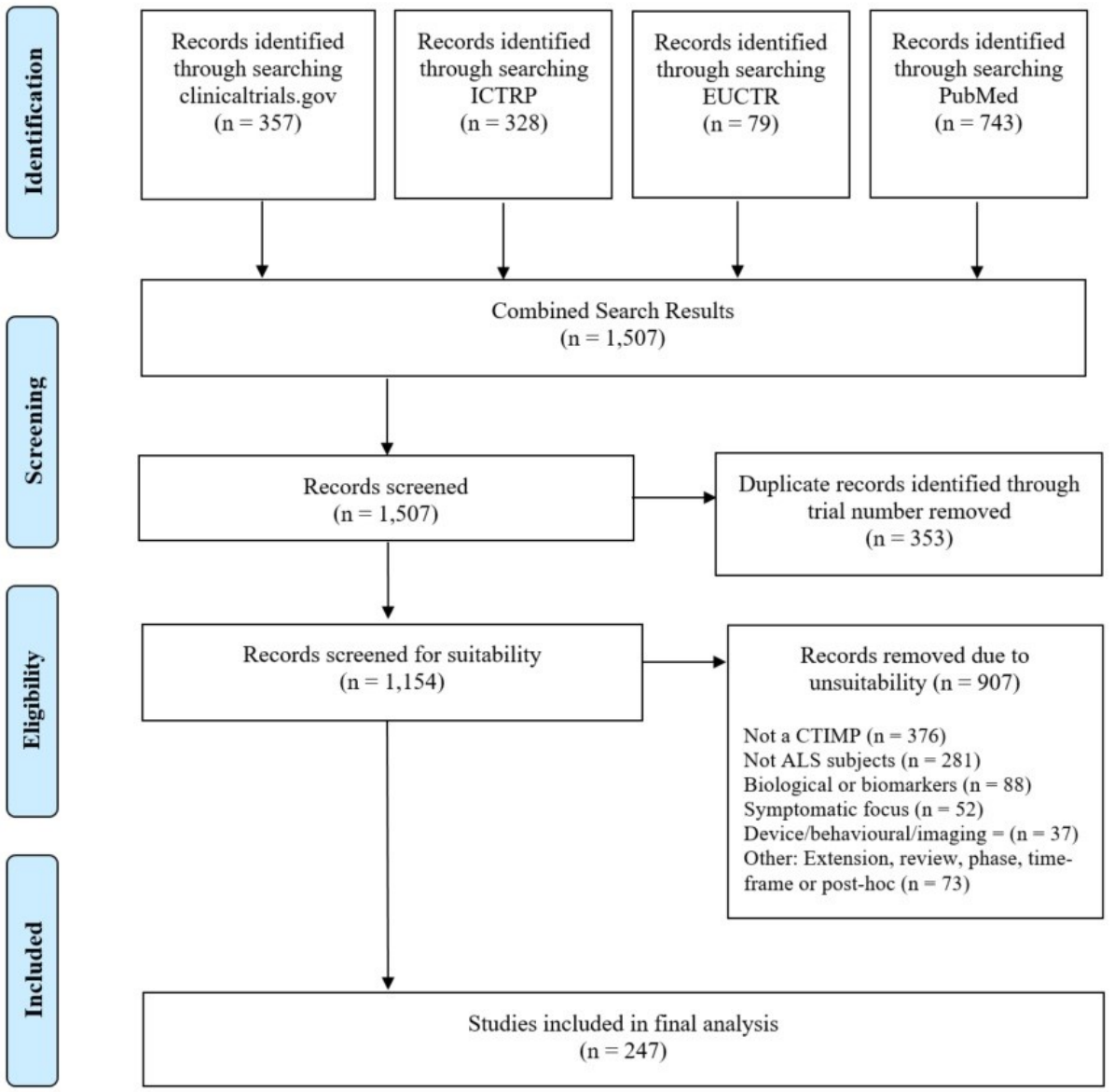
3.5.1 Overview

The search identified 1,507 records, (PRISMA diagram in Figure 3). 353 were removed due to duplication and 907 did not meet inclusion criteria (defined Figure 3); in particular results which were not clinical trials of investigative medicinal products and non-MND subjects. 237 clinical trials remained. These trials were proposed to include over 29,222 trial participants with MND. The non-motor symptoms evaluated in this review are neuropsychiatric, cognitive impairment, behavioural changes, pain, disordered sleep, fatigue, and problematic saliva.

Table 6 summarises the reported prevalence of these symptoms in the MND population, and the pharmacological and non-pharmacological treatments suggested with evidence derived from a Cochrane database systematic review of treatments [62] and United Kingdom National Institute for Clinical Excellence (NICE) clinical care guidelines [61]. The trials forming the main dataset of this review are focused on therapeutic targets for motor-symptoms and improving survival.

Table 7 provides a detailed overview of how frequently each non-motor symptom considered in this review was evaluated in the clinical trials. These seven symptoms were included as outcome measures or evaluated within quality of life measures (QoL) in 206 trials (87%). Neuropsychiatric symptoms were assessed in 75 trials (32%) and cognitive impairment was evaluated as an outcome measure in 16 trials (6.8%) Behavioural change was evaluated in 33 trials (14%), pain in 55 trials (23%) and fatigue in 18 trials (8%).Sleep disturbances were evaluated in 12 trials (5%). Whilst saliva assessment was included in 184 trials (78%) this was part of a composite measure embedded within the either the ALSFRS(R) [170] or the CNS-BFS (Centre for Neurologic Studies Bulbar Function Scale [171]), and the impact of drugs of saliva problems was not assessed specifically. 31 trials (13%) did not include any assessment of saliva, neuropsychiatric, cognitive impairment, behavioural changes, pain, disordered sleep and fatigue as an outcome measure or evaluate within a quality of life measure.

Figure 3: PRISMA Diagram for Record Selection



From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009).
*P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

Table 6: Non-Motor Symptoms, Prevalence and Assessments in MND

Symptom	Details	Reported Prevalence	Non-Pharmacological Interventions	Pharmacological Interventions	References
Neuropsychiatric	• Depression • Anxiety • Suicidal ideation • Emotional lability	Depression 0-44% Anxiety 0-33% Suicidal ideation 13.3% Emotional lability 50%	• Talking therapies • Music therapy • Hypnosis • Mindfulness • Cognitive behavioural therapy	• Benzodiazepines and other anxiolytic medications • Antidepressants (particularly the SSRI and TCA groups) • Dextromethorphan and quinidine combination for emotional lability • Amitriptyline due to additional anticholinergic effects on excessive saliva and insomnia	[68, 172-175]
Cognitive Impairment	• Executive dysfunction • Social cognition • Verbal fluency • Working memory • Language dysfunction	30-50% of people with MND have some level of cognitive impairment 6-14% of people with MND reach threshold for FTD	• Trial of non-invasive ventilation (NIV) to evaluate if cognitive problems may be related to respiratory impairment	• No medications to address AL specific cognitive impairment currently available • Cognitive status must also be considered in prescribing symptom management drugs • Glycopyrrolate as first option of treating sialorrhea in people with MND with cognitive impairment as this has fewer central nervous system side-effects	[61, 62, 71, 79, 176]

Behavioural Change	• Apathy • Impulsivity • Disinhibition • Perseveration • Loss of Sympathy/empathy • Hyper orality and change in eating behaviour	24-69% of people with MND experience some behavioural change Apathy is most common behavioural change, experienced by 28% of people with MND	No ALS-specific but FTD interventions available which may be beneficial: • Environmental management (reducing noise, clutter and stimuli and avoiding potentially problematic situations) • Non-verbal cues • Creating reward systems	• Benzodiazepines	[71, 76, 176]
Pain	• Spasticity • Cramps • Joint immobility • Pressure sores	Up to 57% of people with MND report pain	• Exercise programmes (physiotherapy)	Cramps • Quinine • Levetiracetam • Mexiletine Spasticity • Nonsteroidal anti-inflammatories • Muscle relaxants • Baclofen, tizanidine or • dantrolene • Intrathecal baclofen	[62, 86, 87, 175, 177]
Sleep Disturbances	• Poor quality sleep • Difficulty getting to, or staying, asleep • Daytime sleepiness	Exact prevalence unknown due to multiple potential aetiologies of sleep problems but 45-60% of people with MND report disturbed sleep due to breathing problems	• Non-invasive ventilation	• Amitriptyline (antidepressant with additional benefit of insomnia management) • Sedatives (opioids and benzodiazepines)	[62, 82, 178-180]

Fatigue	• Mental fatigue • Physical fatigue	44% of people with MND experience clinically significant fatigue and this is associated with disease severity	• Resistance exercise • Respiratory exercise • Repetitive transcranial magnetic stimulation (rTMS)	• Modafinil	[61, 62, 83, 181]
Saliva	• Excessive oral secretion • Dry mouth	Problematic saliva 37.5%	• Radiotherapy • Suction • Humidification of NIV	• Hyoscine patches • Amitriptyline • Atropine drops • Glycopyrrolate • Carbocisteine • Botulinum toxin	[61, 62, 91, 175, 182]

Table 7: Non-Motor Symptoms Evaluated and Assessments Used

Tool	Intended Area of Focus	Non-Motor Symptom Assessed	Separate Score for Non-Motor Symptom?	MND-Specific Tool	Symptom-Specific Tool	MND *and* Symptom Specific Tool	Frequency of Use as an Outcome Measure *
C-SSRS (Columbia Suicide Severity Rating Scale)	Suicidality	Neuropsychiatric	Yes	No	Yes	No	4
NPI-Q (Neuropsychiatric Inventory Questionnaire)	Neuropsychiatric	Neuropsychiatric	Yes	No	Yes	No	1
ESAS (Edmonton Symptom Assessment Scale)	Quality of Life	Neuropsychiatric	No	No	No	No	1
		Pain	No	No	No	No	1
		Sleep	No	No	No	No	1
HADS (Hospital Anxiety and Depression Scale)	Anxiety & Depression	Neuropsychiatric	Yes	No	Yes	No	2
ADI-12 (Amyotrophic Lateral Sclerosis Depression Inventory – 12 item)	Depression	Neuropsychiatric	Yes	No	No	Yes	1
HAM-D (Hamilton Depression)	Depression	Neuropsychiatric	Yes	No	Yes	No	3
ALSQOL-R (Amyotrophic Lateral Sclerosis Specific Quality of Life – Revised and Short Form)	Quality of Life	Pain	No	Yes	No	No	33
		Fatigue	No	Yes	No	No	33
		Neuropsychiatric	No	Yes	No	No	33
		Sleep	No	Yes	No	No	33

		Cognition[ɪ]	No	Yes	No	No	33
SF-8, SF-12 and SF-36 (Short Form Health Survey – 8 item, 12 item or 36 item)	Quality of Life	Pain	No	No	No	No	31
		Neuropsychiatric	No	No	No	No	31
SEI-QoL (Schedule for Individual Quality of Life)	Quality of Life	Self-reported (any)	No	No	No	No	1
ALSAQ-5 (Amyotrophic Lateral Sclerosis Assessment Questionnaire – 5 item)	Quality of Life	Neuropsychiatric	No	Yes	No	No	6
ALSAQ-40 (Amyotrophic Lateral Sclerosis Assessment Questionnaire – 40 item)	Quality of Life	Pain	No	Yes	No	No	34
		Neuropsychiatric	No	Yes	No	No	34
EQ-5D-5L and EQ-5D-3L (EuroQol – 5 Dimension – 5 and 3 Level)	Quality of Life	Pain	No	No	No	No	13
		Neuropsychiatric	No	No	No	No	13
McGill or McGill Revised	Quality of Life	Neuropsychiatric	No	No	No	No	9
KFSS (Krupp Fatigue Severity Scale)	Fatigue	Fatigue	Yes	No	Yes	No	3
VAS (Visual Analog Scale)	General	Fatigue	Yes	No	No	No	5
		Pain (cramp)	No	No	No	No	7
		Sleep	No	No	No	No	1
		Behavioural (emotionality)	No	No	No	No	1
		Saliva	No	No	No	No	1
SIP (Sickness Impact Profile)/ALS-19	General	Behaviour	No	No	No	No	5

		Neuropsychiatric	No	No	No	No	5
		Sleep	No	No	No	No	5
ALSFRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale)	Physical function	Saliva	No	Yes	No	No	182
ESS (Epworth Sleepiness Scale)	Sleep	Sleep	Yes	No	Yes	No	2
PSQI (Pittsburgh Sleep Quality Index)	Sleep	Sleep	Yes	No	No	Yes	1
Norris Scale	Physical functioning	Behavioural	No	Yes	No	No	18
ECAS (Edinburgh Cognitive Assessment Screen)	Cognition and Behavioural Change	Behaviour	Yes	No	No	Yes	14
		Cognition	Yes	No	No	Yes	14
FBI (Frontal Behavioural Inventory)	Behavioural Change	Behaviour	Yes	No	Yes	No	1
ACE-III (Addenbrooke's Cognitive Examination – III)	Cognition	Cognition	Yes	No	Yes	No	2
ALS-CBS (Amyotrophic Lateral Sclerosis Cognitive Behavioural Screen)	Cognition and Behavioural Change	Behaviour	Yes	No	No	Yes	2
		Cognition	Yes	No	No	Yes	2
MoCA (Montreal Cognitive Assessment)	Cognition	Cognition	Yes	No	Yes	No	1
Verbal Fluency	Cognition	Cognition	Yes	No	Yes	No	1
CNS-BFS (Centre for Neurologic Bulbar Function Scale)	Physical function	Saliva	No	Yes	No	No	2
CNS-LS (Centre for Neurologic-Lability Scale)	Emotional lability	Behaviour	Yes	No	Yes	No	1

DSM (Diagnostic Statistical Manual) and frontotemporal dementia criteria (FTD)	Diagnosis criteria	Behaviour	No	No	Yes	No	2
Symptom-specific Questionnaires	General	Pain (cramp)	Yes	No	Yes	No	1
		Fatigue	No	No	Yes	No	1
No Data on Assessment Tool	Emergent suicidality	Neuropsychiatric	No	No	No	No	1

** Please be aware that this is the number of times used, not the number of trials, as some trials may have utilised several outcome measures to evaluate the same non-motor symptom or a single outcome measure several times*
[1] Indicates self-reported cognitive problems, not a formal clinician assessment of cognitive function

3.5.2 Symptom Evaluation

3.5.2.1 Neuropsychiatric Symptoms

Neuropsychiatric symptoms were assessed within quality of life measures in 61 trials (26%); 29 (48%) of these trials used MND-specific quality of life measures, 29 (48%) generic and three a combination. Four trials used a combination of generic quality of life measures and neuropsychiatric assessments that were not MND-specific. No data on assessment tool used was available for one trial.

Seven trials used neuropsychiatric measures which were not developed specifically for people with MND; ESAS (Edmonton Symptom Assessment Scale [183]), Hamilton-Depression [184], NPI-Q (Neuropsychiatric Inventory Questionnaire [140]) and C-SSRS (Columbia Suicide Severity Rating Scale [185]). Only one trial utilised an MND-specific neuropsychiatric assessment of depression, the ADI-12 (MND Depression Inventory [141]), in combination with the more widely used HADS (Hospital Anxiety and Depression Scale [138]), the unmodified version.

Trials evaluating neuropsychiatric symptoms within quality of life measures utilised: Edmonton Symptom Scale (ESS [183]), MND Specific Quality of Life (ALSSQOL-R [186]), MND Assessment Questionnaire (ALSAQ [187]), Short Form Health Survey (SF [188]), EuroQol [189], McGill[190] and Sickness Impact Profile (SIP [191]). These quality of life measures did not provide separate scores for the neuropsychiatric symptoms evaluated. Items focusing on neuropsychiatric symptoms

were often limited to binary assessment (present or absent) with scoring reported within the overall quality of life score, making change over time difficult to ascertain.

3.5.2.2 Cognition and Behaviour Change

Cognition was evaluated in 16 trials (7%); within quality of life measures in five trials (Sickness Impact Profile/MND-19 and ALSQOL-R. Seven trials used the ECAS (Edinburgh Cognitive Assessment Screen[161]) and one used the MND-CBS (MND Cognitive Behavioural Screen [144]), both MND-specific measures of cognitive impairment. One of the seven trials using the ECAS also evaluated cognition using the MoCA (Montreal Cognitive Assessment [146]), a measure of global cognition that is not specifically designed for people with MND. Two trials used the ACE-III (Addenbrooke's Cognitive Assessment [145]) and another a test of verbal fluency, both tests of cognitive function which are not disease-specific.

People with MND may lack insight into cognitive and behavioural changes [192], or downplay experiences due to stigma [193]. Objective measures (such as the ECAS, MND-CBS, MoCA, ACE-III, verbal fluency) focus on clinical evaluation and task-based assessments, whereas self-report measures (such as the SIP/MND-19 and ALSQOL-R) are reliant on the person with MND to recognise and disclose their cognitive difficulties.

34 trials (14%) evaluated behavioural symptoms in participants. Five of these were within the context of quality of life measures; SIP and MND-19. Nine were within assessment tools also evaluating cognition, eight trials using measures such as the ECAS and MND-CBS which are specifically designed for MND and one trial using the FBI (Frontal Behavioural Inventory [194]), a non-disease-specific assessment including behavioural items. Emotional lability is a key behavioural change experienced by some individuals with MND and was evaluated in 19 trials; 18 of which used the Norris scale (which includes one item assessing emotional lability [195]) and one the visual analogue scale on emotionality.

3.5.2.3 Pain

Pain was evaluated in 55 trials (23%). Assessment was included in the context of quality of life measures (such as the MND Assessment Questionnaire, EuroQol measures and MND Quality of Life tools) in 46 trials. Frequency of reporting changes in levels of pain are not reported separately when evaluated in quality of life measures. Cramp was specifically addressed in trials using questionnaires or visual analogue scales [196]. Other outcome measures evaluating pain utilised numeric rating

scales, functional assessments (Edmonton Symptom Assessment Scale [183]) and quantification of pain-related adverse events (NCT03690791).

3.5.2.4 Sleep

13 trials (5.5%) evaluated sleep, nine of which utilised only quality of life measures. The quality of life measures did not provide a separate score for sleep-related symptoms as the scores were reported as an overall measure of quality of life. The remaining three trials used the symptom-specific Epworth Sleepiness Scale [81], visual analogue scales and the Pittsburgh Sleep Quality Index [197].

3.5.2.5 Fatigue

18 trials (7.6%) evaluated fatigue as an outcome measure. Eight of these trials measured fatigue within quality of life measures and as a result, no separate scores for each non-motor symptom were reported, only the aggregate score for quality of life. One trial utilised the ESAS, a generic tool to document change in patient-reported symptoms. Nine trials evaluated fatigue specifically, utilising visual analogue scales, presence/absence statements, the Krupp Fatigue Severity Scale [198].

3.5.2.6 Problematic Saliva

182 trials (77%) reported using the MND-FRS or MND-FRS-(R), as an outcome measure that evaluates saliva within the context of physical function. Ten of these trials also utilised additional saliva evaluations; the CNS-BFS (Centre for Neurologic Studies Bulbar Function Scale), a visual analogue scale and the ALSSQOL-R (MND Quality of Life Revised [199]). Aside from the MND-FRS-(R) and CNS-BFS, no measures both disease and symptom-specific measures of saliva symptoms were included in the trials within this review. Neither the MND-FRS nor the CNS-BFS provide scores for the severity or frequency of an individuals' saliva problems.

3.5.3 Assessment Tools

Of the 237 trials included in this study which evaluated non-motor symptoms, 49 versions or combinations assessment tools were used. In this study we categorised assessment tools as MND-specific (designed and validated specifically for people with MND), symptom-specific (focusing only on the non-motor symptom under consideration), both (disease and symptoms specific), and generic

(evaluating the symptom within a general measure, usually a quality of life questionnaire). Six instruments used were MND-specific (designed and validated specifically for people with MND), four were symptom-specific, four were both disease and symptom specific, and seven were symptom-generic (evaluating the symptom within a general measure, for example, QoL, and not specifically evaluating that symptom).

Versions of the MND-FRS-(R) most frequently utilised (182 trials, 77%). A complete list of the assessment tools used, and the frequency that they are included as outcome measures, is available in Table 8. 208 of the 237 trials (88%) included in this study evaluated one of the listed non-motor symptoms. However, 102 (49%) of these can be accounted for with the use of the MND-FRS(R) as a primary or secondary outcome to evaluate physical progression, with a single item on hypersalivation. Table 9 provides a summary of the outcome measures explored in this review.

Table 8: Assessment Tool Characteristics

Domain	Tool Acronym	Tool Name	Administrator	Scoring Affected by Motor Disability or Speech Impairment? (Yes/No)	Disease Specific Impairment Threshold Available? (Yes/No)	Available in Languages other than English? (Yes/No)	Time to administer (Minutes)
Quality of Life	*ALSAQ-5/40*	*Amyotrophic Lateral Sclerosis Assessment Questionnaire – 5 or 40 item*	Clinician or researcher	No	Yes	Yes [200]	5-30
Quality of Life	*SIP/ALS-19*	*Sickness Impact Profile*	Self-report questionnaire	No	Yes	No	10-20
Quality of Life	*ALSSQOL*	*Amyotrophic Lateral Sclerosis Specific Quality of Life*	Self-report questionnaire	No	Yes	Yes [201]	10-20
Disease Burden	*ESAS*	*Edmonton Symptom Assessment Scale*	Self-report questionnaire	No	No	Yes [202]	5-10
Quality of Life	*EQ-5D-5L EQ-5D-3L*	*EuroQol*	Self-report questionnaire	No	No	Yes	5
Quality of Life	*McGill*	*McGill*	Clinician or researcher	No	Yes	Yes	10-20
Physical	*ALSFR(R)*	*Amyotrophic Lateral Sclerosis Functional Rating Scale*	Clinician or researcher	No	Yes	Yes	5-10
Cognition	*ACE-III*	*Addenbrooke's Cognitive Examination – III*	Clinician or researcher	Yes	No	Yes [203]	20-30

Cognition and Behaviour	*ALS-CBS*	*Amyotrophic Lateral Sclerosis Cognitive Behavioural Scale*	Clinician or researcher and caregiver questionnaire	No	Yes	Yes [204]	5-10
Cognition and Behaviour	*ECAS*	*Edinburgh Cognitive ALS Screen*	Clinician or researcher and caregiver semi structured interview	No	Yes	Yes [205, 206]	15-30
Behaviour	*FBI*	*Frontal Behavioural Inventory*	Caregiver questionnaire	No	No	Yes [207]	5-10
Behaviour	*NS*	*Norris Scale (bulbar sub-scale)*	Clinician or researcher	No	No	Yes [208]	10-20
Cognition	*VF*	*Verbal Fluency (No data available on type of test)*	Clinician or researcher	Yes	Yes	Yes	5-10
Behaviour	*CNS-BFS*	*Centre for Neurologic Studies Behavioural Scale*	Self-report questionnaire	No	No	No	10-15
Behaviour	*CNS-LS*	*Centre for Neurologic Studies Lability Scale*	Self-report questionnaire	No	No	No	5
Sleep	*PSQI*	*Pittsburgh Sleep Quality Index*	Self-report and caregiver questionnaire	No	No	Yes [209]	5-10
Sleep	*ESS*	*Epworth Sleepiness Scale*	Self-report questionnaire	No	No	Yes	5
Fatigue	*KFS*	*Krupp Fatigue Severity Scale*	Self-report questionnaire	No	No	Yes	5

3.5.3.1 Quality of Life

70 trials (30%) included quality of life assessments as outcome measures. These quality of life measures frequently contained questions on non-motor symptoms such as mood, pain and fatigue. Often these questionnaires include only a single item evaluating the presence of this non-motor symptom, with no additional information on its impact on the individual, severity or change over time [210, 211].

In the trials included in this review, 20% of the times where non-motor symptoms were assessed, this occurred within a quality of life measure, rather than a scale specifically evaluating that symptom. As a result, often no score for the non-motor symptom is reported. Of the 70 trials that used a quality of life assessment as an outcome measure, only 21 included an additional tool to evaluate non-motor symptoms, which was not the MND-FRS-(R).

A range of quality of life (QoL) measures were used as outcome measures in the trials included in this review. MND-specific measures; Sickness Impact Profile MND, MND Assessment Questionnaires, MND-Specific Quality of Life enable us to evaluate how the candidate drug affects aspects of the individual's life most likely to be affected by MND. Disease and symptom specific measures are more likely to be sensitive and specific enough to detect changes, crucial in clinical trials.

However, findings from drug trials using disease-specific measures are limited in their comparability across neurological conditions. In comparison, more general assessments of quality of life and physical functioning such as the Edmonton Symptom Assessment Scale, Short Form Health Surveys, EuroQol measures, Schedule for Individual QoL and McGill enable researchers to compare findings with existing health-related quality of life and disability data, but at the potential cost of evaluating disease-specific impairment.

3.5.3.2 Symptom-Specific Measures

Neuropsychiatric outcome measure such as the NPI-Q were neither disease-specific nor symptom-specific. Whilst useful to capture the potential presence of broad range of disorders, the utility of this measure to detect change over time is limited due to the dichotomous outcome of Yes/No to presence of disorders. Symptom-specific measures such as the HADS, C-SSRS and HAM-D were used as outcome measures in other included trials, the suitability of these measures for people with MND is uncertain, due to overlap with somatic symptoms and disease progression. This can be mediated through the use of revised disease-specific thresholds of impairment [169]. The ADI-12 is a brief

measure of depressive symptoms, specifically designed and validated for people with MND [141]; evidence base and comparability outside MND is limited.

The ECAS and MND-CBS are disease-specific measures of cognitive and behavioural symptoms in people with MND. Designed and validated for use in this population, they focus on the aspects of cognition and behaviour which are most affected in this condition and are sensitive to detecting changes across repeated assessment [212]. The MoCA and ACE-III are measures of global cognition, whilst not specifically intended to evaluate cognitive impairment in people with MND they may have utility as outcome measures in trials to detect potential changes. However, both of these assessments rely on drawing tasks to evaluate cognitive functioning, the scoring on which may be detrimentally affected by the physical progression characteristic of MND.

Verbal fluency is a measure of a specific aspect of cognition, often affected in people with MND, however, using this assessment in isolation may be insufficient to detect the broad range of cognitive function that can be affected by MND progression.

As MND exists on a disease spectrum with frontotemporal dementia (FTD) [213], measures of behaviours that are included in FTD diagnosis, such as the Frontal Behavioural Inventory and DSM criteria (Diagnostic and Statistical Manual), can be of relevance to evaluating behavioural symptoms in people with MND, even those who do not meet diagnostic threshold for FTD. However, these measures may also miss the nuanced behaviours that can occur in the heterogeneous presentations of MND. Emotional lability can be a commonly experienced symptom of bulbar dysfunction, measures such as the CNS-LS, are beneficial to evaluate disease and symptom-specific outcomes.

Pain was primarily evaluated within quality of life measures, both MND-specific and generic measures. Symptom-specific assessments of pain and cramp prevalence and severity were limited to visual analogue scales and Cramp Questionnaires, which may not be sufficiently objective to detect the nuanced changes occurring within the progression of MND and the potential impact of a candidate drug.

Symptom-specific sleep measures used in the trials in this review are the Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index are beneficial to understand participant perspective and acknowledge that sleep quality is greater than just time spent at rest. However, in MND, disordered breathing and declining respiratory function can be a significant contributor to the multifactorial issue of sleep. In tools which are not MND-specific, the impact of respiratory symptoms may not be accounted for. In MND the Epworth Sleepiness Scale has the additional benefit of indicating the severity of respiratory symptoms.

Contribution of other symptoms and evaluation using symptom-specific scales is also of consideration when evaluating fatigue. Using symptom-specific outcome measures such as the Krupp Fatigue Severity Scale, and the FSS, may not reflect the interwoven contributions to the conceptualisation and causes of physical and mental fatigue experienced in MND.

3.5.3.3 Saliva Assessments

Whilst 184 (78%) trials evaluated saliva, in all of these trials saliva was assessed in the context of a single sub-domain score of the MND-FRS(R) or with other bulbar symptoms, alongside swallowing and speech, in the CNS-BFS. Impact of the candidate drug, separate SALIVA score and change in saliva problems were not reported.

MND-FRS-(R) includes a single item on hypersalivation. CNS-BFS also considers problematic saliva, and the Norris Scale an item on behavioural change. As a result, despite apparent frequent measurement of saliva, as the measurement is within the MND-FRS-(R) we know little about the potential impact of these candidate drugs on the saliva symptoms which can have a significant affect upon people with MND [85].

Of the 206 trials which included an assessment of any non-motor symptom, saliva (using larger physical function or bulbar assessment tools) was the only non-motor symptom assessed in 102 (49%) of these trials. Ultimately, excluding the use of the MND-FRS(R) as a physical function outcome measure, including the single item on salivation, saliva problems were under-evaluated. Only 80 (44%) of the 182 trials using the MND-FRS-(R), evaluating saliva, assessed any additional non-motor symptom.

Table 9: Summary of Non-Motor Outcome Measures

Non-motor Symptom	Assessment Group	Assessment Tools Used to Evaluate	Frequency of Use as an Outcome Measure (% of 237 Total Trials)
Neuropsychiatric	*QoL Measures*	Sickness Impact Profile, SF-8/12/36, ALS-19, ALSQOL, ALSAQ-5/40, ESAS, EQ-5D-5L, EQ-ED-3L, McGill	74 (31)
	Symptom-Specific	ADI-12, HADS, Hamilton-Depression, Columbia Suicide	
Cognitive	*QoL Measures*	Sickness Impact Profile, ALS-19	16 (6.8)
	Cognitive	ACE-III, ALS-CBS, ECAS, MoCA, DSM Criteria (used as dementia diagnostic criteria), Verbal Fluency	
Behavioural	*Quality of Life and Caregiver Burden*	Sickness Impact Profile, ALS-19, Zarit Burden Interview, Caregiver Burden Inventory	37 (15)
	Symptom-specific	ALS-CBS, CNS-LS, ECAS, FTD Criteria, Emotionality Analogue Scale, FBI, Norris Scale	
Pain	*Quality of Life*	ALSQOL, ESAS, EQ-5D-5L/3L, SF-12/36, McGill, ALSAQ-40	55 (23)
	Pain	Cramp Questionnaire, Numeric Rating Scale, Visual Analogue Scale	
Sleep	*Quality of Life*	ALSQOL, Sickness Impact Profile, Edmonton Symptom Assessment Scale	12 (5)
	Sleep	Visual Analogue Scale, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale	
Fatigue	*Quality of Life*	ALSQOL, Edmonton Symptom Assessment Scale	18 7.6)
	Fatigue	Visual Analogue Scale, Presence vs Absence Questions, Krupp Fatigue Severity Scale, Fatigue Severity Scale	
Saliva		ALSFRS(R), Visual Analogue Scale, ALSSQOL-R, CNS-BFS	182 (77)

3.6 Discussion

3.6.1 Overview

As conceptualisation of MND broadens from a motor-only disorder to one of multisystem involvement, it is vital that clinical management guidelines and trial design continue to reflect this. Effective symptom management remains a major priority for MND care, as stated in NICE 2016 care guidelines [61], and clinical management and trial design guidance recommend the inclusion of symptom-focused outcome measures to evaluate potential additional therapeutic benefits [32, 62].

This study considers the evaluation of non-motor symptoms as outcome measures in 237 trials proposed to include over 29,222 trial participants with MND in the last 25 years, since the licensing of riluzole in 1994. The non-motor symptoms included in this review are neuropsychiatric symptoms, cognitive and behavioural changes, pain, disordered sleep, fatigue, and problematic saliva, all of which are prevalent in and impactful in MND [51]. Our findings indicate that non-motor symptoms were not consistently evaluated and where evaluated, assessment tools were not specific to MND, or the non-motor symptom being evaluated.

Evaluating non-motor symptoms and including them as potential therapeutic targets supports the delivery of participant-centric trials and a broader conceptualisation of MND as a multifaceted disorder. Clinical trials are costly, lengthy and require huge personal sacrifices from participants, evaluating the full potential of candidate drugs beyond exclusively motor outcome measures is a vital consideration for future trials to explore the holistic impact of prospective disease modifying therapies. In Chapter 4 we report that people with MND report these symptoms as common and impactful, reducing their frequency and severity will improve the lives of people with MND now, whilst the search for a cure continues.

3.6.2 Evaluation and Management

Effective management and treatment of non-motor symptoms can have a significant impact on the lives of people with MND and their caregivers, reducing disease burden and improving quality of life [61]. Non-motor symptoms can benefit from both non-pharmacological and pharmacological interventions and in conditions such as MND where symptom management is currently the primary focus, managing these non-motor symptoms can benefit those living with MND [175]. Using non-motor assessments in clinical evaluation of people with MND can help us address these symptoms in care planning, disease management and when designing future research.

Under-evaluation of non-motor symptoms using disease specific measures is a potentially missed opportunity when considering the holistic impact of drug candidates on these troublesome symptoms. In our previous work, we found that neuropsychiatric and cognitive symptoms were consistently under-assessed in MND trials [119]. Whilst improvement in motor functioning and prolonging survival remain the main goal in clinical drug trials, additional symptomatic benefit of candidate drugs can be of great interest. An additional benefit of including measures to evaluate these non-motor symptoms in trial design is a better understanding of the potential negative impact of candidate drugs on these aspects of MND. An investigative medicinal product that may result in, or worsen existing, non-motor symptoms and in turn increase disease burden, may offset the potential improvement in motor symptoms for people with MND. Greater knowledge of these side effects can help to inform licensing decisions and future suitability for prescription of the medication to sub-groups of the MND population.

3.6.3 Assessment Tools

In other neurodegenerative conditions, such as Parkinson's disease, where non-motor symptoms are common and impactful, disease-specific and symptom-specific scales such as Parkinson's Disease Fatigue Scale [214], King's Parkinson's Disease Pain Scale [215] and Parkinson's Disease Sleep Scale [216] have clinical utility [217]. As a result, in this review we also considered the intended purpose of each of the tools utilised to evaluate non-motor symptoms. In using assessment tools that are specific to, or adapted for, the population we are evaluating, we are better able to determine the prevalence and progression of non-motor symptoms, whilst accounting for the progressive disability and speech impairments of MND that may influence responses. Including revised impairment thresholds in well-established generic measures can also be a viable alternative to mitigate potential confounding effects of MND.

3.6.4 Conclusion

This study indicates that non-motor symptoms have not been comprehensively or consistently evaluated within clinical trials of MND. An improved understanding of the frequency that these symptoms occur, and their contribution to acquired disability, will enable us to provide a more holistic overview of an MND diagnosis and potential impact of investigative medicinal products. The key strength of this study is that it provides a comprehensive evaluation of MND trials completed, published or registered since 1994. In addition, we provide a detailed overview and critique of the assessment tools used to explore these non-motor symptoms in the included trials. However, a

weakness of the current work is the focus on a limited number of non-motor symptoms in MND, namely neuropsychiatric, cognitive and behavioural changes, pain, disordered sleep and fatigue and problematic saliva. However, the scope of non-motor symptoms can be extended in future studies to assessment of other symptoms including gastrointestinal issues, dysphagia and sexual dysfunction.

We recommend that future clinical trials should include non-motor outcome measures. While it is appropriate that measurement of change in functional decline and improvement in survival remain as primary outcomes in confirmatory trials, we recommend future trials include disease specific secondary outcome measures to establish the effect of investigative medicinal products on non-motor symptoms to enable a more complete profile of how a candidate drug may affect people with MND. Cognitive assessments are already gradually receiving greater prominence in trial design [218], reflective of Airlie House guidance encouraging the use of cognitive or behavioural functioning as primary or secondary outcome measures [32].

Evaluation of the key non-motor symptoms considered in this study was primarily using tools which may not be suitable for people with MND, or generic assessments of physical function or quality of life where symptom-specific changes were not apparent. These non-motor symptoms should be evaluated with assessment tools which are MND-specific or validated for use in people with MND, including disease-specific impairment thresholds where possible.

3.7 Key Findings

- A systematic review of 237 previous, current and planned trials in MND that were proposed to include over 29,222 individuals with MND
- 31 trials (13%) did not include any assessment of non-motor symptoms including saliva, neuropsychiatric symptoms, cognitive impairment, behavioural changes, pain, disordered sleep and fatigue
- Neuropsychiatric symptoms were assessed in 32% of trials (n = 75)
- Cognition outcome measures were included in 6.8% of trials (n = 16)
- Behavioural change was evaluated in 14% of trials (n = 33)
- Pain was assessed in 23% (n = 55), fatigue in 8% (n = 18) and sleep disturbance in 5% (n = 12)
- Problematic saliva was assessed in 78% (n = 184) of trials, however, this was as part of a wider scale on physical function and no results on a drugs' impact on saliva specifically were available

- **Understanding MND as a multi-system, and reflecting this in trial design, will facilitate future trials in evaluating non-motor symptoms as potential additional therapeutic targets**

4 Chapter 4: Experimental Project 1 - Holistic Assessment of Non-Motor Symptoms for People with Motor Neuron Disease (NMS-MND)

The first aim of this thesis was to explore how non-motor symptoms had been assessed in previous trials, what symptoms were impactful and their importance to people with MND to include in future trial design.

To build on the findings from the two systematic reviews (Chapters 2 & 3), both of which indicated that non-motor symptoms are under evaluated in trial design, this study aimed to explore how people with MND experience non-motor symptoms and their opinion about including these symptoms in clinical trials.

As concluded in the systematic reviews, symptoms occurring as a result of, or in addition to, the motor degeneration characteristic of MND offer new avenues for symptom management, improving quality of life and reducing disability. Feedback from prospective participants on how they are affected by MND, their goals for treatment and preferences on methods of assessment helps inform trialists design decisions and deliver participant-centric trials.

Across the systematic review we explored the frequency, and type, of assessment for neuropsychiatric symptoms, cognitive impairment, behavioural change, pain, disturbed sleep, fatigue and problematic saliva. Based upon updated literature on potential non-motor symptoms people with MND may experience, we expanded this in our study to also consider gastrointestinal issues and sexual dysfunction as symptom prompts, whilst also encouraging participants to report any other symptoms they were affected by.

4.1 Abstract

Background: In addition to changes in physical functioning, people with motor neuron disease (MND) often experience non-motor symptoms (NMS). These may occur secondary to, or distinct from, motor degeneration, and can significantly reduce quality of life. NMS that may affect people with MND explored in this study are: pain, fatigue, gastrointestinal issues, poor sleep, low mood, anxiety, problematic saliva, apathy, emotional lability, cognitive impairment and sexual dysfunction.

Aim: This study explored the presence, frequency and impact of NMS. We also asked people with MND's perspective on how frequently these NMS are, and should be, evaluated in clinical care and included trial design. In addition, we considered people with MND's preferences for how data is collected on their symptoms.

Hypothesis: We hypothesise that non-motor symptoms will be common, impactful and occur frequently in people with MND. In addition, we hypothesise that people with MND may not find the frequency that these non-motor symptoms are assessed in clinical care, or evaluated in trial design as sufficient. As a result, we hypothesise that people with MND may be supportive of including non-motor symptom assessment in clinical trial design.

Method: People registered on the Scottish MND register (CARE-MND), who had provided prior consent to be contacted, were invited to complete a questionnaire on their NMS either online or in paper format. Participants also completed a self-reported Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS(R)) on their functional ability. This was supplemented by clinical data from the Scottish MND register.

Results: 120 people participated (91% opted for paper format). All but one participant experienced at least one NMS, with 72% reporting five or more NMS. The non-motor symptoms most often reported were pain and fatigue (76% respectively) and pain was also reported as most frequently occurring in those affected (51%). The symptoms reported to be *most impactful* were pain and problematic saliva (51% respectively). Lower ALSFRS(R) score, older age at onset and being a long survivor (diagnosed over 7 years ago) were associated with reporting more NMS. 73% of respondents were happy with the frequency that NMS were discussed in clinical care. 80% indicated they believe NMS are important to include in trials. The preferred method of assessment was completing questionnaires, at home, about symptoms.

Conclusion: People with MND are frequently affected by NMS. Pain, fatigue, gastrointestinal issues, poor sleep, low mood, anxiety, problematic saliva, apathy, emotional lability, cognitive impairment and sexual dysfunction are common symptoms affecting people with MND. Where reported, these symptoms are frequent, impactful and a priority for people with MND in clinical care and trial design.

Ethical approval was provided for this study on 19th October 2021 (Research Ethics Committee number: 21/YH/0226).

4.2 Lay Summary

The purpose of the study was to improve the understanding of how people with a diagnosis of MND are affected by non-motor symptoms. Non-motor symptoms include problems such as mental health, sleep, cognition, behaviour, fatigue, sexual dysfunction, gastrointestinal disturbance and pain.

The aim was to find out how many people with MND in our sample, taken from the Scottish MND Register (CARE-MND), report a series of non-motor symptoms as present, and if reported as present, how often these symptoms occur and their impact on the individual.

Additionally, the study explored how important people with MND think it is for clinical trials to consider non-motor symptoms, and whether if potential new treatments made non-motor symptoms worse, that would that influence their decision to try new medicines to treat the physical aspects of their disease.

The study involved sending a structured questionnaire to all people living with MND in Scotland who said that they would be interested in participating in research. 120 people responded (approximately 28% of the total number of people living with MND in Scotland).

All but one participant experienced at least one non-motor symptom, with 72% reporting five or more. The most frequently reported symptoms were pain and fatigue (affecting 76% participants). The symptoms which people reported as impacting on their lives the most were pain and problems with saliva.

73% of respondents were happy with how often they discussed non-motor symptoms at their clinical appointments. 80% of participants reported that they believed it was also important to look at how a new drug tested in a clinical trial might affect non-motor symptoms. Worsening physical health, being older when MND began and being diagnosed over seven years ago were all linked to reporting more non-motor symptoms.

4.4 Introduction

4.4.1 Non-Motor Symptoms

Non-motor symptoms such as low mood, anxiety, cognitive impairment, behavioural change, fatigue, pain, disturbed sleep, problematic saliva, sexual dysfunction and gastrointestinal issues are becoming more widely acknowledged as prevalent and impactful features of MND [51, 71].

Non-motor symptoms can be further divided as primary, those being directly a result of MND pathology, and secondary, being symptoms arising as a result of motor dysfunction. Primary symptoms, such as cognitive and behavioural change, occur as a manifestation of the pathology of the disease, associated with frontotemporal cerebral dysfunction [219]. Secondary symptoms, such as inefficient saliva clearance from bulbar motor dysfunction, pain and gastrointestinal issues from inability to move regularly, disturbed sleep to pain or anxiety, may be considered as a result of the impact of motor decline. Additional symptoms, such as low mood, anxiety, fatigue and sexual dysfunction, may be more complex in origin, occurring directly as a result of MND pathology for some people, but as a secondary aspect of the diagnosis and associated disability for others.

Symptoms may also be associated with different neuroanatomical regions [59] broadening understanding of the aetiopathogenesis of MND and provide insights into wider neuroanatomical dysfunction [60]. MND is a multisystem disorder with non-motor symptoms that are poorly understood and their impact on the individual not yet well established or understood.

These symptoms differ in frequency, severity and occurrence in many neurological conditions [51]. Previous service evaluation, quality improvement, and research into non-motor symptoms of neurological conditions has focused on disorders like Parkinson's disease (PD) [58] and multiple sclerosis (MS) [220, 221]. PD and MS research has established these symptoms as core features of those conditions, which may precede the onset of motor symptoms, be predictive of disability and negatively affect prognosis [52, 53]. MND research has confirmed that cognitive impairment often occurs prior to motor presentation and is equally predictive of worse disease impact and prognosis [166].

In a condition such as MND where no cure is currently available, the primary focus of clinical care is to provide symptomatic relief and improve an individual's quality of life [222]. The broad range of non-motor symptoms previously reported [56], and their significant effect on quality of life [222], has highlighted the need for further research into the presence and impact of a broad range of non-motor symptoms in MND.

The current study explores how people with MND experience non-motor symptoms and their perception of the clinical care they receive regarding these issues. This study also considers how

important people with MND report it is to address these non-motor symptoms in clinical trial design; whether this is to explore potential additional therapeutic benefit of candidate drugs or to provide a more complete picture of potential side effects.

4.4.2 Assessment in Clinical Care

In the United Kingdom's NHS, evidence based management of people affected by MND is supported by the National Institute of Clinical Excellence (NICE) 2016 guidelines [61]. Non-motor symptoms are often not adequately reported by patients or addressed in clinical management for MND, with the focus on breathing, muscle weakness, swallowing and speech. Non-motor symptoms are often not reported by patients in clinical consultations more generally, perhaps because of a lack of awareness they relate to the presenting condition [58]. NICE clinical guidance [61] directly addresses cognitive and behavioural changes as symptoms of MND which may precede motor dysfunction, and an aspect of functioning that needs to be continually monitored. Guidelines for managing the psychological and social impact of MND, changes relating to sexual symptoms and intimacy, and problematic saliva, are also provided. Problematic sleep and fatigue are considered as secondary effects of respiratory dysfunction.

Guidelines on symptom-focused treatment [62] encourage a broader conceptualisation of MND as a multi-system disorder with non-motor symptoms as important areas that also require effective consideration, management and treatment.

4.4.3 Evaluation of Non-Motor Symptoms in Clinical Trials

Guidance on designing and running trials for people with MND have encouraged the exploration of non-motor symptoms as additional outcome measures. The Airlie House recommendations on trial design highlight the potential for cognitive or behavioural assessments to be included as primary or secondary outcome measures [32]. The European Medicines Agency ALS Trial Guidelines go further, indicating the importance of evaluating mood [63].

Despite this guidance, we have recently reported that non-motor symptoms are insufficiently addressed in trial design [119, 168] (see Chapter 2 and 3), and where evaluated, this is often with assessment tools not designed to evaluate non-motor symptoms in people with progressive physical decline or communication impairment [119, 168].

4.5 Aims

The aim of this study was to explore how frequently people with MND report symptoms of low mood, anxiety, cognitive impairment, behavioural change, fatigue, pain, disturbed sleep, problematic saliva, sexual dysfunction and gastrointestinal issues occurring.

Specifically, this study aimed to:

- Explore how significant participants considered the impact of each reported non-motor symptom to be on their daily life.
- Explore how often a symptom, when reported as present, occurred in the previous fortnight.
- Report any additional symptoms that people with MND consider to be impactful.
- Evaluate the number of participants reporting satisfaction with how frequently non-motor symptoms were discussed with their clinical care team.
- Evaluate if people with MND considered non-motor symptoms to be important to include in the design of future clinical trials.
- Report any potential side-effects that would be concerning to people with MND when considering a prospective treatment.
- Explore people with MND's preferences for how non-motor symptoms are assessed by inviting them to consider five potential methods of assessment.

4.6 Methods

4.6.1 Participants

We invited all people with MND on the CARE-MND register who had indicated a willingness to receive information on current research, and met study inclusion criteria, to participate. Inclusion and exclusion criteria are available in Table 10.

Potential participants received an invitation pack containing a paper copy of the questionnaires, the participant information sheet, a consent form and an invitation letter with a link to complete the questionnaires online if preferred.

Table 10: NMS-MND Inclusion and Exclusion Criteria

Inclusion	Exclusion
• Over 18 • Confirmed diagnosis of MND (including the following subtypes: ALS by El Escorial Criteria (possible, probable, and definite), Primary Lateral Sclerosis, and Progressive Muscular Atrophy) • Able to provide informed consent (proxy signature accepted if limb dysfunction renders the individual unable to sign) • Fluent in English • Provided prior consent on CARE-MND to be contacted regarding research • Resident in Scotland	• Concerns from the clinical team regarding capacity

4.6.2 Data Collection

Source data from participant-completed questionnaires were collected using two methods, depending on participant preference. These options were selected to maximise accessibility, to ensure participants with physical disability, speech impairment or inexperience with technology were not alienated from participating.

1. *Electronic data collection*
   Online Surveys platform https://www.onlinesurveys.ac.uk/
   The link to the survey was provided on the Participant Invitation Letter.
2. *Paper questionnaires*
   A copy of the questionnaires and a postage-paid return envelope was provided in the postal invitation pack.

Within the questionnaire pack Appendix 3 was the ALS Functional Rating Scale – Revised (ALSFRS(R)), a questionnaire based assessment, evaluating the presence and resultant disability, of physical symptoms commonly affecting people with MND [170]. The self-administered (participant reported) version of the ALSFRS(R) demonstrated high inter-rater and intra-rater reproducibility [223] and was shown to be suitable for remote digital assessment [224]. Where two responses were indicated on a self-reported ALSFRS(R), the response indicating greater impairment was used.

In addition to data collection through questionnaires, this project involved a data request to CARE-MND for clinical information on participants. All study questionnaires and a list of requested CARE-MND variables are in Appendix 4. Requested variables from CARE-MND focused on clinical presentation of MND, use of intervention, cognitive screening, demographics and MND classification.

4.6.3 Study Questionnaire

The questionnaire was developed specifically for this study, and a full copy of is provided in Appendix 3. The questionnaire content was designed with input from members of the multi-disciplinary care team for people with MND, expert neurologists and an MND nurse consultant. In addition, people with MND attending routine NHS clinics provided feedback on the early design. The selection of pre-specified potential non-motor symptoms was based on previous literature, as discussed in the Introduction. People with MND, and their caregivers, provided feedback on the questionnaires in the final stages to ensure the symptom list was comprehensive and questionnaire items suitable for this cohort.

An overview of the study questionnaire content is represented in Table 11.

Table 11: Overview of NMS-MND Questionnaire Content

Area	Overview of Content	Response Structure
Clinical Questions	Date of MND diagnosis. Symptoms of MND. Use of interventions (ventilation, feeding tube, riluzole and referral to speech and language therapy team).	Open-ended response to symptoms experienced. Yes/No to using an intervention.
Presence of Symptoms	List of 11 potential symptoms. Sleep, saliva, pain, low mood, anxiety, fatigue, cognition, apathy, emotional lability, sexual dysfunction and gastrointestinal issues.	Yes/No to experiencing an issue. If 'Yes' participants asked to provide a brief description.
	• How frequently did this symptom happen in the last 2 weeks?	• A few days • Most days • Every day
	• Is this a significant problem for you?	• Yes • No • Unsure
Clinical Care	• Do your clinical team ask you about these symptoms when you go to appointments? • Would you like them to ask you about any of these symptoms more often?	Free-text response to discuss their opinion.
Trial Design	• Is it important to you that trials for new drug treatments also consider symptoms like these as well? • What types of side effects would concern you most about new treatments being investigated in a drug trial? • If a drug being investigated in a clinical trial led to side effects, which side effects would stop you from wanting to take a new drug?	Free-text response to discuss their opinion.
Impactful Symptoms	Participants encouraged to report any symptoms that affect them, including non-motor symptoms previously discussed. For each symptom we invited them to consider: • How often did it affect you in the past 2 weeks? • How much of a problem is it?	Frequency • Over half the days • Under half the days Impact • This is a significant problem for me • This bothers me from time to time • This happens but does not affect me much
Preferred Method of Symptom Assessment	List five options of data collection methods; questionnaires at home, questionnaires in clinic, wearable devices and entering data into a website or app. Indicate if they found each potential method acceptable.	• Acceptable • Not sure • Prefer not to

4.6.4 Non-Motor Symptom Selection

The pre-specified list of eleven symptoms explored in this study were selected based on current literature, with input from MND clinical specialists, people with MND and their caregivers. An opportunity to highlight any symptoms that were impactful to each individual, but not included in the pre-specified list, was also provided in the questionnaire.

The eleven aspects of health explored were pain, fatigue, gastrointestinal issues, poor sleep, low mood, anxiety, problematic saliva, apathy, emotional lability, cognitive impairment and sexual dysfunction.

A recent study suggested that 50-85% of people with MND reported severe pain, which became more problematic over time and reduced their quality of life [85]. However, pain is also an aspect of MND which may be responsive to treatment in the form of physical therapy [86] and pharmacological interventions [87].

Sleep disturbance and poor quality sleep are frequently reported in MND [32] but sleep quality, length of sleep and REM duration can be improved in people with MND utilising non-invasive ventilation [33] potentially indicative that respiratory weakness due to motor decline is a primary cause of these difficulties. Sleepiness is a key aspect of fatigue in people MND, along with reduced alertness, loss of stamina, and lack of energy [7]. Fatigue is reported by up to 44% of pwMND, co-occurring with depression in 15% of individuals [34].

Findings from a recent population based project of multimorbidity in MND in Scotland indicate the presence of neuropsychiatric disorders in 19.7% of people with MND, 70% were mood disorders and 31.67% neurotic disorders (inclusive of anxiety, stress-related and somatoform disorders) [68]. The prevalence of these disorders in people with MND is elevated in comparison to rates in the general population, 6.9% of whom fulfil diagnostic thresholds for major depressive disorder and 14% an anxiety disorder [69, 70].

Cognitive impairment is an additional non-motor feature of motor neuron disease which is prevalent, experienced by 30-50% of pwMND [71] and detrimental to an individual's and a carer's quality of life and prognosis [3, 72]. Apathy is the most commonly reported behavioural change, with 28% of a sample of people with MND showing abnormal levels of apathy on the Dimensional Apathy Scale [76]. An additional behavioural change experienced by some people with MND is emotional lability, with up to 50% experiencing some changes in emotionality and emotion regulation [225].

We have recently reported that problematic saliva production and handling, characterised by thickened saliva and sialorrhea, is experienced by 37.5% of people with MND [91]. Saliva thickening

and excessive drooling can be detrimental to an individual's well-being, increase the risk of respiratory complications and exacerbate dysarthria [92].

Gastrointestinal symptoms such as constipation, nausea, vomiting, acid reflux or excessive flatulence may occur for people with MND[88]. Gastrointestinal abnormalities were reported in 16– 83% of people with MND, depending on the symptom considered and disease stage [89]. These symptoms may occur as a response to interventions (particularly new drug treatments or NIV), secondary to increasingly physical disability or as indicative of wider nervous system degeneration [89, 90].

Although sexual function is not directly affected by MND, the impact of an MND diagnosis on sexuality, intimacy and libido remain highly relevant to exploring the a more holistic impact of non-motor symptoms of the condition on the individual [93], with interest in sex reported to decrease 28% after an MND diagnosis [94]. Despite the significant impact changes in sexual behaviour can have on an individual's quality of life [93], sexuality is often not considered or discussed in routine clinical consultations, and inclusion in research studies might be an important step towards raising this issue.

4.6.5 Statistical Analysis Plan

Descriptive statistics were used to explore the characteristics of the sample, considering demographic, phenotypic and clinical data followed by ascertainment of the total number of non-motor symptoms reported (defined as a 'yes' response to the list of eleven pre-specified symptoms) is associated with age at participation, age at diagnosis, years since diagnosis and ALSFRS(R) score using a series of linear regression models. Analysis of variance and t-tests were used to explore the same association of total number of non-motor symptoms with categorical variables; long survivorship (defined as greater than seven years since diagnosis), use of interventions, gender and disease subtype.

To explore the occurrence of sub-groups in patterns of non-motor symptoms reported, considering if some symptoms were more frequently reported, or if some symptoms tended to co-occur, latent class analysis was used. The descriptions of how participants with MND report experiencing these symptoms, and additional symptoms which they consider impactful, were represented in the open-ended question responses. A binary logistic regression was used to explore if the number of non-motor symptoms an individual reported, is associated with their response to the questionnaire item "Is it important to you that trials for new drug treatments also consider symptoms like these [non-motor symptoms] as well?"

Preference for assessment method was represented using descriptive statistics, to consider the number of response to each preference level for the options of assessment.

4.6.6 REC Feedback

Ethical approval was provided for this study on 19th October 2021 (Research Ethics Committee number: 21/YH/0226). The REC committee provided positive feedback on the relevance of the study, and potential utility in guiding future trial design. The committee acknowledged that as MND is a relatively rare disorder, the sample size should be focused on the number of participants attainable rather than power calculations. The committee recommended that any statistical modelling is limited, and descriptive statistics be presented, as a smaller sample size may yield interesting and relevant results, even if no associations are found through statistical modelling.

4.7 Results

4.7.1 Sample Characteristics

120 people with MND completed the questionnaires; 109 in paper format and 11 online. The studies described in Chapter 4 and Chapter 5 involved different samples of people with MND. This sample represents 23% of the 532 Scottish residents living with MND during the recruitment period, and 39% of this group (n = 311) who have provided prior consent to hear about research and were invited to complete the study. Table 12 provides an overview of the demographic and clinical characteristics of respondents.

Table 12: Characteristics of NMS-MND Participants

Characteristics	**Overall (N = 120)**
Age at participation, mean (SD) (years)	60 (12)
Age at diagnosis, mean (SD) (years)	65 (11)
Survival length, mean (SD) (years) *Long survivor > 7 years (%)*	5 (6) 23 (19)
Males, no. (%)	76 (63)
MND sub-type, no. (%)* *ALS* *PLS* *PBP* *PMA* *Other* *ND*	 70 (58) 21 (18) 11 (9) 5 (4) 4 (3) 9 (8)
Bulbar onset (%)	21 (18)
Current intervention use (%) *Riluzole* *Non-invasive ventilation* *Gastrostomy*	 44 (37) 26 (22) 22 (18)
Referral to Speech and Language Therapy	73 (61)
ALSFRS(R) *Mean* *Range* *SD*	 30 3 – 47 9

*Motor neuron disease (MND), amyotrophic lateral sclerosis (ALS), progressive lateral sclerosis (PLS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), no data (ND)

4.7.2 Total Number of Non-Motor Symptoms Reported

4.7.2.1 Presence, Frequency and Impact

All but one participant with MND (99%) experienced at least one non-motor symptom, with 72% reporting five or more non-motor symptoms. The presence, impact and reported frequency of these symptoms are shown in Table 13 and Figure 4. The most frequently reported non-motor symptoms were fatigue and pain, both affecting 76% of participants. 40% of participants reporting that they experienced pain stated that their pain occurred ‘every day’ in the previous fortnight. The most impactful non-motor symptoms were pain and saliva, with 51% of participants reporting experiencing these symptoms considering them both a ‘significant’ problem. Participants were also asked to describe the effect and impact of these symptoms on them, a small sub-set of these responses are represented in Table 14 to provide an indication of the types of concerns participants raised.

Figure 4: Histogram to Represent Number of Participants Reporting Symptom as Present

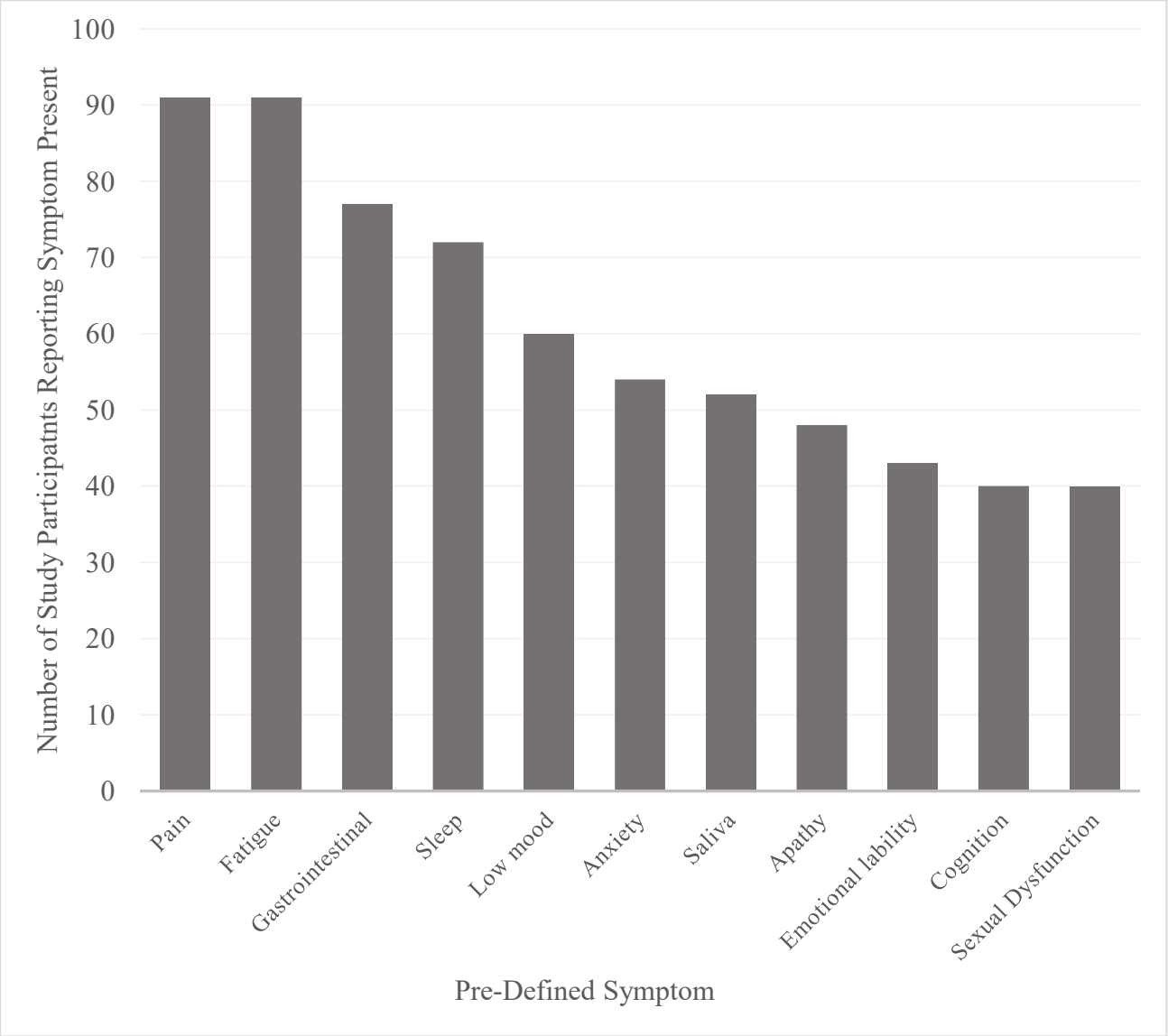


Table 13: Frequency, Severity and Impact of Non-Motor Symptoms

Symptom	Frequency of Reporting as 'Present' n (%)	Frequency of Reporting as 'Significant' n (%)	Frequency of Symptom Occurrence in Previous Fortnight n (%)
Pain	91 (76)	27 (51)	*Every day*, 34 (40) *Most days*, 30 (35) *A few days*, 21 (25)
Fatigue	91 (76)	45 (49)	*Every day*, 32 (36) *Most days*, 24 (27) *A few days*, 32 (36)
Gastrointestinal	77 (64)	42 (54)	*Every day*, 14 (19) *Most days*, 24 (33) *A few days*, 35 (48)
Sleep	72 (60)	28 (39)	*Every day*, 27 (39) *Most days*, 22 (32) *A few days*, 20 (29)
Low mood	60 (50)	45 (48)	*Every day*, 7 (13) *Most days*, 7 (13) *A few days*, 42 (75)
Anxiety	54 (45)	13 (24)	*Every day*, 8 (16) *Most days*, 10 (20) *A few days*, 32 (64)
Saliva	52 (43)	27 (51)	*Every day*, 27 (56) *Most days*, 11 (23) *A few days*, 10 (21)
Apathy	48 (40)	21 (41)	*Every day*, 7 (15) *Most days*, 17 (35) *A few days*, 23 (47)
Emotional lability	43 (36)	15 (33)	*Every day*, 1 (3) *Most days*, 13 (33) *A few days*, 26 (65)
Cognition	40 (33)	18 (41)	*Every day*, 7 (18) *Most days*, 14 (41) *A few days*, 18 (46)
Sexual Dysfunction	40 (33)	20 (43)	*Every day*, 22 (61) *Most days*, 8 (22) *A few days*, 6 (17)

Table 14: Brief Overview of Participant Descriptions of Non-Motor Symptoms

Sleep	"Difficulty getting to sleep"	"Very tired all the time"
	"Cannot get comfortable"	"Never feel refreshed"
Saliva	"Causes choking and coughing"	"Drooling is socially awkward"
	"Thick saliva affects ability to eat"	"Problems clearing throat"
Pain	"Awful pain and terrible cramps"	Frustrating"
	"Limits daily activities"	"Sharp pains in contracted fingers"
Low mood	"Mood has got darker as reality of future hits"	"Makes me sad"
	"Get emotional and have a good cry"	"Takes the joy away from life"
Anxiety	"Anxious about my condition"	"Worry for the future"
	"Small problems worry me"	"Prevents me from relaxing"
Fatigue	"Complete exhaustion, very debilitating"	"Cannot tackle tasks I used to enjoy"
	"I have low energy"	"Just not able to do much"
Cognition	"Difficulty in finding the correct word"	"I forget names of friends"
	"I have a bad memory"	"Struggle to plan ahead"
Apathy	"Get up & go is gone"	"No motivation"
	"No interest in anything much"	"Leads to frustration"
Emotional lability	"Embarrassing and unexpected"	"I explain it is MND"
	"Mostly laughing to excess"	"Noisy emotions when trying to cry"
Sexuality	"Physical difficulties in having sex"	"No libido"
	"Unable to have sex – sad"	"Causes immense frustration"
Gastrointestinal	"Constant abdominal discomfort"	"Feeling of being 'bunged up'"
	"Acid reflux"	"I vomit every day"

4.7.2.2 Participant Characteristics and Non-Motor Symptoms

There was a significant difference in number of non-motor symptoms reported between long survivors (M = 6.8, SD = 2.3) and non-long survivors (M = 5.3, SD = 2.3); t(119) = -2.9, p = 0.005 with long survivors (n = 23) reporting more non-motor symptoms, with independent t-tests in Table 15.

There was a significant relationship between ALSFRS(R) score and total number of non-motor symptoms reported (R2 = 0.056, F(1,111) = 6.60, p < 0.0010, Table 16. As the ALSFRS(R) score decreases (indicative of worsening physical function), the number of non-motor symptoms reported increased significantly ((β = -0.88, p = 0.01), explored in regression models in Table 16.

As the age of the participant increased, their number of reported non-motor symptoms increased significantly (R^2 = 0.001, F(1, 118) = 0.1716, p = 0.0001). The next regression model was statistically significant overall, suggesting that as age at diagnosis and number of years since diagnosis increased, the number of non-motor symptoms reported also increased (R^2 = 0.005, F(2, 117) = 0.273, p = 0.0002). However as Table 16 shows, this effect was not significant for each variable in turn.

There was no significant difference in number of non-motor symptoms reported between men (M = 5.6, SD = 2.4) and women (M = 5.4, SD = 2.2); t(119) = -0.48], p = 0.63 or between disease sub-types (F(5, 112) = 1.04, p = 0.36).

4.7.2.3 Intervention Use and Non-Motor Symptoms

We explored three levels of riluzole, non-invasive ventilations and feeding tube use in analysis of variances in Table 17; never taken, currently taking and discontinued. Use of riluzole (F(3, 117) = 0.22, p = 0.80), non-invasive ventilation (F(3, 117) = 0.69, p = 0.50) or a feeding tube (F(3, 117) = 0.48, p = 0.62) were not associated with the number of non-motor symptoms an individual reported.

Table 15: Independent T-Tests Comparing Long Survivors and Gender with Total Number of Non-Motor Symptoms Reported

	M	**SD**	**M**	**SD**	**t(119)**	**p**
Number of Non-Motor Symptoms Reported	Long Survivor					
	Yes (>7 years)		No (< 7 years)			
	6.8	2.3	5.3	2.3	-2.9	0.005
	Gender					
	Male		Female			
	5.6	2.4	5.4	2.2	0.48	0.63

Table 16: Linear Regressions to Explore ALSFRS(R), Years since Diagnosis and Age with Total Number of Non-Motor Symptoms Reported

	B	**95% CI**	**β**	**r(112)**	**r^2**	**p-value**
Intercept	35.75**	[32.05, 39.44]				<2e-16***
ALSFRS(R)(score)	-0.79*	[-1.40, -0.18]	-0.24	-.24*	0.052	0.0122
Intercept	5.05**	[2.56, 7.55]				
Age at Participation	0.01	[-0.03, 0.05]	0.04	0.04	0.0001	0.0001
Intercept	4.76**	[2.31, 7.20]			0.005	0.0006***
Years Since Diagnosis	0.02	[-0.06, 0.10]	0.05	.04		0.5804
Age at Diagnosis	0.01	[-0.03, 0.05]	0.06	.05		0.5413

Table 17: Analysis of Variance to Explore Intervention Use and Disease Sub-Type with Total Number of Non-Motor Symptoms Reported

	Sum of Squares	**DF**	**Mean Square**	**F(110)**	**η2**	**P-value**
Disease Sub-type	29.3	5	5.85	1.04	0.05	0.40
Riluzole Use	2.4	2	1.22	0.22	0.004	0.80
NIV Use	7.6	2	3.79	0.69	0.50	0.012
Gastrostomy Use	5.3	2	2.65	0.48	0.008	0.62

4.7.3 Pattern of Non-Motor Symptoms Reported

To explore patterns of reported non-motor symptoms we conducted a latent class analysis. For this analysis we used the Yes/No responses to the question asking if participants experienced the ten pre-defined non-motor symptoms.

To determine optimal number of classes the number of classes was increased one at a time until there was no additional model improvement [226] and Bayesian Information Criterion (BIC) was evaluated as a quantitative indicator of model fit [227]. Two classes provided the lowest BIC for our population, presented in Table 18.

Cluster one included 40% of the cohort and was characterised by frequent occurrence of listed non-motor symptoms and we named this High-NMS. Cluster two, including 60% of the cohort, also involved presence of non-motor symptoms but to a lesser extent than cluster one so we named this Medium-NMS.

Participants in the High-NMS cluster had the following probabilities of reporting these non-motor symptoms as present; 80% disturbed sleep, 42% problematic saliva, 89% pain, 96% low mood, 82% anxiety, 90% fatigue, 36% cognition, 67% apathy, 38% emotional liability, 39% sexual dysfunction and 72% probability of reporting gastrointestinal issues.

Participants in the Medium-NMS cluster however, had the following probabilities of reporting the occurrence of the same symptoms; 47% disturbed sleep, 42% problematic saliva, 69% pain, 20% low mood, 21% anxiety, 69% fatigue, 29% cognition, 22% apathy, 34% emotional liability, 35% sexual dysfunction and 58% probability of reporting gastrointestinal issues.

The conditional probability results for all ten non-motor symptoms indicate that whilst both clusters experienced the listed non-motor symptoms frequently, participants in the High-NMS cluster had greater probability of experiencing disturbed sleep, pain, low mood, anxiety, fatigue, cognitive impairment, apathy and gastrointestinal issues. Probability of reporting problematic saliva, emotional lability and sexual dysfunction remained similar in the High-NMS and Medium-NMS clusters.

Table 18: Parameters of Fit of Latent Class Analysis

Clusters (N)	Parameters (N)	Likelihood	AIC	BIC
2	23	-741.7082	1529.416	1591.317
3	35	-719.8475	1509.695	1603.892
4	47	-712.9626	1519.925	1646.418
5	59	-700.3771	1518.754	1677.544

*AIC, Akaike Information Criterion, BIC, Bayesian Information Criterion

4.7.4 Self-Reported Impact of MND

Participants were also invited to list any symptoms that has a significant impact on their daily life. These could be symptoms already listed in the previous non-motor section, or other aspects of functioning affected by MND. The question "Please **describe up to five symptoms** that you experience which affect your life the most" invited respondents to consider aspects of MND that may be problematic to them.

For each symptom participants also considered the frequency of occurrence (over or under half of the days in a given fortnight) and the significance of the problem to them with the questionnaire item "Please indicate how often this symptom occurs for you, and how much of a problem it is for you." These findings are displayed in Table 19.

The most frequently reported motor symptoms were muscle weakness or stiffness (n = 56), loss of limb function (n = 45) and problems with walking (n = 36). Fatigue (n = 33), pain (n = 26) and cramps (n = 19) were the most frequently self-identified non-motor symptoms.

The symptoms that were reported to occur most often (the frequency of participants selecting 'Over Half' of the days in a fortnight) and identified as most significant (the frequency of participants selecting 'Significant Problem') were muscle weakness or stiffness, loss of limb function and problems with walking.

Table 19: Participant Reported Impactful Symptoms

Symptom Grouping	Symptom Reported	Number of Times Symptom is Identified as Present by Participants*	Frequency of Symptom Reported as Occurring in the Past Two Weeks+		Frequency of the Participant Indicating the Significance of the Symptom+		
			Over Half the Days (%)	Under Half the Days (%)	This is a significant problem for me (%)	This bothers me from time to time (%)	This happens but does not affect me much (%)
Muscle	*Weakness/Stiffness*	56	55 (98)	1 (2)	43 (77)	17 (30)	2 (4)
	Fasciculations	8	5 (63)	2 (3)	3 (38)	2 (25)	2 (25)
Mobility	*Loss of Limb Function*	45	42 (93)	1 (2)	32 (71)	8 (18)	1 (2)
	Walking	36	35 (97)	-	33 (92)	1 (3)	1 (3)
	Balance/Falls	16	15 (94)	1 (6)	14 (88)	2 (13)	-
Oral	*Speech*	34	30 (88)	2 (6)	24 (71)	9 (26)	1 (3)
	Swallow/Choking	24	22 (92)	2 (8)	17 (77)	7 (29)	-
	Breathing	23	22 (96)	1 (4)	20 (87)	3 (13)	-
	Saliva	15	13 (87)	1 (7)	11 (73)	3 (20)	-
	Cough	5	4 (8)	1 (20)	3 (60)	2 (40)	-
Tiredness	*Fatigue*	33	31 (94)	2 (6)	21 (64)	11 (33)	1 (3)
	Sleep	14	13 (93)	1 (7)	9 (64)	4 (29)	1 (7)
Pain	*Pain*	26	26 (100)	-	19 (73)	7 (27)	-
	Cramps	19	13 (68)	6 (32)	11 (58)	6 (32)	2 (11)
Quality of Life	*Independence in Activities of Daily Living*	17	17 (100)	-	15 (88)	1 (6)	-
	Quality of Life	4	2 (50)	2 (50)	3 (75)		1 (25)
Cognition or Behaviour	*Behaviour Change*	9	4 (45)	5 (55)	3 (33)	5 (56)	1 (11)
	Emotional Lability	7	3 (43)	4 (57)	3 (43)	4 (57)	-

	Cognition	5	3 (60)	2 (40)	3 (60)	2 (40)	-
Gastrointestinal	*Constipation*	9	4 (45)	5 (55)	3 (33)	5 (56)	1 (11)
	Gastrointestinal (unspecified)	3	2 (67)	1 (33)	2 (67)	1 (33)	-
	Nausea	2	1 (50)	1 (50)	1 (50)	1 (50)	-
	Diarrhoea	2	-	2 (100)	-	2 (100)	-
	Acid reflux	1	-	1 (100)	-	1 (100)	-
Mood	*Low mood*	7	4 (57)	3 (43)	3 (43)	4 (57)	-
	Anxiety	3	2 (67)	1 (33)	-	2 (67)	1 (33)
Continence	*Incontinence*	2	2 (100)	-	2 (100)	-	-
	Nocturia	1	-	-	1 (100)	-	-
	Catheter Use	1	1 (100)	-	-	1 (100)	-

***** Note that due to missing data patterns, frequency of identification may be greater than frequency of occurrence or impact and percentages may not total 100%

[+] Represented as a percentage of the number of people who reported this symptom as occurring to them

4.7.5 Management and Assessment of Non-Motor Symptoms

Of the subgroup (n = 109) who responded to this question, 73% were happy with the frequency with which these symptoms were discussed with their clinical team, reporting that they felt able to raise concerns where needed.

Crucially, 80% of all participants, indicated that they believe non-motor symptoms are important and should be included in future clinical trials; either to be explored in secondary outcome measures as potential additional therapeutic benefits for candidate drugs, or as areas to consider as possible side-effects.

The total number of non-motor symptoms participants reported as not having a significant association with the likelihood of a participant indicating 'Yes' to the question "Is it important to you that trials for new drug treatments also consider symptoms like these as well?", (OR = 1.03, 95% CI = 0.82 to 1.28, p = 0.79).

The lack of association between an individual's own experience of non-motor symptoms and the likelihood of them agreeing that non-motor symptoms were important to include in future trials may suggest that people with MND feel that it is important to include non-motor in future clinical trials, irrespective of if they experience them personally.

Participants also suggested potential side effects that may discourage, or influence their decision to take a new medication to manage MND. The concerns reported were extremely diverse, considering increased physical disability and worsened non-motor symptoms, to a reduction in quality of life or damage to their body or organs. The potential side-effects that participants reported would be of greatest concern are summarised in Table 20.

The potential-side effects most frequently raised as concerning by respondents were concerns that a prospective new treatment might cause, or worsen, nausea/vomiting, gastrointestinal issues or fatigue. 10% of respondents stated that any side-effects would inform their decision-making process, and 10% reported that no side-effects would prevent them from taking a drug.

Table 20: Potential Side Effects of Concern Reported by Participants

Symptom Identified	Number of Times Identified by a Participant
Nausea/vomiting	14
Gastrointestinal	14
Fatigue	10
Mental health	8
Pain/Cramps	8
Cognition	7
Quality of Life	6
Incontinence	5
Organ damage	5
Walking	5
Headache	5
Speech	4
Sleep	4
Sensory loss	3
Coughing/choking	3
Dizziness	3
Balance	3
Delirium	3
Itching	2
Muscle weakness	2
Personality	2
Weight gain	1
Muscle stiffness	1
Eye irritation	1
Appetite	1
Erectile dysfunction	1
Breathing difficulties	1
Allergies	1
Heart problems	1
Panic attacks	1

4.7.6 Assessment Methods

Participants were asked to indicate if they found five types of assessment methods "Acceptable", or if they would "Prefer Not To", "Not Sure" was also available to offer a neutral response option too. These response options were assigned a numerical code, "Acceptable" = 3, "Not Sure = 2" "Prefer Not To" = 1 or in order for responses to be ranked by preference. Acceptability of each method is explored in Table 21.

The most acceptable method of data collection to participants was completing questionnaires themselves remotely, followed by completing questionnaires with the support of the research team or using wearable devices to provide data. After these methods participants indicated a lesser preference for data collection using specialised websites, or participant apps.

Table 21: Assessment Methods Ranked by Preference

Assessment Method	**N**	**Acceptable n (%)**	**Not Sure n (%)**	**Prefer Not To n (%)**
Completing questionnaires, at home, about my symptoms	119	108 (91)	4 (3)	7 (6)
Completing questionnaires in clinic, with the help of a researcher or clinician, about my symptoms	117	83 (71)	12 (10)	22 (19)
Wearing a device on my body which senses movement (similar to a FitBit wristwatch)	116	79 (68)	20 (17)	17 (15)
Type my data into a specialised website	115	66 (57)	19 (17)	30 (26)
Putting data about my symptoms into an app on my smartphone	116	49 (42)	22 (19)	45 (39)

4.8 Discussion

4.8.1 Findings Summary

Chapter 4 presents the results of a structured questionnaire-based study highlighting that people with MND frequently experience non-motor symptoms, which occur in addition to changes in motor function. The high prevalence and impact of these symptoms is consistently reported in systematic reviews [51], symptom-focused research [228] and interventional studies [87]. In this study, all but one participant with MND experienced at least one non-motor symptom, with 72% reporting five or more non-motor symptoms.

Our finding that pain and fatigue were the symptoms participants report most frequently and are most impactful on daily life, aligns with previous research findings on the multifactorial nature and added burden of pain and fatigue for people living with MND [177, 229, 230]. In particular, the finding that pain is a frequently occurring and impactful symptom of MND echoes findings presented by the TONiC group, who in a larger sample of 636 found 69% individuals reported pain and significantly reduced a person's quality of life [54].

The most impactful non-motor symptoms were pain and problematic saliva, with 51% of participants reporting experiencing these symptoms, considering them both a 'significant' problem, aligning with reviews finding that problematic saliva led to feelings of embarrassment, social withdrawal and reduced quality of life [231].

Despite a potential for responder bias, the sample characteristics appear to be representative of the wider MND population; age of participants, site of onset, gender, prevalence of long survivors, region of onset and disease duration and severity [232]. The non-motor symptoms explored in this study (pain, fatigue, gastrointestinal issues, poor sleep, low mood, anxiety, problematic saliva, apathy, emotional lability, cognitive impairment and sexual dysfunction) were common, impactful and occurred frequently for people with MND. Of the 120 individuals who completed questionnaires **99% experienced at least one of these non-motor symptoms and 72% of respondents reporting five or more non-motor symptoms**.

To our knowledge, this is the first study to directly ask participants about their attitudes towards the inclusion of non-motor symptoms in clinical trials. Although symptom-focused trials in MND are beneficial, our recent reviews suggest that the additional potential benefits or side effects of candidate drugs in motor-focused trials are under evaluated. The findings from this study indicate that people affected by MND are also supportive of exploring the holistic impact of MND treatment options when choosing outcome measures.

The vast majority of people with MND supported the consideration of non-motor symptoms when evaluating new drug treatments; offering a synchronous voice to clinical and research guidelines [32] and thereby encouraging a more holistic perspective of the impact, management and treatment of MND. Through focusing on the participant perspective, the findings from this study inform us of the broad range of symptoms that can be experienced in addition to, or secondary from, motor degeneration in MND.

The list of symptoms these participants were asked to indicate if they experienced were based on findings from systematic reviews [51], repurposed questionnaires from other neurological conditions [59] and clinical management guidance [230]. This questionnaire, created specifically for this study, amalgamated symptoms which previous studies had separately found to be present, whilst also offering participants the option to report additional symptoms that they experienced. An additional novel aspect of this questionnaire was the exploration of the impact and frequency of these symptoms. This is an important participant perspective, expanding the understanding of how non-motor symptoms can affect daily life.

4.8.2 Non-Motor Symptoms Reported

Exploring the types of non-motor symptoms experienced by people with MND, irrespective of why they occur, works towards expanding the conceptualisation of MND as an primarily a motor disorder.

Categorising non-motor symptoms as primary, secondary or both, can be useful to inform future research into the causes, impact and potential management of each symptom. Primary symptoms can provide an insight into the heterogeneity of MND, and prospective therapeutic targets. Secondary symptoms enable a better understanding of the impact of MND and the disability which occurs as a result of motor degeneration.

Raising awareness of these additional symptoms helps people with MND, and those who support them, to better understand their condition and changes that they may experience. This in turn helps with informing care planning decisions, managing symptoms to improve quality of life and ultimately reduce the uncertainty involved with facing an MND diagnosis. Including the perspective of people with MND enables symptomatic interventions [233] and trials [85] to be informed by the needs of those they aim to help.

An example of this is the improved understanding over the past decade of cognitive and behavioural change as a common aspect of MND progression, particularly the diagnostic overlap with frontotemporal dementia [77]. In line with clinical care guidelines, the multi-disciplinary team now

routinely screen for cognitive impairment and behavioural symptoms in people with MND, with the opportunity to use specifically developed assessment tools such as the Edinburgh Cognitive and Behavioural ALS Screen [161]. Effective detection of these cognitive and behavioural issues has enabled early intervention so people with MND and their supporters can implement management strategies and adapt care planning accordingly [160].

4.8.3 Evaluation of Non-Motor Symptoms

Integration of non-motor symptoms into trial design is key to offering a holistic evaluation of disease progression and effective treatment options. Including non-motor symptoms either as additional outcome measures, potential therapeutic target or side effect of an investigative medicinal product is supported by the overwhelming majority of respondents, and aligns with current trial design guidance [32, 63]. This study is the first to offer feedback from people affected by MND on integrating non-motor symptoms into trial design, indicating that the majority of respondents are supportive.

Holistic assessment of non-motor symptoms is also crucial in clinical care. Providing space within the multi-disciplinary team, and time within the clinical appointment schedule, is essential to ensure people with MND feel able to discuss their changing health. Non-motor symptoms may not be reported by people with MND, so the clinician must lead discussions in this area, prompting their patient to consider symptoms beyond their motor dysfunction and explain the various ways MND can present [58].

In designing effective research, and delivering efficient clinical care, the way in which all symptoms of MND are assessed must be a balance between patient preference and data quality. Respondents indicated a clear preference for remote data collection through at home questionnaires, reducing the burden of travelling to appointments and enabling people with MND to respond at their own pace. A preference for remote assessment has been indicated in larger surveys considering self-monitoring and device-use as remote options for clinical care and trial delivery [234].

4.8.4 Conclusion and Implications

In conclusion, non-motor symptoms occur frequently and are impactful for people with MND. 99% of people with MND experience at least one non-motor symptom in this generalisable population. The most frequently occurring symptoms are pain and fatigue, reported by 76% of participants, and the

most impactful symptoms are pain and problematic saliva. All but one participant experienced at least one symptom, with 72% reporting five or more symptoms. Evaluation of the holistic impact on function is necessary to understand, manage and ultimately treat the individual. The burden of non-motor symptoms increases with disease duration, being more frequent in longer survivors, age, and also disease severity.

The key novel aspect of this study was the exploration of the attitudes of people with MND towards including the evaluation of non-motor symptoms in clinical trials. Findings indicated that people with MND, prospective participants in these trials, were largely supportive of including non-motor assessments in trials, in line with clinical [61] and trial [32] guidance encouraging a broader conceptualisation of treatment.

Future research in this area may focus on the benefits of assessing non-motor symptoms within current multidisciplinary care teams and evaluating the suitability of new symptom-focused interventions. In addition, exploring the impact of investigative medicinal products on non-motor symptoms will enable clinicians managing people with MND to make informed, evidenced-based, management decisions. These decisions require more randomised controlled trials focusing on the impact of interventions and medication regimens on non-motor symptoms in MND. Finally, future research can explore how non-motor symptoms may be impacted by candidate drugs in trials.

4.9 Key Findings

- A comprehensive structured questionnaire-based study with 120 people with MND reporting the presence, impact and frequency of non-motor symptoms
- The symptoms evaluated were pain, fatigue, gastrointestinal issues, poor sleep, low mood, anxiety, problematic saliva, apathy, emotional lability, cognitive impairment and sexual dysfunction
- 99% of participants reported at least one of these symptoms as present, with 72% reporting five or more symptoms
- Pain and fatigue were most commonly occurring, with 76% reporting each as present
- Pain and problematic saliva were reported to be most impactful by participants
- Lower ALSFRS(R) score, older age at onset and being a long survivor (diagnosed over 7 years ago) were associated with reporting more non-motor symptoms
- 73% of respondents were content with the frequency that these issues were discussed in clinical care
- 80% indicated they believe non-motor symptoms are important to include in trials
- The preferred method of assessment was questionnaires, at home, about symptoms

- **People with MND are frequently and significantly affected by non-motor symptoms, and are supportive of their assessment in clinical care and inclusion in trial design**

5 Chapter 5: Experimental Project 2 - Factors Impacting Trial Participation in People with MND (FIT-P-MND)

The protocol for this experimental project has been published [235] and is available in Appendix 5.

Beswick, Emily, Stella A. Glasmacher, Rachel Dakin, Judith Newton, Alan Carson, Sharon Abrahams, Siddharthan Chandran, and Suvankar Pal. "**Protocol: Prospective observational cohort study of factors influencing trial participation in people with motor neuron disease (FIT-Participation-MND)**" *BMJ Open* 11, no. 3 (2021).

2 citations.

The second overall aim of this thesis was to explore the reason individuals with MND might participate in a clinical trial, and the characteristics of participants compared to non-participants.

A better understanding the characteristics of individuals who participate in clinical trials can enable trialists to make informed design decisions and employ targeted recruitment strategies to ensure more generalisable sub-groups of people with MND have the opportunity to engage with research if they wish to do so. Attrition due to disease progression, negative experiences of the candidate drugs or a change in circumstances are all expected in a clinical trial. However, identifying the characteristics of people who may be at greater risk of attrition, enabling early implementation of additional support, can improve trial participation. Efficient recruitment and retention strategies, tailored to prospective participants, reduce the risk of delayed or discontinued trials, and representative samples improve the generalisability of conclusions drawn from trial data.

The decision to participate in a clinical trial is a multi-faceted, complex and often a collaborative process. Exploring the demographic and clinical characteristics of 'self-selectors', people actively choosing to participate in an interventional clinical drug trial, compared with those who choose to participate in an observational questionnaire-based research project but not a clinical trial, offers an interesting and novel insight into this choice.

5.1 Abstract

Introduction: Motor neuron disease (MND) is a rapidly progressive and fatal neurodegenerative disorder with limited treatment options. The Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial (MND-SMART) is a multi-site UK trial seeking to address the paucity in effective disease modifying drugs for people with MND. Historically, neurological trials have been plagued by suboptimal recruitment and high rates of attrition. Failure to recruit and/or retain participants can cause insufficiently representative samples, terminated trials, or invalid conclusions.

Aim: This study investigates person-specific factors affecting recruitment and retention of people with MND to MND-SMART. Improved understanding of these factors may improve trial protocol design, optimise recruitment and retention.

Hypothesis: We hypothesise that person-specific factors, such as neuropsychiatric symptoms, cognitive impairment, behavioural change, phenotype, quality of life, apathy and physical functioning will significantly impact upon people with MND's decision to participate, and remain in MND-SMART.

Methods: Participants with MND on the Scottish MND Register completed a series of questionnaires to evaluate person-specific characteristics. Participants with MND completed established questionnaires to evaluate neuropsychiatric symptoms and quality of life. In addition, participants completed a novel study-specific questionnaire on Attitudes towards Clinical Trial Participation. Variables on phenotype, cognition and physical functioning were obtained from CARE-MND and MND-SMART. Caregivers completed a brief apathy scale. 12 months after completing the questionnaires we used MND-SMART recruitment data to establish if members of our cohort engaged with the trial.

Results: 120 people with MND completed questionnaires for this study. Mean age at participation was 66 (SD = 9), 14% (n = 17) were categorised as long survivors (defined as over 7 years since diagnosis [5]), with 68% (n = 81) of participants male. 60% (n = 73) of participants had the ALS sub-type of MND, 13% (n = 16) PLS, 12% (n = 15) PBP, 4% (n = 5) PMA and the remaining 11% (n = 11) of people were defined as 'Other' sub-type or had no data available. 73% (n = 88) of people with MND had a caregiver co-participating with them who completed the b-DAS. ALSFRS(R) and ECAS scores were available for 92% (n = 110) and 57% (n = 68) of participants, respectively. Of the 120 FIT-P-MND participants, 50% (n = 60) were randomised into MND-SMART and 78% (n = 94) expressed interest in participating by attending screening, completing online forms or contacting the trial team. After the one-year follow-up period 65% (n = 39) of the 60 randomised participants remained in MND-SMART. One individual chose to withdraw and the remaining participants died during follow

up. Only age was a significant predictor for trial participation, (OR = 0.92, 95% CI = 0.88 to 0.96, p = 0.000488), with the likelihood of participation decreasing as participant age increases. Older age (OR = 0.93, 95% CI = 0.88 to 0.97, p = 0.002), more apathetic behaviours (OR = 0.9, 95% CI = 0.80 to 0.99, p = 0.044) and region of onset (X^2 (5, N = 112) = 17.79, p = 0.003) were associated with reduced likelihood of remaining a trial participant.

Conclusions: The aim of this study was to better understand the person-specific factors that may influence an individual with MND's decision to participate in a clinical trial. The findings suggest that older age, apathy and region of onset may be associated with initial, and continued, engagement as a trial participant. An improved knowledge of the person-specific factors that are relevant in the decision-making process for prospective and current trial participants, can facilitate the delivery of targeted recruitment strategies and additional support to individuals with greater likelihood of withdrawal.

Ethics and Dissemination: Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020.

5.2 Lay Summary

The purpose of this study was to improve understanding of why people with MND choose to participate, or not, in clinical trials of potential new drugs. It also looked at why individuals with MND who are participating in a clinical trial may stop participating in that trial.

The findings from this study aim to better inform research as to potential barriers experienced by people for participating, and remaining, in a clinical trial. Improving understanding of these factors may inform future trial protocol designs to be more inclusive and identify participants who may be 'high-risk' and need more support from the research team to remain in a clinical trial.

There is already evidence to support how 'trial factors' such as the design of a clinical trial, inclusion/exclusion criteria and method of patient follow-up can affect how successful a trial in MND is at recruiting and retaining participants.

MND-SMART is an innovative new multi-arm adaptive trial co-produced alongside people living with MND which addresses many of these 'trial factors' and provides an excellent opportunity to study how 'person-specific factors' may also impact upon how likely people with MND are to get involved in, and stay in, clinical trials.

Participants completed structured questionnaires and the project involved linking these to clinical records on the Scottish MND register, CARE-MND, and the participants' involvement in MND-SMART.

This study investigated the presence of psychiatric symptoms (particularly depression and anxiety), apathy, cognitive impairment, self-reported quality of life, health perception, functional ability and medical history in a sample of people with MND. It evaluated how many of the individuals from the cohort participated in the MND-SMART trial, and if they remained in the trial 12 months later.

Of 120 participants, 50% also joined MND-SMART, and 33% of the FIT-P-MND participants remained in the clinical trial after one year. The study identified that people were less likely to get involved in MND-SMART, and to stay participating, if they were older in age and experienced apathy (a behavioural change that can affect some people with MND meaning that they have difficulty with motivation).

5.3 Introduction

5.3.1 Trials in MND

Despite 125 clinical trials registered between 2008 and 2019, involving 15,647 people with MND, and evaluating 76 investigative medicinal products (IMPs) [20], progress in developing new treatments has been underwhelming [236]. Since its licensing in 1994, riluzole remains the only globally licensed disease modifying treatment, with limited efficacy [237], however, other potentially promising treatments are under investigation [238].

However, in the last decade new directions in MND trials are emerging. Advanced understanding of the biological basis of the condition, novel biomarkers and multiple potential therapeutic targets offer promising avenues of exploration [31]. The 2019 revision of Airlie House consensus guidelines for design and implementation of MND clinical trials encapsulates the new direction of research in this area [32]. On clinicaltrials.gov alone there were 191 interventional trials for people with MND actively recruiting or scheduled to open recruitment, at the time of writing.

The accurate identification of factors that impact upon recruitment, and retention of participants in research studies is important when considering trial design [44]. Recruitment should involve selection of participants who are representative of the target population, in numbers sufficient to fulfil trial-specific power calculations. Previously, whilst restrictive inclusion criteria have been advantageous to stratify a heterogeneous population to detect an effect, results from these studies may not be readily generalisable, and restrict opportunities for research participation. While 83% of people with MND indicated they would be open to participating in research trials [25], surveyed clinicians estimate enrolment figures of 25% in trials, primarily due to unsuitability of people with MND within stated inclusion criteria [26]. Historically trials have utilised narrow inclusion criteria in an attempt to stratify subgroups, however, this may impact on homogenisation of trial outcomes at the cost of inclusivity [23]. As MND-SMART involves broader inclusion criteria than many previous trials we expect higher rates of enrolment, reflecting greater inclusivity of these criteria.

5.3.2 MND-SMART

MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) is a multi-site United Kingdom clinical trial, clinicaltrials.gov (NCT04302870) and EudraCT (Trial record number: 2019-000099-41), which epitomises the new direction of research in this area. MND-SMART aims to evaluate a series of repurposed candidate drugs over the next two decades, within an umbrella trial protocol, with change in ALSFRS(R) [11] (Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised) score and survival as co-primary outcome measures.

In the design of MND-SMART many of the aspects of historical trials that limited engagement have been addressed; including remote appointments to reduce travel burden, liquid medication to avoid swallowing difficulties and inclusive participation criteria. This afforded an exciting unique opportunity to explore additional reasons for, and barriers towards, joining a clinical trial experienced by people with MND.

The multi-arm, multi-stage, adaptive design has been shown to be particularly beneficial in enabling a reduction of patient numbers and time required to test more than one candidate drug in later stage trials of stroke [39] and cancer [40], these may be particularly crucial changes in trial delivery for rare and high-burden diseases such as MND. Broad inclusion criteria intends to promote participation and ensure that the trial is available to a large number of people living with MND, ultimately intending to capture the heterogeneity of this condition and improve the generalisability of findings.

As this is a UK wide trial with five sites in Scotland, and as the CARE-MND register (used for recruitment and additional covariates) includes only people with MND living in Scotland, FIT-Participation-MND will focus on Scottish participants. FIT-Participation-MND utilised recruitment and retention data from MND-SMART to review factors that may contribute to trial recruitment and retention.

5.3.3 Recruitment and Retention

Successful recruitment strategies for a clinical trial involve the engagement of participants who are representative of the wider target population, in numbers that are sufficient to meet the requirements of trial-specific power calculations in efficient time-frames. Equally important is retaining individuals who wish to remain trial participants despite their condition progressing. Attrition is defined as the loss of participating individuals to follow-up or as a result of missing data at one of more time-

points[42]. Whilst some attrition is inevitable, ensuring optimal retention is an important consideration in trial design. Clinical trials in people with MND frequently report attrition rates over 20% [239, 240], risk of bias is high at attrition rates in this threshold [50].

Sub-optimal recruitment and retention can affect a study's power and an insufficient number of participants will have a significant impact upon the conclusions drawn from the data, increasing the probability of Type II error [15]. These methodological issues can lead to trials reporting invalid or inconclusive results, prolonging trial time and potentially result in the trial being terminated prematurely [44, 45]. Trials that do not recruit efficiently, or sufficiently, can have a high social, financial and administrative cost. Understanding who does, and who does not, choose to participate in a clinical trial can have significant beneficial impact on designing informed recruitment and retention strategies to support participants throughout the trial journey.

5.3.4 Factors Impacting Recruitment and Retention in MND Research

A review of clinical trials in oncology [48] identified three areas that impact upon recruitment: patient factors, trial factors and doctor factors. This concept was also reflected in Atassi's [25] review of factors affecting adherence in MND trials; study population characteristics, trial design and site/staff facilities. Focusing on recruitment and retention within a single trial enables us to explore the impact of person-specific factors.

The presence of neuropsychiatric conditions, behaviour change and cognitive impairment pose significant challenges for recruitment and can impact upon a person's ability to give informed consent and protocol adherence [25] [241]. Participants' demographic characteristics [242, 243] and attitudes towards research and health behaviours [244] may be predictive of trial enrolment and attrition

5.3.5 Impact of COVID-19 Pandemic

MND-SMART publicly launched on 15th January 2020, with seven participants recruited at the lead site in Edinburgh, before recruitment was halted due to the first national lockdown as the government required that all non-COVID research was halted. Staff at the Edinburgh site continued to follow up these seven participants until recruitment was re-opened on 13th July 2020, in line with local and government guidance. In parallel the FIT-P-MND study commenced recruitment on 10th August 2020, and continued recruiting until 31st May 2021. At the time of the final data request, regarding

participation in MND-SMART, on the 31st of May 2022, five sites across Scotland were open and had been actively recruiting since 13th July 2020. Therefore, despite the potential impact of COVID-19, the research team are confident that as recruitment to MND-SMART re-opened prior to the commencement of the FIT-P-MND study, the majority of FIT-P-MND participants who would have wanted to join the trial had the opportunity to do so.

5.4 Aims

The general aim of this study was to investigate person-specific factors affecting recruitment and retention of people with MND to MND-SMART.

Specifically, this study aimed to:

- Explore the clinical and demographic characteristics of participants who choose to participate in MND-SMART, in comparison to those who do not become involved in the trial.
- Evaluate the differing responses to, and scores on, assessments of neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), cognition, behavioural change, quality of life, previous study participation and physical functioning of participants who choose to participate in MND-SMART, in comparison to those who do not.
- Explore the clinical and demographic characteristics of FIT-P-MND participants who were also MND-SMART participants, but were not retained one year after FIT-P-MND participation, compared to those who remained trial participants.
- Evaluate the differing responses to, and scores on, assessments of neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), cognition, behavioural change, quality of life, previous study participation and physical functioning of FIT-P-MND participants who were also MND-SMART participants, but were not retained one year after FIT-P-MND participation, compared to those who remained trial participants.
- Explore the responses to a study-specific questionnaire focusing on attitudes towards, barriers to participation and understanding of clinical trials.

5.5 Methods

5.5.1 Overview

Using a range of participant and caregiver questionnaires, clinical data and trial participation information this study evaluated person-specific factors in people with MND that may contribute to decision-making in trial engagement. Factors such as: neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), apathy, attitudes to clinical trials and quality of life were explored through questionnaires completed by the participant or their caregiver. This was supplemented with data derived from CARE-MND or MND-SMART relating to cognition (ECAS [161]), disease phenotype, demographics and physical functioning (ALSFRS(R)).

The study involved three stages of data collection:

1. Questionnaire completion: participants and caregivers questionnaire packs
2. CARE-MND data request: additional covariates collected in routine clinical care
3. MND-SMART data request: trial involvement and participation

Data requests to CARE-MND and MND-SMART for additional data on physical functioning, cognition and clinical phenotype enabled a reduction in in burden for participants by ensuring brevity in study visits. Data on MND-SMART participation was requested a minimum of 12 months after study questionnaires were completed.

5.5.2 Recruitment

All recruitment was conducted through the CARE-MND register. This register contains contact details for people with MND living in Scotland, who have consented to receive information about upcoming research that may be relevant to them. All participants were also asked to identify a caregiver who would be willing to complete the Brief Dimensional Apathy Scale [245] questionnaire on their behaviour. Participants were given the option of completing their questionnaires online, in paper format or a telephone appointment. Due to COVID-19 restrictions, in-person appointments were no longer able to be offered.

In recruitment, study questionnaires were emailed or posted after a consent form for study participation was received. 38 people with MND completed a consent form indicating that they wished to participate but did not complete the study questionnaires. 120 individuals completed study

questionnaires. Eight of these people who consented but did not complete questionnaires died during the data collection time period. The study timeline is presented in Table 22 and inclusion criteria in Table 23.

Follow-up data on trial engagement was collected 12 months from the completion of the final questionnaire. Each participant was followed up for a mean of 18 months (SD = 2.5) after completing their questionnaires, with a minimum of 12 months for each individual. A total of 47 participants died during the follow-up period (overall 12-month survival of 61%).

Table 22: FIT-P-MND Study Timeline

Key Study Stage	Date of Occurrence
Favourable ethical opinion obtained	12th May 2020
Site approval to commence recruitment	8th July 2020
Recruitment commences	10th August 2020
Recruitment closes	31st May 2021
Initial CARE-MND and MND-SMART data request	18th June 2021
Second CARE-MND and MND-SMART data request	31st May 2022

Table 23: Inclusion and Exclusion Criteria for Participants and Caregivers

Inclusion Criteria	
Participant	*Caregiver*
• Over 18 • Confirmed diagnosis of MND (including the following subtypes: amyotrophic lateral sclerosis by El Escorial Criteria (possible, probable, and definite), primary lateral sclerosis, and progressive muscular atrophy) • Able to provide informed consent (proxy signature accepted if limb dysfunction renders the individual unable to sign) • Fluent in English	• Able and willing to complete a brief questionnaire regarding the participant's behaviour • Family member, spouse, relative, friend or partner of an individual with motor neuron disease • Primary caring responsibilities for a person with motor neuron disease • Fluent in English
Exclusion Criteria	
Participant	*Caregiver*
• Diagnosis of Frontotemporal Dementia (FTD-MND) • Unable to provide informed consent to participate • Resident outside Scotland • Under 18	• Paid carers who did not know the person pre-MND diagnosis • Not fluent in English • Unable to provide informed consent • Diagnosis of motor neuron disease

5.5.2.1 Power Calculation

This study recruited 120 individuals with a diagnosis of MND. The required sample size was determined using the primary research aims, which was answered using regression analyses. The sample size calculation is based upon the use of a logistical regression model, as recruitment of people with MND to the MND-SMART clinical trial is a binary outcome variable (Yes/No to participation). An OR (measure of association between an exposure and an outcome) of 1.70 with power at 0.70 provides a sample size estimate of 111.

There are approximately 420 people living with MND in Scotland at any point in time, circa 220 of whom have provided consent on CARE-MND to be contacted about research. All participants on the CARE-MND register who are eligible were invited to participate. Previous research using postal questionnaires in people with MND reported a response rate of 63% [120]. However, we anticipated that adding the options of completion via online survey or telephone would improve response rates, and we were able to recruit over a quarter of people with MND in Scotland.

5.5.3 Study Assessments

Table 24 includes a summary of all assessments included in the study completed by participants, and caregivers, with the full questionnaire schedule in Appendix 6. Also included within Table 24 are the list of additional variables requested from CARE-MND and MND-SMART, with the full data request information available in Appendix 7.

The questionnaire set includes three validated questionnaires on neuropsychiatric symptoms; HADS, STAI-Y, PHQ-9 and two established questionnaires on quality of life, ALSSQOL-20 and CDC HQOL-4. Finally, participants will be asked to complete the Attitudes to Clinical Trials Questionnaire (ACT-Q), developed specifically for this study to evaluate the attitudes and understanding of people with MND towards trial participation. Caregivers were invited to complete the b-DAS to consider behavioural changes of the participant.

Table 24: Assessments and Requested Variables for Participants

Data Source	Name of Assessment
Study Assessment Questionnaires: FIT-Participation-MND Participant with MND	ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire)
	HADS (Hospital Anxiety and Depression Scale) [137, 246]
	STAI-Y (State-Trait Anxiety Inventory-Form Y) [247]
	PHQ-9 (9-Item Patient Health Questionnaire) [248, 249]
	ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [210]
	CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [250]
Study Assessment Questionnaires: Carer/Relative	b-DAS (Brief Dimensional Apathy Scale) [76, 245]
CARE-MND Data Request	Clinical phenotype data • Date of Diagnosis • Age at Diagnosis • Classification of MND • Site of Onset • Previous Research Participation
CARE-MND or MND-SMART Data Request	ALSFRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [251]
	ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [148]
MND-SMART Data Request	• Date MND-SMART Participant Information Sheet given • Date of Screening • Date of Randomisation • Date of Withdrawal • Date of Last Appointment if Withdrawn • Reason for Withdrawal if provided • Status (Alive/Deceased) • Date of Death (if Applicable)

5.5.4 Questionnaire Selection Process

The thresholds for impairment, where applicable, for the included questionnaires and assessment tools are provided in Table 25.

Centre for Disease Control and Prevention - Health-Related Quality of Life (CDC-HRQOL)

This scale is freely available for use and there is a large volume of comparative data available. As it is not disease specific, we were be able to contextualise our findings within other neurological and degenerative conditions [252]. The scale also contained a specific item of interest to the research team regarding self-perceptions of health. HRQOL contains two sections; in the first participants were asked to rate their overall health on a scale of 1-5 from poor to excellent. In the second section participants indicated the number of days in the past month that had been affected by physical and mental health, and the number of days where this poor health affected their ability to engage in activity.

ALS-Specific Quality of Life Questionnaire-Brief Form (ALSSQOL-20)

This scale is free to use with the support of the Penn State Hershey Medical Centre team and enabled us to assess QoL whilst considering disease-specific features [199]. It has also been recently validated for use in people with MND in a comprehensive multi-centre study. The short form of the ALSSQOL contains 20 items with 10-point Likert rating scales for level of agreement. Scores are summed and divided by the number of responses per person, resulting in a score (generally out of 10) for overall self-reported quality of life. Normative data for the ALSSQOL is available in the scoring manual [210], with average scores of 6.5 (SD = 1.1) and a range of 3.7 to 9.3.

9-Item Patient Health Questionnaire (PHQ-9)

The PHQ-9 self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD), developed in the mid-1990s by Pfizer Inc. and is freely available [249]. It has been validated across a wide range of clinical populations [253]. It is suitable for people with neurological conditions as it balances a brief administration time with reasonable sensitivity and specificity [254]. The questionnaire consists of 9 items based directly upon the 9 criteria for depressive disorder diagnosis in the DSM-IV and also includes a specific question on suicidal ideation. The PHQ-9 total scores range

from 0 to 27 a score of 10 or higher considered to indicate ‘mild’ depression, 15 or higher indicates ‘moderate’ depression, and 20 or higher ‘severe’ depression [254].

Hospital Anxiety and Depression Scale (HADS)

The HADS is a brief 14-item measure, with seven statements regarding depressive behaviour and seven on anxiety-related behaviours[255]. Respondents indicate their level of agreement with each statement on a 4-item Likert scale, providing a total score and two sub-scores, with higher scores indicative of more behaviours present. The HADS was selected primarily due to its relatively low reliance on somatic symptoms, which have the potential to be confounded by disease progression in neurological conditions, previous use as an outcome measure in MND trials and disease-specific validation data [169]. Although MND-specific cut-offs are available [169], we opted to use the standardised score cut-offs to facilitate comparison with other disease cohorts and align with data from MND trials [256], specifically MND-SMART, where the full version is used. In the HADS, symptoms of depression and anxiety are scored separately. A sub-score of 8 to 10 suggested mild anxiety or depression, 11 – 14 indicates moderate and 15 – 21 represents severe [257].

State-Trait Anxiety Inventory - Form Y (STAY-Y)

This is a reliable assessment tool for anxiety in people with MND [258] which differentiates between state and trait anxiety. The range of possible scores ranges from a minimum score of 20 to a maximum score of 80 on both the STAI-Trait and STAI-State subscales. Sub-scores are commonly classified as “no or low anxiety” (20-37), “moderate anxiety” (38-44), and “high anxiety” (45-80) [259]. The State-Trait Anxiety Inventory has been previously used for remote data collection in cohorts affected by MND, and was found to be suitable [120].

Brief Dimensional Apathy Scale (BDAS)

The b-DAS was developed to provide a shorter administration time clinical tool for assessing the three subtypes of apathy based upon the Dimensional Apathy Scale [76]. Using data reduction techniques the b-DAS has been shown to differentiate between executive, emotional and initiation apathy alongside awareness and insight deficit [245]. In people with MND initiation apathy, self-generation of thoughts and behaviours, was most impaired [76]. This scale retains the psychometric properties and suitability for people with MND of the DAS, essential for differentiation of apathetic subtypes, whilst offering a shorter administration time [245]. B-DAS total scores range from 0 (least apathetic) to a potential total score of 27.

Edinburgh Cognitive and Behavioural Screen (ECAS)

The ECAS was designed specifically to assess cognitive impairment in people with MND, and ensures cognitive functioning assessment was not impacted by any physical deterioration [79]. The ECAS considers cognitive impairment (providing ALS-specific and ALS non-specific impairment scores to distinguish areas of cognitive decline expected in MND) and behavioural change, as reported by a caregiver.

Total cognitive scores are out of 136, with impairment cut-offs defined as a score at or below 105, and ALS-specific impairment sub-scores are out of 100, with a score below 77 indicating abnormality. ALS non-specific sub-scores are scored out of 36, and impairment is defined as a score below 24 [260].

The ECAS has been shown to be a valid measure of cognition in people with MND [161] and other neurological disorders [261, 262]. The behaviour section provides two scores, a score out of 5 for the presence of 5 potential behavioural changes (disinhibition, apathy, loss of sympathy/empathy, hyper-orality and perseveration) and a score out of 3 for the presence of 3 psychosis indicative behaviours (strange beliefs/behaviours, hallucinations and persecution beliefs) [260].

Most importantly for our study, the ECAS was integrated into routine clinical care for people with MND in Scotland and its administration for research or clinical purposes are recorded on the patient's proforma on CARE-MND. Through data requests to CARE-MND and MND-SMART, we accessed ECAS scores and avoid duplicating cognitive assessments for participants.

ALS Functional Rating Scale (ALSFRS(R))

The ALSFRS(R) comprises 12 items rated on a 5-point Likert scale, providing a total score out of 48, with lower scores indicating more severe symptoms. Domains assessed include: speech, saliva problems, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning

in bed and adjusting bed clothes, walking, climbing stairs, shortness of breath, and respiratory insufficiency. Scoring on the scale has been used to assess functional capability and is widely used as a primary outcome, or co-primary outcome alongside survival, to measure change in function (such as gait difficulties) in clinical trials in MND [263].

Table 25: Impairment Threshold of Covariates

Assessment or Data Included	**Impairment Thresholds**
ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire)	Not applicable
CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [250]	Not applicable
ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [210]	
ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [148]	• Total score is 136 where a higher score indicates better performance. Scores below, or at, 105 are considered abnormal. • ALS-specific score has a maximum of 100, and an abnormality cut off of 77. • ALS non-specific score has a maximum of 36, and an abnormality cut of 24.
b-DAS (Brief Dimensional Apathy Scale) [76, 245]	Each subscale has a minimum score of 0 (least apathy) and a maximum score of 9 (most apathy) Impairment defined as score per subscale: Executive ≥4 Emotional ≥5 Initiation ≥6
ECAS Behavioural Screen Subscale	Carer-Completed Behavioural Change Interview • Indicate Yes/No to symptoms, score 1 for every symptoms present out of 10 Carer-Completed Psychosis Screen Indicate Yes/No to symptoms, score 1 for every symptoms present out of 3

ALSFRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [251]	Twelve tasks rated from 0 (cannot do) to 4 (normal ability). Summed score between 0 (worst) and 48 (best).
HADS (Hospital Anxiety and Depression Scale) [137, 246]	Maximum total score is 24 Total of 12 per subscale (≥9) Severe (7 to 8) Moderate (≤6) Mild
STAI-Y (State-Trait Anxiety Inventory-Form Y) [247]	Total score ranges 20 to 80 (≥60) High (40–59) Moderate (20–39) Low
PHQ-9 (9-Item Patient Health Questionnaire) [248, 249]	Depression: Total score ranges from 0 to 27 (20-27) Severe (15-19) Moderately severe (10-14) Moderate (5-9) Mild (1-4) Minimal Suicidality: Item 9 scores from (0) Not at all 1. Several days 2. More than half the days 3. Nearly every day Scores of **≥1** indicates presence of suicidal ideation

5.5.5 Development of the Attitudes to Clinical Trials Questionnaire

The Attitudes towards Clinical Trial Participation Questionnaire (ACT-Q) is a brief study-specific questionnaire to quantify FIT-Participation-MND's attitudes towards involvement in research, and multi-arm clinical trials in particular (full list of study questionnaires are available in Appendix 6). Developed by the investigators, based on Kessel's survey of participant experience in cancer trials [264] & Ellis' [48] tripartite model on factors impacting cancer trial engagement.

Ellis' review highlights the importance of considering physician influence, participant characteristics and understanding of trial design to inform recruitment and retention strategies which shaped our decision of topics to evaluate [48]. Kessel's survey, although designed for oncology patients, was useful to inform ACT-Q design as the survey focused on trial participation, potential reasons for involvement and barriers that prospective participants may face[264].

The questionnaire involves 19 items on 3 areas of interest;

1. Barriers to Participation
2. Reasons for Participation
3. Understanding of Clinical Trials and Multi-Arm Multi-Stage Design

The questionnaire responses involved 5-point Likert rating scales of the extent to which participants feel each statement is applicable to them, or their level of understanding of a particular research aspect.

Each potential response was scored on the participant's rating of its importance to their decision making process and an overall score for each factor was produced per individual. Items 6, 7 and 13 have been reverse scored, indicating less agreement with the attitude. The final aspect of this questionnaire was evaluating participants' understanding of five key features of trial design. Respondents indicated on a 5-point scale to represent their level of understanding of each design feature.

People with MND provided feedback on the design, content and response structure of the ACT-Q. Respondents were asked to consider the questionnaire structure of the ACT-Q, provided an estimate of the time taken to complete and suggested any additional factors which may influence their attitudes towards trial participation.

5.5.6 Analysis Plan

5.5.6.1 Scoring the ACT-Q

The Attitudes towards Clinical Trial Participation Questionnaire (ACT-Q) is a brief questionnaire developed specifically for use in this study. Each potential response was scored on the participant's rating of its importance to their decision making process and an overall score for each factor will be produced per individual. Items 6, 7 and 13 were reverse scored, indicating less agreement with the attitude. Respondents indicated on a 5-point scale to represent level of understanding for key aspects of the multi-arm multi-stage trial design.

5.5.6.2 Statistical Analysis

The independent variables in this study were the study questionnaires and clinical data from CARE-MND. The binary dependent variable was the decision to participate, or not, in MND-SMART. To determine which factors affected recruitment into the trial, we used logistic regression to model aforementioned independent variables on the dependent variable. Results were presented with odds ratio and 95% confidence intervals.

To determine which factors affected trial retention, we used univariate and multivariable logistic regression to explore the effect of the aforementioned independent variables on withdrawal from the trial at the twelve month time point (dependent variable). Results were displayed as odds ratios and 95% confidence intervals.

As this is an exploratory study with multiple of independent variables and a priori hypotheses, we will not be using an adjusted alpha-level to correct for multi-testing.

5.5.6.3 Missing Data

If particular covariates, certain assessments or questionnaires, are not completed fully by the majority of participants, we considered removing the variable from analysis. If necessary, missing data within individual questionnaires was handled using multiple imputation. Incomplete questionnaires will not be returned to participants. As participants do not require a caregiver to participate, a missing behavioural questionnaire will not be included in thresholds for missing data.

5.5.7 REC Feedback

Ethics and Dissemination: Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020.

The REC committee were extremely positive regarding the need for studies focusing on additional symptoms of motor disorders, particularly those focusing on amplifying the voices of people affected through questionnaires. The committee commented on the questionnaires, and were supportive of the inclusion of open-ended questions to capture the participants' experiences of additional symptoms and their opinions on including these symptoms in clinical assessments and trial design. Based on feedback from the committee we included clarification on the distinction between CARE-MND derived data and medical notes, and the proviso that caregivers could provide support to complete the questionnaires.

5.6 Results

5.6.1 Participant Overview

Between 20th August 2020 and 27th May 2021, 120 people with MND residing in Scotland participated in this observational cohort study. The baseline characteristics of participants are provided in Table 26 and generally representative of the heterogeneity found in MND [5].

Also displayed in Table 26 for comparative purposes are the characteristics of all individuals on CARE-MND who did not participate in the current study but have agreed to share their clinical data for research purposes, 'CARE-MND Data Consent' (N = 295). Within this group of individuals who had consented to share their data, 73% (N = 216) had provided additional consent to be contacted about participating in research. These 216 individuals did not opt into the current study and their characteristics are presented below.

A total of 374 people with MND on the CARE-MND register were invited to participate, 158 (42%) completed consent forms and 120 (32%) went on to participate in the current study.

Table 26: Characteristics of FIT-P-MND Participants and CARE-MND Potential Participants

Characteristics	Study Participants (N = 120)	CARE-MND Data Consent (N = 295)	CARE-MND Contact Consent (N = 216)
Age at participation in years, mean (SD)	66 (9)	N/A	N/A
Age at diagnosis in years, mean (SD)	62 (10)	61 (14)	60 (14)
Survival length (%)			
Long survivors (> 7 years)	17 (14)	55 (19)	39 (18)
Males, no. (%)	81 (68)	172 (58)	136 (63)
MND sub-type, no. (%)*			
ALS	73 (60)	193 (65)	135 (63)
PLS	16 (13)	31 (11)	25 (12)
PBP	15 (12)	25 (8)	18 (8)
PMA	5 (4)	10 (3)	9 (4)
Other	3 (3)	11 (4)	8 (3)
No Data	8 (8)	25 (9)	21 (10)
Bulbar onset (%)	28 (23)	89 (30)	61 (28)

Intervention use (%)			
Riluzole	39 (33)	91 (31)	74 (34)
Non-invasive ventilation	12 (10)	47 (16)	40 (19)
Gastrostomy	19 (16)	67 (23)	45 (21)

5.6.2 Overview of Assessment Scores

Scores for the ALSQOL, CDC-HRQOL, PHQ-9, HADS, STAI-Y, b-DAS, ECAS, ALSFRS(R) and the number of studies previous participated in are available in Table 27.

Participants' scores on the PHQ-9 suggested low frequency of depressive symptoms. 15 participants (13%) were categorised as 'mild', 7 (6%) as 'moderate' and 3 (3%) as 'severe' for frequency of depressive symptoms in the previous fortnight. 22 (18%) participants responded that they had had "Thoughts that you would be better off dead or hurting yourself in some way" several days, or above, in the past fortnight, meeting the PHQ-9 threshold for suicidality present.

For the HADS anxiety sub-score, 80 participants (67%) were in the 'mild' category, a further 16 (13%) in the 'moderate' and 23 (19%) in the 'severe' category. On the HADS depression sub-scale 64 participants (54%) were in the 'mild' category, 28 (24%) in the 'moderate' and 27 (23%) in the 'severe' category.

ALSFRS(R) scores within two years of the questionnaire completion date were available for 111 participants, 98% of which were conducted within one year of study questionnaires. No data was available for 10 participants (12%). CARE-MND participants who had consented to share data but did not participate in the current study (N = 295, n = 195 of whom had ALSFRS(R) scores available) had an average ALSFRS(R) total score of 29. This was lower than the average total score of 33 for study participants, indicating that participants in the current study had overall better averagephysical functioning than the foe all individuals on the CARE-MND register.

Full ECAS data (cognitive and behavioural) was available for 68 participants (57%). Of these 68 participants only cognitive scores were available for 5 participants, resulting in behavioural data available for 63 participants, 53% of the total participants.

41 people (65%) had no behavioural changes, and apathy was the most commonly reported symptom affecting 17 participants (27% of people whom behavioural data was available for). An overview of the frequency that each behavioural symptom occurred is available in Figure 5. Only 2 participants (3%) had any psychosis behaviours on their ECAS, suggesting that few participants experienced behaviours potentially indicative of psychosis.

Study participants' (n = 68) average total ECAS score was 110, with an average ALS non-specific score of 27 and ALS-specific 83. This was comparable to the scores of CARE-MND participants who had consented to share data but did not participate in the current study (N = 295, n = 96 of whom had ECAS scores available), with an average total of 105, an ALS non-specific score of 27 and ALS-specific score of 79.

For participants who had a caregiver participating with them (n = 88), a b-DAS was completed. The frequency of apathy occurring varied greatly depending on apathy sub-type, with 16% of participants above the impairment threshold for executive apathy, 35% for initiation apathy and 8% for emotional apathy.

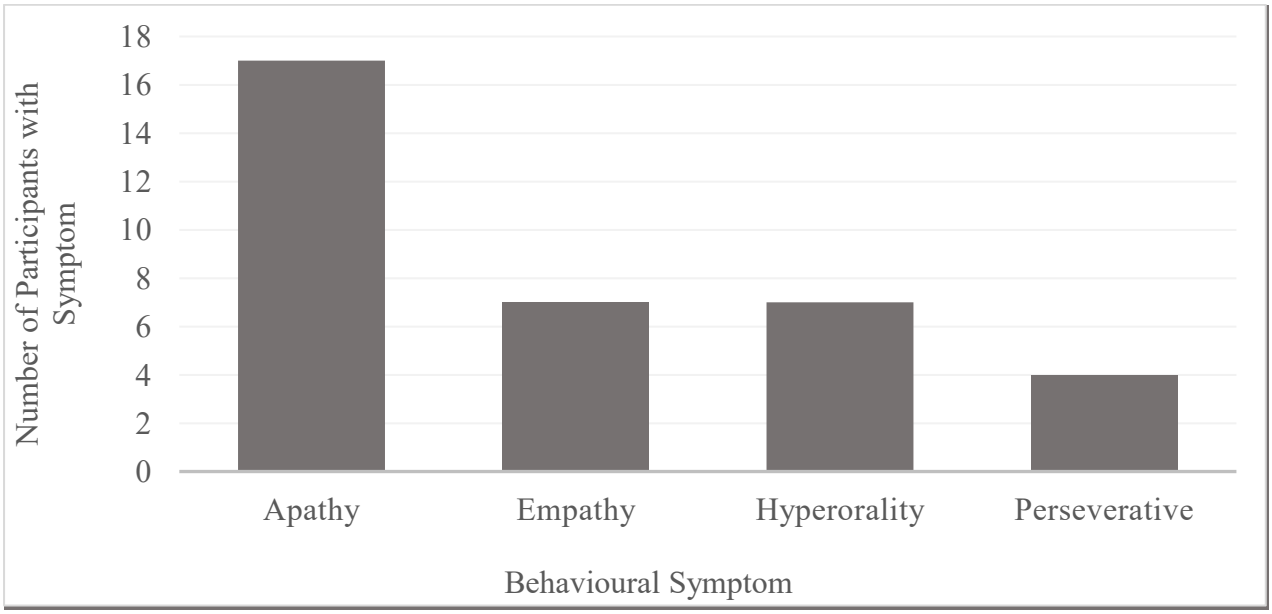
52 (43%) of participants had participated in at least one more research project previously according to their CARE-MND proforma, with 32 participants (27%) involved in two or more studies. Although limited to CARE-MND affiliated studies, this data provides an interesting insight into prior and parallel engagement with clinical trials, observational and genetic research projects in Scotland.

Table 27: Overview of Assessment Scores

Assessment		n	Minimum	Maximum	Mean	SD	Participants (%) Above Abnormality Thresholds
ALSQOL	*Divided Total*	118	1	8.15	4.9	1.4	-
CDC-HRQOL	*Overall Health*	117	1	5	2.8	1.1	-
	Days Affected by Physical Health	106	0	30	14.8	13.1	-
	Days Affected by Mental Health	109	0	30	6.9	9.4	-
	Days where Activities Affected by Health	113	0	30	10.3	12.7	-
PHQ-9	*PHQ Total*	119	0	29	7.0	5.0	3 (2.5) Severe 7 (5.9) Moderately severe
	Suicidality Item	119	-	-	-	-	22 (18) Suicidality present
STAI-Y	*Total*	119	56	112	90.4	10.4	-
	State	119	28	58	45.9	5.9	0 (0) High
	Trait	119	28	60	44.7	6.0	1 (0.8) High
HADS	*Total*	119	1	35	12.3	6.8	-
	Anxiety	119	0	19	5.8	4.1	23 (19.3) Severe
	Depression	119	0	16	6.2	3.4	27 (22.7) Severe
b-DAS	*Total*	88	0	24	7.8	5.1	-
	Executive	88	0	9	1.6	2.1	14 (15.9) Score ≥4
	Initiation	88	0	9	3.7	2.3	31 (35.2) Score ≥5

	Emotional	88	0	9	2.5	1.9	7 (8.1) Score ≥6
ALSFRS(R)	*Total*	111	9	47	32.5	9.1	-
ECAS	*Total*	68	69	132	110.4	13.2	19 (27.9) Score ≤105
	ALS-specific	66	46	99	83.0	10.7	15 (22.7) Score ≤77
	ALS non-specific	66	0	34	27.2	5.3	13 (19.7) Score ≤24
	Behaviour	63	0	4	0.65	1.03	22 (34.9) Symptom present
	Psychosis	63	0	1	0.03	0.18	2 (3.2) Symptom present

Figure 5: Histogram to Represent the Frequency of ECAS Behavioural Symptoms



5.6.3 Assessments Scores with Clinical and Demographic Variables

Independent t-tests Table 28 indicated that the ALSFRS(R), ECAS, HADS, b-DAS, PHQ-9 and ALSQOL scores, STAI state and trait sub-scores, and number of studies previously participated in, did not differ depending on participants' gender or status as a long survivor.

Analyses of variance showed that disease subtype was also not associated with scores on the ALSFRS(R), ECAS, HADS, b-DAS, PHQ-9 and ALSQOL scores, STAI state and trait sub-scores, or the number of studies an individual had previously participated in Table 29.

Table 30 and Table 31 report the results of linear regression models to explore the association of participant age, and number of interventions currently used (a maximum of three; riluzole, non-invasive ventilation and gastrostomy) with assessment scores, respectively.

A multiple regression model evaluating participant age and neuropsychiatric assessments (HADS total score, STAI State, STAI Trait and PHQ-9) was significant overall but not for individual assessment tools. A regression model exploring age and ECAS scores was significant. This suggests that older participants have lower scores and worse cognitive functioning, and inversely that younger people with a diagnosis of MND may have better cognitive functioning.

There was also a significant relationship between age of participants and their ALSFRS(R) score, with an older age associated with higher ALSFRS(R) scores. There was a significant relationship between ALSQOL scores and participant age, suggesting that as the age of participants increased, a lower quality of life was reported. The regression model for the b-DAS was also significant, indicating that as the age of participants increased, b-DAS scores were higher, indicative of more apathetic behaviours, were reported.

The multiple regression model evaluating number of interventions used and neuropsychiatric assessments (HADS total score, STAI State, STAI Trait and PHQ-9) was not significant. The ECAS regression model was also not significant, suggesting no associated between the number of interventions used and cognitive function.

However, a regression model indicated a significant association between ALSFRS(R) scores and intervention use, suggesting that as ALSFRS(R) score lowered (indicating worsened progression) participants used more life-prolonging interventions. The regression model exploring ALSQOL scores and intervention use was also significant, suggesting that intervention use has a positive association with participant-reported quality of life. However, the association between intervention use and b-DAS score was not significant.

Table 28: Gender and Long Survivor T-Tests

	Gender				
	Male	*Female*			
	Mean (SD)	**Mean (SD)**	**DF**	**T-score**	**p**
ALSFRS(R)	32.42 (9.33)	32.65 (8.93)	106	-0.12	0.90
ECAS	109.67 (14.26)	111.76 (11.22)	65	-0.59	0.56
Number of Previous Study Participation	1.09 (1.52)	0.74 (1.22)	117	-0.2	0.22
HADS	12.68 (6.85)	12.12 (6.85)	117	-0.4	0.68
STAI - State	45.57 (5.76)	46.6 (6.27)	117	-0.89	0.38
STAI - Trait	45.71 (5.14)	44.27 (6.35)	117	-1.22	0.22
PHQ-9	6.68 (5.63)	6.87 (4.03)	117	-0.19	0.85
ALSQOL	4.73 (1.51)	5.18 (1.24)	117	-1.62	0.11
b-DAS	8.5 (5.64)	6.53 (3.82)	84	1.75	0.08

	Long Survivor				
	Yes (> 7 Years)	*No (<7 years)*			
	Mean (SD)	**Mean (SD)**	**DF**	**T-score**	**p**
ALSFRS(R)	33.31 (7.37)	32.31 (9.65)	106	-0.38	0.70
ECAS	110.43 (14.04)	110.30 (13.28)	65	-0.03	0.98
Number of Previous Study Participation	2.15 (1.49)	0.63 (1.23)	117	-5.37	3.99
HADS	11.15 (5.54)	12.64 (7.15)	117	1.0	0.32
STAI - State	44.7 (7.0)	46.25 (5.56)	117	1.19	0.23
STAI - Trait	44.15 (7.72)	44.9 (5.44)	117	0.57	0.57
PHQ-9	7.11 (5.16)	6.63 (5.18)	117	-0.42	0.67
ALSQOL	4.89 (1.85)	4.87 (1.31)	117	-0.08	0.93
b-DAS	7.73 (5.13)	7.77 (5.11)	84	-0.58	0.56

Table 29: Subtype and Assessment Scores Analyses of Variance

	Sum of Squares	DF	Mean Square	F(108)	η2	P-value
ANOVAs						
ALSFRS(R)	244	5 (97)	48.88	0.57	0.03	0.72
ECAS	401	4 (61)	100.3	0.54	0.03	0.70
Number of Previous Study Participation	10.07	5 (108)	2.02	0.95	0.04	0.45
ALSQOL	11.55	5 (108)	2.31	1.1	0.05	0.37
b-DAS	42.6	5 (76)	8.51	0.32	0.02	0.90
MANOVAs						
Neuropsychiatric	-		-	0.81	-	0.62
HADS Total	301.8	5 (108)	60.37	1.43	0.062	0.22
PHQ-9 Total	68.14		13.63	0.52	0.023	0.76
STAI	-		-	1.48	-	0.15
Trait	288	5 (108)	57.6	1.58	0.068	0.17
State	350		69.99	2.02	0.086	0.08

Table 30: Regression Models for Participant Age and Assessment Scores

	B	95% CI	β	r(4, 112)	r^2	p-value
Intercept	78.51**	[62.81, 94.22]				<2e-16 ***
HADS Total	-0.19	[-0.52, 0.15]	-0.14	-.11	0.01	0.269
STAI State	-0.24	[-0.58, 0.10]	-0.16	-.15	0.02	0.159
STAI Trait	0.01	[-0.33, 0.35]	0.01	-.06	0.00	0.945
PHQ-9 Total	0.11	[-0.34, 0.56]	0.06	-.06	0.00	0.620
				r(1,117)		
Intercept	71.88	[65.95, 77.82]				<2e-16 ***
ALSQOL	-1.06	[-2.23, 0.10]	-0.16	-0.16	0.03	0.0738
				r(1,84)		
Intercept	65.22	[61.54, 68.89]				<2e-16 ***
b-DAS	0.13	[-0.26, 0.53]	0.07	0.07	0.01	0.509
				r(1, 106)		
Intercept	65.94	[59.29, 72.60]				<2e-16 ***
ALSFRS	0.04	[-0.16, 0.24]	.04	.04	0.001	0.69
				r(1, 65)		
Intercept	69.89	[43.63, 82.15]				1.2e-08 ***
ECAS	0.02	[-0.16, 0.19]	0.02	0.02	0.001	0.856

Table 31: Regression Models for Intervention Use and Assessment Scores

	B	95% CI	β	r(4, 112)	r^2	p-value
Intercept	0.746	[-0.39, 1.88]	-	-	-	0.194
HADS Total	0.014	[-0.01, 0.04]	0.15	0.13	0.01	0.234
STAI State	-0.105	[-0.02, 0.03]	0.04	-0.01	0.00	0.729
STAI Trait	0.004	[-0.03, 0.01]	-0.09	-0.09	0.01	0.391
PHQ-9 Total	-0.005	[-0.04, 0.03]	-0.05	0.05	0.00	0.713
				r(1,117)		
Intercept	-0.05	[-0.46, 0.37]				0.829
ALSQOL	0.13	[0.05, 0.21]	0.28	0.28	0.08	0.002**
				r(1,84)		
Intercept	0.76	[0.49, 1.02]				1.39e-07 ***
b-DAS	-0.01	[-0.04, 0.01]	-0.11	-0.11	0.01	0.293
				r(1, 106)		
Intercept	1.11	[0.66, 1.57]				3.96e-06 ***
ALSFRS	-0.02	[-0.03, -0.00]	-0.23	-0.23	0.052	0.0177 *
				r(1, 65)		
Intercept	-0.15	[-1.35, 1.05]				0.802
ECAS	0.01	[-0.00, 0.02]	0.14	0.14	0.02	0.252

5.6.4 Attitudes to Trials Questionnaire

The Attitudes to Trials Questionnaire (ACT-Q) explored three areas of interest in trial engagement; potential barriers to participation, reasons for participation and understanding of clinical trial design. Mean scores and associated interpretations for each item are displayed in Table 32.

Barriers and reasons for participation are ranked in order of their reported importance to participants. Key barriers to participation identified were; 1) the distance to the clinic, 2) dangers and side effects from trial medications and 3) the time commitment required to participate. Key reasons for participation identified were; **wanting to help others with the same condition**, the **opportunity to contribute to research** and **the possibility of trying new medications** that are not available to all people with MND, **increased contact with medical team**.

Participants' understanding of clinical trials, and the complexities of multi-arm multi-stage design are ranked from best understood to least understood. The best understood areas were necessity of placebos, exclusion criteria and potential treatment efficacy, whilst use of multi-arm design and re-purposed medicines were rated as less well understood.

Table 32: Responses to the ACT-Q

Barriers to Participation*	*Mean score, interpretation (n)*
2) The distance to the clinic is too far	3.2, Slightly Important (118)
1) The time commitment required to participate	2.9, Slightly Important (118)
6) I am concerned about the potential dangers and side effects of trial medications[+]	2.9, Slightly Important (119)
7) I am worried about the possibility of being assigned to the placebo group[+]	2.7, Slightly Important (117)
3) I would not feel well enough to participate because of how my condition affects me	2.6, Slightly Important (119)
5) I may not benefit personally from the development of new drugs	2.4, Not At All (117)
4) I am already participating in other research projects	2.3, Not At All (116)
8) I already feel I have a lot of appointments	2.2, Not At All (118)

Reasons For Participation*	*Mean score, interpretation (n)*
12) I want to help other people with the same condition as me	4.8, Very Important (118)
14) I want the opportunity to contribute to research	4.6, Very Important (119)
9) I may get to try new medicines which are not available to everyone with my condition	4.1, Quite Important (119)
10) I will get additional monitoring of how my condition is changing	3.9, Quite Important (119)
11) I will receive more regular contact with medical staff	3.7, Quite Important (118)
13) I have participated in research before and had a positive experience[+]	2.4, Slightly Important (116)

Understanding of Clinical Trials and Multi-Arm Multi-Stage Design[ı]	*Mean score, interpretation (n)*
15) Why clinical trials often need to have a group of people taking a placebo drug	4.0, Good Understanding (119)
16) Why not everyone may be suitable to participate in a specific clinical trial	4.0, Good Understanding (118)
17) Why researchers believe these experimental treatments may be effective	3.9, Good Understanding (119)
19) Why having multiple 'arms' means we can test more than one drug & why this matters	3.5, Good Understanding, (119)
18) What is a re-purposed medicine and why may it be effective in my condition	3.4, Some Understanding (119)

* 1 = Do not know, 2 = Not at all, 3 = Slightly important, 4 = Quite important, 5 = Very important
[ı] 1 = No understanding, 2 = Little understanding, 3 = Some understanding, 4 = Good understanding, 5 = Full understanding
[+]Items have been reverse scored, indicating less agreement with the attitude

5.6.5 Overview of Recruitment and Retention

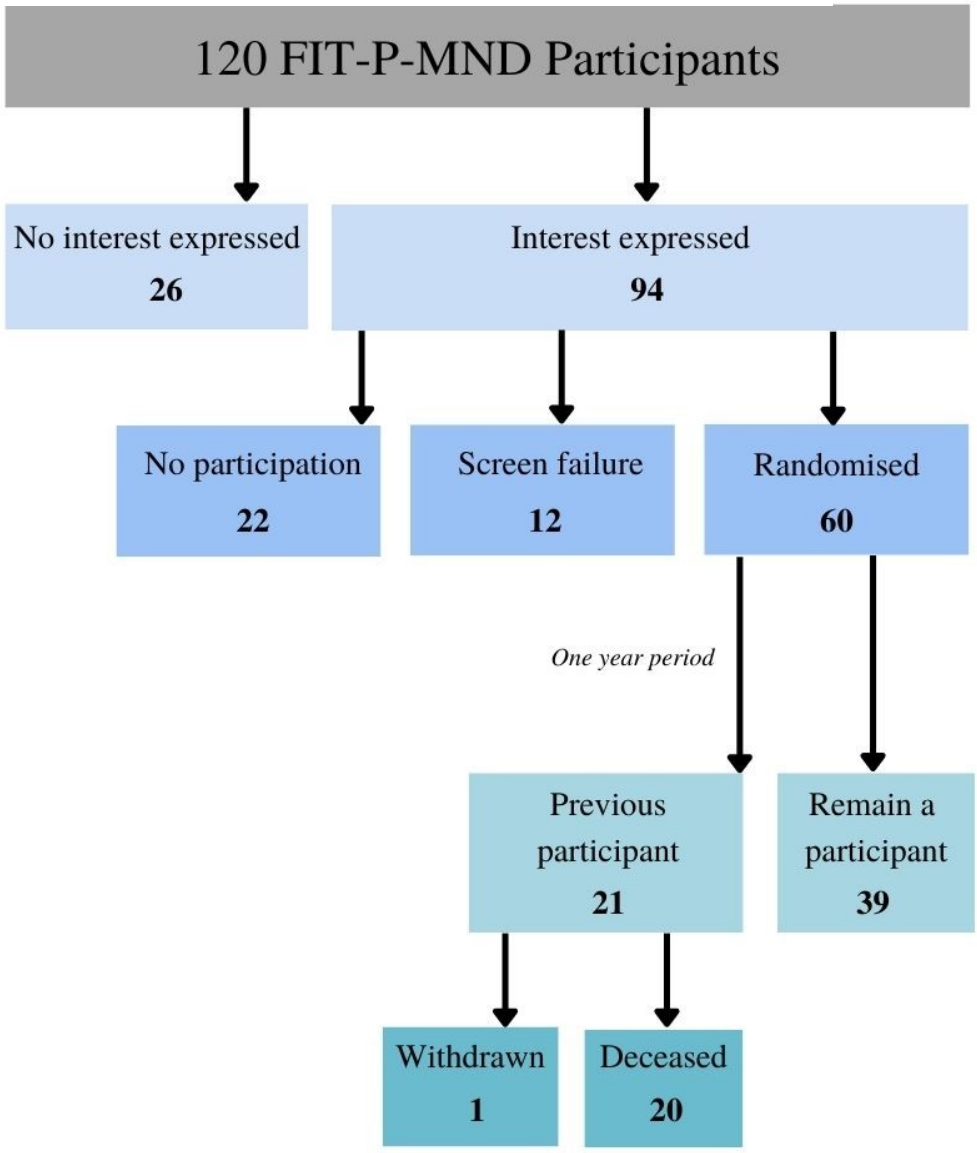
120 people with MND completed the questionnaires and assessments for FIT-P-MND.

Figure 6 details the flow of FIT-P-MND participants' journey to participate, or not, in MND-SMART. Of these individuals, 26 people did not complete online interest forms, or contact the trial team, about potentially participating in MND-SMART and this group was labelled 'No Interest Expressed'. The remaining 94 (78%) expressed some form of interest in engaging, termed 'Interest Expressed'; and 60 (50%) of them went on to be randomised into the trial, termed 'Randomised'. 22 people changed their mind, died or progressed too quickly to become involved, a group labelled 'No Participation', and 12 were unable to join due to not meeting inclusion criteria when screened by the trial team, the 'Screen Failure' group.

After the one year period, data on trial engagement was evaluated. Of the 60 FIT-P-MND participants who were randomised into MND-SMART, 39 (65%) remained as participants at the one-year data collection time-point, in the 'Remain Participant' group. Of the 21 individuals who were no longer participants this was primarily due to death, with only 1 person having withdrawn from the trial, the remaining 20 people had died, included in the 'Previous Participant' group.

Table 33 provides the number of individuals, and their mean scores for study questionnaires and assessments, for each of the trial participation groups.

*Figure 6: Flow of FIT-P-MND Participants into MND-SMART**



*No interested expressed: individual did not register interest on the trial website, did not attend a screening appointment or was never randomised into MND-SMART.

Interest expressed: individual registered interest on the trial website, attended a screening appointment, was randomised into MND-SMART or a combination of these.

No participation: although the individual registered interest on the website, they did not go on to attend a screening appointment or become randomised to MND-SMART.

Screen failure: after an appointment, or pre-appointment check, with the research team the person was deemed ineligible to participate in MND-SMART.

Previous participant: individual was randomised to MND-SMART but at the time of the one-year follow up was no longer a participant as they had withdrawn from the trial, or were now deceased.

Remain a participant: individual was randomised into MND-SMART and remains a current participant at the time of the one-year follow up.

Table 33: Demographics, Clinical Features and Assessment Scores per Trial Group

	Interest in Participation Shown	**Remaining in MND-SMART Participants**	**MND-SMART Participants**	**No Engagement**
	Registered interest with the trial team, were screened for participation or joined MND-SMART	*Participated in MND-SMART and remain participants at 1 year time-point*	*Participated in MND-SMART at some stage in the 1-year time-frame*	*Did not become MND-SMART participants and did not register interest*
	n = 93	n = 38	n = 59	n = 48
Gender				
Male	63	25	41	31
Female	30	13	18	17
Long Survivor				
Yes	19	10	11	15
No	74	28	48	33
Region of Onset				
Lower limb	37	20	25	16
Upper limb	21	10	14	9
Bulbar	18	5	13	16
Respiratory	2	2	2	-
Mixed	9	1	3	5
No data	6	-	2	2
Sub-Type				
ALS	59	24	36	33
PLS	14	8	9	5
PMA	3	2	2	2
PBP	9	2	8	6
MND-FTD	1	-	-	1
Other	2	1	2	-
No Data	5	1	2	1
	Mean (SD)			
Age	64.91 (9.01)	62.66 (10.29)	63.53 (9.35)	70 (7.98)
Number of Interventions Used	0.56 (0.63)	0.53 (0.60)	0.63 (0.64)	0.65 (0.73)
Number of Studies Previously Participated In	0.91 (1.39)	1.13 (1.38)	1.02 (1.47)	1.02 (1.45)
ECAS Total Score	109.73 (13.32)	108.97 (12.85)	109.48 (13.23)	116.17 (10.74)
ALSFRS(R)	32.99 (8.87)	34.58 (7.63)	32.72 (9.02)	30.53 (9.59)
HADS				
Anxiety	5.99 (3.91)	5.79 (4.13)	6.31 (4.20)	5.58 (4.01)
Depression	6.16 (3.56)	5.32 (3.29)	6.00 (3.62)	6.92 (3.04)
Total	12.44 (6.85)	11.34 (7.14)	12.56 (7.31)	12.71 (6.53)

STAI				
State	45.84 (5.54)	46.50 (5.34)	45.92 (5.73)	45.44 (6.25)
Trait	45.24 (5.22)	45.76 (5.13)	45.25 (5.30)	43.65 (6.68)
Total	90.87 (9.44)	92.05 (8.92)	91.03 (9.62)	88.65 (11.05)
PHQ				
Total	6.86 (5.29)	6.89 (4.14)	7.02 (4.55)	7.17 (6.03)
Presence of Suicidality n (%)	18 (19)	4 (11)	11 (19)	11 (23)
ALSQOL	4.80 (1.39)	4.74 (1.46)	4.98 (1.39)	4.96 (1.41)
HRQOL				
*Overall health**	2.86 (1.12)	2.95 (1.06)	2.93 (1.08)	2.46 (1.07)
Physical health symptoms	13.87 (12.86)	14.76 (12.79)	13.14 (12.70)	18.62 (13.15)
Mental health symptoms	7.17 (9.49)	9.38 (11.16)	8.60 (10.42)	5.48 (7.82)
Days impacting usual activities	9.24 (12.25)	10.03 (12.57)	10.28 (12.89)	10.75 (12.71)
bDAS	7.82 (5.27)	6.26 (4.70)	6.77 (4.89)	8.45 (5.21)

*** HQOL ratings of overall health options are;**
5 = Excellent, 4 = Very Good, 3 = Good, 2 = Fair, or 1 = Poor

5.6.5.1 Variables Associated with Recruitment to MND-SMART

Full information on chi square tests and logistic regression are shown in Table 34 and Table 35. **Age was a significant negative predictor of trial participation**, (OR = 0.92, 95% CI = 0.88 to 0.96, p = 0.000488), indicating that **for every increase in 1 year of age, the odds of participating in MND-SMART decreased by 1%**.

Region of onset, disease subtype, long survivor status or number of life-prolonging interventions used were not associated with participation in MND-SMART. The number of studies previously participated in, co-participation with a caregiver and the presence of suicidality as indicated by PHQ response were also not associated. Scores on the ECAS, ALSFRS(R), HADS (total, depression and anxiety sub scores), STAI (total, state and trait sub scores), PHQ Total, ALSQOL and bDAS were not associated with participation in MND-SMART.

Table 34: Chi Square Tests Explore Recruitment to MND-SMART

	N	**X^2**	**df**	**p-value**
Gender	119	0.02	1	0.89
Long Survivor	119	0.68	1	0.41
Region of Onset	112	7.81	5	0.17
Disease Subtype	115	4.76	6	0.57
Caregiver Co-Participating	119	0.12	1	0.72
PHQ Suicidality Presence	119	5.2	1	1.00

Table 35: Logistic Regressions to Explore Recruitment to MND-SMART

	Estimate	OR	95% CI	z	df	p-value
Intercept	-0.57			-0.26	117	0.81
Number of Studies Previously Participated In	0.04	1.04	0.80 - 1.35	0.32		0.75
Intercept	5.46			3.45	117	0.0006 **
Age at Participation	-0.08	0.92	0.88 - 0.96	-3.49		0.0005 **
Intercept	-0.12			-0.49	117	0.63
Number of Interventions	0.17	1.19	0.69 - 2.06	0.63		0.53
Intercept	3.90			1.41	65	0.16
ECAS	-0.02	0.98	0.93 - 1.02	-0.97		0.33
Intercept	-0.122			-0.17	105	0.86
ALSFRS(R)	0.009	1.01	0.97 - 1.05	0.42		0.67
Intercept						
HADS Total	-0.15	1.01	0.96 - 1.06	-0.04	117	0.69
HADS Anxiety	0.01	1.06	0.97 - 1.17	0.40		0.68
HADS Depression	0.06	0.96	0.87 - 1.07	1.32		0.18
Intercept	-1.10			-0.68		0.50
STAI Total	0.01	1.01	0.98 - 1.05	0.67	117	0.50
STAI State	0.001	1.001	0.94 - 1.06	0.03		0.98
STAI Trait	0.03	1.03	0.97 - 1.10	0.94		0.35
Intercept	-0.16			-0.52	117	0.60
PHQ Total	0.02	1.02	0.95 - 1.10	0.58		0.56
Intercept	-0.54			-0.84	117	0.40
ALSQOL	0.11	1.12	0.88 - 1.45	0.84		0.40
Intercept	0.69			1.67	84	0.11
bDAS	-0.08	0.92	0.84 - 1.00	-1.82		0.07

** Indicates significance at $p < 0.01$

5.6.5.2 Variables Associated with Retention to MND-SMART

In our study sample, of the 21 individuals who were no longer MND-SMART participants at the 1 year time-point, only 1 individual withdrew from the trial and the other 20 remained trial participants until their death. As only 1 individual had withdrawn, there was an insufficient sample size for statistical analyses.

Instead we explored the characteristics of those who died during follow-up. Age of the participant was associated with them remaining in MND-SMART at the one year data collection time point, (OR = 0.93, 95% CI = 0.88 to 0.97, p = 0.002). For every increase in one year of age, the odds of remaining a participant in MND-SMART decreased by 1%. In addition, bDAS scores were significantly associated with remaining in MND-SMART , (OR = 0.9, 95% CI = 0.80 to 0.99, p = 0.044), indicating that for each one point increase in apathy severity score the odds of remaining a participant in MND-SMART decreased by 1.1%. No other clinical variables or assessment scores were associated with the likelihood of remaining a participant in MND-SMART or death during follow-up.

Region of onset was associated with remaining a participant in MND-SMART, X^2 (5, N = 112) = 17.79, p = 0.003, with individuals with 'Mixed' symptom onset least likely to remain as an MND-SMART participant at the one-year time-point and more likely to die during the follow-up period.

Figure 7 reports the number of individuals retained in MND-SMART, shown by their reported regions of disease onset.

In Table 37, as further information for the reader, the model intercepts are included. The model intercept comparing retention data to Number of Studies Previously Participated In, Number of Interventions, ALSFRS(R) and PHQ-9 Total Score are noted as significant, however, the regression co-efficient was not significant. The intercept does not provide any information about the relationship between variables, this is gathered from the regression coefficient, which was significant for Region of Onset, Apathy and Age only.

Table 36: Chi Square Tests Explore Retention to MND-SMART

	N	X^2	df	p-value
Gender	119	0.03	1	0.88
Long Survivor	119	0.17	1	0.68
Region of Onset	112	17.79	5	0.003 **
Disease Subtype	115	6.52	6	0.37
Caregiver Co-Participating	119	1.78	1	0.18
PHQ Suicidality Presence	119	1.64	1	0.2
** Indicates significance at p < 0.01				

Figure 7: Percentage of Participants Retained to MND-SMART per Region of Onset

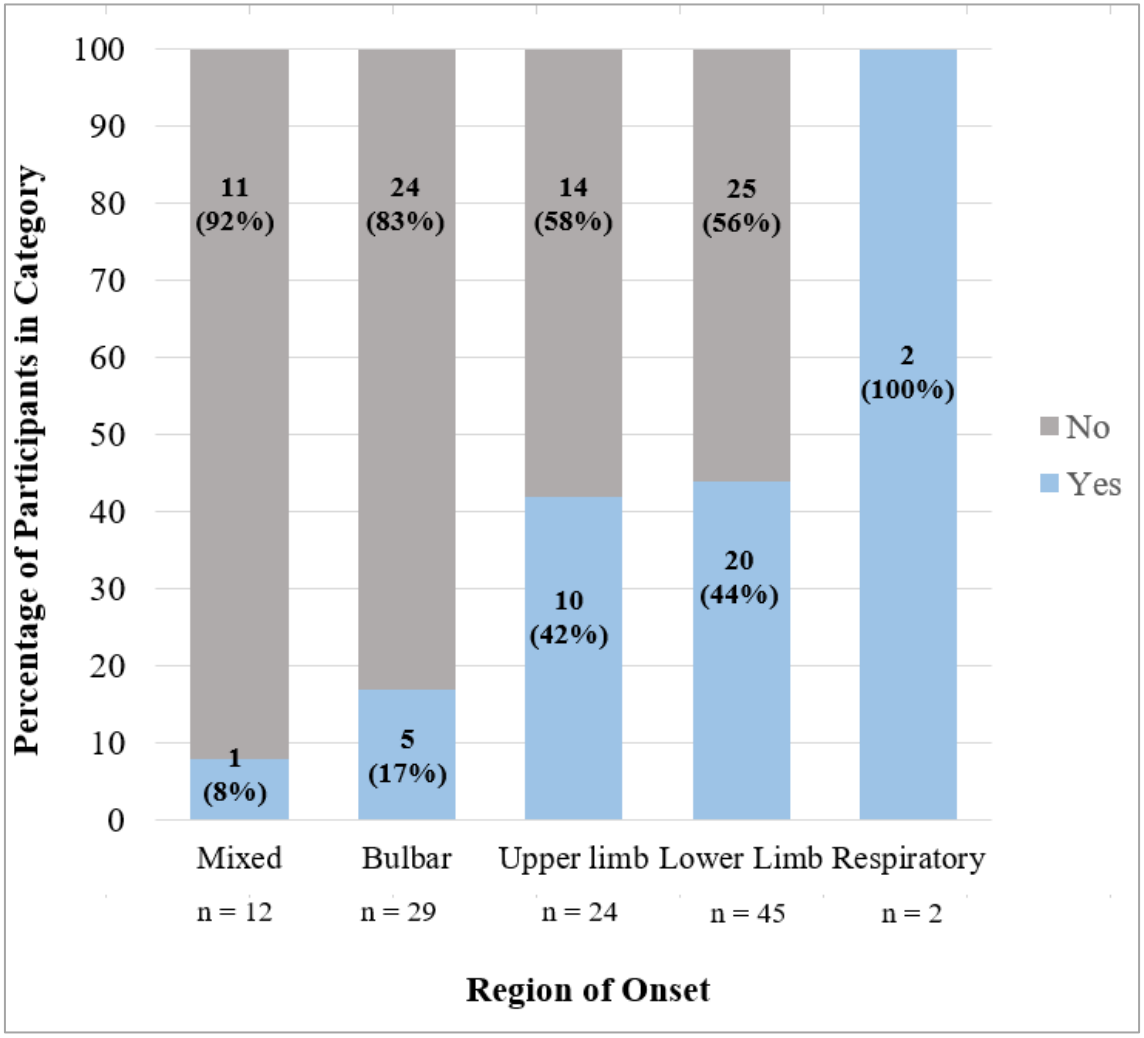


Table 37: Logistic Regressions to Explore Retention to MND-SMART

	Estimate	OR	95% CI	z	df	p-value
Intercept	0.87			-3.60		0.0003 ***
Number of Studies Previously Participated In	0.11	1.11	0.85 - 1.45	0.82	117	0.41
Intercept	4.13			2.62		0.009 **
Age at Participation	-0.07	0.93	0.88 - 0.97	-3.09	117	0.002 **
Intercept	-0.64			-2.47		0.01*
Number of Interventions	-0.21	0.81	0.44 - 1.45	-0.69	117	0.49
Intercept	2.17			1.01		0.31
ECAS	0.02	0.98	0.94 - 1.02	-0.92	65	0.36
Intercept	-2.05			-2.50		0.01*
ALSFRS(R)	0.04	1.05	1.01 - 1.10	1.82	105	0.07
Intercept	-0.37			-0.91		0.36
HADS Total	-0.03	0.97	0.90 - 1.03	-1.05		0.29
HADS Anxiety	-0.002	1.10	0.90 - 1.09	-0.05	117	0.96
HADS Depression	-0.12	0.89	0.78 - 1.10	-1.93		0.05
Intercept	-2.9			-1.59		0.11
STAI Total	0.02	1.02	0.99 - 1.07	1.19		0.23
STAI State	0.03	1.03	0.96 - 1.10	0.76	117	0.45
STAI Trait	0.04	1.05	0.98 - 1.12	1.28		0.20
Intercept	-0.81			-2.51		0.01*
PHQ Total	0.009	1.01	0.93 - 1.09	0.23	117	0.82
Intercept	-0.35			-0.51		0.61
ALSQOL	-0.08	0.92	0.70 - 1.20	-0.61	117	0.54
Intercept	0.19			0.45		0.65
bDAS	-0.10	0.90	0.81 - 0.99	-2.01	84	0.04 *

* Indicates significance at $p < 0.05$
** Indicates significance at $p < 0.01$
*** Indicates significance at $p < 0.00$

5.7 Discussion

5.7.1 Study Summary

The purpose of this study was to gain a better understanding of the person-specific factors that may influence an individual with MND to decide to participate in a clinical trial and remain in the trial. This is the first prospective study exploring characteristics of participants, and non-participants, in an MND trial. Understanding who does, and who does not, participate in such trials enables trialists to make informed and participant-focused decisions about design, recruitment methods and retention strategies. Ultimately, this may have a positive impact to support more people with MND to engage with and remain in trials if they wish to do so.

Although participants had better physical functioning than expected, as evidenced by higher ALSFRS(R) scores, the sample characteristics appear to be representative of the wider MND population for age, site of onset, gender, prevalence of long survivors, region of onset and disease duration [232].

This study was conducted in parallel with the launch of a national multi-arm, multi-stage trial for repurposed candidate drugs, namely MND-SMART. We collected data directly from participants, caregivers and the Scottish MND database, CARE-MND. Questionnaires on neuropsychiatric symptoms, attitudes towards clinical trials, behavioural change and quality of life were combined with clinical, demographic, cognitive and physical functioning data for 120 people with MND.

Of these 120 people, 50% went on to be randomised to MND-SMART. An even greater number, 78%, of FIT-P-MND participants expressed interest in the trial (through completing online interest forms, contacting the trial team or attending screening appointments). Of the 60 FIT-P-MND participants who were randomised to MND-SMART, 65% remained trial participants at the one-year time-point. Only one individual chose to withdraw from the trial, the remaining individuals who were not retained remained trial participants until their death. Participants in MND-SMART were highly motivated to engage with MND-SMART, and when randomised as trial participants remained involved with MND-SMART.

5.7.2 Interpretation of Findings

Reduced likelihood of participation from older age groups has also been identified as a concern in previous research [265]. Previously, older adults have had fewer opportunities to participate in randomised controlled trials, potentially due to narrow inclusion criteria [265], use of technological

outcome measures [266] and reliance on in-person appointments in trial design. Even when many of these barriers were addressed, or minimised, in MND-SMART older adults remained less likely to participate and at higher risk of attrition. Further work to improve the opportunities available for older adults to participate in trials, and addressing the potential person-specific barriers to engagement is essential to recruit and retain this group of prospective participants.

As in our study, previous findings have repeatedly shown that people with MND are highly motivated to engage with research [25], yet only 25% are trial participants [26] and 40% of trials report > 20% attrition [49], suggesting that the identification and removal of barriers to participation and retention must remain a priority across MND.

The availability of literature exploring how apathy may impact research engagement was limited, with a focus on defining and measuring apathy [76], and recommendations for designing trials to evaluate interventions to target apathy [267]. The three sub-types of apathy: initiation, executive and emotional, are evaluated in the b-DAS which was used in the current study due to its shorter administration time.

Apathy is prevalent in MND and other neurodegenerative conditions [268], affecting 28.2% of people with MND in one study [269], but it is heterogeneous and related to differences in pathology, with initiation apathy the most commonly experienced sub-type in MND [76]. The association between increased apathy and reduced likelihood of people with MND remaining in a clinical trial warrants further consideration. In the current study, the b-DAS total score but future research may explore how the presence, or absence, of different sub-types of apathy are associated with trial engagement.

As apathy affects a large proportion of people with MND, facilitating the participation and supporting the retention of apathetic individuals is key to delivering generalisable findings on the efficacy of a candidate drug. Pragmatic trial designs that reduce the burden of participation, and the onus on the individual to attend in-person, through offering remote assessments, using routinely collected clinical data to reduce number of assessments and non-invasive measures may encourage participation and improve likelihood of retention for apathetic individuals.

Region of onset was a clinical characteristics associated with retention rate to MND-SMART with individuals with a mixed onset least likely to be retained, followed by those with bulbar, then upper and lower limb. Both of the two individuals with respiratory onset who participated in MND-SMART were retained at the one-year time-point, which was unexpected as respiratory symptoms are often a predictor for worse prognosis and shorter survival [270], however these individuals may have used non-invasive ventilation systems which have been shown to significantly improve outcomes for this subset of people with MND [271]. Lower retention rates for people with mixed and bulbar onset was

as expected, as these regions of onset are repeatedly linked to speech or swallow problems, and more rapid progression and worse prognosis than limb onset [3].

This negative prognosis for people with mixed or bulbar onset, and those older at time of diagnosis, to be less likely to be retained, due to shorter survival times and greater risk of decline in physical functioning meaning that they are no longer able to attend trial appointments. The use of liquid IMPs and remote assessments, as included in MND-SMART, will likely help to reduce such barriers to participation experienced by individuals those with mixed/bulbar onset, and older adults.

Nonetheless, the majority of person-specific variables explored in this study were not found to be associated with trial recruitment or retention. The finding that ALSFRS(R) scores were not significantly linked to trial engagement is inconsistent with previous study findings which showed better functionality at randomisation was a predictor of trial retention [25]. However, this lack of association may be influenced by our participants' higher functional ability at the point of questionnaire completion. Study participants had a mean ALSFRS(R) total score of 32.5 (SD = 9.1), compared to studies with larger sample sizes, reporting a mean of 26.5 (SD = 10.3).

The lack of association between person-specific variables and trial participation demonstrated in this study suggests that engagement with a clinical trial is also dependent on design factors that are potential barriers to people with MND joining and remaining as participants. Narrow inclusion criteria, travel burden, availability of liquid IMPs and other design facets have all been identified by previous studies [23] and highlighted as important considerations by MND-SMART patient-public representatives. The factors which we have identified may be different for other trials, particularly trials which have more restrictive inclusion criteria or more in-person study visits, potentially with additional person-specific variables impacting participation and retention.

5.7.3 Strengths

A strength of this study is the focused exploration of 28 variables of interest. The decision on which variables to explore was informed through MND and trial design literature, and enabled us to evaluate the study hypotheses that these factors may be associated with the decision to participate, and remain participating, in a clinical trial. The decision to participate and remain engaged with a clinical trial is multifactorial and is often revaluated at various points throughout the trial journey. Our study provides a crucial insight into which person-specific factor were, or were not, associated with recruitment and retention to MND-SMART.

An additional strength of this study was the predominant use of validated instruments to measure these person-specific variables. Although evaluating complex phenomenon such as disease impact, quality of life, and cognitive function will inevitably be reductionist to some extent, validated tools offer a brief, comparable and quantifiable way to explore variation across participants.

Where available, disease-specific measures were used, to mitigate the potential impact of co-occurring physical disability, speech impairment and cognitive impairment on scores [161, 170, 199].

5.7.4 Limitations

However, a potential limitation is that some measures were not designed or adapted for people affected by neurological conditions and scores on these assessments may be influenced by motor and non-motor changes which can affect people with MND [246, 254, 272] although every attempt was made to select symptom-specific measures suitable for this cohort [137, 258].

Another limitation of this study was the assessment of suicidality through a single item within the PHQ-9. Categorising participants as suicidal, or having suicidal intent, based on one question focusing on suicidal ideation within a depression screening measure is insufficient, and may result in type 1 errors [273]. This in turn, may affect the validity of the conclusions drawn regarding the association between the presence of suicidal ideation and trial participation.

The design of this study involved data collection at a single time-point which may be a significant limitation when evaluating people with MND, a condition with rapid and variable progression. The decision to participate in a clinical trial, and the decision to remain a participant, may be continually revaluated as the disease progresses and a person's circumstances change, unlikely to be sufficiently captured by a single point of data collection on trial participation status.

Ultimately, the key limitation of this study is that when the evaluating likelihood of participation in MND-SMART, this study focused on people with MND who had already self-selected as participants in FIT-P-MND. There is a potential bias that is introduced by focusing on trial participation in a subset of people with MND who are already willing to become engaged with another research study. These individuals are inevitably more likely to be interested in ongoing research and physically capable of attending study visits and perhaps supported by a social network likely to facilitate trial engagement.

5.7.5 Future Directions

A key future direction in this area of research is increasing the frequency that person-specific factors and trial engagement are explored. Incorporating studies with a concept similar to FIT-P-MND, either alongside trials, as studies-within-a-trial or sub-studies, can enable trialists to evaluate the characteristics of their own participants. This trial-specific information on who is engaging facilitates targeted recruitment and adaptive retention strategies to support participant retention. Data on demographics, functional ability and clinical characteristics are routinely collected throughout an individuals' trial journey. Secondary outcome measures focusing on neuropsychiatric, cognitive and behavioural symptoms are becoming more prevalent in trial design [49, 119]. Exploring associations between these typically collected variables and trial involvement may offer an important insight into the decision-making process of people with MND.

Another avenue for future research is to focus in more detail on those who choose not to engage with clinical trials. An evident limitation of our findings is that the FIT-P-MND cohort who did not express interest in MND-SMART were still participants in a non-interventional study. The characteristics of self-selecting individuals who were involved FIT-P-MND may be intrinsically different to those people with MND choosing not participate in research at all. Future studies may overcome this sampling bias by exploring the characteristics of this non-engaging sub-group using data collected in routine clinical care, where people have provided permission for this information to be used in research, without a need to rely on active participation.

5.7.6 Conclusion

Our research exemplifies a new, participant-centric, direction for delivering clinical trials to people with MND, as outlined in the Airlie House Guidelines [32]. These findings represent the first direct demonstration of how person-specific factors may be associated with trial engagement for individuals with MND. Ultimately, the decision to participate in a clinical trial is complex, and is often reconsidered repeatedly and renegotiated by the individual and their support network throughout the course of the trial. A greater understanding of this decision-making process can facilitate the delivery of targeted recruitment strategies and retention support, to ensure that all people with MND who wish to participate in a clinical trials remain supported to do so.

5.8 Key Findings

- 120 people with MND and their caregivers completed comprehensive structured questionnaires on neuropsychiatric symptoms, quality of life, apathy and research engagement, this was then combined with clinical data, and data on their participation in MND-SMART
- 50% (n = 60) of study participants were randomised into MND-SMART
- 78% (n = 94) expressed interest in participating by attending screening, completing online forms or contacting the trial team
- After the one-year follow-up period 65% (n = 39) of the 60 randomised participants remained in MND-SMART
- Age was the only predictor for trial participation, with the likelihood of participating decreasing in older age
- Older age, more apathetic behaviours and region of onset (specifically mixed onset) were associated with reduced likelihood of retention to MND-SMART

- **Recruitment and retention strategies, and trial design, which is informed by prospective participants can enable trialists to include individuals who may have historically been excluded from trials or at greater risk of withdrawal**

6 Chapter 6: Systematic Review 3 - A Systematic Review of Digital Technology to Evaluate Motor Function and Disease Progression in MND.

The main body of this work has been published [274] and is available in Appendix 8.

Beswick, Emily, Thomas Fawcett, Zack Hassan, Deborah Forbes, Rachel Dakin, Judith Newton, Sharon Abrahams et al. "**A systematic review of digital technology to evaluate motor function and disease progression in motor neuron disease**." *Journal of Neurology* (2022): 1-15.

A third aim of this thesis was to explore how novel methods of evaluating health, using technology, were changing the landscape of MND research. In other neurological conditions, technology such as activity monitors, inertial measurement units, smartphone apps, gait platforms and movement sensors have been shown to be efficacious and suitable alternative outcome measures.

These types of technology can offer an opportunity to assess motor symptoms outside the clinic environment, decentralising trial delivery and reducing the burden of travel for prospective participants. Devices may also be more sensitive to detecting small changes in functional ability than traditional questionnaire-based rating scales used in neurological trials.

Firstly, we conducted a systematic review to consider how digital technologies had been used in previous research involving participants with MND, specifically focusing on motor symptoms and the types of devices used. We then progressed to exploring the participant-perspective on the acceptability of a wearable accelerometer. To deliver clinical trials, design research and offer clinical care which is person-centric, the perspective and experience of prospective users of any proposed technology is essential.

6.1 Abstract

Background: Amyotrophic lateral sclerosis (ALS) is the most common subtype of motor neuron disease (MND). The current gold-standard measure of progression is the ALS Functional Rating Scale – Revised (ALSFRS(R)), a clinician-administered questionnaire providing a composite score on physical functioning. Technology offers a potential alternative for assessing motor progression in both a clinical and research capacity that is more sensitive to detecting smaller changes in function.

Aims: The aims of this study were to improve understanding of the types of device currently used in research to evaluate motor symptoms in people with MND, and to explore if studies consider the acceptability of devices to participants, and the feasibility their use for routine data collection in MND.

Hypotheses We hypothesise that the majority of studies in this area will be exploratory; using small sample sizes and short follow up periods but will be encouraging for future exploration in research. In addition, we hypothesise that studies have primarily focused on comparing devices to performance on the ALSFRS(R) questionnaire. We hypothesise that people with MND will find these devices acceptable.

Method: We reviewed studies evaluating the utility and suitability of these devices to evaluate motor function and disease progression in people with MND (people with MND). We systematically searched Google Scholar, PubMed, and EMBASE applying no language or date restrictions. We extracted information on devices used and additional assessments undertaken.

Results: 20 studies, involving 1,275 (median 28 and ranging 6 to 584) people with MND, were included. Sensor types included accelerometers (n = 9), activity monitors (n = 4), smartphone apps (n = 4), gait (n = 3), kinetic sensors (n = 3), electrical impedance myography (n = 1) and dynamometers (n = 2). 17 (85%) of studies used the ALSFRS(R) to evaluate concurrent validity. Participant feedback on device utility was generally positive, and has been evaluated in 25% of studies. All studies showed initial feasibility, warranting larger longitudinal studies to compare device sensitivity and validity beyond ALSFRS(R). The risk of bias in the included studies was high, with information to determine study quality unclear.

Conclusions: Measurement of motor pathology and progression using technology is an emerging, and promising area of MND research. Further well-powered longitudinal validation studies are needed.

6.2 Lay Summary

This review considered how wearable devices have been used in previous studies involving people with MND.

Traditionally, how severe a person's symptoms are, and how these change over time, are assessed using questionnaires. This study explores how wearable devices can offer a new way of monitoring physical symptoms. In other neurological conditions, such as Parkinson's disease (PD), wearable devices have been useful to provide detailed measurements of smaller and subtler symptom changes that may not be detected by questionnaires.

In this study twenty studies, involving 1,275 people with MND, were evaluated. Results showed that devices such as activity monitors, smartphone apps and movement sensors offer a promising new direction, but more research needs to be done to understand what devices are suitable for people with MND. Future studies need to consider the experiences of people with MND using these devices, and how acceptable the devices are to this group.

6.3 Introduction

6.3.1 Digital Assessment in MND

In MND there is an urgent clinical need for more effective therapies and many clinical trials are in progress or planned [20]. Accurate measurement of symptom progression in MND is a significant challenge in both clinical and research settings.

The current gold standard for evaluating physical symptom severity and disease progression is the ALSFRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised), a questionnaire based assessment, evaluating the presence and resulting disability, of physical symptoms commonly affecting people with MND. However, the ALSFRS(R) is reliant on clinical judgement, subjective reporting and people with MND's recollection of symptoms [11]. A sensitive measure of disease trajectory is an essential requirement of clinical trial outcome measures. Instruments such as the ALSFRS(R) generate composite scores that may not be sensitive to smaller changes in function, necessitating large trial sample sizes, more frequent assessments points, and longer duration follow up, increasing participant burden [12].

Remote monitoring of function may also improve clinical care delivery [102]. Collecting information between appointments may facilitate delivery of more personalised care [101, 102]. The prognostic capacity of devices is an area of active investigation in a range of neurological conditions [100]. Improved ability to predict disease trajectory, and early identification of impairment may also help with care planning.

MND is characterised by clinical heterogeneity in site of onset and disease progression [275]. The different types of devices available offer the opportunity to evaluate different body regions, whilst enabling each person to act as their own baseline for detecting change and progression [105]. The potential of greater sensitivity for detecting change with these devices and their implementation as alternative outcome measures may lead to significant reduction in sample size requirements for trials by 30.3% and 44.6% for 18-month trials [105]. Smaller sample size requirements for detecting effects of new medicines reduces trial delivery costs, and shortens timelines for trials [105].

Using devices for remote data collection also reduces the need for frequent trial appointments for participants. Decentralized trial delivery offers the opportunity for more frequent assessments, potentially further reducing sample size requirements, for example weekly versus monthly ALSFRS(R) completion [103, 118]. The opportunity for remote data collection also offers trialists the opportunity to reduce the burden of trial participation on people with MND and optimise retention [104].

6.3.2 Types of Health Devices Available

Activity monitors evaluate changes in participants' overall capability for engaging in physical activity [103], whilst wearable devices containing an inertial measurement unit (IMU) enable researchers to provide a picture of an individual's ability to move their limbs [105]. An IMU is contained within a wearable device and used to measure velocity, orientation and gravitational force, which in turn can provide detailed information on the participant's movements. Within the IMU are an accelerometer, gyroscope and magnetometer sensor. Accelerometers measure acceleration from inertia (movement from a resting baseline), gyroscope measure angular rotation (direction of movement) with the magnetometer improving the accuracy of the gyroscope's determination of direction [106].

Smartphones are also used to collate passive (automatically collected by the phone itself) and active (entered by participants into specialised apps or web forms) data on function, symptoms and daily activity [104]. Electrical impedance myography devices apply a low-intensity electrical current to a limb, to evaluate an area of muscle and through repeated measurements we can evaluate changes in the structure and composition of the muscle as it degrades due to disease progression, offering a potential alternative biomarker for people with MND [276]. Dynamometry is also focused on the muscles, evaluating decline through measuring strength of pressure muscles are capable of, this can be focused on a specific area of the body (e.g. hand function and grip strength) or more global decline [277].

In other progressive motor disorders, such as Parkinson's disease, devices have offered an alternative method of continuous and objective monitoring of motor symptoms in both clinical care and trial delivery [108]. The clinical utility of these devices and their potential suitability as trial outcome measures, in people with MND has steadily gained attention in research. In this study, we will explore the current landscape of research in this area; the devices used, aspects of MND evaluated and directions for future work.

6.4 Methods

6.4.1 Search Strategy

A systematic and unbiased literature search was conducted on the 13th June 2022. EMBASE was searched with the terms “amyotrophic lateral sclerosis” OR “motor neuron (e) disease” AND “devices” with the headings expanded to include all relevant sub-headings for devices. PubMed was searched using (amyotrophic lateral sclerosis [MeSH Terms]) OR (motor neuron disease [MeSH Terms]) AND (devices [MeSH Terms]). In addition, Google Scholar was then searched with the search terms "amyotrophic lateral sclerosis" OR “motor neuron(e) disease” AND “wearable devices”, as “devices” alone provided an unmanageable number of results on this database.

Outside of the United Kingdom MND is primarily referred to by its most common subtype, amyotrophic lateral sclerosis (ALS), as a result both terms were included. No language or date restrictions were applied. Reference lists of returned search results were also screened for additional suitable articles.

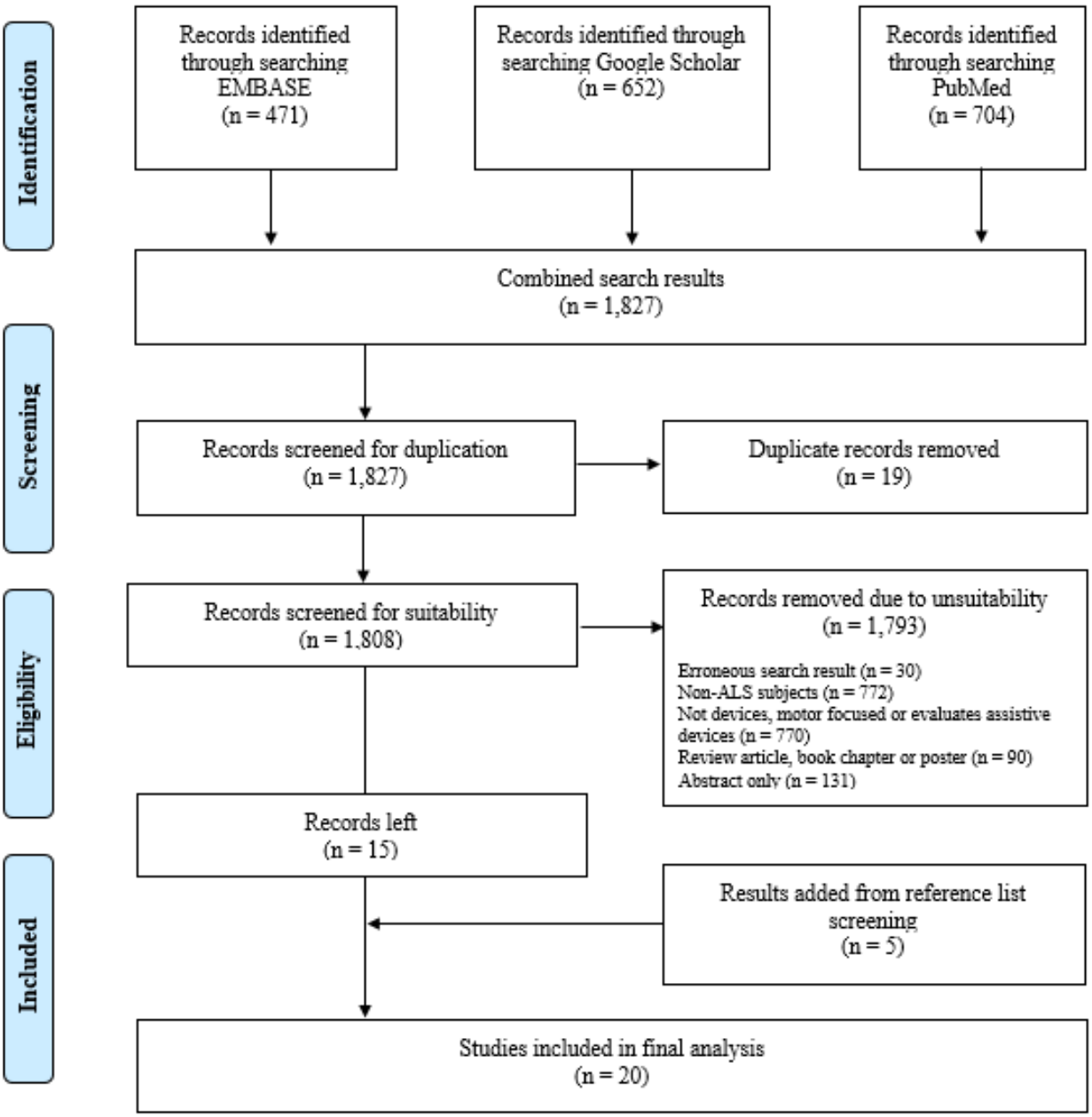
6.4.2 Screening for Eligibility

Results were screened for suitability by two independent reviewers, with any disputes resolved by a third reviewer. Full details of inclusion and exclusion criteria used is provided in Table 38 and the number of results included at each stage in the screening process is outlined in Figure 8.

Table 38: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Cohort study, case-control study, feasibility study, letter, case series or case report AND; • Study population includes people with Motor Neuron Disease (including any of the listed subtypes: Amyotrophic Lateral Sclerosis, Progressive Muscular A trophy, Primary Lateral Sclerosis or Progressive Bulbar Palsy) AND; • The device measures an aspect of motor system pathophysiology (such as movement, strength or impedance) OR; • The device output is used to assess progression of physical symptoms OR; • Gait analysis when focused on progression or evaluation of declining function	• Not including any participants with any form of Motor Neuron Disease • Pediatric or non-human study population • Review articles, conference abstracts, book chapter, poster or clinical trial • Electronic medical device is invasive or implanted • Device measures speech, respiratory function, energy expenditure, cognitive function or an aspect of disease unrelated to motor pathophysiology • Sensor output used for rehabilitative or assistive purposes (e.g. user-computer interface, communication aid, prosthetic) • Gait analysis focused on identifying pathological gait, or differential diagnosis between neurological conditions

Figure 8: PRISMA of Search Records



From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009).
Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

6.4.3 Data Extraction

Two reviewers extracted information from each search result on the devices used and study participant characteristics. We also noted any additional assessments used to evaluate the devices' suitability, and evaluation of participant feedback on the suitability of these devices.

6.4.4 Risk of Bias

Two reviewers independently assessed the methodological quality of all included studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool for quality assessment questionnaire [278]. Studies were judged to either have high or low risk of bias for each domain based on composite assessment of 13 questions. All studies fitting inclusion criteria were included in the review despite their risk for bias.

6.5 Results

6.5.1 Overview of Studies

An overview of the studies included, the specific devices and comparative assessment tools used for concurrent validity are summarised in Table 39. 1,827 search results were identified, of which 20 were studies eligible for inclusion (see PRISMA diagram in Figure 8 for more details).

These 20 studies included 2,044 participants (a mean of 102, range 6 to 584), 1,275 (62%) of whom had MND. The remaining individuals were included as healthy controls or as people with other neurological conditions providing controls. 17 studies (85%) recorded participants' ALSFRS(R) scores [170], to evaluate concurrent validity of the devices [27, 104, 111, 112, 114, 118, 277, 279-287].

Length of follow-up and number of assessment points varied greatly across the studies, from a single time-point of assessment [114] to study duration of 36 months [283]. The median length of follow-up was 6 months, with a mean of 8 months. The number of assessment points, and different tools used, are summarised in Table 2. Devices were used as a part of larger study protocols, such as the Ontario Neurodegenerative Research Initiative (ONDRI), to differentiate presentation and progression across different neurological conditions [283, 288, 289].

Two studies reported on the feasibility of a fully remote research delivery model [118, 285]. Recruitment and informed consent were successfully completed using the internet and electronic

transfer of medical records to confirm eligibility. Remote data collection was a more complex issue. Some participants struggled to set up study platforms independently, with up to 28% of participants with MND unable to record a first measurement [285] and only 15% of participants retained to the 9-month time-point.

Five of the studies explored a form of participant experience on the suitability of the devices to people with MND. Participants completed questionnaires, reported adverse effects, rated the burden of using devices. In one study, semi-structured interviews were undertaken to provide participants with the opportunity to discuss their experiences [290]. Concerns ranged from the fairly innocuous, limited clothing options and worry of losing regarding the ActiGraph [105], to more serious adverse effects of skin and subcutaneous tissue disorders in 6 of 25 participants, resulting in two participants withdrawing from the study [112].

Table 39: Overview of Included Device Studies

Lead Author	Total Number of Participants	Number of Participants with MND	Information on Disease Subtype	Length of Follow Up	Frequency of Data Collection	Function Assessed	Motor Sensor	Additional Assessments	Comparison Devices	Data on Participant Experience Reported?	Company Providing Device	Cost of Device
Andres (2017) [277]	100	100	No subtype data	15 months	Every 5 months	• Upper and lower limb strength	• Accurate Test of Limb Isometric Strength (ATLIS)	• ALSFRS(R)	None	No	ATLIS	No data
Bakers (2021) [279]	88	45	91% ALS 7% PMA 2% PLS	Single time-point	Not applicable	• Upper and lower limb strength	• Portable fixed dynamometer	• ALSFRS(R)	Hand held dynamometer	No	Not applicable	No data
Berry (2019) [104, 291]	23	22	No subtype data	6 months	Every 3 months	• Speech • Cognition • General functioning (self-reported ALSFRS(R), communication and movement logs)	• Smartphone (Beiwe app)	• ALSFRS(R) • ALS-CBS	Vital Capacity (Easy One portable digital spirometer)	No	Onnela Lab at Harvard University	No data

Beukenhorst (2021) [280]	8	8	No subtype data	Three months	Two month-long time periods	• General activity calculated from location data	• Smartphone (Beiwe app)	• ALSFRS(R)	None	No	Onnela Lab at Harvard University	No data
Die Bie (2017) [281]	10	10	No subtype data	12 months	Approximately every 3 months	• Upper limb function	• Reachable workspace (Microsoft Kinect)	• ALSFRS(R)	Forced vital capacity (Puritan Bennett Renaissance II Spirometer)	No	Microsoft	$41
Esser (2011) [292]	72	7	No subtype data	Single time-point	Not applicable	• Lower limb	• Inertial measurement unit	• Gait • Walking speed and distance	None	No	MTx Xsens	No data
Garcia-Gancedo (2021) [111]	25	25	No subtype data	12 months	Every 3 months Wear sensor 3 days a month	• Upper limb function • Speech	• Accelerometer (MegaFaros)	• ALSFRS(R) • Cognition and fine motor skills (9-hole peg test)	• Heart rate variability (Mega Fast Fix electrode patch) Digital speech capture (microphone and computer)	Yes (Reported adverse events, impact on activity and sleep quality)	Mega Electronics	$595
Geronimo (2021) [114]	30	30	84% ALS 14% PLS 2% PMA	Single time-point	Not applicable	• Lower limb	• Accelerometers	• Gait • ALSFRS(R)	• None	No	MetaMotionR	$78

Godkin (2021) [290]	39	5	No subtype data	7 days	Daily	• Upper and lower limb function • ECG	• Accelerometer	• Temperature • Sleep • Mood • Cognition • Rankin scale •	• None	Yes (De-brief interviews to discuss experience)	ActivInsights GENEActiv Originals Bittium Faros	$226
Kelly (2020) [112]	25	25	No subtype data	12 months	Wear device 3 days a month	• Activity • Heart rate variability • Speech	• Accelerometer (Mega Faros 180)	• ALSFRS(R)	• Speech (digital data capture) • Heart Rate variability (Mega Faros 180)	No	Mega Electronics	$596
Londral (2013) [282]	6	3	No subtype data	6 months	Every 3 months	• Upper limb function (typing ability)	• Accelerometer (BioSignals PLUX)	None	None	No	BioSignals Plux	$95
Londral (2016) [293]	45	19	No subtype data	2-20 months	Every 4-6 months depending on progression	• Upper limb function (fine motor typing)	• Accelerometer	ALSFRS(R)	None	No	No data	No data
Montero -Odasso (2017) [283]	500	40	No subtype data	36 months	Annually	• Lower limb function • Balance • Dual tasking (motor and cognitive tasks)	• Gait (GaitRITE® mat or PK Mas electronic walkway) • Accelerometer (GENEActiv)	• Neuro and ocular imaging • Neuropsychology (attention, executive, memory, speech	• None	No	GAIT Rite	$28,500

								production, language, and visuospatial function) • Genomics				
Oskarsson (2016) [284]	27	10	No subtype data	Single time-point	Not applicable	• Upper limb function	• Reachable workspace (Microsoft Kinect)	• ALSFRS(R)	None	No	Microsoft	$41
Rutkove (2019) [285]	141	111	No subtype data	9 months	Daily data collection for 90 days, bi-weekly for 180 days ALSFRS(R) weekly	• Activity	• Activity and sleep tracker (Mi Band) • Smartphone app (ALS AT HOME)	• ALSFRS(R) •	• Spirometer (AirSmart) • Electrical impedance myography (Skulpt Scanner) Speech (ALS AT HOME)	Yes (REDCap survey on patient-reported experience)	Xiaomi	$29
Rutkove (2020) [118]	113	113 61 in analysis	No subtype data	9 months	Daily for 3 months, twice weekly for 6 months ALSFRS(R) weekly	• Activity • Upper limb • Respiratory function • Speech	• Activity tracker (Mi Band)	• ALSFRS(R) • Patient-reported outcome measures •	• Hand grip (Camry Handgrip Dynamometer) • Slow-vital capacity (Air Smart) • Electrical impedance myography (Skulpt Scanner) Speech (ALS at Home app)	Yes (Participant-reported survey on experience)	Xiaomi	$29

Schefner (2018) [27]	106	46	No subtype data	Eight months	Every 2 months	• Detect changes in muscle structure	• Myolex mView	• None	• NDD EasyOneVR Plus Diagnostic Spirometer MicroFet2 VR handheld dynamometer	No	Myolex	No data
Trevizan (2018) [286]	60	30	No subtype data	Single time-point	Not applicable	• Evaluate finger motion	• Microsoft Kinect • Leap Motion Control • Touchscreen laptop	• ALSFRS(R)	• None	No	Microsoft Ultraleap	$41 $247
Van Eijk (2019) [105]	42	42	93% ALS 7% PMA	12 months	Wear sensor 7 days every 2-3 months Questionnaires daily	• Activity level (time active, metabolic equivalent, vector magnitude and movement)	• Accelerometer (ActiGraph GT9X)	• ALSFRS(R) • HADS (Hospital Anxiety and Depression Scale) • Weight •	• None	Yes (Participants rate burden on ten-point scale)	Actigraph	$238
Vieira (2022) [287]	584	584	No subtype data	Single time-point	Not applicable	• Speech • Accelerometer	• Actigraph GT3X devices	• ALSFRS(R)	• None	No	Actigraph	$238

6.5.2 Devices Used

Table 40 reports the devices used, brands of devices and areas of functioning evaluated.

Accelerometers were used in nine studies [105, 112, 114, 282, 283, 287, 290, 292, 293] including those using an accelerometer and additional sensors (gyroscope and magnetometer) in an inertial measurement unit. These sensors were used to evaluate spatio-temporal parameters of gait specifically in three studies [114, 283, 292]. Five studies evaluated lower limb function using accelerometers worn on the waist or ankle during walking tasks [114, 283, 287, 290, 292]; two of which also involved wearing one the wrist to assess upper limb functioning [287, 290]. In addition, two studies used small accelerometers on participants' fingers to evaluate fine motor skills through measuring typing speed, strength and accuracy [282, 293].

The Microsoft Kinect sensor uses a single camera system to evaluate depth and an individual's motion, that can be used to capture reachable workspace [113], a clinically relevant measure of upper-limb function, providing information on capacity to move the arms and reach within their environment. The Microsoft Kinect sensors were used to evaluate upper limb function, through mapping reachable workspace, in three studies [281, 284, 286]. One study explored the suitability of non-immersive virtual reality tasks as a method of assessing upper limb functionality and cognition, comparing touchscreen laptops, Microsoft Kinect motion sensor and finger motion sensor system Leap Motion Control® [286]

Smartphone applications, such as the Beiwe [104, 280] and ALS AT HOME apps were used [118], offering frequent remote data collection, often using a wide range of endpoints. Smartphone data was categorised as active (directly inputted by participants) [294], and passive (using existing smartphone data such as GPS and call logs), used to calculate activity [104, 280]. Participant-completed ALSFRS(R) was supplemented with additional questionnaires, motor tests, digital spirometry and cognitive testing.

Six studies evaluated 'activity monitors' that collect, and present, data on measurements such as time spent active, sleeping, and metabolic equivalent task (MET). MET is a calculation based on body weight to estimate the number of calories burned during an activity or 'task' [295]. Monitoring of general activity using wearable devices in studies also enabled researchers to collect data outside of the artificial clinic environment of changes in the participants' daily functioning, with minimal burden on participants. The Mi Band [118], ActiGraph [105] and Mega Faros sensor [112] were used to evaluate real-world activity levels and heart rate variability during rest and exercise. Activity monitors were combined with additional devices to evaluate respiratory function, such as the AirSmart spirometer [285], and upper limb function, using the Camry digital handgrip dynamometer [118].

Some studies focused on devices specifically aimed to evaluate progression in muscle strength. Electrical impedance myography, which works through the application of low-intensity electrical currents to the muscles, was shown to be potentially suitable to evaluate MND progression [27]. Two studies explored the use of fixed and portable dynamometry devices to assess global and precise muscle strength [277, 279], with hand-held dynamometry devices a common comparison measure to establish the suitability of new exploratory devices [118] [27].

Table 40: Types of Devices Used

Type of Device	Areas of Functioning Evaluated*	Brand Examples in Included Studies	Studies Using
Activity Monitor	• Heart rate • Personal activity • Breathing function • Stress • Sleep • Step count	Mega Fast Fix heartbeat sensor Mi Band Mega Faros Sensor	[111] [118, 285] [112]
Accelerometer	• Activity periods • Wear time • Metabolic rate • Energy expenditure • Steps taken	Actigraph BioSignals Plux Mega Faros 180 MetaMotionR MTXsens GENEActiv Originals Bittium Faros	[105, 287] [282] [112] [114] [292] [283, 290] [290]
Smartphone App	• Behavioral patterns • Sleep data • Social interactions • Physical mobility • Gross motor activity • Cognitive functioning • Speech production	Beiwe ALS AT HOME	[104] [280] [118] [285]
Gait	• Functional walking • Temporal and spatial parameters of movement	MetaMotionR GAIT Rite MTXsens	[114] [283] [292]
Movement Sensor	• Reachable workspace for upper limbs • Fine motor skill on touch screen devices	Microsoft Kinect Leap Motion Control	[281] [284, 286] [286]
Spirometer	• Vital capacity	EasyOne AirSmart Puritan Bennett Renaissance II	[104] [118, 285] [281]

Electrical impedance myography	• Biomarker of neuromuscular health	Skulpt Scanner Myolex mView	[118] [285] [27]
Computerized microphone	• Speech capture	Not specified	[111, 287] [112]
Dynamometry	• Limb and grip strength	Accurate Test of Limb Isometric Strength (ATLIS) Portable fixed dynamometer (PFD) Camry Handgrip Dynamometer	[277] [279] [118] [285]

*Devices may have multiple functionalities and not all functionalities will be automatically enabled

6.5.3 Data Analysis

Accelerometer devices collect raw data in three axes from the primary accelerometer sensor. The raw data is analysed using either data visualisation tools and pre-existing algorithms provided by the vendors or devising new data analysis models [112]. Working with the raw data to generate novel scoring thresholds enables investigators to replicate findings in future studies, compare participants and provide preliminary validity data on the prognostic probability of the devices used.

The data from activity monitors and accelerometers are used to correlate the level of change expected based on standardised tests of disease progression and functionality, in MND studies this is primarily the ALSFRS(R). Other studies use raw data from the devices to quantify the individual's movements when performing a standardised clinical measurement or motor function assessments such as the 6-minute walk test [283], arm raising [284] or typing [282]. Assessments that may be clinically relevant to people with MND may not yet have reliability data on which devices are suitable to evaluate motor functionality during them, a key foundation in considering the suitability of a device to this population.

6.5.4 Risk of Bias in Included Studies

Risk of bias in the included studies is shown in Appendix 9. No study fulfilled all QUADAS-2 criteria for low risk of bias. 31% (126/408) responses were deemed "Unclear" as the information regarding sample decisions, reference and index tests used were not available in the study report, meaning the conclusions regarding risk of bias were affected by a lack of data availability. However, for all of the studies there was low concern that the index test used, the interpretation of the index test or the participants included, differed from the review question.

6.6 Discussion

Digital devices provide an alternative to traditional questionnaire based assessment methods to detect progression in clinical trials [296] and have been used in research studies [297] in a range of neurological disorders. These devices offer a potential new direction for MND research and clinical care. This review explores the current landscape in this area; the device types used and the suitability and acceptability to people with MND. The opportunities offer great promise [298] and research into this area is increasing [274].

The systematic review of Chapter 6 indicates that there are several devices previously used to evaluate motor function in MND that are potentially useful as additional outcome measures in trials. The multi-systemic impact of MND presents multiple potential targets for biomarker evaluation; including speech, motor function, cognition and overall functional ability [299].

6.6.1 Establishing Suitability of Devices

Studies in this review reported that device outcome measures correlated with the ALSFRS(R), suggesting that devices have concurrent validity with traditional measures of disease progression [27, 104, 111, 112, 114, 118, 277, 279-287].

Accelerometer endpoints (average daytime active, percentage of daytime active, total daytime activity score and total 24-hour activity score) showed moderate to strong correlations with ALSFRS(R) scores over a period of 48 weeks [112]. Strong associations between accelerometer endpoints and ALSFRS(R) scores for up to 21 months and accelerometer data indicated less variability over time [105].

Worsening total ALSFRS(R) scores, and declining ALSFRS(R) upper limb sub-scores, were associated with reduced reachable workspace evaluated through Kinect sensors [284]. De Bie et al [281] also demonstrated the potential utility of device outcome measures, as in their study Kinect sensors were able to detect change in upper-limb function when the ALSFRS(R) did not indicate any significant change over a one year period. Scores from activity monitors, specifically the amount of time spent active, correlated with global and motor-specific scores on the ALSFRS(R), suggesting the potential utility of these devices to evaluate function with a low burden on participants [24].

Devices also offer an opportunity to take ALSFRS(R) data collection out of the clinic, with self-reported ALSFRS(R) scores correlating highly with clinic-based assessments [104], working toward

establishing app-based evaluation and fully remote studies [285] as a potentially suitable alternative to burdensome clinic appointments for people with MND involved in research.

However, the sensitivity of the ALSFRS(R) to detect smaller changes in functionality is limited [12]. When establishing the suitability of devices for people with MND, concordant validity with existing measures is a helpful starting point, but should not be the only consideration for a devices' utility in research and clinical evaluation. Responsiveness to change in other physical markers of progression, such as respiratory function and muscle strength, may also be relevant.

6.6.2 Responsiveness to Change over Time

Only three studies explored devices at a single time point [114, 284, 292]. The remaining studies (n = 17) explored changes in motor symptoms over time, with between 2 weeks and 36 months study duration. As when evaluating any progressive disorder, establishing the suitability of these devices to detect change was crucial. Devices were often compared to established measures of disease progression, to establish the ability to detect expected decline and ultimately detect potential treatment effects as biomarkers in clinical trials [27].

The broad range of aspects of function which can be evaluated using devices is particularly useful in a condition such as MND with heterogeneous presentation and progression. Devices offering objective measures of both global and precise decline, have been shown by studies in this review to successfully determine disease progression [105] and discriminate between neurological conditions [292]. Increasing the length of follow-up and the number of measurements to evaluate the reliability of a device across repeated measurements is a key area for future work.

6.6.3 Establishing Acceptability of Devices

Data on the acceptability of devices to people with MND was limited, with only five (36%) studies reporting the participants' experience [105, 111, 118, 285, 290]. For the studies that did report on participant experience, feedback was generally positive with participants reporting low burden, an improved sense of control over their condition and minimal impact on their day-to-day activities [105, 118].

The logistical challenge of remote data collection, any potential risk to participant safety, and shift in onus to the participant to collect the data, must be carefully managed by clinical and trial teams.

Feedback from patients/participants, rates of adverse events and attrition must be closely scrutinised when evaluating the suitability of a potential device for use in this population.

6.6.4 Remote Data Collection

A key benefit of wearable devices and other health technologies to evaluate disease progression in MND is their ability to support remote data collection. A recruitment, consent and data collection process that was either fully or partially remote could significantly reduce the burden placed on individuals who wish to participate in clinical trials. It would also minimise the burden of repeated travel for this vulnerable group, thereby reducing attrition.

Remote data collection using devices presents unique challenges associated with managing and reducing missing data. Studies involving remote data collection reported missing data due to insufficient device charge and participants' lack of adherence to protocol for wearing devices. An inability to use the devices and begin data collection may also be problematic, with one study reporting 13% of healthy controls and 28% of people with MND were unable to obtain a first measurement using the technology provided. Only 15% of participants were retained to the 9-month time-point. With only 15% of participants remaining at the nine-month time-point, drawing conclusions from remotely collected data in these studies must be cautious [118].

6.6.5 Participant-Led Data Collection

The shift to participant-led data collection may be contingent on individuals having a degree of technical knowledge and confidence in their ability to use a device, potentially affecting those who opt to engage [103, 118]. This may bias studies using health technology, for example towards younger individuals, with greater digital literacy and those less affected by upper limb weakness. Clinicians and researchers may pre-emptively address this concern by reducing the skills required for people to participate, providing adequate instructions for use, as well as ongoing technical support. The use of cloud-based data collection methods may also reduce the onus on participants, enabling remote monitoring of adherence and data management from devices.

The inclusion of devices in study design may result in greater participant burden ranging from the intrusion of remembering to wear sensors to attending more remote appointments. It is important that these factors are considered in study design. This burden may also be felt by caregiving relatives and

friends as people with MND experiencing motor decline or cognitive impairment may `need prompting and physical assistance from a caregiver to adhere to study requirements.

6.6.6 Choice of Device

The aim of this study was to systematically review the current landscape of research using devices to monitor motor progression in MND. Device suitability is dependent on the research aims, the intended participant group and project resources. More research into the properties of these devices, and their acceptability to people with MND will help to inform future decisions.

A key aspect requiring consideration is the current lack of consensus regarding choices of device for digital data capture. This lack of consensus, linked to small sample sizes [282] and the low quality of existing evidence [284, 292], introduces uncertainty and may limit uptake in clinical trial design and patient care.

Prospective studies, with larger sample sizes, longer follow-up durations and direct feedback from device users [23] are required to evaluate the utility of devices and establish which devices are most suitable in MND. The development of strategic guidelines would be beneficial to harmonise approaches and inform future study design and clinical care integration. Many devices contain multiple sensors and investigators must balance the benefits of additional data collection with concerns over decrease battery life and greater data storage requirements. If using accompanying software the type available for data analysis and data visualisation is relevant in informing design decisions.

6.6.7 Data Analysis and Management

A further potential challenge for researchers incorporating devices in trial design, and clinicians integrating such devices into care, is how to use device data to evaluate progression. A clear, pre-defined plan for evaluating digitally derived data, correlating this with existing validated outcomes, and determining thresholds of progression are crucial [298].

As with any outcome measure, the findings from studies using devices can be affected by missing data. Data points may be compromised due to technical issues of erroneous recordings, transferring and storage of data. Studies included in this review reported issues with missing data affecting the ability to draw clinical conclusions, due to participants withdrawing early due to adverse effects [111]

or being unable to use the technology to collect data [285]. Investigators must manage the risk of missing data, and develop study-specific plans to account for this in data analysis for future studies.

If investigators intend to use raw data for analysis, how the data is stored and organised and the availability of groups with expertise in this type of data analysis is a crucial consideration. Concerns regarding data security and adherence to privacy regulations may also be a barrier to integrating technologies in study design. Providing detailed data management plans, reviewed by specialists in data security will help to pre-emptively address the concerns of prospective participants, regulatory bodies and funders.

6.6.8 Cost of Devices

A potential concern for prospective users, regulatory bodies, funders, clinicians and research teams is the cost of device technologies. Access to these devices may be limited by the cost of providing equipment such as tablets and computers, or purchasing specialist voice recognition or eye gaze software. Approximate costs for devices, where available, are reported in Table 40. Resource is also required for storage and interpretation of data requiring interdisciplinary collaboration with clinicians, data scientists, information governance, and information technology security. Ensuring future work is not limited in scope by access to devices, is difficult to address without additional funding for MND care and research.

6.6.9 Future Work

Clinicians and trialists designing research to incorporate these devices will face a unique set of considerations and challenges. The body region to be assessed, ease of use, frequency and sensitivity of sampling, reliability, cost to purchase, battery life, and storage capacity of devices must be evaluated. The shift towards telemedicine in clinical care may offer valuable insights into delivering effective remote research opportunities for people with MND [300]. Future work should focus on developing guidelines for clinicians and researchers on available devices, their suitability for MND and which aspects of function are measured.

As there are a number of potentially suitable devices, the decision on what to use must also consider acceptability to participants, cost, area of function to assess and sensitivity to change. Identifying relevant devices, establishing their suitability and providing clear procedures for integration into

health research, specifically for MND, is a unique and complex issue in establishing digital biomarkers [298].

Evaluating the acceptability of devices for 24-hour wear-time periods must consider day-time activities and use during sleep separately. Small-scale feasibility studies like the one outlined in Chapter 7 enable the impact of technical and practical issues with wearing and using these devices on participants, caregivers and researchers to be explored and mitigated prior to launching a large-scale studies, which may be associated with unnecessary cost and participant burden.

6.6.10 Conclusion

Overall, the use of devices for measuring disease progression in MND is a promising direction of research. The reviewed literature was primarily proof-of-concept, exploratory studies with shorter periods of follow-up and smaller sample sizes, limiting the conclusions that can be drawn from the findings. In addition, a large amount of data was unavailable to determine risk of bias accurately, and for the information available, a high risk of bias was indicated. The COVID-19 pandemic has highlighted the importance of implementing remote assessment, using the types of technology discussed in this study, for people with MND [301]. Devices offer an opportunity to decentralise trial delivery and reduce the burden felt by participants previously required to travel to additional appointments.

6.7 Key Findings

- A systematic review of 20 studies, involving 1,275 (median 28 and ranging 6 to 584) people with MND
- The types of technology used varied; accelerometers (n = 9), activity monitors (n = 4), smartphone apps (n = 4), gait (n = 3), kinetic sensors (n = 3), electrical impedance myography (n = 1) and dynamometers (n = 2)
- 17 (85%) of studies used the ALSFRS(R) to evaluate concurrent validity of devices
- Participant feedback on the technology was evaluated in 25% of studies and was generally positive on the devices' utility and acceptability

- **Although including a relatively small number of studies this is a rapidly emerging area. The initial results were promising and technology may offer a new direction for assessing motor function in people with MND**

7 Chapter 7: Experimental Project 3 - Suitability and Acceptability of Wearable Sensors to Evaluate Disease Progression in People with MND.

Results from the systematic review of digital technology to evaluate motor function and disease progression in MND (Chapter 6) indicated that this is an exciting and rapidly evolving new area of MND research. However, it also brings unique challenges, and potential barriers for engagement, which need to be addressed to ensure the delivery of participant-centric research.

The first step understanding, pre-empting and addressing these concerns is exploring feedback on using devices from participants. The findings of our systematic review suggested that only a quarter of motor device studies evaluated, or reported, feedback on user experience. This study explores participants' prior use of technology to evaluate health, their expectations of wearable devices and their experience of using the devices during the study period. Specifically, the participants' perspective of the feasibility and acceptability of using wrist and ankle worn accelerometers during motor tasks, videoconferencing appointments and overnight were evaluated.

7.1 Abstract

Background: Motor neuron disease (MND) progression is traditionally evaluated with the revised ALS Functional Rating Scale (ALSFRS(R)), a questionnaire-based assessment with limited sensitivity to detect change. There is an urgent need for more objective, detailed and sensitive measures of physical function in people with MND to monitor individuals clinically and evaluate the impact of trial interventions. Wearable devices, useful to quantify physical activity and changes in motor function, offer an opportunity to address this need. Accelerometers, such as the ActiGraph, are a type of wearable device that evaluates movement of the limbs and may be useful in degenerative motor disorders.

Aim: To investigate participants with MND's expectations and experiences of wearing a device during motor assessments, daily activity and whilst asleep.

Hypothesis: We hypothesise that people with MND will be supportive of using wearable technologies to monitor health symptoms. Specifically, we hypothesise that a wrist and ankle-worn accelerometer, the ActiGraph, will be acceptable to people with MND as a method of evaluating general activity, overnight to assess sleep, and during standardised motor tasks.

Method: People with MND completed 12 weeks of fortnightly study visits whilst wearing an ActiGraph accelerometer on their right wrist and right ankle. These visits involved completing hand and arm movement tasks, the 6 minute walking test and a 24 hour period of continual wear to explore general activity and sleep. People with MND were invited to complete questionnaires on their use of health devices, expectations for wearable devices and feedback on their experience of the accelerometers, at the beginning, middle and end of the study period.

Results: 10 people with MND participated. All participants completed the full protocol, with seven data-points of motor assessments and 24-hour wear time periods each over the 12 week study. 70% reported having used wearable devices previously. All participants were excited about the prospect of trying a new technology. 80% of participants found wearing the devices to be a positive experience. No one reported side effects, interference with daily living or added burden by study participation. Only one participant reported wearing these devices interfered with their sleep. One participant considered the devices inconvenient or uncomfortable, and one individual reported difficulties putting on their devices which they indicated increased the burden on their caregiver. By week 12, 30% of participants had experienced technical issues with their devices.

Conclusions: All participants remained positive about the experience, reported enjoying the opportunity to try a new device and supportive of the integration of technology to monitor health. The findings of this study suggest that whilst people with MND can benefit from wearable devices, the

suitability of the ActiGraph specifically must be explored further. Participants were a highly motivated, physically well and technologically literate subset of individuals. Hence it may be beneficial for future work to explore how suitable wearable devices are for people affected by MND outside this limited criteria. Considering that one reported issue with the device was that they interfered with sleep, the impact of actions to rectify this is necessary.

Ethics and Dissemination: Ethical approval was provided by the Yorkshire & the Humber - South Yorkshire Research Ethics Committee (21/YH/0226) on 19th October 2021.

7.2 Lay Summary

Ten people with MND were invited to participate in a study that involved wearing an ActiGraph movement device on their right wrist and ankle for one day a fortnight for twelve weeks. Participants were also asked to complete a short series of standardised movement tasks whilst wearing the devices.

The study assessed the acceptability of the devices, and the feasibility for using them to measure changes in movement in people with MND. To explore this, all participants were asked to complete a structured questionnaire at the beginning, middle and end of the study to consider their expectations, experience and feedback on using the devices. The devices used in this study are ActiGraph accelerometers, a small device used to track how the person's body moves. It is possible that devices like these can be a useful alternative to assess physical symptoms in people with MND, and may be more sensitive to detecting small changes in motor symptoms than traditional questionnaire methods (usually the ALSFRS(R)).

Data was collected using a mix of in-person and videoconferencing appointments, over a 12-week period with fortnightly appointments. All participants remained positive about the experience, reported enjoying the opportunity to try a new device and supportive of using technology in healthcare. One individual reported that the devices affected their sleep, and one person reported that they struggled to put on and take off the devices themselves and had to rely on a caregiver. A third of participants reported technical issues with their ActiGraphs.

7.3 Introduction

7.3.1 Measuring Change and Function in MND

Motor neuron disease (MND) is a rapidly progressive, incurable and largely fatal neurodegenerative condition and disease progression has traditionally been assessed in clinical trials using the revised ALS Functional Rating Scale (ALSFRS(R)) administered at face-to-face appointments at one to two month intervals throughout the trial journey [11].

Performance on the scale is used to assess function correlates with quality of life [170]. The ALSFRS(R) has become a widely used primary outcome measure, or co-primary outcome alongside survival, to measure change in functioning (such as gait difficulties) in clinical trials [263]. Whilst the ALSFRS(R) remains an internationally recognised measure of disease progression in MND, its use is associated with poor sensitivity at detecting subtle changes over time (necessitating large numbers of participants and long duration trials), the requirement of researcher-led scoring, most commonly face-to-face in a clinic-based setting [12].

There is an urgent need for a more sensitive and specific outcome measures to objectively measure physical function and disease progression, particularly when evaluating the impact of interventional medicinal products (IMPs) in clinical trials of MND.

7.3.2 Benefits of Wearable Devices in MND

The clinical features of MND include muscle weakness, wasting and spasticity (impacting on mobility and activities of daily living), speech and swallowing difficulties, and respiratory compromise. The schedule of assessments in MND trials often involves numerous and intensive face to face assessments including questionnaires, tests of respiratory function and muscle strength. This may contribute to participant attrition, particularly as the disease progresses, with associated missing data increasing the risk of bias in reported studies [25].

Objective remote monitoring of motor function using a wearable device offers an opportunity to gather supplementary information relating to disease progression for potential use as an outcome measure in clinical trials. These devices can provide objective assessment data, with a potential for mapping a range of motor symptoms, including gait disturbance and impairment in upper limb strength, movement, and dexterity. Movement devices have already been successfully used to

quantify mobility and activities of daily living in people with Parkinson disease [302], multiple sclerosis [303] and stroke [304].

Wearable devices containing inertial measurement units (IMUs) enable the assessment of limb movement [105]. IMUs comprise an accelerometer measuring acceleration from inertia (movement from a resting baseline), gyroscope (measuring angular rotation) and a magnetometer device (which improves accuracy of the gyroscope's determination of direction) [106].

We used the ActiGraph, a portable device which can be worn on the chest, limbs or waist to evaluate body movement. Due to battery life constraints only the accelerometer function in the IMU was enabled as this provided detailed information on limb-specific movement which was the area of interest. Data from accelerometers can be used to correlate the level of change expected based on standardised tests of disease progression and functionality primarily the ALSFRS(R).

7.3.3 New Directions of Device-Based Assessment in MND

Non-invasive wearable devices also allow the completion of measurements in the community, where clinical care for people with MND is traditionally centred in the advanced stages of disease, reducing the need for burdensome repeated clinic attendances. The COVID-19 pandemic highlighted the need for safe evaluation of people with MND in the community using remote assessments.

Previous studies supported the potential utility of ActiGraph accelerometers in people with MND [105, 287]. Strong associations between daily-wear accelerometer endpoints (average daytime active, percentage of daytime active, total daytime activity score and total 24-hour activity score) and ALSFRS(R) scores for up to 21 months. Further, ActiGraph accelerometer data indicated less variability over time [105]. The ActiGraph was also able to identify disease progression, providing preliminary evidence of an ability to evaluate motor symptom changes over time [105]. ActiGraph data from limb-specific motor exercises in a large cohort of people with MND offered predictive value of ALSFRS(R) decline when used in machine learning models [287]. Initial findings on the acceptability of wearing these devices in the community is promising, with wear-time adherence of 93% and a mean rating of burden at 1.3, on a scale of 0 (low burden) to 10 (high burden) [105].

The purpose of this study was to explore these acceptability findings in greater detail considering the prior expectations people with MND have about wearing devices to monitor health, how their perception of burden changes over time and if the limb-focused wear locations affects acceptability. Ultimately, the purpose is to consider how acceptable participants find these devices for motor assessments conducted over video-conferencing, and whilst wearing overnight to gather sleep data.

7.3.4 Hypotheses

1) People with MND will be supportive of using technology to monitor disease progression
2) People with MND will already be using wearable devices to monitor physical health
3) Wrist and ankle worn ActiGraphs will be acceptable to people with MND
4) ActiGraphs will be acceptable to wear during sleep for people with MND
5) Using ActiGraph during motor tasks will be acceptable to people with MND
6) There may be attrition due to adverse effects of wearing the devices
7) People with MND participating in this study may find adherence to the requested schedules of wear time and motor assessments challenging
8) People with MND will be supportive of continuing to use the ActiGraph wearable accelerometer

7.4 Methods

7.4.1 Participants

10 people with a confirmed diagnosis of MND by El Escorial criteria were invited to participate. All had provided prior consent to be contacted about ongoing research projects on the Scottish CARE-MND (Clinical Audit Research and Evaluation) register [9, 10] and met study inclusion criteria outlined in Table 41. All provided informed written consent ahead of participating.

Table 41: MND Devices Study Inclusion and Exclusion Criteria

Inclusion	**Exclusion**
• Ambulant at the time of recruitment • Participant can be using NIV, gastrostomy and communicative devices • Participant must have arm and leg function sufficient to complete required motor assessments	• People with slowly progressing subtypes of MND including PLS and PMA, and long surviving ALS (> 7 years post diagnosis) will be accepted at the investigator's discretion • Conditions other than MND which may impact on upper and lower limb functioning • Significant cognitive impairment • Receiving invasive ventilation • Implantable cardiac device in situ

7.4.2 Assessments Used

Participants completed a 12-week schedule of assessments with fortnightly study visits (Table 42). At the first, middle and final visits participants completed questionnaires to provide feedback on their experience of the wearables devices and participating in the study. At each study visit participants completed a standardised series of movements (detailed in Sections 7.3.6. and 7.3.7). The day after their study visit participants wore the ActiGraph for a 24 hour period of real-world activity, including overnight during sleep. This was completed the day before the final study visit, to facilitate the return of devices.

The primary method of data collection was using questionnaires on acceptability of the devices and measurements from ActiGraph devices. ALSFRS(R) scores at the beginning and end of the study were also collected.

Data on participants' demographics, clinical phenotype and cognition was sourced from CARE-MND records to explore participant characteristics. Scores from the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) were used to report participants' cognitive function [260]. All study questionnaires, ALSFRS(R) and CARE-MND variables requested are available in the Appendices.

Table 42: Study Assessment Schedule

Week	Location	Assessments
0	In-person	• Screening for eligibility • Informed consent process and opportunity to ask questions • Information on using the devices and appointment schedule • Questionnaire 1: expectations and concerns on device use • First set of motor assessments • Complete ALSFRS(R) with researcher • Day after the appointment – wear the device for 24 hours (from the time they wake up, all day and overnight until they wake the next day)
2	Video conferencing	• Fortnightly motor assessment series • Day after the appointment – wear the device for 24 hours
4	Video conferencing	• Fortnightly motor assessment series • Day after the appointment – wear the device for 24 hours
6	In-person	• Questionnaire 2 on the participant's experience so far • Fortnightly motor assessment • Research team to check data recording, charge and download data • Day after the appointment – wear the device for 24 hours
8	Video conferencing	• Fortnightly motor assessment series • Day after the appointment – wear the device for 24 hours
10	Video conferencing	• Fortnightly motor assessment series • Day after the appointment – wear the device for 24 hours
12	In-person	• Day before the appointment – wear the device for 24 hours • Final motor assessment • Complete ALSFRS(R) with researcher • Participant returns devices to the research team • Questionnaire 3 on their experience of wearing devices

7.4.3 Questionnaires on Device Acceptability

Questionnaires investigating the experience and acceptance of devices were designed specifically for this study (available in Appendix 10).

1. Questionnaire 1: Participant Expectations at Screening

2. Questionnaire 2: Participant Evaluations Mid-Study

3. Questionnaire 3: Participant Evaluations at End of Study

Questionnaires contained a series of statements regarding potential benefits, concerns and barriers to using wearable devices, with 'Yes', 'No' and 'Unsure' options for participants to indicate their level of agreements. There was also a 'Prefer Not to Say' to ensure participants were able to decline to respond to any items.

In addition, each questionnaire included a free-text response item for participants to expand on any areas of feedback. Thematic analysis was used to explore the content of these responses, focusing on themes raised by participants; with a particular interest in any expectations, concerns or relevant aspects of their experience of study participation.

7.4.4 Wearable Devices

The wearable device used in this study was the ActiGraph GT9X. This is a wearable accelerometer which can be placed on the body to evaluate movement.

This device is available to purchase and can be used for both research and commercial purposes (https://actigraphcorp.com/actigraph-link/). Support on setting up and putting on their devices, and an explanation of how and when to wear them was provided to the participants at the week 0 visit. The ActiGraph GT9X was used for its licensed purposes in this study; acceleration, activity monitoring and step count.

Each participant received two ActiGraph devices for the duration of their involvement in the study. These devices were worn by the participants using a strap on their right wrist and right ankle. Participants were asked to wear both the upper and lower limb devices for the duration of their motor assessments and the 24 hour general activity evaluation.

7.4.5 Activity Data

The day after the motor assessment appointment (or the day before the final visit) participants were asked to wear both of their ActiGraph devices for 24 hours. This was defined as from when they woke that morning, throughout the day, overnight and taking them off when they woke the next morning. The lower-limb device was secured on the participant's right ankle and the upper-limb device on their right wrist as the participant continued with usual activities for that day and night.

The ActiGraphs were worn overnight to collect preliminary data on the acceptability and feasibility of using the devices for an extended period of time and during sleep. In addition data was collecting regarding participants' sleep/wake activity, time of sleep onset, sleep latency, amount of sleep, and sleep efficiency.

7.4.6 Lower Limb Assessment

The lower-limb ActiGraph was secured to the participant's right ankle using the strap provided. Participants were asked to complete a 6 minute walking test (6MWT), a standardised assessment paradigm validated as an alternative outcome measure in MND [305].

A short timed walk enables comparison of the step count, distanced travelled and gait data from the participants' lower limb as they move as a viable alternative to more detailed and lengthy monitoring periods [98].

During the in-person appointment the researcher and participant could walk around the clinic or the appointment room. An additional timer was used to record the length of time spent walking and a wheeled measurement tool was used to record the distance walked. For the remote appointments using videoconferencing software the participant was asked to remain in view of the researcher, walking as far and as quickly as they can do safely whilst the researcher timed six minutes.

7.4.7 Upper Limb Assessment

The upper-limb ActiGraph was worn on the participants' right wrists, and secured using a strap. Participants were asked to complete a series of movements to evaluate arm and hand function, the fist open/close and pronation/supination of the hand [306]. The research team were able to facilitate this by demonstrating the movements and reminding participants of the series to complete.

Figure 9: Open and close the fist 5 times for each hand. Begin with hand open (left of figure) and count each fist shape (right of figure). Encourage participants to make a fist as tightly as they can and to complete the series quickly, but accurately.

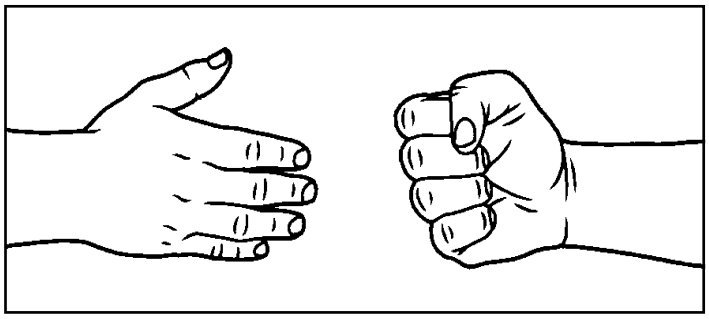


Figure 9: Hand Function Assessment

Figure 10: Begin with palm-up (left of figure) then move to palm-down (right of figure). Repeat movement 5 times on a hard surface (chair arm or table). Encourage participants to be quick but accurate and aim to finish with their palm up.

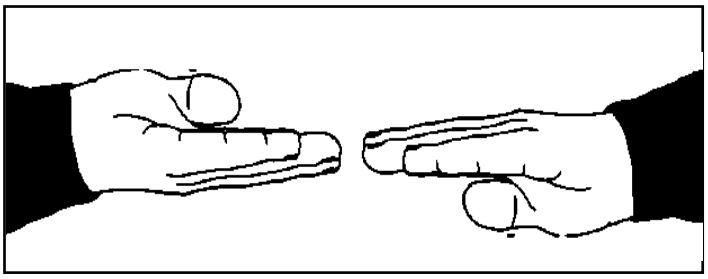


Figure 10: Hand Movement Assessment

Figure 11: Series of arm movements repeated 5 times. Begin standing with arms by their side (left of figure), move to arms straight out in front with palms facing down (middle) and pause for approximately one second. Then as the participant to raise arms above their head and clap palms together (right), lower arms back to their side (left). Repeat entire series 5 times, arms must be back down their side for the series to be considered complete.

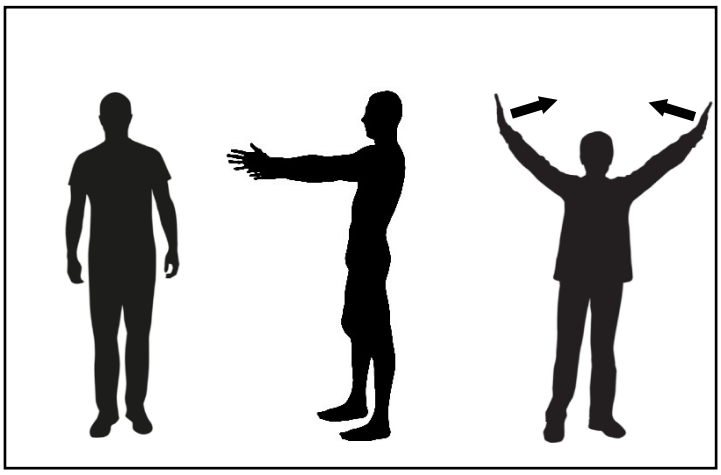


Figure 11: Arm Movement Assessment

7.4.8 REC Feedback

Ethical approval was provided by the Yorkshire & the Humber - South Yorkshire Research Ethics Committee (21/YH/0226) on 19th October 2021.

The REC were supportive of the new direction in technology-focused outcome measures for people with MND and expressed interest in the potential of the wearable devices. Ultimately, the committee were positive about plans for a study focusing on the participant perspective of the suitability of the devices, agreeing that the acceptability of these devices to participants must be a primary consideration. The committee requested clarification on the CE approval of the devices and clarification that ActiGraph's products abided with the Medical Device Directive 93/42/EEC and Radio Equipment Directive 2014/53/EU. Based on REC feedback we also provided information on how the study visits would be conducted within COVID-19 guidance to ensure participant risk was minimised.

7.5 Results

7.5.1 Characteristics of Participants

10 individuals with MND participated in this study. All participants completed the full 12 weeks of data collection with no missing study visits or 24-hour wear periods. The demographic characteristics of the participants are summarised in Table 43 with Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and ALSFRS(R) scores also included.

Table 43: Characteristics of Participants

Characteristics	**Overall**
Age at participation, mean (SD) (years)	62 (12)
Survival length, mean (SD) (years) *Long survivor > 7 years (%)*	3 (3) 2 (20)
Males, n (%)	8 (80)
Right handedness (%)	9 (90)
MND sub-type, no. (%)* *ALS* *PLS* *ND*	 5 (50) 2 (20) 3 (30)
Bulbar onset (%)	1 (10)
Current intervention use (%) *Riluzole* *Non-invasive ventilation* *Gastrostomy*	 1 (10) 0 (0) 0 (0)
ALSFRS(R) at Baseline *Mean* *Range* *SD*	 40 31 – 46 6
Edinburgh Cognitive and Behavioural Screen (ECAS) *Range* *Mean (SD)*	 88 – 125 112 (11)

7.5.2 Participant Expectations of Devices

A full exploration of participant response frequency is available in Table 44. All participants reported that they were excited about the prospect of trying new technology and the majority (90%) thought that wearable devices were a useful option to track changes in symptoms. 70% had used some sort of wearable device before, and were supportive that using these devices may mean less appointments in the clinic in the future.

No participants reported concerns over the time commitment or extra appointments relating to participation, or concerns regarding side effects or possible interference of using devices. No participants were concerned about being able to use the devices independently, adding burden to their caregivers or remembering to wear the devices.

Table 44: Questionnaire 1 Responses on Participant Expectations of Devices

Response Item	**Total N of Responses**		
	Yes	*No*	*Unsure*
I think wearable devices will be a useful option to track changes in my physical symptoms	9	0	1
I have used wearable devices before (e.g. blood pressure checker, step counter, heart-rate monitor)	7	3	0
I am happy that using devices means I do not have to attend as many trial appointments in the clinic	7	1	2
I am excited about the prospective of trying new technology	10	0	0
I am concerned about the additional time commitment required for participation in this study	0	10	0
I am concerned that participating in this study will mean I have extra appointments to remember	0	10	0
I am concerned about wearing devices/batteries near my skin	0	10	0
I am concerned that wearable devices may interfere with my daily activities	0	10	0
I am concerned that I will not remember to wear the device	0	10	0
I am concerned that I will not be able to work the device as I do not feel confident with new technology	0	10	0
I am concerned that remembering to use the device will be extra work for my caregiver	0	10	0
I am concerned that I may struggle to put on and take off the devices without help	0	10	0
I am concerned about side effects from wearing the devices	0	10	0

7.5.3 Participant Feedback on Devices

Table 45 considers participant responses from the two questionnaires, at the beginning and end of the study period, exploring experiences of using the devices.

80% of participants found wearing the devices to be a positive experience. This differed across the location of the devices with all participants happy to wear the wrist device at both time-points, but one participant reporting an issue with their ankle device in the final week of the study.

90% of participants reported they would be happy to wear the devices for a longer time period. 60% of participants indicated that they would be happy to wear the device for longer time periods overnight, which then increased to 80% by the end of the study. At the 6 and 12-week time-points only one person (10%) reported disturbed sleep due to wearing the devices overnight, with 80% of participants happy to wear the devices overnight for longer time periods.

No participants reported any side effects, concerns over remembering to charge the devices, interference with daily activities or additional burden from study participation. Despite one individual reporting at both time-points that they found the devices inconvenient or uncomfortable, all participants remained happy that they had the opportunity to try a new device.

At the 6-week time-point only one individual had experienced technical issues with their device, however this had risen to three, and 30% of participants, by week 12, important when considering future studies with larger samples.

One individual reported difficulties putting on and taking off the devices independently, and in turn felt that using the devices had added burden to their caregivers. Opinions on the suitability of the devices compared to completing questionnaires on physical symptoms varied across the time-points. At the mid-study time-point 80% reported that they preferred wearing a device to completing regular questionnaires about physical symptoms, but this changed to 50% supportive and 50% unsure by the end of the study.

At the end of the study, all participants were supportive of using wearable devices to track symptoms. However, 70% were unsure if they found wearable devices helpful to monitor their own MND symptoms, which we posit may be due to the lack of person-specific feedback we were able to provide.

Comments on the expectations and experiences of the participants are explored in Table 46.

Table 45: Participant Experiences of Devices

Response Item	Total N of Responses						
	Questionnaire 2: Week 6				Questionnaire 3: Week 12		
	Yes	*No*	*Unsure*	*No Data*	*Yes*	*No*	*Unsure*
I have found wearing the devices to be a positive experience	8	0	2	0	8	0	2
I was happy to wear a device on my wrist	10	0	0	0	10	0	0
I was happy to wear a device on my ankle	10	0	0	0	9	1	0
I would be happy to wear a device for longer time periods (eg several days)	9	0	1	0	9	0	1
I would be happy to wear a device overnight for longer time periods (eg several nights)	6	0	4	0	8	0	2
I found wearable devices to be a helpful option for monitoring my physical MND symptoms	5	1	4	0	3	0	7
I found wearing a device overnight disturbed my sleep	1	9	0	0	1	9	0
I preferred wearing a device to completing regular questionnaires about my physical symptoms	8	1	1	0	5	0	5
I am supportive of the use of wearable devices for tracking physical symptoms	9	1	0	0	10	0	0
I enjoyed the opportunity to try a new device	10	0	0	0	10	0	0
I found wearing a device inconvenient or uncomfortable	1	9	0	0	1	9	0
I needed help to put on and take off the devices	1	9	0	0	1	9	0
I felt that wearing a device has added more responsibilities onto my caregivers	0	9	0	1	0	9	1
I found wearing a device interfered with my daily activities	0	10	0	0	1	9	0
I have found the additional appointments from participating in this study to be inconvenient	0	10	0	0	0	10	0

I have experienced technical issues with my device	1	9	0	0	3	7	0
I struggled to remember to charge the device	0	10	0	0	0	10	0
I have experienced some side-effects/problems from wearing the devices	0	10	0	0	0	10	0

Table 46: Participant Comments on Devices

Content Theme	Comments to Illustrate
Positive Comments on Using Technology in Research	Technology is the way ahead.
	Happy to carry on.
	Encourages movement and keeps me more active.
	Wearable devices would be helpful as feeling he is being followed up/monitored and not just left for his MND to progress.
	Good for family as well.
Feedback on Devices and Data	He found the device too 'chunky' and quite large to wear.
	Would like to receive feedback from wearing the devices
Enjoyment of Research Participation	Happy to help out on any trial for MND.
	Enjoyed the experience!
	No problems and happy to be in the study.
	Happy to take part if it helps MND research.
Difficulty Using Wrist and Ankle Straps	People without carers might struggle to use this because buckles are difficult to use. Perhaps Velcro watches would be better.
	Practicalities of putting the straps on, there is too much of the strap that is left loose and can catch on things.
	Could maybe use an elastic strap / magnetic strap.
	Ankle strap is a bit more uncomfortable because of the excess strap, forms a lump on the ankle and is a bit annoying especially overnight.
Concerns of Device Accuracy	Not sure how the devices will assess muscle weakness as opposed to muscle activity.
	Unsure of how what comes off of the device will match with his MND symptoms.
Impact on Sleep	Worse sleep when wearing devices.
	Can be slightly uncomfortable at night on the ankle but did not interfere with sleep.
Faults with Technology	Faulty charger
	Wrist strap broke
	Charger sometimes did not work
	Casing from wrist strap has broken - needs to be attached with tape.

7.5.4 Changes in ALSFRS(R)

The ALSFRS(R) is a rating scale to evaluate 12 aspects of physical symptoms in people with MND, specifically focused on assessing progression. Scores range from 48 to 0, with a lower score indicating greater impairment.

Rate of progression varies greatly, but is expected to decline by approximately one point a month [307]. Participants in this study completed a researcher-led ALSFRS(R) at their Week 0 visit, and three months later at their final Week 12 study visit, with all scores shown in Table 47. The participants in this study tended to be progressing more slowly in their disease, and we were unsure if any difference in their ALSFRS(R) scores would be observed. However, eight participants did show a difference in scores across the three-month time-frame, it was the directionality which was of particular interest. Three participants, 30% of the sample, indicated an improvement in their ALSFRS(R) score between the Week 0 and Week 12 assessment, perhaps indicative of existing concerns regarding the fallibility of this measure and its accuracy in detecting change, particularly in limited time-frames without frequent repeated assessments [12].

Table 47: ALSFRS(R) Scores across the 12-Week Study Period

Study ID	Total Score at Week 0	Total Score at Week 12	Difference in Scores*
WMND-001	40	44	-4
WMND-002	46	46	0
WMND-003	31	29	2
WMND-004	44	40	4
WMND-005	45	44	1
WMND-006	29	32	-3
WMND-007	42	44	-2
WMND-008	44	41	3
WMND-009	46	46	0
WMND-010	37	30	7

* A negative difference in scores indicates an increased (improved) score

7.5.5 Wear Time an Indicator of Adherence

An additional area used to explore acceptability of these devices to people with MND is the wear time, indicative of adherence to the study protocol. The wear-time explored here is specifically focused on the 24-hour time period after each study visit, where participants were asked to wear their devices on the right wrist and right ankle continually, including during sleep.

Adherence to the protocol was excellent, with participants wearing their wrist devices for a median on 95.7% of the requested time, and 87.3% for the ankle devices. In addition, median wear-time steadily improved over the time period, indicating a high-level of engagement from participants in Table 48. A Wilcoxon signed-rank test indicated that wear time in wrist and ankle were significantly different, T = 96, z = -5.56, p = 2.663e-08.

The full dataset of wear-time, in minutes and as a percentage of the 24-hour period, is displayed in Table 49. Across six assessment time-points for ten participants, with two limb measurements each, 140 measurements of 24-hour wear times were taken. Overall, 33% of these (n = 46) were fully complete with no missing minutes of data.

Table 48: Median Wear Time for 24-Hour Time Periods

Device Location	**Week 0 (Minutes)**	**Week 12 (Minutes)**	**Total Wear Time (Minutes)**
Wrist	1338	1440	1378
Ankle	1212	1277	157

Table 49: Wear Time Data per Participant

Study ID	Wear Time in Minutes (% of Total Wear Time)													
	Week 0		**Week 2**		**Week 4**		**Week 6**		**Week 8**		**Week 10**		**Week 12**	
	Wrist	*Ankle*	*Wrist*	*Ankle*	*Wrist*	*Ankle*	*Wrist*	*Ankle*	*Wrist*	*Ankle*	*Wrist*	*Ankle*	*Wrist*	*Ankle*
WMND-001	1358 (94.3)	1097 (76.2)	1364 94.7)	1028 71.3)	1440 (100)	1169 (81.1)	1305 (90.6)	1151 (79.9)	1372 (95.3)	1239 (86)	1440 (100)	755 (52.4)	1148 (79.7)	1318 (79.7)
WMND-002	1318 (91.5)	1440 (100)	1440 (100)	1324 (91.9)	1380 (95.8)	1354 (94)	1440 (100)	1440 (100)	1440 (100)	1440 (100)	1294 (89.8)	1372 (95.3)	1440 (100)	1255 (87.2)
WMND-003	1440 (100)	1440 (100)	1311 (91)	1440 (100)	1358 (94.3)	1440 (100)	1440 (100)	1440 (100)	1431 (93.4)	1434 (99.5)	1379 (95.8)	1239 86)	1332 (92.5)	1332 (92.5)
WMND-004	1375 (95.5)	1264 (87.8)	1275 (88.5)	1440 (100)	1440 (100)	1440 (100)	1440 (100)	1280 (88.9)	1440 (100)	1207 (83.1)	1352 (93.9)	1259 (87.4)	1440 (100)	1440 (100)
WMND-005	1229 (85.3)	1229 (85.3)	1440 (100)	1440 (100)	1440 (100)	1440 (100)	1440 (100)	1241 (86.2)	1440 (100)	1260 (87.5)	1440 (100)	1440 (100)	1440 (100)	1440 (100)
WMND-006	1309 (90.9)	1194 (82.9)	1359 (94.4)	933 (64.8)	1318 (91.5)	1046 (72.6)	1368 (95)	1049 (72.8)	1243 (86.3)	1275 (88.5)	1172 (81.4)	1135 (78.8)	1229 (85.3)	1035 (71.9)
WMND-007	180 (95.8)	1102 (76.5)	1440 (100)	1100 (76.4)	1440 (100)	1155 (80.2)	1440 (100)	1096 (76.1)	1373 (95.3)	1008 (70)	1378 (95.7)	939 (62.2)	1371 (95.2)	1286 (89.3)
WMND-008	1162 (80.7)	886 (61.5)	1212 (84.2)	1054 (73.2)	1316 (91.4)	1104 (76.7)	1357 (94.2)	1260 (87.5)	1374 (95.4)	1376 (95.6)	1440 (100)	1440 (100)	1440 (100)	1268 (88)
WMND-009	1440 (100)	1369 (95)	1440 (100)	1359 (94.3)	1307 (90.8)	1217 (84.5)	1440 (100)	1440 (100)	1372 95.2)	1440 (100)	1377 (95.6)	1377 (95.6)	1440 (100)	1440 (100)
WMND-010	1303 (90.5)	1005 (69.8)	1212 (84.2)	964 (67)	1432 (99.5)	1067 (74)	1196 (83)	1081 (75)	1242 (86.3)	993 (69)	1080 (75)	897 (62.3)	1440 (100)	1168 (81.1)

7.6 Discussion

This study suggests that a significant subgroup of people with MND are motivated to engage with research into technology to evaluate health, and generally find wrist and ankle worn smart-watch style devices acceptable to use. Conducting a standardised series of motor tasks over videoconferencing software was shown to be feasible for, and satisfactory to, people with MND, whilst reducing the need for clinical appointments. This aligns with findings from previous studies, indicating the feasibility of fully remote, technological device outcome and for research delivery for people with MND [103, 285].

These findings add a participant-focused narrative to the current landscape of digital technology to evaluate motor function in MND, explored in this recent review [274]. This review found that whilst initial results of the 20 studies exploring device efficacy were promising, only 36% of studies reported on the acceptability of devices to participants [274].

7.6.1 Expectations of Participants

The ten individuals who participated in this study were engaged with technology as a current and potential method of evaluating health symptoms. The prominence of these technologies in everyday life is also true for people with MND, with a recent study reporting 82% of their surveyed participants used some form of digital device daily [308]. Seven of the ten participants reported having used wearable devices previously. As these technologies become more ubiquitous in everyday life we can aim to reflect this social change in research and clinical care.

A clear benefit of wearable technologies becoming more prevalent is the increased trust participants have in device safety. No participants reported any concerns over potential side-effects of wearing the devices, and unanimously considered them to be safe to wear, with similarly positive findings on safety in other device-focused studies [105, 111]. Although participants did not report any apprehension over the security of the data provided by the wearable devices, this is an important point to consider in future studies using such devices. Ensuring we have robust data management policies, which clearly adhere to General Data Protection Regulations (GDPR), and are able to articulate these clearly to the participants whose data we are responsible for, is essential.

7.6.2 Remote Data Collection

Although the majority of study visits were conducted remotely, participants did attend appointments in-person at the Anne Rowling Regenerative Neurology Clinic in Edinburgh. The requirement to attend a clinical appointment may have been a barrier to participation for some people with MND, however fully-remote delivery brings its own unique challenges [285].

Despite being a sub-set of people with MND physically capable of attending in-person appointments, 70% of participants expressed that the potential reduction in clinic appointments was a benefit of wearable devices. This study suggests that remote appointments to conduct motor assessments whilst wearing devices, using videoconferencing software, is a viable and beneficial alternative to research visits.

However, in aspects of remote data collection such as the 24-hour time period, which were not researcher-led, we must be cautious about the shift of onus of data collection onto the participant. Ensuring participants receive regular reminders, have access to technical support and reassurance to reduce potential worries, will alleviate concerns some individuals may feel when control of data collection is with them.

The impact of a shift towards remote data collection, particularly in groups of participants who often require caregiver support in activities of daily living, must also consider the level of support available to participants. It is essential that researchers mitigate the potential added burden to participants' caregivers that can result from supporting participation; minimising practical and technical assistance that caregivers need to assist with.

7.6.3 Adherence to Protocol

The findings on burden were mixed. Wear time indicated excellent adherence to the protocol. The acceptability of the devices remained stable. However, a third of participants reported technical issues, half of participants reported a negative impact on sleep and one individual reported increased burden on their caregiver, which is of concern. Previously studies utilising the ActiGraph reported low levels of burden due to wearing devices for participants [105], perhaps suggesting that focusing on a reduction of technical issues, and developing effective management strategies for when they do occur, should be the focus when addressing issue of burden. In larger scale studies with longer time-frames, these issues may result in attrition, missing data and complication of participants' daily lives.

When interpreting the findings from this small-sample exploratory study, it is important to remember that these participants represent a sub-set of those affected by MND. MND is a highly heterogeneous condition, presenting and progressing differently. The ten people who provided feedback on the ActiGraph devices were motivated to engage with research, able to travel to clinical appointments, were generally progressing slowly and were physically capable of completing motor assessments. When attempting to extrapolate these findings on acceptability, the relative wellness and independence of these people with MND must be considered.

7.6.4 Technical and Practical Issues

Concerns over charging the devices was the primary technical problem experienced by participants. The majority of problems reported by participants focused on practical issues; difficulty putting on the devices and faulty straps, with the large size of the device affecting comfort. These issues must be addressed in future device studies as they can cause frustration for participants, ultimately affecting both their ability and willingness to adhere to the study protocols and reduce their motivation to participate.

The research team also experienced several technical issues with the devices. Difficulties with charging devices, connecting to computers and saving data resulted in frequent concerns that the devices were not collecting data and that this data would not be successfully captured.

Within this small-scale study these issues could be managed and had minimal impact on data collection and accuracy. However, in a larger-scale study with more participants, such issues are multiplied. Conducting small-scale feasibility studies investigates, identifies and addresses such technical and practical issues identified by participants and researchers, before implementing larger studies which require more resources. Attrition and the resultant sample bias has affected previous technology research, with one study reporting up to 85% attrition after 9 months of data collection [285]. Ultimately, we hope that improving participant satisfaction will reduce the risk of missing data and drop-out that has affected some studies in this area and improve the validity of conclusions that can be drawn.

7.6.5 Sleep

The acceptability of wearing the ActiGraph during sleep was a novel aspect of this study. Evaluating sleep in MND can provide insight into a person's breathing and physical functioning, with an

opportunity for early intervention, for example with non-invasive ventilation to reduce the number of times someone is awoken by respiratory insufficiency. Disturbed or non-refreshing sleep, either due to breathing or movement difficulties, occurring secondary to motor degeneration, can have a significant impact on fatigue, quality of life, prognosis and wellbeing [51].

Wearable devices offer a unique opportunity to evaluate changes in sleep, taking continual or repeated measures of sleep parameters such as time asleep, time to fall asleep, awakenings and movement whilst asleep [290]. However, to avoid further disruption to rest, assessing the acceptability of these devices during sleep, distinctly from day-time wear, is important.

By the end of this 12-week study, with seven nights of data collection, one participant reported disturbed sleep from wearing these devices. Finding devices which cause minimal interference, whilst still able to collect relevant and detailed data, is a balance where feedback from people with MND is as crucial as device efficacy [111].

7.6.6 Future Work

Broadening the concept of wearable devices beyond the watch format to include smart rings, ear-bud headphones, headbands, glasses and clothing, will enable us to utilize the continuous innovations in technology to better understand and support people with MND. However, the familiarity of 'off-the-shelf' devices such as wrist-worn accelerometers, activity monitors and cardiac monitors may help engage people with MND in device research who are less confident in technology. As these devices are more commonly used in daily life and continue to grow in popularity, there may be more trust in their safety and suitability already established.

A drawback of wearable technology research identified by participants in this study, and prevalent in such studies generally, is the difficulty of providing person-specific feedback. As these studies are often exploratory in nature, participants cannot always access their data as we often do not have enough information on expected disease progression to provide clinical context to any findings. Future research focusing on establishing normative progression data from wearable devices will be of huge benefit to participants and researchers alike.

Family, friends or professionals with caregiving responsibilities may also need to provide support for people with MND to use wearable devices. Their contribution to this type of research is vital. Particularly in the later stages of MND, it is important to remember that participation often occurs in a participant-caregiver dyad, with the acceptability of devices to caregivers being as essential as

participant ratings. Involving and implementing their feedback simultaneously will be necessary for progress.

Directions for future research into the implementation of digital technologies in clinical care and trial design recommend establishing reliable digital parameters to evaluate MND progression, and disseminate the information from these devices in a clinically relevant and participant-accessible manner [298]. Based on the findings from this thesis we also recommend that future work must prioritise the acceptability of any candidate devices to people with MND. This can be done alongside, or prior to, exploring a devices' suitability in evaluating MND presentation and progression. Including feedback from prospective users is a key element to making informed decisions on device selection.

In addition, when designing studies to establish the responsiveness of a device, future research should also evaluate how a device is able to monitor progression of each currently affected area of the body. Relying only on covariance with total scores from existing measures of progression, such as the ALSFRS(R), to establish device suitability will limit advancement in this area. The ALSFRS(R) has limited suitability to evaluate individual impaired domains as it provides a summed score, and inadequate sensitivity to detect smaller changes in functioning [12].

7.7 Key Findings

- Ten people with MND wore an accelerometer on their wrist and ankle for a 24 hour period, and during a series of motor tasks, once a fortnight for 12 weeks and completed questionnaires to provide feedback on their experiences
- All participants completed the full protocol of study visits
- Participants were excited about the prospective of trying a new technology and remained supportive of the integration of technology to monitor health
- 80% of participants found wearing the devices to be a positive experience.
- No one reported side effects, interference with daily living or added burden from study participation but one person reported devices interfered with their sleep
- 30% of participants had experienced technical issues with their devices but the end of the study
- One individual reported that the devices increased caregiver burden

- **This study provided positive and promising initial feedback from a subset of people with MND on the acceptability of wearable devices, their suitability for motor assessment via video conferencing and the comfort of wearing overnight to evaluate sleep**

8 Chapter 8: General Discussion

8.1 Thesis Aims

To improve understanding of how we can deliver more effective and participant-centred trials in MND, this project aimed to explore how non-motor symptoms and digital tools may offer potential new directions in assessing MND trial outcomes. Two systematic reviews identified the previously reported use of non-motor outcome measures in MND trials, forming the basis of an additional questionnaire-based study to evaluate people with MND's perspective on additional non-motor outcome measures in trials, and their experience of these symptoms.

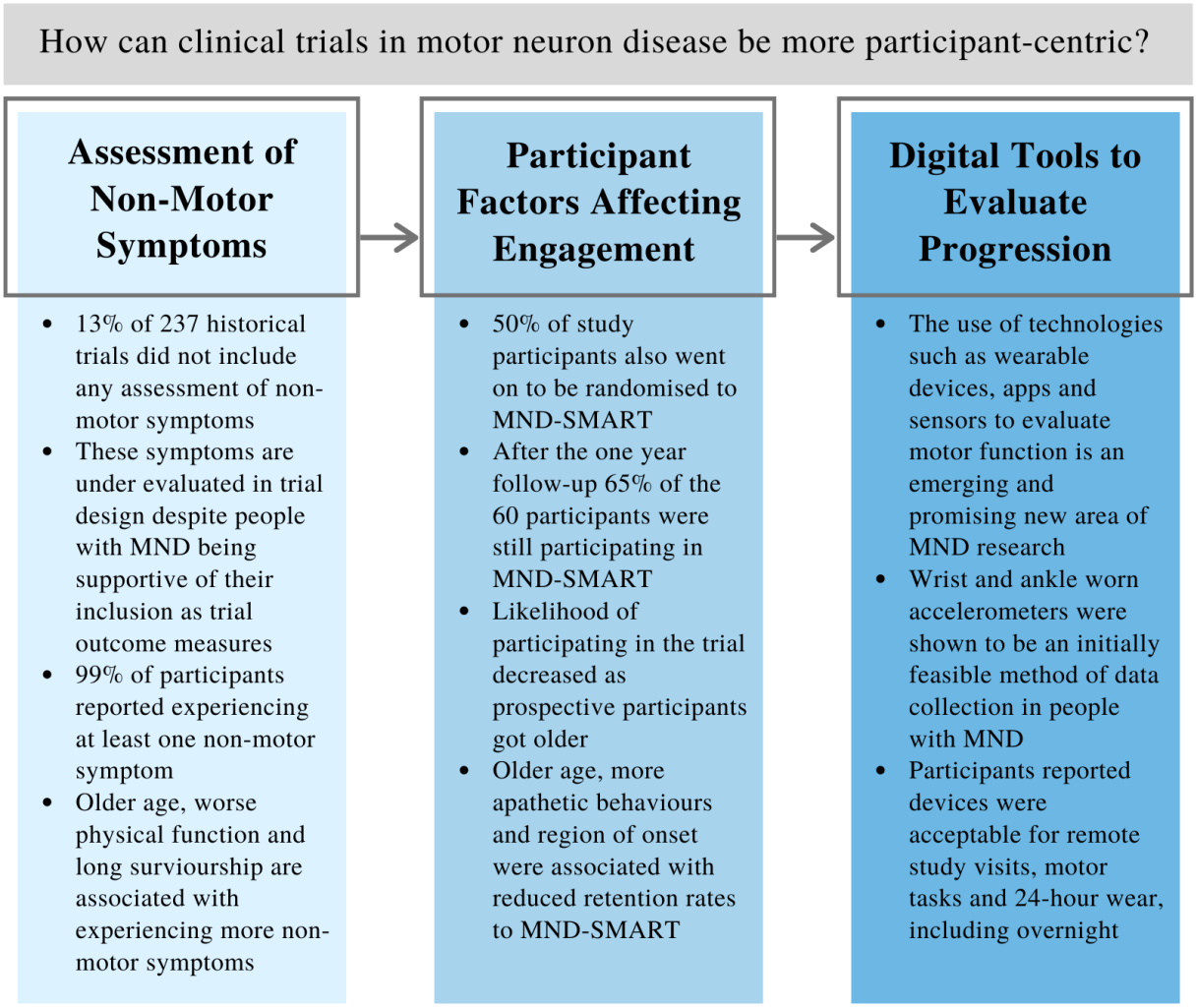
In addition, this PhD thesis aimed to evaluate person-specific characteristics of people with MND who chose to participate, or not, in a clinical trial. This was achieved through a prospective cohort study assessing clinical and demographic characteristics of a group of people with MND, and exploring if they engaged with a clinical trial after a one-year follow-up period.

A third systematic review was used to summarise the current landscape of digital technology research to evaluate motor progression. The findings from this review informed the design of a final study evaluating the acceptability of a wearable device, to enable us to accomplish the thesis aim of exploring the potential of digital tools for people with MND.

8.2 Key Findings

The key findings for each review or study are summarised at the end of each Chapter, with an overview provided in Figure 12.

Figure 12: Overview of Thesis Findings



8.3 Recommendations

We recommend the inclusion of non-motor outcome measures in all future MND clinical trials, as additional secondary assessments, to provide a full profile of a candidate drugs' potential benefits and side effects. To evaluate cognitive impairment and behavioural change we recommend using the ECAS, as this tool is specifically designed for people experiencing motor and speech dysfunction, and multiple validated versions allow for repeated assessment with mitigation of any learning effect [161, 212]. We believe that this is the best measure available to measure this aspect of MND based on current evidence.

Whilst the potential profile of neuropsychiatric symptoms in people with MND is complex and varied, participants in a questionnaire-based study of non-motor symptom presence described in Chapter 4, reported low mood and anxiety as frequent. Based on our findings that 50% of participants report low mood, and 45% report anxiety, we recommend the inclusion of measures to evaluate the presence of these symptoms in people with MND participating in trials. In addition, the evaluation of these symptoms in clinic, and providing space for a broader discussion of the holistic impact of MND on the individual, is crucial.

We also recommend prioritising the assessment of pain and fatigue as secondary outcome measures in trial design, using symptom-specific tools. Assessment tools such as the Fatigue Severity Scale [309], have previously used in people with MND [181], or the Brief Pain Inventory [310] that is an established clinical trial outcome measure for other conditions [311].

Based upon the findings from Chapter 5, we recommend that when designing and delivering recruitment strategies trialists focus on engaging older people with MND and those with more apathetic behaviours to participate, and remain in, clinical trials.

The Attitudes to Clinical Trials Questionnaire (ACT-Q) was particularly informative as an insight into the potential barriers, reasons for engagement and understanding of trial design reported by prospective participants. We recommend that trialists focus on delivering clear informative guidance on repurposed drugs, multiple study arms and the benefits of novel trial designs to help potential participants make informed decisions. The distance to travel to clinic for trial appointments was highlighted by FIT-P-MND participants as the primary barrier to participation. Trialists should strive to minimise travel and include remote assessment visits as often as possible.

Based on these findings, we recommend that future trials have allied studies, such as FIT-P-MND, associated with them to inform recruitment and retention strategies within future protocol iterations. Based on the findings presented in Chapter 5 and 7, we recommend that these future trials include

remote study visits, broad inclusion criteria and repeated engagement with participants to gather feedback on their trial experiences.

Travel burden was also highlighted as an area of concern by participants in Chapter 7, exploring the acceptability of wearable devices for people with MND. We recommend prioritising research into digital tools that enable remote assessment of disease progression. Participants in our study reported in Chapter 7 found wrist and ankle worn accelerometers to be an acceptable to assess 24-hour activity in the community, and for use during videoconferencing appointments. On this basis we recommend further use of this type of device.

8.4 Future Directions

Future research in this area must focus on establishing the efficacy of existing and novel outcome measures to evaluate disease severity and progression, in people with MND. The potential benefits of biomarkers to reliably diagnose conditions that may co-occur with MND, such as depression, is evident. Biomarkers to support a diagnosis reduce reliance on subjective measures of self-reported questionnaires and clinical assessments, proffering quantifiable markers of decline to evaluate non-motor symptoms as additional outcome measures.

Whilst biomarkers remain the ideal method of measurement, current focus on evaluating the validity and suitability of existing assessment tools for use specifically in people with MND is a priority. Establishing disease-specific thresholds of impairment, providing normative data and exploring how appropriate existing assessment tools are for people with potential motor, speech and cognitive impairment is a necessary first step to ensuring accurate evaluation of these symptoms as trial outcomes.

A secondary step is the development of new assessment tools to address gaps in measurement, where no symptom-specific or disease-suitable assessments are available. Developing new tools, or adapting existing tools, to ensure they are suitable to evaluate non-motor symptoms in individuals affected by a heterogeneous motor disorder is a complex task. A greater understanding of how differently these symptoms present and their impact on, people with MND is needed to ensure informed decisions are made regarding assessment design and tool selection. The perspective of people with MND is essential at every stage, with preferences on type, method and content of assessment important to develop non-motor outcome measures that evaluate symptoms accurately.

A key priority for research into technology for people with MND is addressing the gap in knowledge about which devices are suitable to evaluate progression in MND. The systematic review presented in Chapter 6 found that whilst early studies were promising, there were a significant number of

unknowns in terms of device efficacy, accuracy and sensitivity to detect impairment and progression. Establishing concurrent validity with the ALSFRS(R) is inadequate to determine suitability of prospective devices as the ALSFRS(R) is in itself an insufficient measure of MND progression [12]. Future studies should focus on all aspects of validity, device reliability, the acceptability to people with MND and the longitudinal data collection capabilities of devices under consideration.

8.5 Strengths and Limitations

A methodological strength of this thesis, specifically focusing on the two prospective studies reported in Chapter 4 and 5, is the relatively large sample size for a condition classified as a rare disorder based on prevalence data [5, 312]. 120 different samples of people with MND completed questionnaires and assessments for each study, providing us with an extensive and representative sample for analysis, amounting to approximately 23% of the 532 Scottish residents living with MND over the recruitment periods.

An exploration of the participant perspective throughout this thesis is its ultimate strength. The attitudes, differences and experiences of people with MND are at the forefront of the aims, study design and methods. The study reported in Chapter 4 focuses on how people experience MND, exploring their views on how symptoms are assessed and evaluated, Chapter 5 also aims to put participant characteristics and decisions at the forefront of trial design. The participant voice is paramount in Chapter 7, where questionnaires are used to gauge participant experience and acceptance of a wearable device, and use this feedback as a priority when exploring prospective device suitability. Conducting research for, and with, people with MND is a strength of this thesis throughout.

A limitation of the studies in this thesis, and indeed any studies involving participant recruitment, is the bias towards individuals who are willing, and able, to participate. This is particularly relevant in Chapter 5, which considers the person-specific factors impacting the decision to participate in a clinical trial in a sub-set of individuals who have already chosen to engage with a research study. This was mitigated by providing prospective participants with multiple completion methods in these studies, to moderate potential barriers to engagement.

The ability to draw conclusions from findings of the studies in this thesis is also limited by sample size. Chapter 3 and 5 involved 120 people with MND each respectively, meeting recruitment targets based on power calculations from statistical analyses involving the full sample. This represents approximately 28% of people living with MND in Scotland (based on 422 prevalence cases [5]), a large sample for MND research. However, analyses on subsets of participants are exploratory in

nature, and inferences must be made accordingly. Chapter 7 reports the findings from a small pilot study exploring the acceptability of a wearable device to ten participants with MND, these conclusions will be used to inform the suitability of these devices for use in larger responsiveness studies.

A limitation of this general area of research is the difficulty of defining non-motor symptoms, and the subjectivity of how these symptoms can affect are reported by people with MND. Different people may report the presence and impact of these symptoms different which impacts on their measurement. Quantification of non-motor symptoms, to enable comparison across participants, may be a reductionist method of assessment. Concepts such as mood and diagnoses such as depression are difficult to define and often overlap with other symptoms of MND. This issue is a general concern in human research that must be accounted for when interpreting any findings.

8.6 Alternative Designs

A hypothetical review of the projects included in the thesis, and their design and analysis prompted a consideration of changes that could have been made to potentially improve the conclusions drawn. For Experimental Project 1, the non-motor survey presented in Chapter 4, I would have included a broader range of potential symptoms. Although it is likely that many of these symptoms would have been experienced by only a small subset of participants, findings from open-ended questions on symptoms experienced indicated that there were many other symptoms impactful to people with MND which were not included in our pre-defined list of symptoms.

Regarding Experimental Project 2, the factors impacting trial participation study reported Chapter 5, the primary change to improve this study would be to include a participant-reported ALSFRS(R) in the questionnaire packs. In this study we relied on ALSFRS(R) data from CARE-MND or MND-SMART which was often undertaken at a different time to the study questionnaires. The lack of association between physical functioning and trial participation or retention was unexpected. Hence this methodological change might improve our ability to ascertain the validity of this finding. In addition, I would rethink the validated measures used in the initial participant data collection. The STAI-Y was long to complete and caused some confusion to participants regarding the state versus trait conditions, which may have impacted the accuracy of responses. Based on findings from the non-motor study I would have included questionnaires exploring the participants' experiences of pain and fatigue, to evaluate how impactful these symptoms were on trial engagement.

Finally, with the study presented in Chapter 7, focusing on participant acceptance for wearable accelerometers, a methodological change I would implement would be more frequent periods of

device use. In the current study, devices were worn for a 24-hour period once a fortnight, for the 12 week study. However, feedback from participants indicated that they would be willing to wear the devices more frequently. Including weekly 24-hour wear periods would have increased the amount of data available, and enabled us to explore how more frequent assessment points affected the level of burden participants reported, and the acceptability of the devices.

8.7 Impact of COVID-19

The national lockdown due to the COVID-19 pandemic occurred around 6 months into this PhD, with a halt to all non-COVID related research approvals and recruitment. Unfortunately, this resulted in a delay of several months for commencing recruitment to the FIT-P-MND study presented in Chapter 5. In addition, we were no longer able to offer in-person appointments for the FIT-P-MND or NMS-MND studies due to concerns over the participants' safety. The focus of my PhD shifted towards remote data collection, with a focus on online and paper questionnaires, in an attempt to future proof against potential future lockdowns and minimise delays. As the final study, exploring acceptability of wearable devices in Chapter 7 commenced recruitment, national COVID-19 restrictions were easing. We were able to invite participants in to attend in-person appointments. However, recruitment was affected as many individuals were understandably cautious about additional visits to the clinic when many people with MND had been advised to shield at the height of the pandemic. Minimising the potential risk to prospective participants, ensuring data collection could be done remotely and conducting systematic reviews in case experimental chapters were no longer feasible, shaped the thesis structure, due changes necessitated by COVID-19.

8.8 Conclusion

In summary, although non-motor symptoms have previously been under evaluated in clinical trial design, people with MND report them as frequent, impactful and important to include in future trials. Older age, region of onset and presence of apathy were the participant specific factors associated with the decision not to participate, or remain, in a clinical trial. Half of the study participants went on to also participate in MND-SMART and withdrawal, unrelated to death, was minimal. Digital technology is a promising, and rapidly growing, area of focus in MND research. Feedback on the acceptability of any device from prospective users is essential to inform device selection and study design. The findings from this thesis will help inform recruitment and retention strategies for MND clinical trials, provide justification for the future inclusion of additional non-motor outcome measures

and inform future research into the suitability of digital technology to evaluate motor symptoms in people with MND.

8.9 Personal Training

Within the timeframe of the PhD I have developed and progressed my skills as an independent and collaborative researcher. My first project as a PhD student was to conduct a systematic review of trial databases, where I learnt how to select search terms and screen results. This was also my first experience of the publication process, and a lesson in persistence. I collaborated with co-authors on multiple manuscript drafts and gained experience on writing, editing and revising based on reviewer feedback. During the PhD I had the opportunity to design my own research projects, select assessment tools and learn how to develop research ideas into testable hypotheses. I also completed training and gained personal experience of how to develop a study protocol and ensure a study design was robust enough to receive sponsor and ethical approval. Alongside my PhD I had the opportunity to attend several conferences, academic meetings and participant engagement events to present posters and discuss research plans. Feedback from people affected by MND, and those working to help them, was essential to shape the project plan for the whole PhD journey. At the end of my PhD I began compiling papers, protocols and projects into a thesis. Writing the thesis was another important lesson in persistence. Bringing three years of work together into a cohesive narrative, to explain how the studies combine to address the research aims, provided an experience in determination, conducting statistical analysis in R and presenting study findings.

8.10 Student Contributions

Chapter 2:
A Systematic Review of Neuropsychiatric and Cognitive Assessments in Clinical Trials of MND

EB defined search terms, led on data collection and screened search results with a second reviewer. EB summarised findings and wrote the manuscript with support and feedback from all co-authors listed in the first publication available in the Appendices.

Chapter 3:
A Systematic Review of Non-Motor Symptom Evaluation in Clinical Trials for MND.

EB defined the search terms, led on data collection and screened search results with a second reviewer. EB summarised findings and wrote the manuscript with support and feedback from all co-authors listed in the second publication available in the Appendices.

Chapter 4:
Holistic Assessment of Non-Motor Symptoms for People with MND (NMS-MND).

EB designed the study protocol and questionnaires, with feedback from the supervisory team and wider clinical team. With support from the data processor at the Anne Rowling Regenerative Neurology Clinic, which hosts the CARE-MND research register, EB sent invitation packs and study questionnaires to all eligible people with MND in Scotland. EB then collated all questionnaire responses and analysed the data. EB conducted the statistical analyses and summarised findings, with essential feedback from the supervisory team received at every stage.

Chapter 5:
Factors Impacting Trial Participation in People with MND (FIT-P-MND).

EB selected the participant assessments, designed the study protocol and designed the ACT-Q, with input from people with MND and advice from the supervisory team. With help from the data processor at the Anne Rowling Regenerative Neurology Clinic, which hosts the CARE-MND research register, EB sent invitation packs and study questionnaires to all eligible people with MND in Scotland. EB then collated all questionnaire responses and combined this with clinical and research participation from CARE-MND and MND-SMART. EB conducted the statistical analyses and summarised findings, with advice and input from the supervisory team throughout. EB was not involved in data collection for MND-SMART.

Chapter 6:
A Systematic Review of Digital Technology to Evaluate Motor Function and Disease Progression in MND.

EB defined the search terms, led on data collection and screened search results with the help of a second reviewer. EB summarised findings and wrote the manuscript with support and feedback from all co-authors listed in the publication available in the Appendices.

Chapter 7:
Suitability and Acceptability of Wearable Sensors to Evaluate Disease Progression in People with MND.

EB selected the ActiGraph devices and coordinated international purchasing contracts. EB designed the study protocol and assessment schedule, with input from the lead supervisor throughout. EB worked with the Anne Rowling Clinic team to recruit study participants and collect data on ActiGraph wear, motor tasks and device acceptability. EB summarised and analysed responses to study questionnaires and wrote the manuscript with input from the lead supervisor at each stage.

8.11 Statistical Training and Contributions

Through the Institute for Academic Development statistical consultancy support I met with Dr Niall Anderson, a senior lecturer in medical statistics at the University of Edinburgh. He kindly provided advice on research design and analysis plans for the study presented in Chapter 5.

In addition, through the School of Psychology, I met with Dr Josiah King and Dr Umberto Noe, both senior teaching coordinators in statistics. They provided invaluable advice on when latent class analysis is a suitable method to represent study data, which as a result was included Chapter 4.

The support from these University staff was essential in shaping study design and informing planned analysis, however, no study data was shared with these individuals. All statistical analyses were performed, using R, by the student.

Statistics Courses Undertaken:

- Healthy R: R for Health Care Data Analysis *(May 2020)*
- Edinburgh eCRF Medical Statistics *(May 2021)*

9 References

1. Yedavalli, V.S., A. Patil, and P. Shah, *Amyotrophic lateral sclerosis and its mimics/variants: a comprehensive review.* Journal of clinical imaging science, 2018. **8**.
2. Talbot, K., *Motor neuron disease: the bare essentials.* Practical neurology, 2009. **9**(5): p. 303-309.
3. Chio, A., et al., *Prognostic factors in ALS: a critical review.* Amyotrophic lateral sclerosis, 2009. **10**(5-6): p. 310-323.
4. Kiernan, M.C., et al., *Amyotrophic lateral sclerosis.* The lancet, 2011. **377**(9769): p. 942-955.
5. Leighton, D.J., et al., *Changing epidemiology of motor neurone disease in Scotland.* Journal of neurology, 2019. **266**(4): p. 817-825.
6. Hobson, E.V., et al., *Management of sialorrhoea in motor neuron disease: a survey of current UK practice.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013. **14**(7-8): p. 521-527.
7. Alonso, A., et al., *Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study.* European journal of neurology, 2009. **16**(6): p. 745-751.
8. Black, H.A., et al., *Genetic epidemiology of motor neuron disease-associated variants in the Scottish population.* Neurobiology of aging, 2017. **51**: p. 178. e11-178. e20.
9. Hern, J., et al., *The Scottish Motor Neuron Disease Register: a prospective study of adult onset motor neuron disease in Scotland. Methodology, demography and clinical features of incident cases in 1989.* Journal of Neurology, Neurosurgery and Psychiatry, 1992. **55**(7): p. 536-541.
10. Leighton, D., et al., *Clinical audit research and evaluation of motor neuron disease (CARE-MND): a national electronic platform for prospective, longitudinal monitoring of MND in Scotland.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019. **20**(3-4): p. 242-250.
11. Rooney, J., et al., *What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis.* Journal of Neurology, Neurosurgery & Psychiatry, 2017. **88**(5): p. 381-385.
12. van Eijk, R.P., et al., *An old friend who has overstayed their welcome: the ALSFRS-R total score as primary endpoint for ALS clinical trials.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2021: p. 1-8.
13. Bensimon, G., et al., *A controlled trial of riluzole in amyotrophic lateral sclerosis.* New England Journal of Medicine, 1994. **330**(9): p. 585-591.
14. Group II, R.S., et al., *Dose-ranging study of riluzole in amyotrophic lateral sclerosis.* The Lancet, 1996. **347**(9013): p. 1425-1431.
15. Abe, K., et al., *Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial.* The Lancet Neurology, 2017. **16**(7): p. 505-512.
16. Mora, J.S., et al., *Masitinib as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomized clinical trial.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020. **21**(1-2): p. 5-14.
17. Paganoni, S., et al., *Survival analyses from the CENTAUR trial in amyotrophic lateral sclerosis: Evaluating the impact of treatment crossover on outcomes.* Muscle & Nerve, 2022.
18. Miller, T.M., et al., *Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS.* New England Journal of Medicine, 2022. **387**(12): p. 1099-1110.
19. McCluskey, L. and D. Falcone, *Familial amyotrophic lateral sclerosis.* Waltham, MA: UpToDate Inc, 2019.
20. Wong, C., et al., *Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective.* Brain communications, 2021. **3**(4): p. fcab242.
21. Mitsumoto, H., *Clinical trials: present and future.* Amyotroph Lateral Scler Other Motor Neuron Disord, 2001. **2 Suppl 1**: p. S10-4.

22. Miller, R.G., J.D. Mitchell, and D.H. Moore, *Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).* Cochrane database of systematic reviews, 2012(3).
23. van Eijk, R.P., et al., *Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials.* Neurology, 2019. **92**(5): p. e451-e460.
24. Chiò, A., et al., *ALS clinical trials: do enrolled patients accurately represent the ALS population?* Neurology, 2011. **77**(15): p. 1432-1437.
25. Atassi, N., et al., *Analysis of start-up, retention, and adherence in ALS clinical trials.* Neurology, 2013. **81**(15): p. 1350-1355.
26. Bedlack, R.S., et al., *Scrutinizing enrollment in ALS clinical trials: room for improvement?* Amyotrophic Lateral Sclerosis, 2008. **9**(5): p. 257-265.
27. Shefner, J.M., et al., *Reducing sample size requirements for future ALS clinical trials with a dedicated electrical impedance myography system.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018. **19**(7-8): p. 555-561.
28. Stamate, C., et al., *The cloudUPDRS app: A medical device for the clinical assessment of Parkinson's Disease.* Pervasive and mobile computing, 2018. **43**: p. 146-166.
29. Vesterinen, H.M., et al., *Drug repurposing: a systematic approach to evaluate candidate oral neuroprotective interventions for secondary progressive multiple sclerosis.* PloS one, 2015. **10**(4): p. e0117705.
30. Grill, J.D. and J. Karlawish, *Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials.* Alzheimer's research & therapy, 2010. **2**(6): p. 1-11.
31. Bowser, R., M.R. Turner, and J. Shefner, *Biomarkers in amyotrophic lateral sclerosis: opportunities and limitations.* Nature Reviews Neurology, 2011. **7**(11): p. 631-638.
32. Van Den Berg, L.H., et al., *Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials.* Neurology, 2019. **92**(14): p. e1610-e1623.
33. *Clinical investigation of medicinal products for treatment of amyotrophic lateral sclerosis (ALS).* Eur Neuropsychopharmacol, 2001. **11**(2): p. 187-9.
34. Food, U. and D. Administration, *Amyotrophic lateral sclerosis: developing drugs for treatment guidance for industry.* US Food and Drug Administration: Silver Spring, MD, USA, 2019.
35. Mehta, A.R., et al., *Trials for neurodegenerative diseases: time to innovate.* Lancet Neurol, 2021. **20**(12): p. 984.
36. Wong, C., et al., *Protocol: Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART): a multi-arm, multi-stage, adaptive, platform, phase III randomised, double-blind, placebo-controlled trial of repurposed drugs in motor neuron disease.* BMJ Open, 2022. **12**(7).
37. Wong, C., et al., *Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective.* Brain Commun, 2021. **3**(4): p. fcab242.
38. Wong, C., et al., *Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART): a multi-arm, multi-stage, adaptive, platform, phase III randomised, double-blind, placebo-controlled trial of repurposed drugs in motor neuron disease.* BMJ Open, 2022. **12**(7): p. e064173.
39. Jaki, T. and J.M. Wason, *Multi-arm multi-stage trials can improve the efficiency of finding effective treatments for stroke: a case study.* BMC cardiovascular disorders, 2018. **18**(1): p. 215.
40. Sydes, M.R., et al., *Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: the MRC STAMPEDE trial.* Trials, 2009. **10**(1): p. 39.
41. Kiernan, M.C., et al., *Improving clinical trial outcomes in amyotrophic lateral sclerosis.* Nature Reviews Neurology, 2021. **17**(2): p. 104-118.
42. Dumville, J.C., D.J. Torgerson, and C.E. Hewitt, *Reporting attrition in randomised controlled trials.* Bmj, 2006. **332**(7547): p. 969-971.
43. Kieser, M. and T. Friede, *Re-calculating the sample size in internal pilot study designs with control of the type I error rate.* Statistics in medicine, 2000. **19**(7): p. 901-911.

44. Gul, R.B. and P.A. Ali, *Clinical trials: the challenge of recruitment and retention of participants.* Journal of clinical nursing, 2010. **19**(1-2): p. 227-233.
45. Gross, D. and L. Fogg, *Clinical trials in the 21st century: The case for participant-centered research¶.* Research in nursing & health, 2001. **24**(6): p. 530-539.
46. Berger, A.M., D.E. Neumark, and J. Chamberlain. *Enhancing recruitment and retention in randomized clinical trials of cancer symptom management*. in *Oncology nursing forum*. 2007.
47. Grill, J.D. and J. Karlawish, *Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials.* Alzheimer's research & therapy, 2010. **2**(6): p. 34.
48. Ellis, P., *Attitudes towards and participation in randomised clinical trials in oncology: a review of the literature.* Annals of Oncology, 2000. **11**(8): p. 939-946.
49. Wong, C., et al., *Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective.* Brain Communications, 2021. **3**(4).
50. Polit, D. and B. Hungler, *Essentials of nursing research: Principles and methods*. 2001, Philadelphia: Lippincott Williams &Williams.
51. Fang, T., F. Jozsa, and A. Al-Chalabi, *Nonmotor symptoms in amyotrophic lateral sclerosis: a systematic review.* International Review of Neurobiology, 2017. **134**: p. 1409-1441.
52. Forsaa, E.B., et al., *What predicts mortality in Parkinson disease?* A prospective population-based long-term study, 2010. **75**(14): p. 1270-1276.
53. Chaudhuri, K.R., et al., *The movement disorder society nonmotor rating scale: Initial validation study.* Movement Disorders, 2020. **35**(1): p. 116-133.
54. Edge, R., et al., *Do pain, anxiety and depression influence quality of life for people with amyotrophic lateral sclerosis/motor neuron disease? A national study reconciling previous conflicting literature.* Journal of neurology, 2020. **267**: p. 607-615.
55. Young, C.A., et al., *Quality of life in multiple sclerosis is dominated by fatigue, disability and self-efficacy.* Journal of the neurological sciences, 2021. **426**: p. 117437.
56. van Groenestijn, A.C., et al., *Associations between psychological factors and health-related quality of life and global quality of life in patients with ALS: a systematic review.* Health and Quality of Life Outcomes, 2016. **14**(1): p. 107.
57. Ando, H., R. Cousins, and C. Young. *Perceptions of quality of life in motor neurone disease: views of patients and patient family support group. Qualitative results from the Trajectories of Outcome in Neurological Conditions study*. in *JOURNAL OF NEUROLOGY*. 2013. SPRINGER HEIDELBERG TIERGARTENSTRASSE 17, D-69121 HEIDELBERG, GERMANY.
58. Chaudhuri, K.R., D.G. Healy, and A.H. Schapira, *Non-motor symptoms of Parkinson's disease: diagnosis and management.* The Lancet Neurology, 2006. **5**(3): p. 235-245.
59. Günther, R., et al., *Non-motor symptoms in patients suffering from motor neuron diseases.* Frontiers in neurology, 2016. **7**: p. 117.
60. Christidi, F., et al., *Clinical and radiological markers of extra-motor deficits in amyotrophic lateral sclerosis.* Frontiers in neurology, 2018. **9**: p. 1005.
61. National, C.G.C.U., *Motor Neurone Disease: Assessment and Management.* 2016.
62. Ng, L., et al., *Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease.* Cochrane Database of Systematic Reviews, 2017(1).
63. Agency, E.M., *Clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis.* EMA/531686/2015, Corr.1, 2015.
64. Kanner, A.M. and J.J. Barry, *The impact of mood disorders in neurological diseases: should neurologists be concerned?* Epilepsy & Behavior, 2003. **4**: p. 3-13.
65. Johnston, M., et al., *Mood as a predictor of disability and survival in patients newly diagnosed with ALS/MND.* British Journal of Health Psychology, 1999. **4**(2): p. 127-136.
66. McDonald, E.R., et al., *Survival in amyotrophic lateral sclerosis: the role of psychological factors.* Archives of Neurology, 1994. **51**(1): p. 17-23.
67. de Wit, J., et al., *Caregiver burden in amyotrophic lateral sclerosis: a systematic review.* Palliative medicine, 2018. **32**(1): p. 231-245.

68. McHutchison, C.A., et al., *Relationship between neuropsychiatric disorders and cognitive and behavioural change in MND.* Journal of Neurology, Neurosurgery & Psychiatry, 2020. **91**(3): p. 245-253.
69. Ohayon, M.M., et al., *The prevalence of depressive disorders in the United Kingdom.* Biological psychiatry, 1999. **45**(3): p. 300-307.
70. Wittchen, H.-U., et al., *The size and burden of mental disorders and other disorders of the brain in Europe 2010.* European neuropsychopharmacology, 2011. **21**(9): p. 655-679.
71. Benbrika, S., et al., *Cognitive, emotional and psychological manifestations in amyotrophic lateral sclerosis at baseline and overtime: a review.* Frontiers in neuroscience, 2019. **13**: p. 951.
72. Chiò, A., et al., *Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life.* European journal of neurology, 2010. **17**(10): p. 1298-1303.
73. Abrahams, S., et al., *Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS).* Neuropsychologia, 2000. **38**(6): p. 734-747.
74. Girardi, A., S.E. MacPherson, and S. Abrahams, *Deficits in emotional and social cognition in amyotrophic lateral sclerosis.* Neuropsychology, 2011. **25**(1): p. 53.
75. Taylor, L.J., et al., *Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis?* J Neurol Neurosurg Psychiatry, 2013. **84**(5): p. 494-498.
76. Radakovic, R., et al., *Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale.* Journal of Neurology, Neurosurgery & Psychiatry, 2016. **87**(6): p. 663-669.
77. Burrell, J.R., et al., *The frontotemporal dementia-motor neuron disease continuum.* Lancet, 2016. **388**(10047): p. 919-31.
78. Strong, M.J., et al., *Amyotrophic lateral sclerosis-frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria.* Amyotrophic lateral sclerosis and frontotemporal degeneration, 2017. **18**(3-4): p. 153-174.
79. Goldstein, L.H. and S. Abrahams, *Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment.* The Lancet Neurology, 2013. **12**(4): p. 368-380.
80. Raaphorst, J., et al., *A systematic review of behavioural changes in motor neuron disease.* Amyotrophic Lateral Sclerosis, 2012. **13**(6): p. 493-501.
81. Johns, M.W., *A new method for measuring daytime sleepiness: the Epworth sleepiness scale.* sleep, 1991. **14**(6): p. 540-545.
82. Katzberg, H.D., et al., *Effects of noninvasive ventilation on sleep outcomes in amyotrophic lateral sclerosis.* Journal of Clinical Sleep Medicine, 2013. **9**(4): p. 345-351.
83. McElhiney, M., et al., *Prevalence of fatigue and depression in ALS patients and change over time.* Journal of Neurology, Neurosurgery & Psychiatry, 2009. **80**(10): p. 1146-1149.
84. Lou, J.-S., et al., *Fatigue and depression are associated with poor quality of life in ALS.* Neurology, 2003. **60**(1): p. 122-123.
85. Raheja, D., et al., *Patient-reported problematic symptoms in an ALS treatment trial.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016. **17**(3-4): p. 198-205.
86. Aksu, S. and I. Citak-Karakaya, *Effect of exercise therapy on pain complaints in patients with amyotrophic lateral sclerosis.* The pain clinic, 2002. **14**(4): p. 353-359.
87. McClelland III, S., et al., *Intrathecal baclofen for spasticity-related pain in amyotrophic lateral sclerosis: efficacy and factors associated with pain relief.* Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 2008. **37**(3): p. 396-398.
88. Toepfer, C.F., A Klauser, RL Riepl, W Muller-Felber, D Pongratz, M, *Gastrointestinal dysfunction in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, 2000. **1**(1): p. 15-19.
89. Nash, Y. and M. Sitty, *Non-Motor Symptoms of Amyotrophic Lateral Sclerosis: A Multi-Faceted Disorder.* Journal of Neuromuscular Diseases, 2021(Preprint): p. 1-15.
90. Ahmed, R.M., et al., *Physiological changes in neurodegeneration—mechanistic insights and clinical utility.* Nature Reviews Neurology, 2018. **14**(5): p. 259.

91. Pearson I, G.S., Newton J, Mehta A, Beswick E, Davenport R, Chandran S, *The prevalence and management of saliva problems in motor neuron disease: A 4-year analysis of the Scottish MND Register.* Neurodegenerative Diseases, 2021(In Press).
92. Garuti, G., et al., *Sialorrhea in patients with ALS: current treatment options.* Degenerative neurological and neuromuscular disease, 2019. **9**: p. 19.
93. Poletti, B., et al., *Sexuality and intimacy in ALS: systematic literature review and future perspectives.* Journal of Neurology, Neurosurgery & Psychiatry, 2019. **90**(6): p. 712-719.
94. Wasner, M., et al., *Sexuality in patients with amyotrophic lateral sclerosis and their partners.* Journal of neurology, 2004. **251**(4): p. 445-448.
95. Mueller, C., et al., *Assessment and Management of Neuropsychiatric Symptoms in Parkinson's Disease.* CNS Drugs, 2018. **32**(7): p. 621-635.
96. van Groenestijn, A.C., et al., *Cognitive behavioural therapy and quality of life in psychologically distressed patients with amyotrophic lateral sclerosis and their caregivers: Results of a prematurely stopped randomized controlled trial.* Amyotroph Lateral Scler Frontotemporal Degener, 2015. **16**(5-6): p. 309-15.
97. Díaz, J.L., et al., *Effect of a short-term psychological intervention on the anxiety and depression of amyotrophic lateral sclerosis patients.* J Health Psychol, 2016. **21**(7): p. 1426-35.
98. van Eijk, R.P.A., T. Kliest, and L.H. van den Berg, *Current trends in the clinical trial landscape for amyotrophic lateral sclerosis.* Current Opinion in Neurology, 2020. **Publish Ahead of Print**.
99. Glasper, A., *A long-term plan for embracing digital healthcare technology.* British Journal of Nursing, 2019. **28**(3): p. 204-205.
100. Cohen, A.B., B.V. Nahed, and K.N. Sheth, *Mobile medical applications in neurology.* Neurology: Clinical Practice, 2013. **3**(1): p. 52-60.
101. Hobson, E.V., et al., *Using technology to improve access to specialist care in amyotrophic lateral sclerosis: a systematic review.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016. **17**(5-6): p. 313-324.
102. Hobson, E.V., et al., *The TiM system: developing a novel telehealth service to improve access to specialist care in motor neurone disease using user-centered design.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018. **19**(5-6): p. 351-361.
103. Rutkove, S., et al., *Accelerating clinical therapeutic trials in ALS through frequent at-home data collection. (4921).* Neurology, 2020. **94**(15 Supplement): p. 4921.
104. Berry, J.D., et al., *Design and results of a smartphone-based digital phenotyping study to quantify ALS progression.* Annals of clinical and translational neurology, 2019. **6**(5): p. 873-881.
105. van Eijk, R.P.A., et al., *Accelerometry for remote monitoring of physical activity in amyotrophic lateral sclerosis: a longitudinal cohort study.* J Neurol, 2019. **266**(10): p. 2387-2395.
106. Ahmad, N., et al., *Reviews on various inertial measurement unit (IMU) sensor applications.* International Journal of Signal Processing Systems, 2013. **1**(2): p. 256-262.
107. Boe, A.J., et al., *Automating sleep stage classification using wireless, wearable sensors.* NPJ digital medicine, 2019. **2**(1): p. 1-9.
108. Ossig, C., et al., *Wearable sensor-based objective assessment of motor symptoms in Parkinson's disease.* J Neural Transm (Vienna), 2016. **123**(1): p. 57-64.
109. Kourtis, L.C., et al., *Digital biomarkers for Alzheimer's disease: the mobile/wearable devices opportunity.* npj Digital Medicine, 2019. **2**(1): p. 9.
110. Casey, B., S. Coote, and A. Donnelly, *Objective physical activity measurement in people with multiple sclerosis: a review of the literature.* Disability and Rehabilitation: Assistive Technology, 2018. **13**(2): p. 124-131.
111. Garcia-Gancedo, L., et al., *Objectively Monitoring Amyotrophic Lateral Sclerosis Patient Symptoms During Clinical Trials With Sensors: Observational Study.* JMIR Mhealth Uhealth, 2019. **7**(12): p. e13433.

112. Kelly, M., et al., *The use of biotelemetry to explore disease progression markers in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020. **21**(7-8): p. 563-573.
113. Kurillo, G., et al., *Evaluation of upper extremity reachable workspace using Kinect camera.* Technology and Health Care, 2013. **21**(6): p. 641-656.
114. Geronimo, A., A.E. Martin, and Z. Simmons, *Inertial sensing of step kinematics in ambulatory patients with ALS and related motor neuron diseases.* Journal of Medical Engineering & Technology, 2021. **45**(6): p. 486-493.
115. Tacchino, A., et al., *A new app for at-home cognitive training: description and pilot testing on patients with multiple sclerosis.* JMIR mHealth and uHealth, 2015. **3**(3): p. e85.
116. Jongstra, S., et al., *Cognitive testing in people at increased risk of dementia using a smartphone app: the iVitality proof-of-principle study.* JMIR mHealth and uHealth, 2017. **5**(5): p. e6939.
117. Rutkove, S.B., et al., *Improved ALS clinical trials through frequent at-home self-assessment: a proof of concept study.* Annals of Clinical and Translational Neurology, 2020. **7**(7): p. 1148-1157.
118. Rutkove, S.B., et al., *Improved ALS clinical trials through frequent at-home self-assessment: a proof of concept study.* Ann Clin Transl Neurol, 2020. **7**(7): p. 1148-1157.
119. Beswick, E., et al., *A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis.* Journal of Neurology, 2020: p. 1-12.
120. Wicks, P., et al., *Prevalence of depression in a 12-month consecutive sample of patients with ALS.* European journal of neurology, 2007. **14**(9): p. 993-1001.
121. Zucchi, E., N. Ticozzi, and J. Mandrioli, *Psychiatric symptoms in amyotrophic lateral sclerosis: beyond a motor neuron disorder.* Frontiers in neuroscience, 2019. **13**.
122. Gonçalves, D.C., N.A. Pachana, and G.J. Byrne, *Prevalence and correlates of generalized anxiety disorder among older adults in the Australian National Survey of Mental Health and Well-Being.* Journal of affective disorders, 2011. **132**(1-2): p. 223-230.
123. Katon, W., E.H. Lin, and K. Kroenke, *The association of depression and anxiety with medical symptom burden in patients with chronic medical illness.* General hospital psychiatry, 2007. **29**(2): p. 147-155.
124. Caga, J., et al., *Apathy and its impact on patient outcome in amyotrophic lateral sclerosis.* Journal of neurology, 2018. **265**(1): p. 187-193.
125. Watermeyer, T.J., et al., *Impact of disease, cognitive and behavioural factors on caregiver outcome in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2015. **16**(5-6): p. 316-323.
126. Bock, M., et al., *Cognitive-behavioral changes in amyotrophic lateral sclerosis: screening prevalence and impact on patients and caregivers.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016. **17**(5-6): p. 366-373.
127. Goldstein, L., et al., *Predictors of psychological distress in carers of people with amyotrophic lateral sclerosis: a longitudinal study.* Psychological medicine, 2006. **36**(6): p. 865-875.
128. Bhandari, R. and A. Kuhad, *Edaravone: a new hope for deadly amyotrophic lateral sclerosis.* Drugs of today (Barcelona, Spain: 1998), 2018. **54**(6): p. 349-360.
129. Pillinger, T., et al., *Altered glutamatergic response and functional connectivity in treatment resistant schizophrenia: the effect of riluzole and therapeutic implications.* Psychopharmacology, 2019. **236**(7): p. 1985-1997.
130. De Carvalho, M., et al., *A randomized, placebo-controlled trial of memantine for functional disability in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis, 2010. **11**(5): p. 456-460.
131. Group, U.-L.S., *Lithium in patients with amyotrophic lateral sclerosis (LiCALS): a phase 3 multicentre, randomised, double-blind, placebo-controlled trial.* The Lancet Neurology, 2013. **12**(4): p. 339-345.
132. Miller, R., et al., *Phase II/III randomized trial of TCH346 in patients with ALS.* Neurology, 2007. **69**(8): p. 776-784.

133. Gold, J., et al., *Safety and tolerability of Triumeq in amyotrophic lateral sclerosis: the Lighthouse trial.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019. **20**(7-8): p. 595-604.
134. Beck, A.T., et al., *An inventory for measuring depression.* Archives of general psychiatry, 1961. **4**(6): p. 561-571.
135. Nilsson, M.E., et al., *Columbia–suicide severity rating scale scoring and data analysis guide.* CSSRS Scoring Version, 2013. **2**: p. 1-13.
136. Sharp, R., *The Hamilton Rating Scale for Depression.* Occupational Medicine, 2015. **65**(4): p. 340-340.
137. Gibbons, C.J., et al., *Rasch analysis of the hospital anxiety and depression scale (HADS) for use in motor neurone disease.* Health and quality of life outcomes, 2011. **9**(1): p. 82.
138. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta psychiatrica scandinavica, 1983. **67**(6): p. 361-370.
139. Cummings, J.L., et al., *The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia.* Neurology, 1994. **44**(12): p. 2308-2308.
140. Kaufer, D.I., et al., *Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory.* The Journal of neuropsychiatry and clinical neurosciences, 2000. **12**(2): p. 233-239.
141. Hammer, E.M., et al., *Validity of the ALS-Depression-Inventory (ADI-12)—a new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis.* Journal of affective disorders, 2008. **109**(1-2): p. 213-219.
142. Atassi, N., et al., *Depression in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis, 2011. **12**(2): p. 109-112.
143. Murphy, J., et al., *Cognitive-behavioral screening reveals prevalent impairment in a large multicenter ALS cohort.* Neurology, 2016. **86**(9): p. 813-20.
144. Woolley, S.C., et al., *Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS™).* Amyotrophic Lateral Sclerosis, 2010. **11**(3): p. 303-311.
145. Mioshi, E., et al., *The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening.* International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences, 2006. **21**(11): p. 1078-1085.
146. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment.* Journal of the American Geriatrics Society, 2005. **53**(4): p. 695-699.
147. Osborne, R.A., et al., *Screening for frontal lobe and general cognitive impairment in patients with amyotrophic lateral sclerosis.* J Neurol Sci, 2014. **336**(1-2): p. 191-6.
148. Abrahams, S., et al., *Screening for cognition and behaviour changes in ALS.* Amyotrophic lateral sclerosis and frontotemporal degeneration, 2014. **15**(1-2): p. 9-14.
149. KERTESZ, A., et al., *The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia.* Journal of the International Neuropsychological Society, 2000. **6**(4): p. 460-468.
150. Murphy, J., F. Ahmed, and C. Lomen-Hoerth, *The UCSF screening exam effectively screens cognitive and behavioral impairment in patients with ALS.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2015. **16**(1-2): p. 24-30.
151. Dick, J., et al., *Mini-mental state examination in neurological patients.* Journal of Neurology, Neurosurgery & Psychiatry, 1984. **47**(5): p. 496-499.
152. Wang, Y.-P. and C. Gorenstein, *Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II.* Clinics, 2013. **68**(9): p. 1274-1287.
153. Mottram, P., K. Wilson, and J. Copeland, *Validation of the Hamilton Depression Rating Scale and Montgommery and Asberg Rating Scales in terms of AGECAT depression cases.* International Journal of Geriatric Psychiatry, 2000. **15**(12): p. 1113-1119.
154. Posner, K., et al., *The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults.* American journal of psychiatry, 2011. **168**(12): p. 1266-1277.

155. Giddens, J.M., K.H. Sheehan, and D.V. Sheehan, *The Columbia-Suicide Severity Rating Scale (C–SSRS): Has the "gold standard" become a liability?* Innovations in clinical neuroscience, 2014. **11**(9-10): p. 66.
156. Lai, C.K., *The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders.* Clinical interventions in aging, 2014. **9**: p. 1051.
157. Mathuranath, P., et al., *A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia.* Neurology, 2000. **55**(11): p. 1613-1620.
158. Wechsler, D., *The measurement and appraisal of adult intelligence.* 1958.
159. Phukan, J., N.P. Pender, and O. Hardiman, *Cognitive impairment in amyotrophic lateral sclerosis.* The Lancet Neurology, 2007. **6**(11): p. 994-1003.
160. Hodgins, F., S. Mulhern, and S. Abrahams, *The clinical impact of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and neuropsychological intervention in routine ALS care.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019: p. 1-8.
161. Niven, E., et al., *Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): a cognitive tool for motor disorders.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2015. **16**(3-4): p. 172-179.
162. Mitsumoto, H., et al., *ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS): study methodology, recruitment, and baseline demographic and disease characteristics.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014. **15**(3-4): p. 192-203.
163. Murphy, J., et al., *Cognitive-behavioral screening reveals prevalent impairment in a large multicenter ALS cohort.* Neurology, 2016. **86**(9): p. 813-820.
164. Woolley, S., et al., *Longitudinal screening detects cognitive stability and behavioral deterioration in ALS patients.* Behavioural Neurology, 2018. **2018**.
165. Crockford, C., et al., *ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS.* Neurology, 2018. **91**(15): p. e1370-e1380.
166. Elamin, M., et al., *Cognitive changes predict functional decline in ALS: a population-based longitudinal study.* Neurology, 2013. **80**(17): p. 1590-1597.
167. Abrahams, S., P. Leigh, and L. Goldstein, *Cognitive change in ALS: a prospective study.* Neurology, 2005. **64**(7): p. 1222-1226.
168. Beswick, E., et al., *A systematic review of non-motor symptom evaluation in clinical trials for amyotrophic lateral sclerosis.* Journal of Neurology, 2021.
169. Gibbons, C.J., et al., *Rasch analysis of the hospital anxiety and depression scale (HADS) for use in motor neurone disease.* Health Qual Life Outcomes, 2011. **9**: p. 82.
170. Cedarbaum, J.M., et al., *The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III).* J Neurol Sci, 1999. **169**(1-2): p. 13-21.
171. Smith, R.A., et al., *Assessment of bulbar function in amyotrophic lateral sclerosis: validation of a self-report scale (Center for Neurologic Study Bulbar Function Scale).* European journal of neurology, 2018. **25**(7): p. 907-e66.
172. Kurt, A., et al., *Depression and anxiety in individuals with amyotrophic lateral sclerosis.* CNS drugs, 2007. **21**(4): p. 279-291.
173. Díaz, J.L., et al., *Effect of a short-term psychological intervention on the anxiety and depression of amyotrophic lateral sclerosis patients.* Journal of Health Psychology, 2016. **21**(7): p. 1426-1435.
174. Silva-Moraes, M.H., et al., *Suicidal behavior in individuals with amyotrophic lateral sclerosis: A systematic review.* J Affect Disord, 2020. **277**: p. 688-696.
175. Hobson, E.V. and C.J. McDermott, *Supportive and symptomatic management of amyotrophic lateral sclerosis.* Nature Reviews Neurology, 2016. **12**(9): p. 526.
176. Caga, J., et al., *The impact of cognitive and behavioral symptoms on ALS patients and their caregivers.* Frontiers in neurology, 2019. **10**: p. 192.
177. Chiò, A., et al., *Pain in amyotrophic lateral sclerosis: a population-based controlled study.* European Journal of Neurology, 2012. **19**(4): p. 551-555.

178. Boentert, M., *Sleep disturbances in patients with amyotrophic lateral sclerosis: current perspectives.* Nature and science of sleep, 2019. **11**: p. 97.
179. Chio, A. and A. Cicolin, *Sleep in ALS: more than discomfort or respiratory breathing disorder*. 2021, BMJ Publishing Group Ltd.
180. Lo Coco, D., et al., *Sleep–wake problems in patients with amyotrophic lateral sclerosis: implications for patient management.* Neurodegenerative Disease Management, 2012. **2**(3): p. 315-324.
181. Gibbons, C., et al., *Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease.* Cochrane Database of Systematic Reviews, 2018(1).
182. Bradley, W.G., et al., *Current management of ALS: comparison of the ALS CARE Database and the AAN Practice Parameter.* Neurology, 2001. **57**(3): p. 500-504.
183. Chang, V.T., S.S. Hwang, and M. Feuerman, *Validation of the Edmonton symptom assessment scale.* Cancer: Interdisciplinary International Journal of the American Cancer Society, 2000. **88**(9): p. 2164-2171.
184. Williams, J.B., *A structured interview guide for the Hamilton Depression Rating Scale.* Archives of general psychiatry, 1988. **45**(8): p. 742-747.
185. Posner, K., et al., *Columbia-suicide severity rating scale (C-SSRS).* New York, NY: Columbia University Medical Center, 2008. **10**.
186. Simmons, Z., et al., *The ALSSQOL: balancing physical and nonphysical factors in assessing quality of life in ALS.* Neurology, 2006. **67**(9): p. 1659-1664.
187. Jenkinson, R.F., Cathy Brennan, Michael Swash, Crispin, *Evidence for the validity and reliability of the ALS assessment questionnaire: the ALSAQ-40.* Amyotrophic Lateral Sclerosis and other motor neuron disorders, 2000. **1**(1): p. 33-40.
188. Ware Jr, J.E. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection.* Medical care, 1992: p. 473-483.
189. Rabin, R. and F.d. Charro, *EQ-SD: a measure of health status from the EuroQol Group.* Annals of medicine, 2001. **33**(5): p. 337-343.
190. Cohen, S.R., et al., *The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability.* Palliative medicine, 1995. **9**(3): p. 207-219.
191. Bergner, M., et al., *The Sickness Impact Profile: development and final revision of a health status measure.* Medical care, 1981: p. 787-805.
192. Woolley, S.C., D.H. Moore, and J.S. Katz, *Insight in ALS: awareness of behavioral change in patients with and without FTD.* Amyotroph Lateral Scler, 2010. **11**(1-2): p. 52-6.
193. Werner, P., et al., *Help-seeking for dementia: a systematic review of the literature.* Alzheimer Disease & Associated Disorders, 2014. **28**(4): p. 299-310.
194. Kertesz, A., W. Davidson, and H. Fox, *Frontal behavioral inventory: diagnostic criteria for frontal lobe dementi.* Canadian Journal of Neurological Sciences, 1997. **24**(1): p. 29-36.
195. Couratier, P., F. Torny, and M. Lacoste, *[Functional rating scales for amyotrophic lateral sclerosis].* Rev Neurol (Paris), 2006. **162**(4): p. 502-7.
196. Weiss, M.D., et al., *A randomized trial of mexiletine in ALS: Safety and effects on muscle cramps and progression.* Neurology, 2016. **86**(16): p. 1474-81.
197. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.* Psychiatry research, 1989. **28**(2): p. 193-213.
198. Schwartz, J.E., L. Jandorf, and L.B. Krupp, *The measurement of fatigue: a new instrument.* Journal of psychosomatic research, 1993. **37**(7): p. 753-762.
199. Simmons, Z., et al. *Validation of a shorter ALS-specific quality of life instrument: the ALSSQOL-R*. in *Neurology*. 2010. LIPPINCOTT WILLIAMS & WILKINS 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
200. Palmieri, A., et al., *Quality of life and motor impairment in ALS: Italian validation of ALSAQ.* Neurological research, 2010. **32**(1): p. 32-40.
201. Oh, J., et al., *Translation and psychometric evaluation of a Korean version of the amyotrophic lateral sclerosis-specific quality of life–revised.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017. **18**(1-2): p. 92-98.

202. Carvajal, A., et al., *The Spanish version of the Edmonton Symptom Assessment System-revised (ESAS-r): first psychometric analysis involving patients with advanced cancer.* Journal of pain and symptom management, 2013. **45**(1): p. 129-136.
203. Mekala, S., et al., *Dementia diagnosis in seven languages: the Addenbrooke's Cognitive Examination-III in India.* Archives of Clinical Neuropsychology, 2020. **35**(5): p. 528-538.
204. Tremolizzo, L., et al., *ALS Cognitive Behavioral Screen (ALS-CBS): normative values for the Italian population and clinical usability.* Neurological Sciences, 2019: p. 1-7.
205. Mora, J.S., et al., *Spanish adaptation of the edinburgh cognitive and behavioral amyotrophic lateral sclerosis screen (ECAS).* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018. **19**(1-2): p. 74-79.
206. Poletti, B., et al., *The validation of the Italian Edinburgh cognitive and behavioural ALS screen (ECAS).* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016. **17**(7-8): p. 489-498.
207. Alberici, A., et al., *The Frontal Behavioural Inventory (Italian version) differentiates frontotemporal lobar degeneration variants from Alzheimer's disease.* Neurological Sciences, 2007. **28**(2): p. 80-86.
208. Oda, E., et al., *Reliability and factorial structure of a rating scale for amyotrophic lateral sclerosis.* No to shinkei= Brain and nerve, 1996. **48**(11): p. 999-1007.
209. Hita-Contreras, F., et al., *Reliability and validity of the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) in patients with fibromyalgia.* Rheumatology international, 2014. **34**(7): p. 929-936.
210. Felgoise, S.H., et al., *Amyotrophic lateral sclerosis–specific quality of life–short form (ALSSQOL-SF): A brief, reliable, and valid version of the ALSSQOL-R.* Muscle & nerve, 2018. **58**(5): p. 646-654.
211. Jenkinson, C., et al., *Development and validation of a short measure of health status for individuals with amyotrophic lateral sclerosis/motor neurone disease: the ALSAQ-40.* Journal of neurology, 1999. **246**(3): p. III16-III21.
212. Crockford, C., et al., *Measuring reliable change in cognition using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS).* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018. **19**(1-2): p. 65-73.
213. Strong, M.J., et al., *Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis, 2009. **10**(3): p. 131-146.
214. Brown, R., et al., *The Parkinson fatigue scale.* Parkinsonism & related disorders, 2005. **11**(1): p. 49-55.
215. Chaudhuri, K.R., et al., *King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation.* Movement disorders, 2015. **30**(12): p. 1623-1631.
216. Trenkwalder, C., et al., *Parkinson's disease sleep scale—validation of the revised version PDSS-2.* Movement Disorders, 2011. **26**(4): p. 644-652.
217. Schapira, A.H., K.R. Chaudhuri, and P. Jenner, *Non-motor features of Parkinson disease.* Nature Reviews Neuroscience, 2017. **18**(7): p. 435.
218. Beswick, E., et al., *A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis.* Journal of Neurology, 2020.
219. Chenji, S., et al., *Neuroanatomical associations of the Edinburgh cognitive and Behavioural ALS screen (ECAS).* Brain Imaging and Behavior, 2021. **15**(3): p. 1641-1654.
220. Fernández-Jiménez, E. and P.A. Arnett, *Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: A relative importance analysis.* Multiple Sclerosis Journal, 2015. **21**(11): p. 1468-1472.
221. Chalah, M.A., et al., *Theory of mind in multiple sclerosis: a neuropsychological and MRI study.* Neuroscience letters, 2017. **658**: p. 108-113.
222. Young, C.A., et al., *The relationships between symptoms, disability, perceived health and quality of life in amyotrophic lateral sclerosis/motor neuron disease.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019. **20**(5-6): p. 317-327.

223. Bakker, L.A., et al., *Development and assessment of the inter-rater and intra-rater reproducibility of a self-administration version of the ALSFRS-R.* Journal of Neurology, Neurosurgery & Psychiatry, 2020. **91**(1): p. 75-81.
224. Meyer, T., et al., *Remote digital assessment of amyotrophic lateral sclerosis functional rating scale–a multicenter observational study.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2022: p. 1-10.
225. Gibbons, Z.C., et al., *Behaviour in amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis, 2008. **9**(2): p. 67-74.
226. Nylund, K.L., T. Asparouhov, and B.O. Muthén, *Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study.* Structural equation modeling: A multidisciplinary Journal, 2007. **14**(4): p. 535-569.
227. Schwarz, G., *Estimating the dimension of a model.* The annals of statistics, 1978: p. 461-464.
228. Ferentinos, P., et al., *Prevalence of major depression in ALS: comparison of a semi-structured interview and four self-report measures.* Amyotrophic lateral sclerosis, 2011. **12**(4): p. 297-302.
229. Rivera, I., et al., *Prevalence and characteristics of pain in early and late stages of ALS.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013. **14**(5-6): p. 369-372.
230. Wallace, V.C., et al., *The evaluation of pain in amyotrophic lateral sclerosis: a case controlled observational study.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014. **15**(7-8): p. 520-527.
231. James, E., et al., *Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis.* Cochrane Database of Systematic Reviews, 2022(5).
232. Chiò, A., et al., *ALS phenotype is influenced by age, sex, and genetics: a population-based study.* Neurology, 2020. **94**(8): p. e802-e810.
233. Weeks, K.R., et al., *Needs and preferences for psychological interventions of people with motor neuron disease.* Amyotrophic lateral sclerosis and frontotemporal degeneration, 2019. **20**(7-8): p. 521-531.
234. Helleman, J., et al., *Patient perspectives on digital healthcare technology in care and clinical trials for motor neuron disease: an international survey.* Journal of neurology, 2022: p. 1-11.
235. Beswick, E., et al., *Prospective observational cohort study of factors influencing trial participation in people with motor neuron disease (FIT-participation-MND): a protocol.* BMJ Open, 2021. **11**(3): p. e044996.
236. Mitsumoto, H., B.R. Brooks, and V. Silani, *Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved?* The Lancet Neurology, 2014. **13**(11): p. 1127-1138.
237. Andrews, J.A., et al., *Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020: p. 1-10.
238. Miller, T.M., et al., *Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS.* New England Journal of Medicine, 2022. **387**(12): p. 1099-1110.
239. Min, J.H., et al., *Oral solubilized ursodeoxycholic acid therapy in amyotrophic lateral sclerosis: a randomized cross-over trial.* J Korean Med Sci, 2012. **27**(2): p. 200-6.
240. Beghi, E., et al., *Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS.* Amyotroph Lateral Scler Frontotemporal Degener, 2013. **14**(5-6): p. 397-405.
241. Friedman, L.M., et al., *Fundamentals of clinical trials*. Vol. 4. 2010: Springer.
242. Cooley, M.E., et al., *Challenges of recruitment and retention in multisite clinical research.* Cancer nursing, 2003. **26**(5): p. 376-386.
243. Hunninghake, D.B., C.A. Darby, and J.L. Probstfield, *Recruitment experience in clinical trials: literature summary and annotated bibliography.* Controlled clinical trials, 1987. **8**(4): p. 6-30.
244. Madsen, S.M., et al., *Attitudes towards clinical research amongst participants and nonparticipants.* Journal of internal medicine, 2002. **251**(2): p. 156-168.
245. Radakovic, R., et al., *The brief Dimensional Apathy Scale: A short clinical assessment of apathy.* The Clinical Neuropsychologist, 2020. **34**(2): p. 423-435.

246. Crawford, J.R., et al., *Normative data for the HADS from a large non-clinical sample.* Br J Clin Psychol, 2001. **40**(4): p. 429-34.
247. Spielberger, C.D., *State-Trait anxiety inventory.* The Corsini encyclopedia of psychology, 2010: p. 1-1.
248. Sjonnesen, K., et al., *Evaluation of the 9-item Patient Health Questionnaire (PHQ-9) as an assessment instrument for symptoms of depression in patients with multiple sclerosis.* Postgrad Med, 2012. **124**(5): p. 69-77.
249. Spitzer, R.L., K. Kroenke, and J.B. Williams, *Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire.* Jama, 1999. **282**(18): p. 1737-44.
250. Hennessy, C.H., et al., *Measuring health-related quality of life for public health surveillance.* Public health reports, 1994. **109**(5): p. 665.
251. Scale, A.L.S.F.R., *Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. The ALS CNTF treatment study (ACTS) phase I-II Study Group.* Arch Neurol, 1996. **53**: p. 141-7.
252. Yin, S., et al., *Summarizing health-related quality of life (HRQOL): development and testing of a one-factor model.* Population health metrics, 2016. **14**(1): p. 1-9.
253. Moriarty, A.S., et al., *Screening and case finding for major depressive disorder using the Patient Health Questionnaire (PHQ-9): a meta-analysis.* General hospital psychiatry, 2015. **37**(6): p. 567-576.
254. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* Journal of general internal medicine, 2001. **16**(9): p. 606-613.
255. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
256. Chiò, A., L. Mazzini, and G. Mora, *Disease-modifying therapies in amyotrophic lateral sclerosis.* Neuropharmacology, 2020. **167**: p. 107986.
257. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale: an updated literature review.* Journal of psychosomatic research, 2002. **52**(2): p. 69-77.
258. Siciliano, M., et al., *Assessing anxiety and its correlates in amyotrophic lateral sclerosis: The state-trait anxiety inventory.* Muscle & nerve, 2019. **60**(1): p. 47-55.
259. Spielberger, C., et al., *Manual for the State-Trait Anxiety Inventory; Palo Alto, CA, Ed.* Palo Alto: Spielberger, 1983.
260. Abrahams, S., et al., *Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener 15: 9–14*. 2014.
261. Foley, J.A., et al., *Sensitivity and specificity of the ECAS in Parkinson's disease and progressive supranuclear palsy.* Parkinson's Disease, 2018. **2018**.
262. Kourtesis, P., et al., *The Edinburgh cognitive and behavioral amyotrophic lateral sclerosis screen (ECAS): sensitivity in differentiating between ALS and Alzheimer's disease in a Greek population.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2020. **21**(1-2): p. 78-85.
263. Paganoni, S., M. Cudkowicz, and J.D. Berry, *Outcome measures in amyotrophic lateral sclerosis clinical trials.* Clinical investigation, 2014. **4**(7): p. 605.
264. Kessel, K.A., et al., *Cancer clinical trials–Survey evaluating patient participation and acceptance in a university-based Comprehensive Cancer Center (CCC).* Clinical and translational radiation oncology, 2018. **13**: p. 44-49.
265. Ford, J.G., et al., *Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review.* Cancer: Interdisciplinary international journal of the American cancer society, 2008. **112**(2): p. 228-242.
266. Wildenbos, G.A., L. Peute, and M. Jaspers, *Aging barriers influencing mobile health usability for older adults: A literature based framework (MOLD-US).* International journal of medical informatics, 2018. **114**: p. 66-75.
267. Cummings, J., et al., *Apathy in neurodegenerative diseases: recommendations on the design of clinical trials.* Journal of geriatric psychiatry and neurology, 2015. **28**(3): p. 159-173.

268. Radakovic, R. and S. Abrahams, *Multidimensional apathy: evidence from neurodegenerative disease.* Current Opinion in Behavioral Sciences, 2018. **22**: p. 42-49.
269. Santangelo, G., et al., *Apathy in amyotrophic lateral sclerosis: insights from dimensional apathy scale.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017. **18**(5-6): p. 434-442.
270. Shoesmith, C.L., et al., *Prognosis of amyotrophic lateral sclerosis with respiratory onset.* Journal of Neurology, Neurosurgery & Psychiatry, 2007. **78**(6): p. 629-631.
271. Bourke, S.C., et al., *Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial.* The Lancet Neurology, 2006. **5**(2): p. 140-147.
272. Spielberger, C.D., *State-trait anxiety inventory for adults.* 1983.
273. Altura, K.C., et al., *Suicidal ideation in persons with neurological conditions: prevalence, associations and validation of the PHQ-9 for suicidal ideation.* General hospital psychiatry, 2016. **42**: p. 22-26.
274. Beswick, E., et al., *A systematic review of digital technology to evaluate motor function and disease progression in motor neuron disease.* Journal of Neurology, 2022: p. 1-15.
275. Beghi, E., et al., *The epidemiology and treatment of ALS: focus on the heterogeneity of the disease and critical appraisal of therapeutic trials.* Amyotrophic Lateral Sclerosis, 2011. **12**(1): p. 1-10.
276. Rutkove, S.B., et al., *Electrical impedance myography as a biomarker to assess ALS progression.* Amyotrophic Lateral Sclerosis, 2012. **13**(5): p. 439-445.
277. Andres, P.L., et al., *Fixed dynamometry is more sensitive than vital capacity or ALS rating scale.* Muscle & nerve, 2017. **56**(4): p. 710-715.
278. Whiting, P.F., et al., *QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies.* Annals of internal medicine, 2011. **155**(8): p. 529-536.
279. Bakers, J.N., et al., *Portable fixed dynamometry: towards remote muscle strength measurements in patients with motor neuron disease.* Journal of Neurology, 2021. **268**(5): p. 1738-1746.
280. Beukenhorst, A.L., et al., *Smartphone data during the COVID-19 pandemic can quantify behavioral changes in people with ALS.* Muscle & nerve, 2021. **63**(2): p. 258-262.
281. de Bie, E., et al., *Longitudinal evaluation of upper extremity reachable workspace in ALS by Kinect sensor.* Amyotroph Lateral Scler Frontotemporal Degener, 2017. **18**(1-2): p. 17-23.
282. Londral, A., et al. *A Method to Detect Keystrokes using Accelerometry to Quantify Typing Rate and Monitor Neurodegenerative Progression*. in *NEUROTECHNIX*. 2013.
283. Montero-Odasso, M., et al., *Motor Phenotype in Neurodegenerative Disorders: Gait and Balance Platform Study Design Protocol for the Ontario Neurodegenerative Research Initiative (ONDRI).* J Alzheimers Dis, 2017. **59**(2): p. 707-721.
284. Oskarsson, B., et al., *Upper extremity 3-dimensional reachable workspace assessment in amyotrophic lateral sclerosis by Kinect sensor.* Muscle Nerve, 2016. **53**(2): p. 234-41.
285. Rutkove, S.B., et al., *ALS longitudinal studies with frequent data collection at home: study design and baseline data.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2019. **20**(1-2): p. 61-67.
286. Trevizan, I.L., et al., *Efficacy of different interaction devices using non-immersive virtual tasks in individuals with Amyotrophic Lateral Sclerosis: a cross-sectional randomized trial.* BMC neurology, 2018. **18**(1): p. 1-10.
287. Vieira, F.G., et al., *A machine-learning based objective measure for ALS disease severity.* NPJ digital medicine, 2022. **5**(1): p. 1-9.
288. Farhan, S.M.K., et al., *The Ontario Neurodegenerative Disease Research Initiative (ONDRI).* Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, 2017. **44**(2): p. 196-202.
289. Vert, A., et al., *Detecting accelerometer non-wear periods using change in acceleration combined with rate-of-change in temperature.* BMC medical research methodology, 2022. **22**(1): p. 147-147.

290. Godkin, F.E., et al., *Feasibility of a continuous, multi-sensor remote health monitoring approach in persons living with neurodegenerative disease.* Journal of neurology, 2021: p. 1-14.
291. Berry, J.D., et al., *Design and results of a smartphone-based digital phenotyping study to quantify ALS progression.* Ann Clin Transl Neurol, 2019. **6**(5): p. 873-881.
292. Esser, P., et al., *Assessment of spatio-temporal gait parameters using inertial measurement units in neurological populations.* Gait & posture, 2011. **34**(4): p. 558-560.
293. Londral, A., S. Pinto, and M. de Carvalho, *Markers for upper limb dysfunction in Amyotrophic Lateral Sclerosis using analysis of typing activity.* Clin Neurophysiol, 2016. **127**(1): p. 925-931.
294. *Theme 11: Improving diagnosis, prognosis and disease progression.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017. **18**(sup2): p. 261-279.
295. Canosa, A., et al., *Lifetime sport practice and brain metabolism in Amyotrophic Lateral Sclerosis.* NeuroImage: Clinical, 2020. **27**: p. 102312.
296. Capecci, M., et al., *Clinical effects of robot-assisted gait training and treadmill training for Parkinson's disease. A randomized controlled trial.* Annals of physical and rehabilitation medicine, 2019. **62**(5): p. 303-312.
297. Gijbels, D., et al., *Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures.* Multiple Sclerosis Journal, 2010. **16**(5): p. 618-626.
298. van Eijk, R.P.A., et al., *A Road Map for Remote Digital Health Technology for Motor Neuron Disease.* J Med Internet Res, 2021. **23**(9): p. e28766.
299. Ramanarayanan, V., et al., *Speech as a Biomarker: Opportunities, Interpretability, and Challenges.* Perspectives of the ASHA Special Interest Groups, 2022: p. 1-8.
300. Pugliese, R., et al., *Emerging technologies for management of patients with amyotrophic lateral sclerosis: from telehealth to assistive robotics and neural interfaces.* Journal of Neurology, 2022. **269**(6): p. 2910-2921.
301. Bombaci, A., et al., *Telemedicine for management of patients with amyotrophic lateral sclerosis through COVID-19 tail.* Neurological Sciences, 2021. **42**(1): p. 9-13.
302. Lu, R., et al., *Evaluation of wearable sensor devices in Parkinson's disease: A review of current status and future prospects.* Parkinson's Disease, 2020. **2020**.
303. Sparaco, M., et al., *The role of wearable devices in multiple sclerosis.* Multiple sclerosis international, 2018. **2018**.
304. Rozanski, G.M., et al., *Consumer wearable devices for activity monitoring among individuals after a stroke: a prospective comparison.* JMIR cardio, 2018. **2**(1): p. e8199.
305. Russo, M., et al., *The 6-min walk test as a new outcome measure in Amyotrophic lateral sclerosis.* Scientific Reports, 2020. **10**(1): p. 1-9.
306. D'Ascenzo, C., et al., *Parkinson-like features in ALS with predominant upper motor neuron involvement.* Amyotrophic Lateral Sclerosis, 2012. **13**(1): p. 137-143.
307. Thakore, N.J., et al., *Trajectories of impairment in amyotrophic lateral sclerosis: insights from the Pooled Resource Open-Access ALS Clinical Trials cohort.* Muscle & Nerve, 2018. **57**(6): p. 937-945.
308. Hobson, E.V., et al., *"Anything that makes life's journey better." Exploring the use of digital technology by people living with motor neurone disease.* Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017. **18**(5-6): p. 378-387.
309. Krupp, L.B., et al., *The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus.* Archives of neurology, 1989. **46**(10): p. 1121-1123.
310. Cleeland, C.S. and K. Ryan, *The brief pain inventory.* Pain Research Group, 1991. **20**: p. 143-147.
311. Atkinson, T.M., et al., *The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations.* Pain Medicine, 2010. **11**(3): p. 337-346.
312. Logroscino, G., B. J. Traynor, O. Hardiman, P. Couratier, J. D. Mitchell, R. J. Swingler, and E. Beghi., *Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues.* Journal of Neurology, Neurosurgery & Psychiatry, 2008. **79**(1): p. 6-11.