Practical Management of Behavioural Impairment in Motor Neurone Disease: MiNDToolkit Feasibility Study

Statistical Analysis Plan (SAP)

Version 1.0

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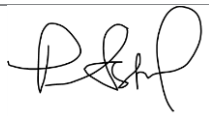
Polly Ashford	Trial Manager		23/05/2023

SAP REVISION HISTORY

Document Name	Version No.	Reason for Revision	Effective Date

PURPOSE:

The Statistical Analysis Plan (SAP) is consistent with the guidance provided by Gamble et al., *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials*, JAMA;2017:318;2337-2343. It provides details of the analyses to be carried out for this study prior to any analyses being performed.

RESPONSIBILITY:

The Trial Statistician is responsible for the writing and maintenance of the SAP but may delegate responsibilities to other, appropriate, team members. The plan should be written in collaboration with the Chief Investigator and Trial Manager both of whom should approve the plan.

1.0 Administrative Information

Sponsor :	University of East Anglia
Sponsor Reference :	R202920
Funder :	Motor Neurone Disease Association
Funder Reference :	Mioshi 934-794
Trial Registration :	ISRCTN15746123
Trial Identifier :	N/A
NRES :	19/LO/0692 Queen Square REC
IRAS:	260290
Chief Investigator :	Eneida MIOSHI
Trial Statistician :	Lee SHEPSTONE
UKCRC Trials Unit :	Norwich CTU
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2.0 Introduction

2.1 Background and Rationale

Motor Neurone Disease (MND) is known to affect the motor system and other circuitry in the central nervous system. It is well established that up to 15% of people with MND can develop Frontotemporal Dementia (FTD), displaying complex changes in 'personality'/behaviour and cognitive functioning (i.e. planning, concentration and language ability). There is evidence that MND patients can also present with non-motor symptoms, which are defined as cognitive and behavioural changes or impairments, even without full-blown MND-FTD (MND combined with FTD). Furthermore, the National Institute for Health and Care Excellence (NICE) MND guidelines published in February 2016, place an emphasis on the importance of non-motor cognitive and behavioural symptom assessment in the scope of disease management (NICE, 2016a). This is further supplemented with new publication of diagnostic guidelines for MND-FTD, with a stronger emphasis on detection of cognitive and behavioural symptoms that could occur in up to 50% of MND patients (Strong et al., 2017), known as MND with cognitive impairment and/or behavioural impairment.

There are multiple, quick and effective screening methods available for cognitive and behavioural impairment in MND, which have been noted in a systematic review of literature (Simon & Goldstein, In Press). These include the Edinburgh Cognitive and behavioural ALS Screen (ECAS; Abrahams et al., 2014), ALS Cognitive Behavioral Screen (ALSCBS; Woolley et al., 2010), Mini-Addenbrooke's Cognitive Examination (Mini-ACE; Hsieh et al., 2015) and Motor Neuron Disease Behavioural Instrument (MiND-B; Mioshi et al., 2014). With these tools, there is increased awareness, more routine assessment and improved detection of cognitive and behaviour changes in MND for healthcare professionals (HCPs). A recent systematic review showed that behavioural impairment (such as lack of motivation or impulsivity) were associated with increased burden (de Wit et al., 2018). Earlier research has shown that behaviour, as well as cognitive impairment, impacts burden in family members (e.g. Burke et al., 2015; Watermeyer et al. 2015). In dementia, impairments relating to cognition or behaviour are manageable through codes of practice applicable to specialist clinics and community teams (NICE, 2016b). Therefore, it is timely to explore tools that might help manage these impairments for both families and HCPs in MND.

The MiNDToolkit was created for management of behavioural impairment in MND. This Toolkit was comprehensively created through surveying research literature and multiple consultations with allied HCPs (e.g. Occupational Therapists, Speech and Language Therapists, Specialist Nurses), internationally expert clinicians, international expert researchers, family members of people living with MND-FTD and also people living with MND.

For carers, the MiNDToolkit comprises several psychoeducational online modules that are tailored for the symptoms they are dealing with. For HCPs, the MiNDToolkit is a composition of tools inclusive of educational information, structured interactive clinical reasoning and techniques for management of behavioural change of people with such impairments or MND-FTD.

2.2 Trial Objectives

Before conducting a large-scale randomized controlled trial of the MiNDToolkit as an intervention, it is important to answer the question “Can this study be done?” (NIHR, 2019). Therefore, there is need for a feasibility study to inform the design of future trials.

This feasibility study aims:

1) To test the feasibility of the MiNDToolkit online intervention in MND Specialist Settings;

2) To explore the potential of several outcome measures for future evaluation studies (trials).

3.0 Study Methods

3.1 Trial Design

This study is a pilot, small-scale, open-label, randomised controlled trial to determine the feasibility of the MiNDToolkit for use by carers (family carer/relative/live-in professional carers) with optional support from HCPs.

3.2 Allocation

After completion of pre-intervention assessments, eligible participants will be randomized by the Norwich CTU, using a randomisation table provided by the study statistician. Participants will be allocated to either the MiNDToolkit intervention group or usual care group, the control group. The platform will automatically notify MiNDToolkit-trained HCPs at sites of participants assigned to the MiNDToolkit intervention group.

3.3 Sample Size

The sample size is not based upon any statistical considerations but upon practical considerations and typical sample sizes for feasibility studies. The MiNDToolkit intervention will involve up to 30 carers (family carer/relative/live-in professional carer) of people with MND, with additional behavioural impairments. This requires 2 to 3 participants per site.

3.4 Interim analyses and stopping guidance

No formal interim analyses or stopping rules based upon efficacy are planned.

3.5 Timing of outcome assessments

Assessments will be made at baseline prior to randomization and post intervention (within one month of the end of the intervention period of 3 months).

4.0 Statistical Principles

4.1 Treatment Adherence

No definition of treatment adherence is provided and no definition is required to define any analysis population. Assessing adherence is an objective of the study.

4.2 Protocol deviations

All major deviations from protocol will be recorded and should be reported as part of the study output. These may inform the design of a future trial.

4.3 Analysis populations

All participants randomised to the study will represent the study population for analyses related to efficacy outcomes and follow-up, excluding any participants who withdraw and do not provide or agree to use of relevant data. An Intention-to-Treat (ITT) approach will be used when making group comparisons as an estimate of intervention effect.

5.0 Trial Population

Potential participants are carers of people with MND with additional behavioural symptoms. For more details see eligibility section below. Participants are identified nationally. The intention is to secure 10 sites across England and Wales.

5.1 Screening data

Participants complete the screening and baseline assessment questionnaires online. Some measures (e.g. ALSFRS-R adapted) are modified in terms of sentence construction, as they are being completed by the carer.

This assessment will include the Motor Neuron Disease Behavioural Instrument (MiND-B; Mioshi et al., 2014).

Additional information to characterize the screened group includes:

- Carer socio-demographic details.
- ALS-Functional Rating Scale Revised (ALSFRS-R; Cedarbaum et al., 1999), adapted for completion by carer.

5.2 Eligibility

Eligibility to the study is decided based upon the following entry criteria.

5.2.1 Inclusion Criteria:

1) Participants are family carers, relatives or live-in professional carers of:

• Patients with a diagnosis of MND with cognitive impairment or behavioural impairment, based on Strong et al. (2017) diagnostic criteria, or

• Patients with a diagnosis of MND-FTD based on Strong et al. (2017) diagnostic criteria.

2) Carers will have at least 7 hours of contact with the person with MND per week and be willing to participate in research activities.

3) Carers must be aged 18 years or over.

5.2.2 Exclusion Criteria:

1) Inability to read or communicate in English (with or without support).

2) Participant is a carer of a patient who already has a carer recruited into the study.

5.3 Recruitment and participant flow

Figure 1 indicates the pre-trial planned participant flow.

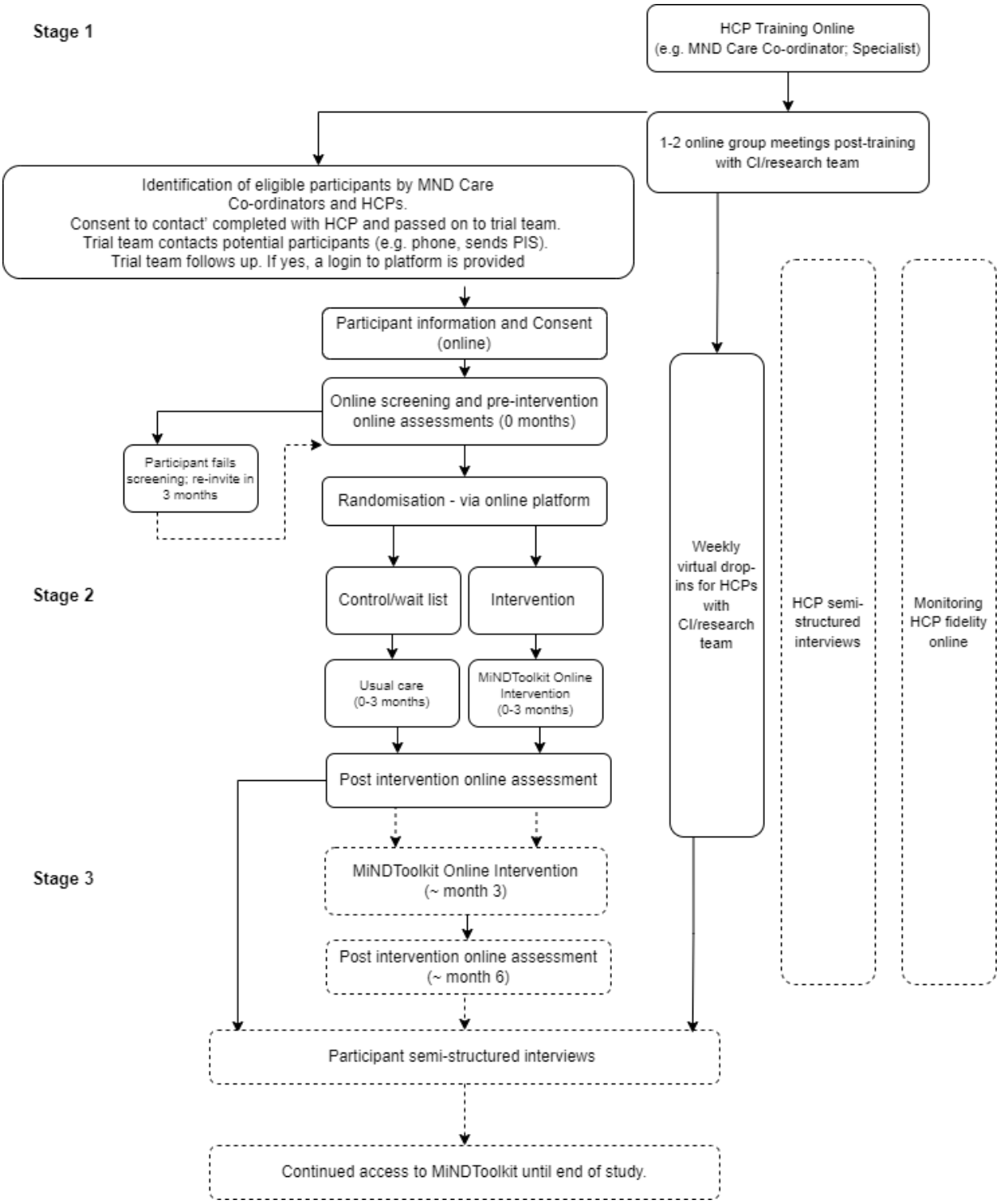

Figure 1: Participant Flow

5.5 Baseline participant characteristics

The characteristics of all participants at baseline will be compared between treatment group. No formal hypothesis testing will be carried out.

The following characteristics will be summarised using descriptive statistics:

- Demographic details.
- Person with MND clinical phenotype.
- Information regarding care provided by the carer.
- The Patient Health Questionnaire 9 (PHQ-9; Kroenke et al., 2003) for the carer.
- The Generalized Anxiety Disorder Questionnaire 7 (GAD-7; Kroenke et al., 2007) for the carer.
- The Carer Experience Scale (CES; Al-Janabi et al., 2008).
- ICEpop CAPability measure for Adults (ICECAP-A; Al-Janabi et al., 2012) for the carer.
- Acceptance and Action Questionnaire II (AAQ-II; Bond et al., 2011).
- Motor Neuron Disease Behavioural Instrument (MiND-B), with additional FRS adapted questions

5.6 Withdrawal information

Where possible, the time and reason for withdrawal from the study will be ascertained and reported. Reasons may be grouped and frequencies reported by treatment group.

6.0 Analysis

6.1 Framework and levels of statistical significance

Statistical analyses will use a classical frequentist approach. Statistical significance will be set at the conventional two-sided 5% level. Confidence intervals will be of corresponding 95% size.

6.2 Outcomes

No primary efficacy outcome is defined and the main outcomes of interest will relate to trial feasibility.

6.2.1 Feasibility Outcomes

Feasibility outcomes will be collected to enable an estimation of key parameters to inform a future trial, and to provide preliminary information about the impact of the intervention. These are:

- Numbers of potentially eligible participants.
- Number of participants subsequently recruited into the study.
- Attrition rate and reason for withdrawals.
- Use of the MiNDToolkit by carers:
    - engagement with the platform: number of times assessed;
    - length of time spent logged in;
    - which modules have been repeated and frequency of replay.

- Use of the MiNDToolkit by HCPs:
    - frequency of use,
    - duration and time taken;
    - which modules have been repeated and frequency of replay.

- Completion of online outcome measures:
    - time to completion;
    - number of non-completed outcomes (i.e. 'abandoned' before completion)

6.2.2 Efficacy Outcomes

The following outcome efficacy variables, all related to the carer of the person with dementia, are collected within one month of the end of the intervention.

- Patient Health Questionnaire 9
- Generalized Anxiety Disorder Questionnaire 7
- Carer Experience Scale
- ICEpop CAPability measure for Adults

6.3 Analysis Methods

The primary set of analyses will be related to the feasibility information on participant 'flow' and outcome data availability to inform the design of a future trial. Numbers of eligible participants, recruitment, and attrition rates will be compared with those of published studies in MND interventions, to evaluate if the MiNDToolkit was well accepted by families and professionals, and feasible for professionals. Formally, we will estimate, where possible, each rate with an associated 95% confidence interval. Of note, current published studies may not provide the ideal estimates for comparison to our proposed study, given the differences in the nature of the intervention. For this reason, we will have a cautious approach in the interpretation of attrition rates for the MiNDToolkit.

The distribution of each measure will be inspected to assess the possibility of 'ceiling' or 'flooring' effects, which would make an outcome inappropriate for a trial. The standard deviation, for Normally distributed variables, will be estimated with 95% confidence intervals, for use in future sample size calculations.

In addition, initial estimates of efficacy will also be provided. These will be estimated as between-group differences from a general linear model with appropriate link function and error distribution. Each model will include the baseline value of the outcome variable at baseline where available.

A number of individuals continued to access the online toolkit post the main follow-up time point and complete questionnaires. These will also be summarized but not included in any estimate of efficacy.

6.4 Missing Data and Invalid data

Trial questionnaires are completed online and a participant cannot 'advance' from one item until it is completed. However, it is possible for a participant to abandon entry online and not complete all questionnaries. The proportion doing this will be calculated together with a 95% confidence interval. Also, not all online entry was completed within the intended 30 days of six month follow-up. The number falling outside of 30 days will be calculated, again with a 95% confidence interval.

6.5 Additional analyses

Currently no additional subgroup or sensitivity analyses are planned.

6.5 Software

Statistical analyses will be carried out using SAS version 9.4.

7.0 References

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