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# Factors Influencing Trial Participation in Motor Neuron Disease (FIT-Participation-MND)



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# Factors Influencing Trial Participation in Motor Neuron Disease (FIT-Participation-MND)

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# 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 trial participants can result in insufficiently representative samples [1], terminated trials, or invalid conclusions [2].

**Aim:** This study seeks to investigate patient-specific factors that affect recruitment and retention of people with MND to MND-SMART. An improved understanding of these factors will improve trial protocol design, optimise recruitment and minimise attrition.

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

**Methods:** People with MND on the Scottish MND Register, Clinical Audit Research and Evaluation MND (CARE-MND), will be sent invitation packs. Participants with MND will complete the HADS, PHQ-9, STAI-Y, ALSSQOL-20, CDC-HQOL-4 and a novel questionnaire on Attitudes towards Clinical Trial Participation (ACT-Q). Additional clinical data will be extracted from participants' CARE-MND or MND-SMART records. Caregivers will be asked to complete the b-DAS apathy scale. After 12 months we will complete a data request to MND-SMART to evaluate how many participants were recruited and how many remain involved.

**Analysis:** Descriptive statistics will be used to summarise and compare assessment tools and the number of participants reaching pre-defined impairment thresholds. Variable groupings include: attitudes, quality of life cognitive impairment, behavioural change, physical functioning, neuropsychiatric and phenotype. To explore the association with participation in MND-SMART, and withdrawal. We will use univariate and multivariable logistic regression; presented as odds ratio and 95% confidence intervals.

**Ethics and Dissemination:** Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020. The results of this study will be published in a peer-reviewed journal and presented at academic conferences. Participants who wish to receive one will be sent a summary of the findings and the results will also be presented at patient engagement events.

**Key Words:** Motor neuron disease, amyotrophic lateral sclerosis, clinical trials, recruitment, retention, attrition

# 2. Article Summary

*Strengths and limitations of this study*

- Strength: The first study prospectively assessing factors influencing people with MND to participate, and remain in, a clinical trial
- Strength: Better understanding of factors that affect recruitment and retention can inform future trial design
- Limitation: Impossible to account for all potential influences on the variability in human behaviour

# 3. Introduction

Motor neuron disease (MND) is a rapidly progressive incurable and uniformly fatal neurodegenerative disorder. Mean age of onset is 65.3 years and only 51.3% of people with MND survive more than 12 months from diagnosis [3]. The disorder has a significant impact on multiple aspects of an individual's life necessitating a holistic approach to clinical care and trial design.

This study will specifically investigate how the presence and severity of symptoms of depression, anxiety, suicidality, cognitive and behavioural change, impact upon recruitment and retention within the context of the first multi-arm multi-centre UK clinical trial in MND.

### *3.1. The Clinical Audit Research and Evaluation of MND platform (CARE-MND)*

Established in 1989, the Scottish Motor Neuron Disease Register was the first population-based register for MND in the world [4]. In 2015 the register was re-launched as the electronic platform Clinical Audit Research and Evaluation of MND (CARE-MND).This has facilitated detailed longitudinal phenotyping of people with MND in Scotland from diagnosis to death, with allied tissue and brain banks, and a research interest register allowing people with MND the ability to register interest in future observational and interventional studies. [5]. The CARE-MND register has 99% case ascertainment for people with MND in Scotland where there is an incidence of 180-220 new cases a year, and a prevalence of approximately 450 people with MND (pwMMD). [5]. The FIT-Participation-MND project will use CARE-MND to facilitate recruitment, access clinical features, and details of trial involvement for participants.

### *3.2. Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial (MND-SMART)*

There is an urgent need for new therapies in MND. Only one disease modifying therapy, Riluzole, has been approved for treatment in the United Kingdom, with limited impact on survival [6]. MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) is a multi-site United Kingdom clinical trial, which seeks to evaluate the effects of repurposed medicines with potential neuroprotective properties (EudraCT Number: 2019-000099-41). Primary objectives are to assess the impact of these candidate drugs on functional ability, as measured using the ALS-FRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised) [7], and also on survival. Secondary outcomes include the impact of these medicines on cognition, respiratory functioning, affective symptoms, and quality of life in people with MND.

In a rare disease such as MND, the multi-arm, multi-stage, adaptive design is particularly beneficial in enabling a reduction of patient numbers and time required to test more than one candidate drug in both phase 2 and 3. Establishing multiple stages with pre-defined interim analysis also reduces the chance of a patient taking an ineffective drug for longer than necessary, crucial in a condition with such a short life expectancy. FIT-Participation-MND will utilise recruitment and retention data from MND-SMART to review factors that may contribute to trial recruitment and retention.

### *3.3. Recruitment and Retention*

The accurate identification of factors that impact upon recruitment, and retention of participants in research studies is important when considering trial protocol design [2]. Recruitment should involve selection of participants representing the entire target population, in numbers sufficient to fulfil trial-specific power calculations. Historically many trials have focussed on specific subgroups, utilising narrow inclusion criteria. Whilst restrictive inclusion criteria may be 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 in significant numbers. While 83% of pwMND indicated they would be open to participating in research trials [8], actual enrolment figures of 25% are reported for clinical trials [9].Whilst some attrition is inevitable, ensuring optimal retention is an important consideration in trial design. Clinical trials in pwMND frequently report attrition rates over 20% [10, 11]. The risk of bias is substantial when attrition rates exceed 20% [12].

Suboptimal recruitment and retention can affect a study's power, which in turn will have a significant impact upon the conclusions drawn from the data [13]. These methodological issues can lead to trials reporting invalid

or inconclusive results, prolong trial time and potentially result in the trial being terminated prematurely [2, 14]. Further investigation of factors that may account for variability in recruitment and retention, particularly within trial of MND therapies, is essential to devise strategies to address issues in enrolment and attrition to improve clinical trial delivery.

### *3.4. Factors Affecting Trial Participation*

A review of clinical trials in Oncology [15] identified three areas that impact upon recruitment: patient factors, trial factors and doctor factors. This concept was also reflected in Atassi's [8] review of historical MND-trials which summarise three factors impacting upon protocol adherence; study population characteristics, trial design and site & staffing facilities. MND-SMART seeks to address aspects of trial design which may affect participation; through inclusive participant criteria to encapsulate the heterogeneity of MND, remote follow-up appointments to address progressive disability and liquid medication to minimise potential swallowing difficulties. Focusing on recruitment and retention within a single trial, particularly MND-SMART which utilised feedback from pwMND and their representatives to address potential barriers to participating the in the design process, enables us to explore the impact of patient-specific factors.

The presence of neuropsychiatric conditions such as depression, anxiety or suicidality, behavioural changes such as apathy, or cognitive impairment pose significant challenges for recruitment as these can also impact upon a person's ability to give informed consent and ability to engage with a clinical trial [8]. Psychological comorbidities and cognitive impairment can significantly impact upon a participant's adherence to protocol during participation in a clinical trial, irrespective of the condition identified [16]. Previous research has indicated that participants' demographic characteristics [17, 18] and attitudes towards research and health behaviours [19] may be predictive of trial enrolment and attrition.

Using a range of assessments this study will evaluate patient-specific factors in people with MND: neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), apathy, attitudes to clinical trials and quality of life. This will be supplemented with data derived from CARE-MND or MND-SMART relating to cognitive impairment (Edinburgh Cognitive and Behavioural ALS Screen scores), disease phenotype, demographic characteristics, physical functioning and comorbidities. To explore how variation within these patient-specific factors impact upon both recruitment into trials and attrition from trials we will link these data to reports from MND-SMART on participant enrolment and retention.

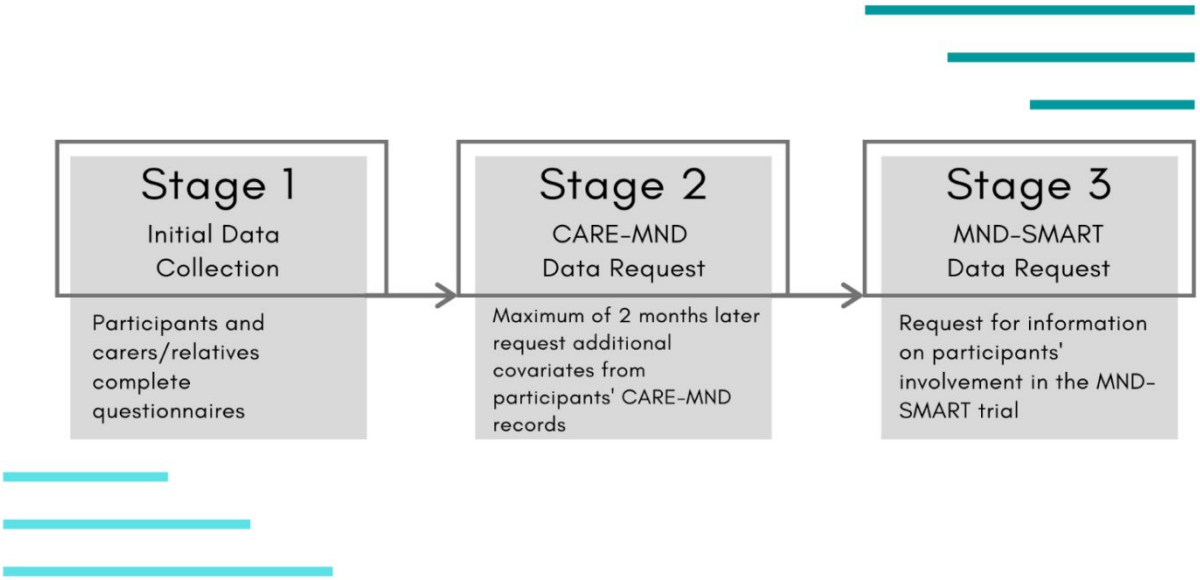
# 4. Methods

## 4.1. Stages of Study

This study will involve three stages of data collection (Figure 1):

1. Questionnaire completion: participants and caregivers complete questionnaire packs
2. CARE-MND data request: additional covariates collected in routine clinical care from each individual's CARE-MND record
3. MND-SMART data request: information on trial involvement and continued participation

*Figure 1: Stages of Data Collection in FIT-P-MND*




## 4.2. Recruitment

Potential participants will receive a postal pack with information on the study and a Consent Form. They will also be asked to identify a caregiver who would be willing to complete a questionnaire about the participant's behaviour. Caregiver will receive a separate Consent Form and Information Sheet. Participants can indicate on their Consent Form their preferred completion method for the questionnaires. These options have been selected to maximise accessibility, to ensure participants with physical disability, speech impairment and inexperience with technology are not alienated from participating.

4. Link to Online Survey to complete questionnaires online
5. Postal paper questionnaire pack
6. Telephone appointment with the lead researcher to go through the questionnaire pack (this can be posted in advance)
7. For participants who can attend the Anne Rowling Regenerative Neurology Clinic in Edinburgh, in-person appointments with the lead researcher

## 4.3. Sample Size Considerations

This study will aim to recruit a convenience sample of 100 individuals with a diagnosis of motor neuron disease. All participants on the CARE-MND register who are eligible will be invited to participate. Previous research

using postal questionnaires in people with MND report response rate of 63% [20]. However, we anticipate that adding the options of completion via online survey or telephone will positively impact on recruitment.

## 4.4. Study Assessments

Table 1 includes a summary of all study assessments included in participant and caregiver engagement and data requests. The questionnaire set for people with MND will include three validated questionnaires; HADS, STAI-Y and PHQ-9. Participants will also be invited to complete two established questionnaires on quality of life, ALSSQOL-20 and CDC HQOL-4. Finally, participants will be asked to complete the ACT-Q developed specifically for this study to evaluate the attitudes and understanding of people with MND towards trial participation. Carers/relatives will be invited to complete the b-DAS to consider behavioural changes of the participant.

*Table 1: Study Assessments, CARE-MND and MND-SMART Data Requests*

| Data Source | Name of Assessment |
|---|---|
| Study Assessment Questionnaires: Participant with MND | ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire) |
| | HADS (Hospital Anxiety and Depression Scale) [21, 22] |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [23] |
| | PHQ-9 (9-Item Patient Health Questionnaire) [24, 25] |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [26] |
| | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [27] |
| Study Assessment Questionnaires: Carer/Relative | b-DAS (Brief Dimensional Apathy Scale) [28, 29] |
| CARE-MND Data Request | Clinical phenotype data<br>• Date of Diagnosis<br>• Age at Diagnosis<br>• Classification of MND<br>• Site of Onset<br>• Family History |
| MND-SMART Data Request | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [7] |
| | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [30] |
| | MND-SMART recruitment and retention data<br>• Date Participant Information Sheet given<br>• Date of Screening<br>• Date of Randomisation<br>• Date of Withdrawal<br>• Date of Last Appointment if Withdrawn<br>• Reason for Withdrawal if provided<br>• Status (Alive/Deceased)<br>• Date of Death (if Applicable) |

## 4.5. Inclusion/Exclusion Criteria

*Table 2: Criteria for Study Participants and Caregivers*

| **For Participant with MND** | |
|---|---|
| *Inclusion Criteria* | • Over 18<br>• 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)<br>• Able to provide informed consent (proxy signature accepted if limb dysfunction renders the individual unable to sign)<br>• Fluent in English |
| *Exclusion Criteria* | • Diagnosis of Frontotemporal Dementia (FTD-MND)<br>• Unable to provide informed consent to participate<br>• Resident outside Scotland |
| **For Caregiver** | |
| *Inclusion Criteria* | • Able and willing to complete a brief questionnaire regarding the participant's behaviour<br>• Family member, spouse, relative, friend or partner of an individual with motor neuron disease<br>• Primary caring responsibilities for a person with motor neuron disease<br>• Fluent in English |
| *Exclusion Criteria* | • Paid carers – excluded to ensure they know the person pre-MND diagnosis<br>• Not fluent in English<br>• Unable to provide informed consent<br>• Diagnosis of motor neuron disease |

## 4.6. Public and Patient Involvement Statement

Patients were first involved in the research when they were emailed the ACT-Q, Participant Information Sheet and Consent Form and asked to provide feedback. Patients were asked to consider the questionnaire structure of the ACT-Q, provide an estimate of the time taken to complete and asked to suggest any additional factors which may influence their attitudes towards trial participation.

Patients were invited to provide feedback on the Participant Information Sheet and Consent Form , particularly clarity of study aims, and additional aspects of MND which may potentially affect trial participation. Feedback from patients was used to refine the list of exploratory covariates in the study, and particularly the items included on the ACT-Q. The time required to participate in the research was based on feedback from patients, existing time-to-complete data for each of the established questionnaires, with additional time to allow for potential communication or physical difficulties frequently experienced by this population.

All participants in the study, who select this option on their consent form, will be sent a copy of the study findings. Either to themselves or their representatives. Patients will be consulted regarding the best way to disseminate findings and provide feedback on initial versions of the study summary documents to ensure clarity of presentation and suitability for this audience.

# 5. Analysis Plan

The study questionnaires will be grouped into domains to reduce the number of candidate variables in the analysis as shown in Table 3. The total scores of individual questionnaires will be summed into an overall summary score for each domain, which will be included in the subsequent analysis. As all scores represent the same directionality (higher score indicates greater impairment) a summed score will provide an overall indication of the level of impairment for each individual per grouped domain.

We will present the mean scores for each assessment, displayed in the factor groupings discussed above, with ranges and standard deviation.

*Table 3: Grouping of Exploratory Covariates*

| **Grouping** | **Assessment or Data Included** | **Impairment Thresholds** |
|---|---|---|
| Attitudes | ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire) | Not applicable |
| Quality of Life | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [27] | Not applicable |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [26] | |
| Cognitive Impairment | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [30] | • Total score is 136 where a higher score indicates better performance. Scores below 105 are considered abnormal<br>• |
| Behavioural Change | b-DAS (Brief Dimensional Apathy Scale) [28, 29] | Each subscale has a minimum score of 0 (least apathy) and a maximum score of 9 (most apathy)<br>Impairment defined as score per subscale:<br>Executive ≥4<br>Emotional ≥5<br>Initiation ≥6 |
| | ECAS Behavioural Screen Subscale | Carer-Completed Behavioural Change Screen<br>• Indicate Yes/No to symptoms, score 1 for every symptoms present out of 10<br><br>Carer-Completed Psychosis Screen<br>Indicate Yes/No to symptoms, score 1 for every symptoms present out of 3 |
| Physical Functioning | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [7] | Twelve tasks rated from 0 (cannot do) to 4 (normal ability). Summed score between 0 (worst) and 48 (best). |
| Neuropsychiatric | HADS (Hospital Anxiety and Depression Scale) [21, 22] | Maximum total score is 24<br>Total of 12 per subscale<br>(≥9) Severe<br>(7 to 8) Moderate<br>(≤6) Mild |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [23] | Total score ranges 20 to 80<br>(≥60) High<br>(40–59) Moderate<br>(20–39) Low |

| | | |
|---|---|---|
| | PHQ-9 (9-Item Patient Health Questionnaire) [24, 25] | Depression:<br>Total score ranges from 0 to 27<br>(20-27) Severe<br>(15-19) Moderately severe<br>(10-14) Moderate<br>(5-9) Mild<br>(1-4) Minimal<br><br>Suicidality:<br>Item 9 scores from<br>(0) Not at all<br>1. Several days<br>2. More than half the days<br>3. Nearly every day<br>Scores of **≥1** indicates presence of suicidal ideation |
| Clinical Phenotype | • MND classification | Not applicable |
| | • Site of onset (spinal, bulbar, pure respiratory) | |
| | • Age at diagnosis | |

## 5.2. Scoring the ACT-Q

The Attitudes towards Clinical Trial Participation Questionnaire (ACT-Q) is a brief trial-specific questionnaire to quantify participant's attitudes towards involvement in research, and multi-arm clinical trials in particular (Table 4). It was developed by the investigators, based upon Kessel's survey for evaluating oncology patient acceptance and participation in clinical trials [31] & Ellis' tripartite model of factors that may influence trial participation [15].
The scoring system is designed to encompass the main themes of the attitudes considered. Focusing on potential factors which may influence a participant's attitude towards, and likelihood of participating in a clinical trial whilst simultaneously evaluating their understanding of a complex trial design. Each potential response is 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. -1 (Not at all), 0 = (Do not know), 1 = (Slightly important), 2 = (Quite important) and 3 (Very important). Items 6, 7 and 13 will be reverse scored as they indicate less agreement with the attitude category.

The final aspect of this questionnaire is evaluating participants' understanding of five key features of the MND-SMART design; placebo condition, eligibility, potential efficacy, repurposed medicines and multiple arms. Participants will respond on a 5-point scale from 0 (No understanding) to 5 (Full understanding) and a total score to represent level of understanding will be produced for each participant, for each trial aspect.

*Table 4: Items of the Attitudes to Clinical Trials Questionnaire (ACT-Q) and Grouping*

| Category | Item |
|---|---|
| Practical Burden | 1) The time commitment required to participate |
| | 2) The distance to the clinic is too far |
| | 3) I already feel I have a lot of appointments |
| Disease Burden | 4) I would not feel well enough to participate because of how my condition affects me |
| | 5) I am concerned about the potential dangers and side effects of trial medications |
| Altruistic Motivations | 6) I may not benefit personally from the development of new drugs |
| | 7) I am worried about the possibility of being assigned to the placebo group |
| | 8) I want to help other people with the same condition as me |
| | 9) I want the opportunity to contribute to research |
| Practical Benefits | 10) I will get additional monitoring of how my condition is changing |
| | 11) I will receive more regular contact with medical staff |
| | 12) I may get to try new medicines which are not available to everyone with my condition |
| Research Engagement | 13) I am already participating in other research projects |
| | 14) I have participated in research before and had a positive experience |

## 5.43. Impact of neuropsychiatric factors on recruitment

We will use logistic regression to model the impact of the aforementioned independent variables on the participant's decision to enrol or not enrol in MND-SMART. All variables will be considered in univariate and subsequently multivariable analysis. Results will be presented as odds ratio and 95% confidence intervals.

## 5.5. Impact of neuropsychiatric factors on retention

12 months after the obtaining the questionnaire responses, we will extract participation data from MND-SMART. MND-SMART being an ongoing trial, it is likely that some individuals will not have withdrawn but will do so later; these individuals will be considered censored at the point of analysis.

We will use univariate and multivariable logistic regression to explore the effect of the aforementioned independent variables withdrawal from the trial at the 12 month time point. Results will be displayed as odds ratios and 95% confidence intervals.

## 5.6. Missing Data

Missing data management will be dependent upon the pattern of missing data identified. If missing at random we will delete participants with over 10% of overall missing data using list wise deletion method.

If particular covariates, certain assessments or questionnaires, are not completed by a significant number (10%) of participants, we will consider removing this variable from analysis. The 10% threshold has been selected as it has been suggested that level of missing data over this threshold can bias statistical analysis and affect our ability to correctly estimate the amount of variability in the data [32].

If data are missing not at random, multiple imputation (e.g. by chained equations) will be used; generating a minimum of 5 imputed datasets.

# 6. Management of Potential Risk

All participants, and carers/relatives, will be required to provide informed consent and acknowledge that they have read the study information. The participant-facing documentation highlights the voluntary nature of the study and the requirements of participation. If there is any doubt about the person's capacity to provide informed consent they will not be recruited. There are no direct risks involved in participating, however, as some of the questionnaires focus on mental health we acknowledge this may be distressing for some participants. To mitigate this participants will be made aware of the inclusion of mental health questionnaires in the study before consenting to participate and asked to acknowledge that their MND nurse-specialist will be informed of any clinically significant scores. The individual's GP will also be contacted to inform them of the person's involvement in the study.

A potential issue is fatigue, a common problem for people with MND, which may be induced by the length of assessment administration. Participants will be encouraged to inform the researcher if they are experiencing any issues and breaks can be taken if required in telephone or in-person appointment. The option to complete at home enables participants who have significant issues with physical and mental fatigue to take breaks and complete the questionnaires at their own pace.

Data management and confidentiality of participants will be managed by assigning Participant ID codes to anonymise responses. The paper Consent Form and the Participant ID code break spreadsheet will be the only documents with identifiable information. Additional source data will be identified using Participant ID numbers.

# 7. Ethics and Dissemination

This research is co-sponsored by the University of Edinburgh and NHS Lothian. Representatives from the Academic and Clinical Central Office for Research and Development (ACCORD) have reviewed and approved this project. Ethical approval was provided by the West of Scotland Research Ethics Committee 3 on 12th May 2020 (REC Reference: 20/WS/0067).

Only people with MND who have provided prior consent to be contacted about ongoing research on their CARE-MND record will be invited to participate. The Anne Rowling Regenerative Neurology Clinic hosts the register, the data processor at the clinic will contact the potential participants' clinical MND nurse-specialist to ensure it is still suitable to contact each person with MND prior to posting recruitment packs.

At the end of the study a lay summary will be sent to the participants, or their nominated representative, for individuals who have indicated they would like to receive one on their Consent Form. The results will also be disseminated to the wider MND community at research engagement events at the Anne Rowling Clinic and Euan MacDonald Centre and on their social media platforms. Fully anonymised raw data will be uploaded to a persistent DOI under the lead researcher's account at the Open Science Framework associated with the ORCID ID 0000-0001-9843-0778: https://osf.io/fxnwv/. This is in line with Open Science practice, to enhance the value of the research data to the scientific community. Agreement with this data storage policy is included in the Consent Form. Additionally we intend to publish the results of this project in a peer-reviewed journal and presented at academic conferences.

# 8. Author Statement

Each author has contributed significantly to one or more aspects of the study. All authors contributed to study development and design. EB, JN and SP will lead participant recruitment. EB and SP will contribute to data acquisition. EB and SP drafted the manuscript and all authors provided critical revisions and approved the final version.

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# A Study Protocol for Factors Influencing Trial Participation in Motor Neuron Disease (FIT-Participation-MND)



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# A Study Protocol for Factors Influencing Trial Participation in Motor Neuron Disease (FIT-Participation-MND)

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# 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 (pwMND). 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. This study investigates patient-specific factors affecting recruitment and retention of pwMND to MND-SMART. Improved understanding of these factors may improve trial protocol design, optimise recruitment and retention.

**Methods and Analysis:** PwMND on the Scottish MND Register, CARE-MND, will be sent invitation packs. Participants with MND will complete the HADS, PHQ-9 and STAI-Y to evaluate neuropsychiatric symptoms, the ALSSQOL-20 and CDC-HQOL-4 for quality of life and a novel study-specific questionnaire on Attitudes towards Clinical Trial Participation (ACT-Q). Variables on phenotype, cognition (ECAS) and physical functioning (ALS-FRS(R)) will be requested from CARE-MND or MND-SMART. Caregivers will complete the b-DAS apathy scale. After 12 months we will complete a data request to MND-SMART to evaluate how many participants were recruited and how many remain involved. Descriptive statistics will be used to summarise and compare assessment tools and the number of participants reaching pre-defined impairment thresholds. Variable groupings: attitudes, quality of life, cognition, behaviour, physical functioning, neuropsychiatric and phenotype. Univariate and multivariable logistic regression will explore the association with participation/withdrawal in MND-SMART; presented as odds ratios and 95% confidence intervals.

**Ethics and Dissemination:** Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020. The results of this study will be published in a peer-reviewed journal, presented at academic conferences and disseminated to participants and the public.

**Key Words:** Motor neuron disease, amyotrophic lateral sclerosis, clinical trials, recruitment, retention, attrition

# 2. Article Summary

*Strengths and limitations of this study*

- Strength: The first study prospectively assessing factors influencing people with MND to participate, and remain in, a clinical trial
- Strength: Better understanding of factors that affect recruitment and retention can inform future trial design
- Limitation: Impossible to account for all potential influences on the variability in human behaviour
- Limitation: As the population is Scotland-based there may be additional barriers to participation or factors affecting attrition in trial sites across the United Kingdom.

# 3. Introduction

Motor neuron disease (MND) is a rapidly progressive incurable and uniformly fatal neurodegenerative disorder. Mean age of onset is 65.3 years and only 51.3% of people with MND survive more than 12 months from diagnosis [1]. The disorder has a significant impact on multiple aspects of an individual's life necessitating a holistic approach to clinical care and trial design.

This study will specifically investigate how the presence and severity of symptoms of depression, anxiety, suicidality, cognitive and behavioural change, impact upon recruitment and retention within the context of the first multi-arm multi-centre UK clinical trial in MND.

### *3.1. The Clinical Audit Research and Evaluation of MND platform (CARE-MND)*

Established in 1989, the Scottish Motor Neuron Disease Register was the first population-based register for MND in the world [2]. In 2015 the register was re-launched as the electronic platform Clinical Audit Research and Evaluation of MND (CARE-MND). This has facilitated detailed longitudinal phenotyping of people with MND in Scotland from diagnosis to death, with allied tissue and brain banks, and a research interest register allowing people with MND the ability to register interest in future observational and interventional studies. [3]. The CARE-MND register has 99% case ascertainment for people with MND in Scotland where there is an incidence of 180-220 new cases a year, and a prevalence of approximately 450 people with MND (pwMMD). [3]. The FIT-Participation-MND project will use CARE-MND to facilitate recruitment, access clinical features, and details of trial involvement for people with MND living in Scotland.

### *3.2. Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial (MND-SMART)*

There is an urgent need for new therapies in MND. Only one disease modifying therapy, riluzole, has been approved for treatment in the United Kingdom, with limited impact on median survival [4] . The recently published Airlie House guidelines encapsulate the new direction of trials in this area; with clear recommendations to rethink outcome measures, stratify participant characteristics and use academic consensus and historical trial findings to inform future design [5].

MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) is a multi-site United Kingdom clinical trial, which seeks to evaluate the effects of repurposed medicines with potential neuroprotective properties. Full details of the trial design and selection criteria is available at clinicaltrials.gov (NCT04302870) and EudraCT (Trial record number: 2019-000099-41). MND-SMART is a long-running trial, expected to evaluate several candidate repurposed drugs over the next two decades under a single umbrella protocol. Currently, Memantine and Trazodone are being evaluated against placebo.
Primary objectives are to assess the impact of these candidate drugs on functional ability, as measured using the ALS-FRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised) [6], and also on survival. Secondary outcomes include the impact of these medicines on cognition, respiratory functioning, affective symptoms, and quality of life in 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 [7] and cancer [8], 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.

Establishing multiple stages with pre-defined interim analysis also reduces the chance of a patient taking an ineffective drug for longer than necessary, crucial in a condition with such a short life expectancy.

MND-SMART is a Scotland-led trial with sites in Scotland opening first, then expanding across the rest of the UK. At the time of writing FIT-Participation-MND only Scottish sites have commenced recruitment, and as the CARE-MND register (which will be used for recruitment and additional covariates) includes only on Scottish pwMND, FIT-Participation-MND will focus on Scottish participants. FIT-Participation-MND will utilise

recruitment and retention data from MND-SMART to review factors that may contribute to trial recruitment and retention.

### *3.3. Recruitment and Retention*

The accurate identification of factors that impact upon recruitment, and retention of participants in research studies is important when considering trial design [9]. Recruitment should involve selection of participants 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 (pwMND) indicated they would be open to participating in research trials [10], surveyed clinicians estimate enrolment figures of 25% in trials, primarily due to unsuitability of pwMND within stated inclusion criteria [11]. 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 [12]. As MND-SMART involves broader inclusion criteria than many previous trials we expect higher rates of enrolment, reflecting greater inclusivity of these criteria.

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[13]. Whilst some attrition is inevitable, ensuring optimal retention is an important consideration in trial design. Clinical trials in pwMND frequently report attrition rates over 20% [14, 15], risk of bias is high at attrition rates in this threshold [16]. 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.

Suboptimal recruitment and retention can affect a study's power, in turn significantly impacting conclusions [17]. These methodological issues can lead to trials reporting invalid or inconclusive results, prolonged trial times and potential premature termination [9, 18]. 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.

### *3.4. Factors Affecting Trial Participation*

A review of clinical trials in oncology [19] identified three areas that impact upon recruitment: patient factors, trial factors and doctor factors. This concept was also reflected in Atassi's [10] review of factors affecting adherence in MND trials; study population characteristics, trial design and site/staff facilities. MND-SMART seeks to address these through inclusive trial participant criteria, remote follow-up appointments to address progressive disability and liquid medication to minimise potential swallowing difficulties. Focusing on recruitment and retention within a single trial enables us to explore the impact of patient-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 [10] [20]. Participants' demographic characteristics [21, 22] and attitudes towards research and health behaviours [23] may be predictive of trial enrolment and attrition.

Using a range of assessments this study will evaluate patient-specific factors in people with MND: neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), apathy, attitudes to clinical trials and quality of life. This will be supplemented with data derived from CARE-MND or MND-SMART relating to cognition(ECAS), disease phenotype, demographics and physical functioning. To explore how these patient-specific factors impact upon recruitment and retention in MND-SMART. Descriptive statistics will be used to explore reasons for attrition and group individuals who withdraw from the trial due to loss-to-follow-up, disease progression, death and withdrawal of study arm.

### *3.5. Aims and Hypothesis*

1. Evaluate the characteristics of individuals who do, or do not, participate in MND-SMART.
2. Characteristics of FIT-P-MND participants who remain enrolled on MND-SMART after 12 months or lost to follow-up

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

# 4. Methods

## 4.1. Stages of Study

This study will involve 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

## 4.2. Study Timeline

Timeline for the current study was impacted by the COVID-19 pandemic, as non-COVID research and recruitment was temporarily halted. Table 1 provides an overview for key time-points in the study, and projected dates for recruitment and data collection.

*Table 1: Overview of FIT-Participation-MND Study Timeline*

| Key Study Aspect | Actual or Projected Date |
|---|---|
| Favourable ethical opinion obtained | 12th May 2020 |
| Site approval to commence recruitment | 8th July 2020 |
| Recruitment commences | 10th August 2020 |
| Recruitment planned to close | February 2021 |
| CARE-MND data request | February-March 2021 |
| MND-SMART data request | February-March 2022 |

## 4.2. Recruitment

All individuals on the CARE-MND register who have consented to receive information on studies which they may be eligible for will be invited to participate in FIT-Participation-MND via a postal invitation pack.

Potential FIT-Participation-MND participants will receive this postal pack with information on the study and a Consent Form. They will also be asked to identify a caregiver who would be willing to complete a behaviour questionnaire and they will receive a separate Consent Form and Information Sheet.

Participants can indicate on their Consent Form their preferred completion method; online survey, in-person appointment in Edinburgh, postal or telephone. These options have been selected to maximise accessibility and inclusivity.

## 4.3. Sample Size Considerations

This study will aim to recruit a sample of 130 individuals with a diagnosis of MND.

The required sample size was determined using the primary research objectives, which will be answered using regression analysis. The 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 odds ratio (measure of association between an exposure and an outcome) of 1.70 with power at 0.75 provides a sample size estimate of 126.

There are around 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 will be invited to participate.

Previous research using postal questionnaires in people with MND report response rate of 63% [24]. However, we anticipate that adding the options of completion via online survey or telephone will improve response rates. As a result we expect 130 individuals to be an obtainable sample size, based on a 60% response rate estimate.

Across all Scottish sites the MND-SMART projected recruitment is 100 participants per year, with attrition due to death or withdrawal predicted at 20% annually. We estimate that 80% of the 130 participants in FIT-P-MND will also enrol in MND-SMART, 104 people. Based on projected annual attrition rates of 20% for MND-SMART we expect 80 of these individuals to remain in MND-SMART 12-months later.

As this is an exploratory study, looking at 9 variables (using grouping to simplify analysis and presentation), and a relatively rare condition sample size is based on the number of potential participants available and descriptive analysis methods will be utilised to explore the data.

## 4.4. Study Assessments

Table 2 includes a summary of all study assessments included in FIT-Participation-MND participant and caregiver engagement and data requests. The questionnaire set for people with MND will take around 45 minutes, depending on physical decline and speech impairment, and include three validated questionnaires; HADS, STAI-Y and PHQ-9. FIT-Participation-MND participants will also be invited to complete two established questionnaires on quality of life, ALSSQOL-20 and CDC HQOL-4. Finally, participants will be asked to complete the ACT-Q developed specifically for this study to evaluate the attitudes and understanding of people with MND towards trial participation. Carers/relatives will be invited to complete the b-DAS to consider behavioural changes of the participant (circa 5 minutes). Questionnaires will take around 50 minutes in total.

Data requests to CARE-MND and MND-SMART for additional data on physical functioning, cognition and clinical phenotype enable us to reduce burden on participants by ensuring brevity in study visits. We will use ALSFRS(R) and ECAS scores from CARE-MND, or MND-SMART if the individual is also a trial participant, to ensure we collect scores closest to the time-point that the FIT-Participation-MND study assessments are undertaken.

*Table 2: Study Assessments, CARE-MND and MND-SMART Data Requests*

| 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) [25, 26] |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [27] |
| | PHQ-9 (9-Item Patient Health Questionnaire) [28, 29] |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [30] |
| | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [31] |
| Study Assessment Questionnaires: Carer/Relative | b-DAS (Brief Dimensional Apathy Scale) [32, 33] |
| CARE-MND Data Request | Clinical phenotype data<br>• Date of Diagnosis<br>• Age at Diagnosis<br>• Classification of MND<br>• Site of Onset<br>• Family History |
| CARE-MND or MND-SMART Data Request | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [6] |
| | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [34] |
| MND-SMART Data Request | MND-SMART recruitment and retention data<br>• Date MND-SMART Participant Information Sheet given<br>• Date of Screening<br>• Date of Randomisation<br>• Date of Withdrawal<br>• Date of Last Appointment if Withdrawn<br>• Reason for Withdrawal if provided<br>• Status (Alive/Deceased)<br>• Date of Death (if Applicable) |

## 4.5. Inclusion/Exclusion Criteria

Table 3 summarises the inclusion and exclusion criteria for people with MND and their caregivers who wish to participate in FIT-Participation-MND. These criteria have been primarily selected to align with the criteria for MND-SMART to ensure maximum overlap in the two participant groups.

*Table 3: Criteria for FIT-Participation-MND Participants and Caregivers*

| **For FIT-Participation-MND Participant with MND** | |
|---|---|
| *Inclusion Criteria* | • Over 18<br>• 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)<br>• Able to provide informed consent (proxy signature accepted if limb dysfunction)<br>• Fluent in English |
| *Exclusion Criteria* | • Diagnosis of Frontotemporal Dementia (FTD-MND)<br>• Unable to provide informed consent<br>• Resident outside Scotland |
| **For Caregiver** | |
| *Inclusion Criteria* | • Able and willing to complete a brief questionnaire regarding the participant's behaviour<br>• Family member, spouse, relative, friend or partner for pwMND<br>• Primary caring responsibilities for pwMND<br>• Fluent in English |
| *Exclusion Criteria* | • Paid carers – excluded to ensure they know the person pre-MND diagnosis<br>• Not fluent in English<br>• Unable to provide informed consent<br>• Diagnosis of MND |

## 4.6. Public and Patient Involvement Statement

PwMND were first involved in the research when they were emailed the ACT-Q, Participant Information Sheet and Consent Form and asked to provide feedback. People with MND were asked to consider the questionnaire structure of the ACT-Q, provide an estimate of the time taken to complete and asked to suggest any additional factors which may influence their attitudes towards trial participation.

PwMND were invited to provide feedback on Participant Information Sheets and Consent Forms, particularly clarity of study aims, and additional aspects of MND which may potentially affect trial participation. Feedback from these individuals was used to refine the list of exploratory covariates in the study, and particularly the items included on the ACT-Q. Time required to participate in the research was based on feedback from patients, existing time-to-complete data for each of the established questionnaires, with additional time for potential communication or physical difficulties.

All participants in the study, who chose to, will be sent a copy of the study findings. PwMND and their caregivers will be consulted regarding the best way to disseminate findings and provide feedback on initial versions of the study summary documents to ensure clarity of presentation and suitability for this audience.

# 5. Analysis Plan

The study questionnaires will be grouped into domains to reduce the number of candidate variables in the analysis as shown in Table 3. The total scores of individual questionnaires will be summed into an overall summary score for each domain, which will be included in the subsequent analysis. As all scores represent the same directionality (higher score indicates greater impairment) a summed score will provide an overall indication of the level of impairment for each individual per grouped domain.

We will present the mean scores for each assessment, displayed in the factor groupings discussed above, with ranges and standard deviation.

*Table 4: Grouping of Exploratory Covariates*

| **Grouping** | **Assessment or Data Included** | **Impairment Thresholds** |
|---|---|---|
| Attitudes | ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire) | Not applicable |
| Quality of Life | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [31] | Not applicable |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [30] | |
| Cognitive Impairment | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [34] | • Total score is 136 where a higher score indicates better performance. Scores below 105 are considered abnormal<br>• |
| Behavioural Change | b-DAS (Brief Dimensional Apathy Scale) [32, 33] | Each subscale has a minimum score of 0 (least apathy) and a maximum score of 9 (most apathy)<br>Impairment defined as score per subscale:<br>Executive ≥4<br>Emotional ≥5<br>Initiation ≥6 |
| | ECAS Behavioural Screen Subscale | Carer-Completed Behavioural Change Screen<br>• Indicate Yes/No to symptoms, score 1 for every symptoms present out of 10<br><br>Carer-Completed Psychosis Screen<br>Indicate Yes/No to symptoms, score 1 for every symptoms present out of 3 |
| Physical Functioning | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [6] | Twelve tasks rated from 0 (cannot do) to 4 (normal ability). Summed score between 0 (worst) and 48 (best). |
| Neuropsychiatric | HADS (Hospital Anxiety and Depression Scale) [25, 26] | Maximum total score is 24<br>Total of 12 per subscale<br>(≥9) Severe<br>(7 to 8) Moderate<br>(≤6) Mild |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [27] | Total score ranges 20 to 80<br>(≥60) High<br>(40–59) Moderate<br>(20–39) Low |

| | | |
|---|---|---|
| | PHQ-9 (9-Item Patient Health Questionnaire) [28, 29] | Depression:<br>Total score ranges from 0 to 27<br>(20-27) Severe<br>(15-19) Moderately severe<br>(10-14) Moderate<br>(5-9) Mild<br>(1-4) Minimal<br><br>Suicidality:<br>Item 9 scores from<br>(0) Not at all<br>1. Several days<br>2. More than half the days<br>3. Nearly every day<br>Scores of **≥1** indicates presence of suicidal ideation |
| Clinical Phenotype | • MND classification | Not applicable |
| | • Site of onset (spinal, bulbar, pure respiratory) | |
| | • Age at diagnosis | |

## 5.1. Scoring the ACT-Q

The Attitudes towards Clinical Trial Participation Questionnaire (ACT-Q) is a brief trial-specific questionnaire to quantify FIT-Participation-MND's attitudes towards involvement in research, and multi-arm clinical trials in particular (Table 4). Developed by the investigators, based upon Kessel's survey [35] & Ellis' tripartite model [19] on factors impacting trial engagement.
Each potential response is 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 will be reverse scored, indicating less agreement with the attitude.

The final aspect of this questionnaire is evaluating FIT-Participation-MND participants' understanding of five key features of design. Respondents will indicate on a 5-point scale to represent level of understanding.

*Table 4: Items of the Attitudes to Clinical Trials Questionnaire (ACT-Q) and Grouping*

| Category | Item |
|---|---|
| Practical Burden | 1) The time commitment required to participate |
| | 2) The distance to the clinic is too far |
| | 3) I already feel I have a lot of appointments |
| Disease Burden | 4) I would not feel well enough to participate because of how my condition affects me |
| | 5) I am concerned about the potential dangers and side effects of trial medications |
| Altruistic Motivations | 6) I may not benefit personally from the development of new drugs |
| | 7) I am worried about the possibility of being assigned to the placebo group |
| | 8) I want to help other people with the same condition as me |
| | 9) I want the opportunity to contribute to research |
| Practical Benefits | 10) I will get additional monitoring of how my condition is changing |
| | 11) I will receive more regular contact with medical staff |
| | 12) I may get to try new medicines which are not available to everyone with my condition |
| Research Engagement | 13) I am already participating in other research projects |
| | 14) I have participated in research before and had a positive experience |

## 5.2. Statistical Analysis

We will use logistic regression to model the impact of the aforementioned independent variables on the FIT-Participation-MND participant's decision to enrol or not enrol in MND-SMART. All variables will be considered in univariate and subsequently multivariable analysis. Results will be presented as odds ratio and 95% confidence intervals.

12 months after the obtaining the questionnaire responses, we will extract participation data from MND-SMART. MND-SMART

We will use univariate and multivariable logistic regression to explore the effect of the aforementioned independent variables withdrawal from the trial at the twelve month time point. Results will be displayed as odds ratios and 95% confidence intervals.

As this is an exploratory study with 9 categories of covariates, we will not be using an adjusted alpha-level to correct for multi-testing. The Bonferroni method of correcting p-values may not be suitable for this analysis as hypotheses are pre-defined, not all variables must be significant to reject the null hypothesis and descriptive statistics will also be of relevant when interpreting the findings [36].

## 5.3. Missing Data

If particular covariates, certain assessments or questionnaires, are not completed fully by the majority of participants, we will consider removing this variable from analysis. Missing data within individual questionnaires will be 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. The covariate of behavioural change will be included where possible.

# 6. Management of Potential Risk

All FIT-Participation-MND participants, and caregivers, will provide informed consent and acknowledge they have read the study information. Participant-facing documentation highlights the voluntary nature of the study and requirements of participation. If there is any doubt about the person's capacity to provide informed consent they will not be recruited. There are no direct risks involved in participating, however, as some of the questionnaires focus on mental health we acknowledge this may be distressing and this will be clearly stated and participants will be asked to acknowledge that their clinical team will be informed of any significant scores. The individual's GP will also be contacted to inform them of study involvement.

A potential issue is fatigue, which may be induced by the length of assessment administration. Participants will be encouraged to inform the researcher if they are experiencing any and the option to complete at home enables participants who have significant issues with physical and mental fatigue to take breaks and complete the questionnaires at their own pace.

Data management and confidentiality of FIT-Participation-MND participants will be managed by assigning Participant ID codes to anonymise responses. Use of identifiable information will be minimised.

# 7. Ethics and Dissemination

This research is co-sponsored by the University of Edinburgh and NHS Lothian. Representatives from the Academic and Clinical Central Office for Research and Development (ACCORD) have reviewed and approved this project. Ethical approval was provided by the West of Scotland Research Ethics Committee 3 on 12th May 2020 (REC Reference: 20/WS/0067).

Only people with MND who have provided prior consent to be contacted about ongoing research on their CARE-MND record will be invited to participate. The Anne Rowling Regenerative Neurology Clinic hosts the register, the data processor at the clinic will contact the potential participants' MND nurse prior to posting recruitment packs.

At the end of the study a lay summary will be sent to the participants, or their nominated representative, for individuals who have indicated they would like to receive one on their Consent Form. The results will be disseminated to the community at engagement events and social media. Fully anonymised data will be uploaded to a persistent DOI at the Open Science Framework; ORCID ID 0000-0001-9843-0778: https://osf.io/fxnwv/. In line with Open Science practice, to enhance the value of the research data to the scientific community. Agreement with this data storage policy is included in the Consent Form. We intend to publish the results of this project in a peer-reviewed journal and presented at academic conferences.

# 8. Author Statement

Each author has contributed significantly to one or more aspects of the study.
EB, SP, SG, JN, RD, AC, SA and SC contributed to study development and design of the protocol. In addition, EB, JN and SP will lead participant recruitment and contribute to data acquisition.
EB SG, JN, SC, SA, AC and SP drafted this work and provided critical revisions and approved the final version of this protocol. In addition, SG provided advice on analysis plans and EB and SP made significant contributions to planned interpretation of the data.

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# A Prospective Observational Cohort Study of Factors Influencing Trial Participation in People with Motor Neuron Disease (FIT-Participation-MND): A Protocol



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# A Prospective Observational Cohort Study of Factors Influencing Trial Participation in People with Motor Neuron Disease (FIT-Participation-MND): A Protocol

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**Competing interests:** Professor Carson is a paid editor at Journal of Neurology, Neurosurgery and Psychiatry, and gives independent testimony in Court on a range of neuropsychiatric topics.

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**Orchid ID:** Emily Beswick: 0000-0001-9843-0778

**Data statement:** Data will be uploaded o the Open Science framework, associated with the lead author's Orchid ID.

# 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 (pwMND). 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. This study investigates patient-specific factors affecting recruitment and retention of pwMND to MND-SMART. Improved understanding of these factors may improve trial protocol design, optimise recruitment and retention.

**Methods and Analysis:** PwMND on the Scottish MND Register, CARE-MND, will be invited to participate in a prospective observational cohort study that investigates factors affecting trial participation and attrition. We hypothesise that patient-specific factors will significantly affect trial recruitment and retention. Participants will complete the HADS, PHQ-9 and STAI-Y to evaluate neuropsychiatric symptoms, the ALSSQOL-20 and CDC-HQOL-4 for quality of life and a novel study-specific questionnaire on Attitudes towards Clinical Trial Participation (ACT-Q). Clinical data on phenotype, cognition (ECAS) and physical functioning (ALS-FRS(R)) will also be collated. Caregivers will complete the b-DAS apathy scale. After 12 months a data request to MND-SMART will evaluate recruitment and retention. Descriptive statistics will summarise and compare assessments and participants reaching impairment thresholds. Variable groupings: attitudes, quality of life, cognition, behaviour, physical functioning, neuropsychiatric and phenotype. Univariate and multivariable logistic regression will explore association with participation/withdrawal in MND-SMART; presented as odds ratios and 95% confidence intervals.

**Ethics and Dissemination:** Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020. The results of this study will be published in a peer-reviewed journal, presented at academic conferences and disseminated to participants and the public.

**Key Words:** Motor neuron disease, amyotrophic lateral sclerosis, clinical trials, recruitment, retention, attrition

# 2. Article Summary

*Strengths and limitations of this study*

- Strength: The first observational cohort study prospectively assessing factors influencing people with MND to participate, and remain in, a clinical trial
- Strength: Better understanding of factors that affect recruitment and retention can inform future trial design
- Limitation: Impossible to account for all potential influences on the variability in human behaviour
- Limitation: As the population is Scotland-based there may be additional barriers to participation or factors affecting attrition in trial sites across the United Kingdom.

# 3. Introduction

### *3.1. Clinical Trials in Motor Neuron Disease*

Motor neuron disease (MND) is a rapidly progressive incurable and uniformly fatal neurodegenerative disorder. Mean age of onset is 65.3 years and only 51.3% of people with MND survive more than 12 months from diagnosis [1]. The disorder has a significant impact on multiple aspects of an individual's life necessitating a holistic approach to clinical care and trial design.

There is an urgent need for new therapies in MND. Only one disease modifying therapy, riluzole, has been approved for treatment in the United Kingdom, with limited impact on median survival [2] . The recently published Airlie House guidelines encapsulate the new direction of trials in this area; with clear recommendations to rethink outcome measures, stratify participant characteristics and use academic consensus and historical trial findings to inform future design [3].

### *3.2. Recruitment and Retention in MND Trials*

The accurate identification of factors that impact upon recruitment, and retention of participants in research studies is important when considering trial design [4]. Recruitment should involve selection of participants 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 (pwMND) indicated they would be open to participating in research trials [5], surveyed clinicians estimate enrolment figures of 25% in trials, primarily due to unsuitability of pwMND within stated inclusion criteria [6].

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 [7]. As MND-SMART involves broader inclusion criteria than many previous trials we expect higher rates of enrolment, reflecting greater inclusivity of these criteria.

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[8]. Whilst some attrition is inevitable, ensuring optimal retention is an important consideration in trial design. Clinical trials in pwMND frequently report attrition rates over 20% [9, 10], risk of bias is high at attrition rates in this threshold [11]. 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.

Suboptimal recruitment and retention can affect a study's power, in turn significantly impacting conclusions [12]. These methodological issues can lead to trials reporting invalid or inconclusive results, prolonged trial times and potential premature termination [4, 13]. 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.

### *3.3. New Directions in MND Trials*

MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) is a multi-site United Kingdom clinical trial, which seeks to evaluate the effects of repurposed medicines with potential neuroprotective properties. Full details of the trial design and selection criteria is available at clinicaltrials.gov (NCT04302870) and EudraCT (Trial record number: 2019-000099-41). MND-SMART is a long-running trial, expected to evaluate several candidate repurposed drugs over the next two decades under a single umbrella protocol. Currently, memantine and trazodone are being evaluated against placebo.

Primary objectives are to assess the impact of these candidate drugs on functional ability, as measured using the ALS-FRS(R) (Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised) [14], and also on survival.

Secondary outcomes include the impact of these medicines on cognition, respiratory functioning, affective symptoms, and quality of life in 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 [15] and cancer [16], 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. Establishing multiple stages with pre-defined interim analysis also reduces the chance of a patient taking an ineffective drug for longer than necessary, crucial in a condition with such a short life expectancy.

### *3.4. Rationale*

A review of clinical trials in oncology [17] identified three areas that impact upon recruitment: patient factors, trial factors and doctor factors. This concept was also reflected in Atassi's [5] review of factors affecting adherence in MND trials; study population characteristics, trial design and site/staff facilities. MND-SMART seeks to address these through inclusive trial participant criteria, remote follow-up appointments to address progressive disability and liquid medication to minimise potential swallowing difficulties.

In MND-SMART many of the trial and doctor-specific factors that have previously affected engagement with MND trials have been addressed. This provides us with a unique opportunity to explore how patient-specific factors can also influence trial participation decisions. Although focused on a single trial, we believe these findings will inform future trial design, promote inclusivity and support trial teams in retaining participants.

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 adhere to study protocol [5] [18]. Participants' demographic characteristics [19, 20] and attitudes towards research and health behaviours [21] may also be predictive of trial enrolment and attrition.

However, we currently have no knowledge of how prevalent and impactful these patient-specific factors are on people with MND and their decision to participate and remain in a clinical trial. This study will seek to address this knowledge gap, exploring what factors define the trial 'participant' and are associated with retention at follow-up.

### *3.5. Aims and Hypothesis*

This prospective observational cohort study will investigate how patient-specific factors impact upon recruitment and retention within the context of the first multi-arm multi-centre UK clinical trial in MND.

*Aims:*

1. Evaluate the characteristics of individuals who do, or do not, participate in MND-SMART.
2. Compare the characteristics of FIT-P-MND participants who remain enrolled on MND-SMART after 12 months and those who are lost to follow-up

*Hypothesis:*

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

# 4. Methods

## 4.1 Study Design

This prospective observational cohort study will evaluate how patient-specific factors in people with MND affect their participation in MND-SMART, a multi-arm UK-wide clinical trial.

Using a range of assessments this study will evaluate patient-specific factors in people with MND at a specific point in time: neuropsychiatric symptoms, (specifically depression, anxiety and suicidality), apathy, attitudes to clinical trials and quality of life. This will be supplemented with clinical care data and trial participation data derived from the individual's CARE-MND register (Clinical Audit Research and Evaluation in MND) record, and MND-SMART data if they choose to also participate in the trial.

After 12 months we will use an additional data request to MND-SMART to explore which of the FIT-P-MND participants also joined the trial, and of these, who remains enrolled in the trial after 12 months. This study will explore how the patient-specific factors, evaluated through questionnaires and clinical data, impacted upon the recruitment to, and retention of, this cohort of people with MND to MND-SMART.

### *4.1.1. CARE-MND Register*

The FIT-Participation-MND project will use CARE-MND to facilitate recruitment, access clinical features, and details of trial involvement for people with MND living in Scotland.

Established in 1989, the Scottish Motor Neuron Disease Register was the first population-based register for MND in the world [22]. In 2015 the register was re-launched as the electronic platform Clinical Audit Research and Evaluation of MND (CARE-MND). This has facilitated detailed longitudinal phenotyping of people with MND in Scotland from diagnosis to death, with allied tissue and brain banks, and a research interest register allowing people with MND the ability to register interest in future observational and interventional studies. [23]. The CARE-MND register has 99% case ascertainment for pwMND in Scotland where there is an incidence of 180-220 new cases a year, and a prevalence of approximately 450 people with MND [23]. FIT-Participation-MND will focus on Scottish participants.

## 4.2. Stages of Study

This study will involve three time-points of data collection, with participants directly involved in the first stage only:

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

## 4.3. Study Timeline

Timeline for the current study was impacted by the COVID-19 pandemic, as non-COVID research and recruitment was temporarily halted. Table 1 provides an overview for key time-points in the study, and projected dates for recruitment and data collection.

*Table 1: Overview of FIT-Participation-MND Study Timeline*

| Key Study Aspect | Actual or Projected Date |
|---|---|
| Favourable ethical opinion obtained | 12th May 2020 |
| Site approval to commence recruitment | 8th July 2020 |

| | |
|---|---|
| Recruitment commences | 10th August 2020 |
| Recruitment planned to close | February 2021 |
| CARE-MND data request | February-March 2021 |
| MND-SMART data request | February-March 2022 |

## 4.4. Recruitment

All individuals on the CARE-MND register who have consented to receive information on studies which they may be eligible for will be invited to participate in FIT-Participation-MND via a postal invitation pack.

Potential FIT-Participation-MND participants will receive this postal pack with information on the study and a Consent Form. They will also be asked to identify a caregiver who would be willing to complete a behaviour questionnaire and they will receive a separate Consent Form and Information Sheet.

Participants can indicate on their Consent Form their preferred completion method; online survey, in-person appointment in Edinburgh, postal or telephone. These options have been selected to maximise accessibility and inclusivity.

## 4.5. Sample Size Considerations

This study will aim to recruit a sample of 130 individuals with a diagnosis of MND.

The required sample size was determined using the primary research objectives, which will be answered using regression analysis. The 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 odds ratio (measure of association between an exposure and an outcome) of 1.70 with power at 0.75 provides a sample size estimate of 126.

There are around 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 will be invited to participate.

Previous research using postal questionnaires in people with MND report response rate of 63% [24]. However, we anticipate that adding the options of completion via online survey or telephone will improve response rates. As a result we expect 130 individuals to be an obtainable sample size, based on a 60% response rate estimate.

Across all Scottish sites the MND-SMART projected recruitment is 100 participants per year, with attrition due to death or withdrawal predicted at 20% annually. We estimate that 80% of the 130 participants in FIT-P-MND will also enrol in MND-SMART, 104 people. Based on projected annual attrition rates of 20% for MND-SMART we expect 80 of these individuals to remain in MND-SMART 12-months later.

As this is an exploratory study, looking at 9 variables (using grouping to simplify analysis and presentation), and a relatively rare condition sample size is based on the number of potential participants available and descriptive analysis methods will be utilised to explore the data.

## 4.6. Study Assessments

Table 2 includes a summary of all study assessments included in FIT-Participation-MND participant and caregiver engagement and data requests. The questionnaire set for people with MND will take around 45 minutes, depending on physical decline and speech impairment, and include three validated questionnaires; HADS, STAI-Y and PHQ-9. FIT-Participation-MND participants will also be invited to questionnaires on quality of life, ALSSQOL-20 and CDC HQOL-4. Finally, participants will be asked to complete the ACT-Q to

evaluate attitudes towards trial participation. Caregivers will be invited to complete the b-DAS to consider behavioural changes of the participant (circa 5 minutes). Questionnaires will take around 50 minutes in total.

Data requests to CARE-MND and MND-SMART for additional data on physical functioning, cognition and clinical phenotype enable us to reduce burden on participants by ensuring brevity in study visits. We will use ALSFRS(R) and ECAS scores from CARE-MND, or MND-SMART if the individual is also a trial participant, to ensure we collect scores closest to the time-point that the FIT-Participation-MND study assessments are undertaken.

*Table 2: Study Assessments, CARE-MND and MND-SMART Data Requests*

| 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) [25, 26] |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [27] |
| | PHQ-9 (9-Item Patient Health Questionnaire) [28, 29] |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [30] |
| | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [31] |
| Study Assessment Questionnaires: Carer/Relative | b-DAS (Brief Dimensional Apathy Scale) [32, 33] |
| CARE-MND Data Request | Clinical phenotype data<br>• Date of Diagnosis<br>• Age at Diagnosis<br>• Classification of MND<br>• Site of Onset<br>• Family History |
| CARE-MND or MND-SMART Data Request | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [14] |
| | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [34] |
| MND-SMART Data Request | MND-SMART recruitment and retention data<br>• Date MND-SMART Participant Information Sheet given<br>• Date of Screening<br>• Date of Randomisation<br>• Date of Withdrawal<br>• Date of Last Appointment if Withdrawn<br>• Reason for Withdrawal if provided<br>• Status (Alive/Deceased)<br>• Date of Death (if Applicable) |

## 4.6. Inclusion/Exclusion Criteria

Table 3 summarises the inclusion and exclusion criteria for people with MND and their caregivers who wish to participate in FIT-Participation-MND. These criteria have been primarily selected to align with the criteria for MND-SMART to ensure maximum overlap in the two participant groups.

*Table 3: Criteria for FIT-Participation-MND Participants and Caregivers*

| **For FIT-Participation-MND Participant with MND** | |
|---|---|
| *Inclusion Criteria* | • Over 18<br>• 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)<br>• Able to provide informed consent (proxy signature accepted if limb dysfunction)<br>• Fluent in English |
| *Exclusion Criteria* | • Diagnosis of Frontotemporal Dementia (FTD-MND)<br>• Unable to provide informed consent<br>• Resident outside Scotland |
| **For Caregiver** | |
| *Inclusion Criteria* | • Able and willing to complete a brief questionnaire regarding the participant's behaviour<br>• Family member, spouse, relative, friend or partner for pwMND<br>• Primary caring responsibilities for pwMND<br>• Fluent in English |
| *Exclusion Criteria* | • Paid carers – excluded to ensure they know the person pre-MND diagnosis<br>• Not fluent in English<br>• Unable to provide informed consent<br>• Diagnosis of MND |

## 4.7. Public and Patient Involvement Statement

PwMND were first involved in the research when they were emailed the ACT-Q, Participant Information Sheet and Consent Form and asked to provide feedback. People with MND were asked to consider the questionnaire structure of the ACT-Q, provide an estimate of the time taken to complete and asked to suggest any additional factors which may influence their attitudes towards trial participation.

PwMND were invited to provide feedback on Participant Information Sheets and Consent Forms, particularly clarity of study aims, and additional aspects of MND which may potentially affect trial participation. Feedback from these individuals was used to refine the list of exploratory covariates in the study, and particularly the items included on the ACT-Q. Time required to participate in the research was based on feedback from patients, existing time-to-complete data for each of the established questionnaires, with additional time for potential communication or physical difficulties.

All participants in the study, who chose to, will be sent a copy of the study findings. PwMND and their caregivers will be consulted regarding the best way to disseminate findings and provide feedback on initial versions of the study summary documents to ensure clarity of presentation and suitability for this audience.

# 5. Analysis Plan

The study questionnaires will be grouped into domains to reduce the number of candidate variables in the analysis as shown in Table 4. The total scores of individual questionnaires will be summed into an overall summary score for each domain, which will be included in the subsequent analysis. As all scores represent the same directionality (higher score indicates greater impairment) a summed score will provide an overall indication of the level of impairment for each individual per grouped domain.

We will present the mean scores for each assessment, displayed in the factor groupings discussed above, with ranges and standard deviation.

*Table 4: Grouping of Exploratory Covariates*

| **Grouping** | **Assessment or Data Included** | **Impairment Thresholds** |
|---|---|---|
| Attitudes | ACT-Q (Attitudes towards Clinical Trial Participation Questionnaire) | Not applicable |
| Quality of Life | CDC HQOL-4 (Centre for Disease Control and Prevention - Health-Related Quality of Life) [31] | Not applicable |
| | ALSSQOL-20 (ALS-Specific Quality of Life Questionnaire-Brief Form) [30] | |
| Cognitive Impairment | ECAS (Edinburgh Cognitive and Behavioural ALS Screen) [34] | • Total score is 136 where a higher score indicates better performance. Scores below 105 are considered abnormal<br>• |
| Behavioural Change | b-DAS (Brief Dimensional Apathy Scale) [32, 33] | Each subscale has a minimum score of 0 (least apathy) and a maximum score of 9 (most apathy)<br>Impairment defined as score per subscale:<br>Executive ≥4<br>Emotional ≥5<br>Initiation ≥6 |
| | ECAS Behavioural Screen Subscale | Carer-Completed Behavioural Change Screen<br>• Indicate Yes/No to symptoms, score 1 for every symptoms present out of 10<br><br>Carer-Completed Psychosis Screen<br>Indicate Yes/No to symptoms, score 1 for every symptoms present out of 3 |
| Physical Functioning | ALS-FRS (R) (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) [14] | Twelve tasks rated from 0 (cannot do) to 4 (normal ability). Summed score between 0 (worst) and 48 (best). |
| Neuropsychiatric | HADS (Hospital Anxiety and Depression Scale) [25, 26] | Maximum total score is 24<br>Total of 12 per subscale<br>(≥9) Severe<br>(7 to 8) Moderate<br>(≤6) Mild |
| | STAI-Y (State-Trait Anxiety Inventory-Form Y) [27] | Total score ranges 20 to 80<br>(≥60) High<br>(40–59) Moderate<br>(20–39) Low |

| | | |
|---|---|---|
| | PHQ-9 (9-Item Patient Health Questionnaire) [28, 29] | Depression:<br>Total score ranges from 0 to 27<br>(20-27) Severe<br>(15-19) Moderately severe<br>(10-14) Moderate<br>(5-9) Mild<br>(1-4) Minimal<br><br>Suicidality:<br>Item 9 scores from<br>(0) Not at all<br>1. Several days<br>2. More than half the days<br>3. Nearly every day<br>Scores of **≥1** indicates presence of suicidal ideation |
| Clinical Phenotype | • MND classification<br>• Site of onset (spinal, bulbar, pure respiratory)<br>• Age at diagnosis | Not applicable |

## 5.1. Scoring the ACT-Q

The Attitudes towards Clinical Trial Participation Questionnaire (ACT-Q) is a brief trial-specific questionnaire to quantify FIT-Participation-MND's attitudes towards involvement in research, and multi-arm clinical trials in particular (Table 5). Developed by the investigators, based upon Kessel's survey [35] & Ellis' tripartite model [17] on factors impacting trial engagement.
Each potential response is 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 will be reverse scored, indicating less agreement with the attitude.

The final aspect of this questionnaire is evaluating FIT-Participation-MND participants' understanding of five key features of design. Respondents will indicate on a 5-point scale to represent level of understanding.

*Table 5: Items of the Attitudes to Clinical Trials Questionnaire (ACT-Q) and Grouping*

| Category | Item |
|---|---|
| Practical Burden | 1) The time commitment required to participate |
| | 2) The distance to the clinic is too far |
| | 3) I already feel I have a lot of appointments |
| Disease Burden | 4) I would not feel well enough to participate because of how my condition affects me |
| | 5) I am concerned about the potential dangers and side effects of trial medications |
| Altruistic Motivations | 6) I may not benefit personally from the development of new drugs |
| | 7) I am worried about the possibility of being assigned to the placebo group |
| | 8) I want to help other people with the same condition as me |
| | 9) I want the opportunity to contribute to research |
| Practical Benefits | 10) I will get additional monitoring of how my condition is changing |
| | 11) I will receive more regular contact with medical staff |
| | 12) I may get to try new medicines which are not available to everyone with my condition |
| Research Engagement | 13) I am already participating in other research projects |
| | 14) I have participated in research before and had a positive experience |

## 5.2. Statistical Analysis

We will use logistic regression to model the impact of the aforementioned independent variables on the FIT-Participation-MND participant's decision to enrol or not enrol in MND-SMART. All variables will be considered in univariate and subsequently multivariable analysis. Results will be presented as odds ratio and 95% confidence intervals.

12 months after the obtaining the questionnaire responses, we will extract participation data from MND-SMART. MND-SMART

We will use univariate and multivariable logistic regression to explore the effect of the aforementioned independent variables withdrawal from the trial at the twelve month time point. Results will be displayed as odds ratios and 95% confidence intervals.

As this is an exploratory study with 9 categories of covariates, we will not be using an adjusted alpha-level to correct for multi-testing. The Bonferroni method of correcting p-values may not be suitable for this analysis as hypotheses are pre-defined, not all variables must be significant to reject the null hypothesis and descriptive statistics will also be of relevant when interpreting the findings [36].

## 5.3. Missing Data

If particular covariates, certain assessments or questionnaires, are not completed fully by the majority of participants, we will consider removing this variable from analysis. Missing data within individual questionnaires will be 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. The covariate of behavioural change will be included where possible.

# 6. Management of Potential Risk

All FIT-Participation-MND participants, and caregivers, will provide informed consent and acknowledge they have read the study information. Participant-facing documentation highlights the voluntary nature of the study and requirements of participation. There are no direct risks involved in participating, however, as some of the questionnaires focus on mental health we acknowledge this may be distressing, clinical teams will be informed of any significant scores. The individual's GP will also be contacted to inform them of study involvement.

A potential issue is fatigue, which may be induced by the length of assessment administration. Participants will be encouraged to inform the researcher if they are experiencing any and the option to complete at home enables participants who have significant issues with physical and mental fatigue to take breaks and complete the questionnaires at their own pace.

Data management and confidentiality of FIT-Participation-MND participants will be managed by assigning Participant ID codes to anonymise responses. Use of identifiable information will be minimised.

# 7. Ethics and Dissemination

This research is co-sponsored by the University of Edinburgh and NHS Lothian. Representatives from the Academic and Clinical Central Office for Research and Development (ACCORD) have reviewed and approved this project. Ethical approval was provided by the West of Scotland Research Ethics Committee 3 on 12th May 2020 (REC Reference: 20/WS/0067).

Only people with MND who have provided prior consent to be contacted about ongoing research on their CARE-MND record will be invited to participate. The Anne Rowling Regenerative Neurology Clinic hosts the register, the data processor at the clinic will contact the potential participants' MND nurse prior to posting recruitment packs.

At the end of the study a lay summary will be sent to the participants, or their nominated representative, for individuals who have indicated they would like to receive one on their Consent Form. The results will be disseminated to the community at engagement events and social media. Fully anonymised data will be uploaded to a persistent DOI at the Open Science Framework; ORCID ID 0000-0001-9843-0778: https://osf.io/fxnwv/. Agreement with this data storage policy is included in the Consent Form. We intend to publish the results of this project in a peer-reviewed journal and presented at academic conferences.

# 8. Author Statement

Each author has contributed significantly to one or more aspects of the study.
EB, SP, SG, JN, RD, AC, SA and SC contributed to study development and design of the protocol. In addition, EB, JN and SP will lead participant recruitment and contribute to data acquisition.
EB SG, JN, SC, SA, AC and SP drafted this work and provided critical revisions and approved the final version of this protocol. In addition, SG provided advice on analysis plans and EB and SP made significant contributions to planned interpretation of the data.

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