COMMEND

Full study title:

A randomised controlled trial of Acceptance and Commitment Therapy for people with motor neuron disease (COMMEND)

Short study title:

An RCT of ACT for people with MND (Phase 2: RCT)

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Authorised by:

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Sheffield Clinical Trials Research Unit (CTRU)

A randomised controlled trial of Acceptance and Commitment Therapy for people with motor neuron disease

An RCT of ACT for people with MND (Phase 2: RCT)

This document describes a trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

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Abbreviations

AE	Adverse Event
ACT	Acceptance and Commitment Therapy
ALS	Amyotrophic Lateral Sclerosis
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
HRA	Health Research Authority
MND	Motor Neuron Disease
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
PPI	Patient and Public Involvement
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust

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Protocol version history

Version number	Date	Protocol update finalised by (insert name of person):	Reasons for update
2	15.04.19	Rebecca Gould	Feedback from Research Ethics Committee, Trial Steering Committee and Data Monitoring and Ethics Committee
2.1	19.06.19	Rebecca Gould	Minor clarifications
2.2	30.03.20	Rebecca Gould	Amendment to therapy delivery relating to Covid-19
3.0	22.05.20	Rebecca Gould	Amendment for remote consent, eligibility and baseline assessments relating to Covid-19. Amendments to protocol, supporting documents.
3.1	10.06.20	Rebecca Gould	Minor clarification relating to Covid-19
3.2	23.09.22	Rebecca Gould	Minor clarifications

Trial summary

Motor neuron disease (MND) is a rapidly progressive, fatal neurological disease with no known cure. It affects parts of the brain and spinal cord, and results in loss of the ability to move, speak, swallow and breathe. Many people with MND experience distress due to the disease's nature, impact and outlook.

The COMMEND project will adapt a psychological therapy called Acceptance and Commitment Therapy (ACT) for people with MND and assess whether, along with usual multidisciplinary clinical care, it improves their psychological health in comparison to usual care alone. ACT is a form of psychological therapy that helps people to learn new ways of handling distressing thoughts and feelings. It also helps people to develop ways of taking part in activities that are important and meaningful to them.

Phase 1 of the project involved developing ACT for people with MND through a series of workshops and interviews with people with MND, their caregivers and healthcare professionals who work with them. Following this an open uncontrolled feasibility study was conducted to test the acceptability and feasibility of the newly developed intervention.

Phase 2 of the project is a randomised controlled trial (RCT) of the newly developed intervention, and is outlined in this protocol. We will recruit people with MND for 20 months at approximately 14 sites. We intend to recruit 188 people with MND overall. Participants with MND will be randomised to receive either ACT plus usual multidisciplinary clinical care or usual multidisciplinary care alone. The primary caregivers of participants with MND will also be invited to take part in the study. Participants with MND in both arms will complete a series of questionnaires at the outset, 6 months and 9 months. Caregivers will also complete a series of questionnaires at the outset, 6 months and 9 months. The primary outcome measure for participants with MND is psychological health as measured by the total score on the McGill Quality of Life Questionnaire-R[1,2,] at 6 months post-randomisation. Qualitative data will be collected from participants with MND and study therapists, who will complete an anonymous satisfaction questionnaire to further examine the acceptability and feasibility of the intervention (or usual multidisciplinary care for both intervention and control arms).

1. Introduction

1.1 Background

The problem: MND is a rapidly progressive, fatal neurodegenerative disease predominantly affecting motor neurons from the motor cortex to the spinal cord, causing progressive wasting and weakening of bulbar, limb, abdominal and thoracic muscles. Prognosis is poor in MND and median survival is 2-3 years following onset: only 4-10% survive more than 10 years[3–5]. There is no cure, and riluzole, the sole disease-modifying UK-licensed drug, prolongs median survival for only 2-3 months at 1 year[6]. Unsurprisingly, prevalence rates of 44% for depression and 30% for anxiety have been observed, with MND being found to be the most frequent cause of assisted suicide[7–9]. Although shorter survival times, poorer quality of life and increased risks of suicide and mortality have been reported in those experiencing psychological distress[10–14], guidance on improving the psychological health of people with MND is lacking.

How psychological health is currently managed in people with MND: Formal psychotherapy is not routinely part of standard care within services for people with MND, even in MND Care Centres/clinics. While the value of informal psychosocial support is highlighted in NICE MND guidelines, particular psychological therapies or approaches are not specified[15]. People with MND may be able to access formal psychological therapies such as Cognitive Behavioural Therapy through Improving Access to Psychological Therapy services[16]. However, typically these cannot meet their specific psychological, physical and communication needs in a timely fashion due to issues such as the rapid disease course and mobility problems limiting access.

How the problem will be addressed: A manualised psychotherapy intervention based on ACT[17] has been developed specifically for people with MND through a series of qualitative workshops and individual interviews (approved by University College London (UCL) Research Ethics Committee on 1/12/2017, ref. 12213/001). The feasibility and acceptability of delivering the intervention to this population within the NHS has been assessed in an open uncontrolled feasibility study (approved by London – Dulwich REC on 12/03/2018, ref. 18/LO/0227). We will now assess the clinical and cost effectiveness of adapted ACT, modified for people with MND, plus usual multidisciplinary care vs. usual multidisciplinary care alone for improving psychological health in people with MND in an RCT with an internal pilot phase.

1.2 Rationale

Why ACT is being proposed: ACT is an acceptance-based behaviour therapy[17] with a strong evidence base for improving outcomes (such as functioning, quality of life and mood) in chronic pain[18], and a growing evidence base in chronic disease[19] and mental health[20] contexts. It is an alternative form of psychological therapy to traditional therapies such as Cognitive Behavioural Therapy, taking a different approach to difficulties and using different therapeutic techniques[21]. Cognitive Behavioural Therapy is focused on alleviating distress or symptoms, and involves changing how one thinks and behaves in emotional situations. It is conventionally offered for common mental health problems following NICE clinical guidelines[16]. The phrase "catch it, check it, change it" in relation to negative thoughts captures the essence of conventional Cognitive Behavioural Therapy. In contrast, ACT is focused on increasing personally meaningful behaviour in the presence of distress and symptoms (though distress or symptoms may improve as a by-product of therapy). Consequently, it uses a variety of methods to increase a person's willingness to experience uncomfortable or difficult thoughts and feelings so that they can do things that are important to them. These methods include helping people to: i) become more aware of their experiences and focused on the here-and-now rather than dwelling on the past or worrying about the future; ii) be more open to and accepting of their experiences rather than engaging in ineffective struggles or fighting with them; and iii) commit to doing things guided by what really matters to them rather than by things they want to avoid. The phrase "*A*ccept your experiences and be present, *C*hoose a meaningful direction for your life, and *T*ake action" sums up ACT in a nutshell.

It has been argued that ACT is particularly suited to improving outcomes in objectively difficult or immutable situations, such as living with MND and other chronic diseases[22–26]. As it is not possible to cure people with MND, helping them to adopt a focus on what is possible and live their life as best they can is likely to be a more pragmatic approach than trying to control or get rid of distressing or difficult experiences. Furthermore, it has been argued that ACT may better meet the needs of people with disabling long-term conditions and life-limiting illnesses such as muscle disorders and cancer than conventional Cognitive Behavioural Therapy for several reasons[22–26]. First, ACT therapists are not

required to challenge negative thoughts or solve problems as in conventional Cognitive Behavioural Therapy. This is especially relevant in MND because multiple losses (e.g. health, roles and aspirations), unsolvable problems and a stark prognosis may render such techniques ineffective and reduce engagement with therapy. Second, psychological flexibility (akin to coping in conventional Cognitive Behavioural Therapy), which is a fundamental component of psychological health that ACT aims to enhance[27,28], predicts quality of life, mood and adjustment in MND and other progressive and incurable conditions[29,30]. Third, there is emerging preliminary evidence that ACT might have advantages over conventional Cognitive Behavioural Therapy through improved engagement, retention and durability of effects[31–34]. Fourth, ACT includes mindfulness techniques (not used in conventional Cognitive Behavioural Therapy), and there is evidence suggesting that meditation and mindfulness-based approaches are beneficial for people with MND[35,36]. ACT, with its inclusion of behavioural change and motivation-based techniques, as well as mindfulness- and acceptance-based techniques, may be even more beneficial for people with MND than mindfulness-based approaches alone.

Why this research is needed now: A recent systematic review of psychotherapy for people with MND[37] identified four studies that have been conducted to date[38–42]: an RCT of expressive disclosure vs. no disclosure with no therapist input (N = 48); a non-randomised controlled trial of counselling Cognitive Behavioural Therapy vs. no intervention (N = 54); and two uncontrolled studies of life review (N = 29) and hypnosis (N = 8). Although small short-term gains in wellbeing were observed in three of the studies, benefits were not maintained at follow-up or were not assessed, and none assessed the cost-effectiveness of the interventions. Furthermore, the quality of completed studies was variable, but generally poor. A few studies have since been published - a prematurely stopped multicentre RCT of Cognitive Behavioural Therapy vs. usual care (N = 15;[43]) and a protocol and qualitative study of meditation training[35,36] - but none of these have examined ACT.

ACT has been applied to a wide range of mental and physical health conditions relevant to people with MND, including muscle disorders, chronic pain, anxiety and depression, with beneficial effects being reported[18,19,26,44,45]. Systematic reviews of ACT have indicated promising post-intervention improvements in outcomes (e.g. functioning, quality of life, mood) for a range of chronic diseases, life-limiting illnesses, and long-term conditions[18,19]. However, there have been no trials of ACT for MND and trials of ACT for some conditions are limited to case series or small feasibility RCTs – meaning that it cannot be generalised from other conditions that ACT will be effective in MND. Nonetheless, the potential utility of an ACT approach in MND is highlighted by previous empirical work demonstrating that ACT processes (such as psychological flexibility - akin to coping in Cognitive Behavioural Therapy) predict functioning and quality of life in MND[29] and other progressive, incurable, life-limiting conditions: muscle disorders[30,46,47], Duchenne muscular dystrophy[48], and palliative care populations[49]. Indeed, it has been found that even those with illnesses at their most advanced and disabling stage can still find ways to undertake personally meaningful activity, even while holding negative beliefs about their condition, situation or prognosis, and such a focus appears to engender a better quality of life[30,46,47].

2. Aims and objectives

2.1 Aims

To determine the clinical and cost effectiveness of ACT, modified for people with MND, plus usual multidisciplinary care in comparison to usual multidisciplinary care alone for improving psychological health in people with MND.

2.2 Objectives

1. To establish the clinical and cost effectiveness of ACT plus usual multidisciplinary care for people with MND compared to usual multidisciplinary care alone, via an RCT with an internal pilot phase.

2. To evaluate the effect of ACT plus usual multidisciplinary care for people with MND compared to usual multidisciplinary care alone on caregivers of people with MND.

3. To examine perceived mechanisms of impact and the context in which the intervention is delivered by collecting qualitative data from people with MND and study therapists.

3. Trial design

COMMEND is a multi-centre, parallel, 2-arm RCT with outcome assessors intended to be blind. The RCT will include a 10-month internal pilot phase to assess the feasibility of referral rates and acceptability of randomisation. The stop/go criteria are defined as recruitment of 71 people with MND (or 0.51 people with MND per site per month), with ≥70% of participants in the ACT arm completing at least 2 sessions. Recruitment to the RCT is expected to start in July 2019 and will continue until February 2021. Participant follow-up will continue until November 2021.

4. Selection of participants

4.1 Eligibility criteria

4.1.1 Inclusion criteria

For participants with MND:

1. Aged 18 years and over.
2. Diagnosis of definite, laboratory-supported probable, clinically probable, or possible familial or sporadic ALS (which is diagnostically synonymous with MND[50]) using the World Federation of Neurology's El Escorial criteria[51], and additionally the Progressive Muscular Atrophy (PMA) and Primary Lateral Sclerosis (PLS) variants where appropriate investigation has excluded mimics of MND.

It should be noted that all people with MND will be eligible to participate with respect to the presence or absence of mood symptoms, irrespective of whether they are currently experiencing symptoms of depression or anxiety.

For caregivers:

1. Aged 18 years and over.
2. Primary informal caregiver of a person with MND who has consented to participate in the trial (either living with the person with MND or a close family member or friend).

For study therapists:

1. Aged 18 years and over.
2. Therapists who are involved in delivering the intervention to people with MND in the trial.

4.1.2 Exclusion criteria

1. Need for any form of gastrostomy feeding or non-invasive ventilation (NIV). That is, if a participant has a current clinical need then they will not be eligible to participate. For the RCT, a clinical need is defined as the participant being dependent upon percutaneous endoscopic gastronomy to meet all their nutrition and hydration needs, or meeting the NICE criteria for the offer of a trial of non-invasive ventilation as defined in NICE Guidance NG42, section 1.14.17([15]). (These are markers of significantly reduced life expectancy and more advanced disease stage, and hence an indicator that participants might not survive the duration of the study.) Potential participants who use PEG feeds or receive NIV at earlier points in the disease course because of local practice or for reasons other than their MND diagnosis should not be excluded.
2. Diagnosis of dementia using standard diagnostic guidelines (e.g. [52,53]). (This would impede engagement with the intervention.)
3. Currently receiving ongoing formal psychological therapy delivered by a formally trained psychologist or psychotherapist, and unwilling to refrain from engaging in such formal psychological therapy during the receipt of ACT. (Concurrent engagement may lead to conflicts in therapeutic approaches and goals.)
4. Insufficient understanding of English to enable engagement in ACT and completion of screening measures and patient-reported outcome measures. (Translators will not be employed due to difficulties inherent in ensuring adequate translation of discussions in therapy sessions,

therapy materials, screening measures and outcome measures, insufficient time within the study time frame for materials to be translated, and unpredictable availability of interpreters.)
5. Lacking capacity to provide fully informed written consent, verbal consent (for those who cannot provide written consent), or consent via the use of a communication aid.
6. Need for treatment for severe psychiatric disorder such as schizophrenia or bipolar disorder, or expressing suicidal ideation with active plans/suicidal behaviours and imminent intent (hereafter defined as reports of plans to end one's life within the next 2 weeks). (Other forms of treatment would be indicated in such instances.)
7. Other medical factors that could compromise full study participation such as intellectual disabilities or severe sensory deficits (e.g. visual blindness).
8. Previous participation in Phase 1 of COMMEND (feasibility study).

It is common to include a psychotropic drug stabilisation period as one of the inclusion criteria for those who are prescribed psychotropic medications in psychotherapy studies (e.g. a stable dose for at least two months). This is in order to allow for spontaneous recovery, and to control for the potential confound of pharmacotherapy on mental wellbeing. However, this will not be included in the current trial given that it can often take a number of months before a stable dose is achieved. This could have a negative impact on recruitment if potential participants were unwilling to wait for drug stabilisation to occur before receiving psychotherapy. Instead, all psychotropic drug use will be monitored during the course of therapy.

4.2 Approach

For participants with MND and their caregivers:
Both people with MND and their caregivers, where applicable, will be approached about the study. Absence of a participating caregiver will not preclude a person with MND taking part. Potentially eligible participants will be recruited from approximately 14 MND Care Centres/clinics. They will be identified and approached about the trial in one of four ways.

1. Clinicians will approach potentially eligible participants with MND and their caregivers attending routine clinic appointments at the MND Care Centres/clinics about the trial using the patient and caregiver information sheets (which can also be sent to them prior to their appointment by the clinicians).
2. Clinicians from MND Care Centres/clinics will identify potentially eligible participants with MND and their caregivers from clinic databases, and a trial invitation letter and patient and caregiver information sheets will be sent to them. Prior to sending the trial information, clinicians may call the participants to gauge levels of interest as to whether they would like to receive information about the trial. The information sent in the post will include details of how patients and caregivers can discuss the trial further with a member of the local research team or a research nurse from the local Clinical Research Network. The clinicians from MND Care Centres/clinics will follow up the information sent in the post via a telephone call approximately one week later.
3. Potential participants with MND who have provided consent for contact about ongoing research studies will be identified by clinicians from clinic databases (where this information is available), and then contacted by a member of the local research team or a research nurse from the Clinical Research Network.
4. Leaflets will be distributed in MND Care Centres, neurology clinics, and community support groups for people with MND, and advertisements will be posted on online MND-related fora (e.g. MND Association Forum). In addition, the study will be promoted through talks and presentations at meetings in MND Care Centres/clinics and local support groups for people with MND.

Once potential participants with MND and their caregivers have been identified, consent for contact will be sought by the clinician (either verbally or with the use of a communication aid). If consent is obtained, a member of the local research team or a research nurse from the Clinical Research Network will contact them to discuss the trial further (either in the clinic or patient's home, or via telephone or videoconference, depending on patient preference). The trial will be described to them and patients with MND and their caregivers will be given the opportunity to ask any questions or discuss any concerns. If they express an interest in participating in the trial then they will be given a patient or caregiver information sheet, if they do not already have one. They will then be given as long as they feel is needed to consider the information prior to being contacted by a member of the local research team or a research nurse from the Clinical Research Network to determine whether they are still interested in participating

in the trial. Participants will also be asked if they are planning on leaving the country for an extended period of time in the next 9 months. If they are, then they will be advised that they should delay engagement in the study until they return to the UK. This is in order to maximise their chances of receiving the intervention within 6 months (if randomly allocated to the treatment arm) and completing outcome measures at 6- and 9-month follow-up.

If participants with MND and their caregivers are interested in taking part in the study then they will be invited to attend a screening appointment with a member of the local research team or a research nurse from the Clinical Research Network (either in person in the clinic or patient's home, by telephone, or by videoconference, depending on patient preference). Eligibility for inclusion in the trial will be determined during the screening appointment, and fully informed consent will be sought from eligible participants.

For therapists:
Therapists will be recruited from the group of study therapists who will be involved in delivering the intervention to people with MND. They will be approached about completing the qualitative satisfaction questionnaire by a research assistant based in the central study team. If they express an interest in completing the qualitative satisfaction questionnaire then the research assistant will discuss this with them via telephone or email, depending on therapist preference. Completion of the qualitative satisfaction questionnaire will be described to them and therapists will be given the opportunity to ask any questions or discuss any concerns. If they express an interest in participating in this aspect of the trial then they will be given a therapist information sheet. They will then be given as long as they feel is needed to consider the information prior to being contacted by the research assistant to determine whether they are still interested in completing the qualitative satisfaction questionnaire. Fully informed consent will be sought from therapists wishing to complete this.

Recruitment of participants with MND, their caregivers and study therapists at a site will only commence when the study has:
ii) Received Health Research Authority (HRA) approval;
ii) Received confirmation of capability and capacity from the participating NHS Trust;
iii) Received the green light from the Sponsor (or its delegated representative).

4.3 Informed consent procedures

Participants with MND, their caregivers and therapists will be consented in line with the Sheffield Clinical Trials Research Unit (CTRU) Informed Consent Standard Operating Procedure (SOP) (SSU001). All potential participants (patients, caregivers and study therapists) will be given a relevant information sheet and will have the opportunity to discuss the trial, ask questions and request further information for as long as needed before being asked to provide fully informed written consent, verbal consent (for those who cannot provide written consent, or if verbal consent is being obtained by telephone or videoconference), or consent via the use of a communication aid. An independent witness will be asked to sign the consent form to verify the consent taken in all cases where non-written consent is obtained in-person.

Where verbal consent is obtained by telephone or videoconference, the researcher will read each statement from the consent form and ask the potential participant (patient, caregiver or study therapist) to state whether or not they consent to the statement. The researcher will initial each box where consent is agreed. A copy of the consent form will be sent to the potential participant, along with the relevant information sheet, so that they can also read the statements as they are being read out aloud. Once all statements have been agreed to, the potential participant will state their name and the date will be stated by the researcher obtaining consent. With the potential participant's agreement, the conversation regarding consent will be audio recorded using an encrypted digital voice recorder either by the researcher, or by a member of Sheffield CTRU staff joining the call. Once the researcher has signed the consent form, a copy will be sent to the participant for their records, and the encrypted audio file will be uploaded to a secure server within Data Safe Haven. This is a system that satisfies the highest level of security requirements of NHS trusts.

A different consent procedure will be used in cases where the potential participant is unable to provide written consent due to physical limitations, and it is not possible for an independent witness to verify the consent in person (for example, due to the patient and/or caregiver shielding from Covid-19). In these

cases, where consent is provided by videoconference using a communication device without speech output, an independent witness will verify consent for each statement by observing the text output from the potential participant's communication device by videoconference, and providing a verbal confirmation. This verbal confirmation will be audio recorded using an encrypted digital voice recorder. The independent witness will state their name and the researcher will state the date and the name of the participant. The researcher will initial each box where consent is agreed, sign the consent form and send a copy to the participant.

If a person with MND who uses a communication device is unable to provide written consent due to physical limitations AND they do not have access to the internet (and so cannot provide consent via videoconference or digital consent), then a teleconference will be set up between the person with MND, their carer, an independent witness and a member of the research team. Verbal consent will be audio recorded using an encrypted digital voice recorder. Confirmation of consent by the independent witness and documenting of consent will be completed as described in the preceding paragraph.

To accommodate the varying physical limitations of the participant group, two options to provide digital consent will be offered if this is the preference of the person with MND. Following a consent appointment by telephone or videoconference, a digital consent form will be emailed to the potential participant, who can complete the form electronically, provide a simple digital signature in the form of a typewritten signature and return the form to the researcher by email. Alternatively, they will be emailed an individualised link to an online consent form which can be completed using the same method and submitted online. Finally, those participants who do not have access to the internet will be able to sign a paper copy of the consent form and return to a member of the research team via post.

Fully informed written or verbal consent to participate in the trial will also be sought from the caregiver of the person with MND and study therapists using the procedures listed above. The information sheets can be provided to the participant and caregiver at the same time; however, consent from the participant must be obtained prior to the caregiver providing consent. If there is no caregiver or the caregiver decides not to take part, this will not affect whether the person with MND can participate in the trial.

Participants with MND, their caregivers and therapists will be asked to provide consent in accordance with the Mental Capacity Act (2005). It is expected that potential participants will be able to provide informed consent for participation, provided that appropriate time and care has been taken by the member of the local research team or research nurse from the Clinical Research Network to explain the research, and that the potential participant has sufficient time to make a decision and communicate this. Participants will not be included in the study if they are unable to provide fully informed consent for participation. It will be explained that participants are under no obligation to enter the trial and that they can withdraw at any time, without having to give a reason and without their subsequent care or legal rights being affected. It will be made clear to participants that no disadvantage will accrue if they choose not to participate in the trial. It is not expected that participants will lose the capacity to provide informed consent during the course of the trial. If they do, then they will be withdrawn from the trial. Current guidance from the British Psychological Society on evaluation of capacity when seeking consent will be followed, which is regarded as a continuing process rather than a one-off decision. Willingness to continue participating will be continually checked through discussion with participants during the trial.

It will be the responsibility of the Principal Investigator, or a person delegated by the Principal Investigator, to obtain written or verbal informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards. The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the Principal Investigator/Co-Investigator on the delegation of tasks. It must be recorded in the medical notes when the participant information sheet has been given to participants with MND. Capacity to provide consent will be determined at the screening and baseline assessment. No trial procedures will be conducted prior to the participant giving consent to participate in the trial. Screening and baseline assessments will only be completed after fully informed consent is given by the participant (either via written consent, verbal consent, or consent via the use of a communication aid). A copy of the signed consent form will be given or sent to the participant. The original signed form will be retained in the trial file at the recruitment site and a copy of the participant with MND's form will be placed in the medical notes.

5. Assignment of interventions

5.1 Sequence generation

Participants with MND will be allocated in equal proportions to one of the two groups using a computer generated pseudo-random list. Randomisation will use blocks of varying length, stratified by recruitment site.

5.2 Allocation concealment

The allocation sequence will be hosted by the Sheffield CTRU in accordance with their standard operating procedures and will be held on a secure server. Access to the allocation sequence will be restricted to those with authorisation. The sequence will be concealed until recruitment and data collection are complete. Allocation concealment will also be achieved by requiring the details of participants with MND to be entered onto the system before the randomly allocated treatment is revealed.

5.3 Implementation

A CTRU statistician will supply the allocation ratio (1:1) and block sizes to the CTRU randomisation system, but neither statistician nor other trial team members will be able to view the randomisation list during the trial. Once the eligible participant with MND provides fully informed consent and baseline measures have been taken, the participant will be randomised. A member of site staff, signed onto the delegation log (not the blind outcome assessor at the site), will log into the remote, secure internet-based randomisation system and enter basic demographic information, after which the allocation will be revealed. Participants with MND and their GPs will be informed of the allocation by telephone, letter or face to face by the member of site staff.

5.4 Blinding

The trial statisticians will be blinded to allocation as per Sheffield CTRU SOPs (ST001 and ST005). The outcome assessor will be intended to be blind to treatment allocation for the duration of the trial (see section 7.3). Participants, carers, study therapists and clinicians will be aware of the treatment allocation for the trial.

The DMEC will have access to unblinded data at their request during the trial; these data will be prepared by the data management team in the CTRU, aided by another CTRU statistician not involved in the trial when required. The TMG and TSC data report will provide summary outcome data by site but not allocation arm, as per Sheffield CTRU SOP GOV001 and GOV002. As such no member of the trial team other than data management will have access to outcomes in relation to the allocation arm until the end of the trial.

Any instances of un-blinding will be recorded, including information on who was un-blinded, the source of un-blinding, and the reason for un-blinding.

6. Trial intervention

6.1 Name and description of intervention under investigation

6.1.1 ACT

This section describes the development of the manualised intervention ('manual development'), which has been approved by UCL's Research Ethics Committee (ref no. 12213/001), and the intervention procedures as they were implemented in the open uncontrolled feasibility study approved by London Dulwich Research Ethics Committee (ref no. 18/LO/0227).

The intervention has been designed for people with MND only – participating caregivers will not receive the intervention, but will be able to have access to supplementary materials such as audio files.

Previously successful strategies for adapting ACT to clinical populations relevant to people with MND (e.g. CanACT[24,54] and ACTMuS[55]) were used to create a manualised intervention for people with MND. This was developed in conjunction with a Patient/Caregiver Advisory Group, Patient and Public Involvement (PPI) groups in London and Sheffield, and UK MND healthcare professionals to ensure

deliverability across different areas (inner city/rural) and services (clinical psychology, neuropsychology and Improving Access to Psychological Therapy services). It was developed through a combination of workshops and individual qualitative interviews with 14 people with MND, 10 former or current caregivers of people with MND and 12 MND healthcare professionals. Discussions explored: i) facilitators/barriers to engagement in a psychological intervention for people with MND (including potential ways of overcoming barriers); ii) positive and negative experiences of previous psychotherapy for MND (for those who have previously engaged in these approaches); iii) how best to adapt ACT for people with MND (for example, which components of ACT interventions are considered suitable or most relevant for people with MND, which will require adaptation, and which general adaptations to therapy would be most helpful for people with MND); iv) ways of optimising engagement (e.g. using peer mentors to provide support during therapy); and v) how best to promote the intervention to people with MND not currently experiencing distress, as they may perceive less of a need for such an intervention. These PPI discussions informed development of a manualised intervention based on existing ACT approaches[17], comprising a patient workbook, online material, manual and training for therapists.

The intervention has been developed so that it can be tailored to the psychological, physical, communication and cognitive needs of people with MND. Modules focus on the six core evidence-based processes of psychological flexibility (akin to coping in conventional Cognitive Behavioural Therapy) as a basis for improving daily performance and wellbeing. These include: i) reducing avoidance of difficult or uncomfortable experiences where such behaviour might be a barrier to life enriching activity (e.g. avoiding thinking about prognosis or end-of-life issues, avoiding the physical experience of symptoms, and avoiding personally meaningful activities because of difficult emotions/thoughts in addition to physical/communication impairments); ii) reducing the amount of time people are "stuck in their head" ruminating about the past (e.g. who they used to be before their diagnosis) or worrying about the future (e.g. prognosis; symptom development); iii) reducing the degree to which people are caught up in negative or unhelpful thoughts about themselves (e.g. "I'm a burden", " I can't do anything anymore"), their situation ("it's hopeless") or their identity and roles (e.g. "I'm not the person I used to be", "I'm no longer a father or husband"); iv) identifying what really matters to them in their lives (e.g. family, their community); and v) committing to doing personally meaningful activities that support what they value (e.g. spending quality time with family). Each module has been associated with a set of skills, metaphors, experiential exercises and homework tasks specifically adapted for people with MND and designed to increase psychological flexibility. The intervention also incorporates an initial assessment aimed at developing a shared understanding of a person's current difficulties within an ACT framework, and relapse prevention aimed at reviewing any gains made and ways of maintaining these.

The intervention has been adjusted to accommodate physical and communication difficulties by drawing on theoretical principles of 'Selective Optimisation with Compensation'[56]. These involve strategies for helping people to choose the best functional domains to focus their resources on, engage in tasks that they perform best, and find ways of compensating for losses. Although these principles were originally developed to aid adaptation to the challenges of ageing, they can be similarly applied to people with MND of all ages to help them to participate as fully as possible in their lives in ways that are meaningful to them, and have been successfully applied in ACT for chronic pain[57]. For example, principles applied to ACT include limiting goals to those that are most valued and in the best functional domains, and using alternative strategies to achieve valued goals to compensate for losses in function due to MND-related difficulties. The intervention also addresses mild cognitive difficulties (predominantly involving executive or language dysfunction) as these have been reported in approximately 50% of people with MND[58]. Standard therapeutic strategies have been used to compensate for communication issues and mild cognitive difficulties such as working with communication aids, providing a workbook and session summaries as a reminder of the content of the sessions, clarifying and repeating key concepts and skills within and between sessions (e.g. recapping on the previous session at the beginning of the next session), working at a slower pace, and providing appointment reminders. Finally, it has been ensured that the intervention is relevant to all participants and not just those experiencing symptoms of depression and/or anxiety by maintaining a focus on helping people with MND to participate as fully as possible in their lives in meaningful ways, in keeping with the overall aim of ACT, rather than on reducing symptoms of depression and/or anxiety.

The intervention to be implemented in this RCT will comprise up to eight 1:1 sessions, each lasting up to 1 hour, over the course of four months, with a minimum of four being face-to-face (delivered within the MND clinic, GP surgery or participant's home, or via videoconference, depending on patient preference and therapist availability) and up to four being delivered via online audio material/CDs

(followed by therapist support via videoconference, instant messaging, telephone or email, depending on patient preference). In exceptional circumstances, all sessions may be delivered via telephone where videoconference facilities are not available (e.g. due to Covid-19). Hard copies of online audio material will be used for those unable to operate or access equipment. A phased ending to the sessions will be incorporated such that they will be approximately weekly for the first six sessions and then approximately fortnightly for the last two sessions in order to avoid participants perceiving that they have been abandoned due to therapy ending abruptly. The therapist should make initial contact (e.g. to arrange a date for the first session) with the participant within 2 weeks after randomisation. The stipulation of four months to complete the intervention allows for this phased ending, as well as breaks in sessions due to ill-health or hospital appointments. However, should participants not complete their sessions within the four month period, they will still be offered the opportunity to complete up to 8 sessions and the number of weeks taken to deliver the intervention will be recorded. Methods for handling intervention uptake outside of the planned window will be analysed as described in section 9.3.

The flexible delivery of the intervention will ensure the following issues can be accommodated: i) physical and communication deficits, fatigue and other symptoms, as online audio materials can be completed at a time most convenient to people with MND; ii) mild cognitive difficulties, as audio content can be revisited; iii) difficulties in travelling, as all sessions can be completed at home, if necessary; iv) the complexity of each person's presenting problems, as therapy will be delivered individually rather than in groups; v) those with or without internet or PC access, as hard copies of audio content will be available for those who do not have access to or cannot access online materials; and vi) restricted access to psychological therapy in some geographical locations as face-to-face, individual sessions can be delivered by videoconference or telephone in exceptional circumstances, if absolutely necessary. It also ensures the most cost-efficient use of therapist time, while not overburdening people with MND with therapy sessions. Although ACT can be delivered purely online, disadvantages of this would include potential reduced engagement and retention[59–64]. Indeed, a recent RCT of online Cognitive Behavioural Therapy for depression observed poor uptake and no impact on outcomes compared to usual care[65]. Thus, a blended approach of face-to-face sessions supplemented by online audio materials will minimise burden on people with MND (and caregivers) while ensuring sufficient therapist support to maximise engagement and retention, maintain therapeutic alliance and achieve benefits.

All therapy sessions will be recorded using encrypted digital voice recorders in order to monitor adherence to the treatment manual. The treatment manual represents a guide to intervention delivery and, as such, some ACT-consistent deviations from the manual will be expected in order to ensure the intervention meets the unique needs of individual participants. For example, exercises within the modules may be substituted for others, depending on what is most appropriate for the individual. All deviations will be recorded and rated for consistency with the ACT approach as part of the completion of the ACT Treatment Integrity Coding Manual[66] (see below). It will not be possible to review all recordings of therapy sessions in supervision sessions due to time limitations. Consequently, recordings will only be reviewed if an ACT-inconsistent deviation from the manual is identified from the ACT Treatment Integrity Coding Manual[66] or via therapist self-report, or if the therapist/supervisor thinks this would be helpful in resolving difficulties in delivering the intervention. In addition to using the checklist to monitor treatment adherence, 10% of sessions will be randomly selected and assessed for treatment fidelity by an independent ACT therapist using an adapted form of the ACT Treatment Integrity Coding Manual[66]. The random selection of sessions will be stratified according to therapist, phase of the intervention (early, middle or late), and phase of study recruitment (early, middle or late), as previously recommended[67]. If necessary, the ACT therapist will be trained in the use of the ACT Treatment Integrity Coding Manual and good inter-rater reliability will be established with members of the Trial Management Group prior to sessions being rated.

6.1.2 Intervention providers

The intervention has been developed so that it can be delivered by therapists identified to work with people with MND via clinical psychology, neuropsychology and Improving Access to Psychological Therapies services. Therapists will be Band 7 or Band 8 clinical psychologists, counselling psychologists, counsellors or psychotherapists with training in Cognitive Behavioural Therapy or accredited Cognitive Behavioural Therapy therapists, with a minimum of 1 year experience in delivering psychotherapy interventions. Ideally, therapists who are already trained in ACT will be recruited (for example, there have been ACT training initiatives in some Improving Access to Psychological Therapies services), but as therapists are not routinely trained in this approach in the NHS at present, training will be provided by

members of the research team, where necessary. Furthermore, although initial knowledge and/or experience in working with people with MND will be desirable, training in delivering the intervention to this specific population will also be provided by members of the research team, where necessary. This will focus on an overview of MND, as well as communication and physical impairments and mild cognitive difficulties typically seen in people with MND. It will also discuss the practicalities of working with people with augmentative and alternative communication devices, and provide therapists with the opportunity to practice delivering therapy using such devices. Therapists will be identified prior to the trial starting. Where necessary, therapists will attend a 4-day experientially-based training workshop on the use of ACT in people with MND, supplemented by freely available online ACT resources and copies of the newly-developed patient workbook, therapist manual and online videos. Therapists who received 4-day training in Phase 1 will be invited to attend a 1-day top-up training course to review and consolidate skills rather than the full 4-day training workshop. As for previous and ongoing trials of ACT[33,58], training that was developed as part of Phase 1 will be delivered by members of the research team with expertise and experience in ACT and MND. Training will also include two interested members of the Patient/Caregiver Advisory Group, where possible. After completing training and achieving satisfactory competence in ACT delivery, therapists will deliver ACT for people with MND under fortnightly group supervision via telephone from a Band 8 equivalent clinical psychologist or psychotherapist trained in ACT, with a minimum of five years' experience in delivering this therapy. Therapists will also attend a 1-day top-up training course after 12 months to review and consolidate skills in delivering ACT to people with MND. This degree of training is supported by evidence that ACT can be successfully delivered by novice therapists[34,68,69].

6.1.3 Usual care

All participants with MND will receive all aspects of usual multidisciplinary care in Phase 2, with the exception of formal psychological therapies such as Cognitive Behavioural Therapy for those receiving ACT. However, it is likely that all participants with MND will receive informal psychosocial support from healthcare professionals within MND/palliative care services given the holistic care approach typically adopted by these services. Treatment as usual will comprise standard care as outlined in NICE Clinical Guideline NG42 for MND[15]. This will include medication for managing MND and MND-related symptoms, treatments for MND-related symptoms (e.g. physiotherapy, non-invasive ventilation and gastrostomy), and equipment and adaptations to aid activities of daily living, communication and mobility. Coordinated care will be delivered by multidisciplinary healthcare professionals within MND and palliative care services (including neurologists, nurses, dieticians, physiotherapists, occupational therapists, respiratory physiologists, speech and language therapists, and healthcare professionals with expertise in palliative care), and will include access to other services (including clinical psychology and neuropsychology, counselling, social care, respiratory ventilation, palliative care gastroenterology, orthotics, mobility/assistive technology/communication equipment services and community neurological care teams). All of the MND Care Centres/clinics involved as recruiting sites are endorsed by the MND Association, and therefore are audited against the standard of care outlined in NICE Clinical Guideline NG42 for MND[15]. Thus, treatment as usual delivered by the Care Centres/clinics will be as homogeneous as is practically possible. As some variations in care may occur, treatment as usual will be monitored using a modified form of the Client Service Receipt Inventory[70]. Participants receiving ACT will be asked to refrain from receiving concurrent formal psychological therapies during the receipt of ACT as this may lead to conflicts in therapeutic approaches and goals. Other than this, participants will not be actively discouraged from seeking treatment outside of the trial for ethical reasons, but all such interventions will be recorded as part of the modified Client Service Receipt Inventory.

6.2 Concomitant medication

For participants with MND:
At screening, current medications will be recorded (dose and frequency) and a medications log will also be completed at the 6 and 9 month follow up visits, if there are any changes to the medications recorded at screening. This information will be collected via participants' self-reports or extracted from GP medical records and/or MND care centre records, with participants' consent. Participants in the intervention arm will be asked to refrain from engaging in other forms of psychotherapy during the delivery of the intervention as engaging in two types of psychotherapy concurrently may lead to conflicts in therapeutic approaches and goals. Other psychological or psychosocial interventions that participants engage in during the course of the study will be recorded within the CRF at 6 and 9 months, along with any interventions that participants are referred for after receiving the intervention.

6.3 Unblinding

It is not anticipated that an outcome assessor will need to know the treatment allocation, however, if the situation arises, the site staff should discuss this with the Chief Investigator and Trial Manager. Any instances of unblinding will be documented within the CRF and be included as a secondary outcome for the trial. In the event of accidental unblinding, this will be recorded at 6 and 9 months, when the outcome assessors are asked to guess each participant with MND's allocated group.

7. Assessments and procedures

7.1 Primary outcome measure

The primary outcome is psychological health as measured by the total score on the McGill Quality of Life Questionnaire-R[1,2] at 6 months post-randomisation. This is a global measure of quality of life that has good psychometric properties[1,2], and has been shown to be sensitive to change (e.g. it was able to distinguish between days rated as bad, average and good in people with cancer[71,72]). It has also been validated in people with MND[73,74]. It consists of 15 items: a single item measuring overall quality of life, and subscales measuring quality of life across 4 domains: Existential (4 items), Psychological (4 items), Physical (3 items), and Social (3 items).

7.2 Secondary outcome measures

This section describes all proposed secondary outcome measures, which will be completed at baseline (0 months), following confirmation of eligibility and consent, 6-month follow-up, and 9-month follow-up, with three exceptions. The Satisfaction with Therapy and Therapist Scale-Revised will only be collected at 6-month follow-up, adverse events will only be collected at 6 and 9 months, and survival data will be collected at 9 months only. Data collection will be conducted via telephone, videoconference, post, email, online or via face-to-face interview so as to accommodate the varied needs of people with MND. Mode of administration will be recorded as this may impact on the collection of some outcome measures.

Patient-reported outcome measures:

1. Hospital Anxiety and Depression Scale[75]: This is a 14-item self-report measure of depression and anxiety, which provides separate scores for depression and anxiety, as well as an overall score. For the purpose of analysis and, following validation in people with MND and subsequent published recommendations[76], a subset of data will be analysed which omits one item on the depression scale that assesses psychomotor retardation and one item on the anxiety scale that assesses restlessness as these overlap with physical symptoms of MND. This will be used as an additional measure of psychological health;
2. Acceptance and Action Questionnaire-II[77]: A 7-item self-report measure of psychological flexibility (an ACT-specific coping measure), which is commonly used in ACT studies;
3. EQ-5D-5L[78]: A 5-item self-report measure of health-related quality of life, used to calculate utility scores for use in economic evaluations. Each of the 5 items is rated on a 5-point scale from no problems to extreme problems;
4. Non-physical adverse events and physical self-harm. Physical adverse events other than physical self-harm will not be recorded as people with MND will experience many physical adverse events that will be unrelated to the intervention;
5. ALS Functional Rating Scale-Revised[79]: The self-administered version of a 12-item measure of function that has been developed for people with MND that can be used as an indicator of disease progression. It is important to include this measure as level of function may influence engagement with the intervention, as well as to measure symptom progression;
6. Existential and Psychological subscales of the McGill Quality of Life Questionnaire-R[1,2]: These subscales have been included as secondary outcome measures as quality of life in MND (and hence psychological health) has been found to be more associated with psychological/existential factors than physical function/strength[74];
7. Survival at 9 months. It is important to examine this variable as engagement in ACT may indirectly prolong survival through improved self-management of symptoms and decision making in relation to protective health behaviours (e.g. uptake of life prolonging interventions such as non-invasive ventilation), as shown in previous studies of other health conditions[80].
8. Satisfaction with Therapy and Therapist Scale-Revised[81]: A 12-item self-report measure of satisfaction with therapy and satisfaction with the therapist, rated on a 5-point scale from 1 (strongly disagree) to 5 (strongly agree). Six items relate to satisfaction with therapy and six to

satisfaction with the therapist. There is no set definition of what constitutes "satisfactory" and so this will be defined as a total score of 18 or more on the Satisfaction with Therapy subscale. As an indicator, if a participant rated all items on the Satisfaction with Therapy subscale as 3 (i.e. neutral) then they would score 18.

Caregiver-reported outcome measures (absence of a caregiver to complete these measures will not negate a person with MND's participant in the trial):

9. EQ-5D-5L[78];
10. Zarit Burden Interview[82]: A well-validated 22-item self-report measure of caregiver burden, necessary as supporting people with MND to engage in ACT may place extra burden on them.

Cost-effectiveness-related measures:

11. Client Service Receipt Inventory[70] modified for people with MND. This information will be extracted from participants' self-reports, GP medical records and/or MND care centre records, with participants' consent.
12. Quality-adjusted life years and resource use to inform the cost-effectiveness analysis.

7.3 Measures of bias

Expectations about treatment, adherence to the intervention by therapists, patients' preferences for treatment, and use of other forms of treatment during the trial are all potential sources of bias that can affect treatment outcomes. Consequently, the following measures will be included;

13. Credibility/Expectancy Questionnaire[83]: It is important to evaluate treatment credibility/expectancy when developing a new intervention as this can have a significant impact on uptake and dropout rates. The Credibility/Expectancy Questionnaire is a 6-item self-report measure that assesses the credibility of the rationale for therapy and expectations about treatment, which has been adapted for people with MND. Four items are rated on a 9-point scale from 1 to 9 (lower scores are worse) and 2 items are scored on an 11-point scale from 0 to 100%. As the measure includes items rated on two scales, the items will be standardised and summed to form separate composite scores for credibility and expectancy;
14. ACT Treatment Integrity Coding Manual[66]: A coding system that has been developed to assess treatment integrity in ACT interventions, which has been used in previous RCTs of ACT (e.g.[84]). In this coding system, the frequency and depth of coverage of major components of ACT, together with overall adherence and overall therapist competence, are rated on a five-point scale from 1 (not at all) to 5 (extensively). Coding will be completed by an independent ACT therapist for 10% of sessions selected at random;
15. Patients' preferences for treatment (collected on a four point Likert scale from 0 to 3): Prior to randomisation, participants will be asked the following questions: i) Although you will be chosen at random to have either Acceptance and Commitment Therapy or usual multidisciplinary care alone, if you could choose what treatment you received, how much would you hope to receive Acceptance and Commitment Therapy plus usual multidisciplinary care? They will be asked to rate this on a 4-point scale from 0 (not at all) to 3 (completely); and ii) How much would you hope to receive usual multidisciplinary care alone (i.e. without Acceptance and Commitment Therapy)? They will be asked to rate this on a 4-point scale from 0 (not at all) to 3 (completely);
16. Assessment of blindness at 6 and 9 months, as outcome assessors will be blinded to treatment allocation at follow-up: Although participants will be asked not to reveal their allocation to outcome assessors, some may accidentally reveal this and some outcome assessors may be able to guess this. Consequently, we will ask outcome assessors to guess whether they think the participant was allocated to the intervention or control arm. Outcome assessors will be asked to do the following: Please guess which treatment condition the participant has been allocated to (Acceptance and Commitment Therapy plus usual multidisciplinary care or usual multidisciplinary care alone). To what extent are you certain of the participant's treatment allocation? They will be asked to rate this on a scale from 0 (not sure at all) to 4 (very sure);
17. Contamination in the control group is another potential source of bias: That is, use of therapies (pharmacological or behavioural) other than the trial intervention, which may in turn attenuate the true effect of ACT. We will undertake additional exploratory data analysis to assess the impact of these therapies if used by a substantial proportion of participants.

7.4 Screening and collection of sociodemographic and clinical data

For participants with MND:
Participants will be asked to provide consent prior to data collection (see Section 4.3). Socio-demographic and clinical data collected at screening will include: age, date of birth, diagnosis of ALS, PLS or PMA, need for gastrostomy feeding or non-invasive ventilation, comorbid severe psychiatric diagnoses (including dementia, schizophrenia and bipolar disorder), risk of self-harm (e.g. suicidal ideation with active suicidal behaviours/plans, either assisted or non-assisted, and intent), current engagement in formal psychological therapy and willingness to refrain from engaging in formal psychological therapy during the receipt of ACT in the RCT, and need for translators. An identification log stored on the Sheffield CTRU database (Prospect) will collect sex, age, postcode (excluding the final two letters) for all patients screened for eligibility. Additional socio-demographic and clinical data collected at baseline for all those people with MND who meet eligibility criteria and provide consent will include: i) sex, ethnicity, marital status, highest level of educational qualification, current occupation, and highest level of occupational attainment; ii) ongoing medication use (dose and frequency), time since ALS diagnosis and time since symptom onset; and iii) cognitive and behavioural difficulties using the Edinburgh Cognitive Behavioural ALS Screen (ECAS)[85,86]. The exception to this is if the consent and eligibility visit is conducted by telephone or videoconference, and there is no remote version of the ECAS available, in which case the ECAS assessment will not be collected. Where an ECAS assessment has been completed within 12 weeks (of baseline) by the MND Care team, and data are recorded in full in the patient's notes, this can be added to the case report form and used for the trial. If a potential participant indicates a risk of self-harm, a screening version of the Columbia-Suicide Severity Rating Scale (C-SSRS)[84] will be administered.

For caregivers:
Participants will be asked to provide consent prior to data collection (see Section 4.3). Socio-demographic data collected at screening will include: age, date of birth, and caregiver status. Additional socio-demographic data collected at baseline for all those caregivers of people with MND who meet eligibility criteria and provide consent will include: sex, ethnicity, relationship to the participant with MND, marital status, highest level of educational qualification, current occupation, highest level of occupational attainment, length of time spent as the primary caregiver of the participant with MND, and the average number of hours per week involved in caregiving.

For therapists:
Participants will be asked to provide consent prior to data collection (see Section 4.3). Socio-demographic data collected at screening will include: age, date of birth, and study therapist status. Additional socio-demographic data collected for all those study therapists who meet eligibility criteria and provide consent will include: sex, ethnicity, highest level of educational qualification, current occupation, highest level of occupational attainment, number of years since qualifying as a therapist, and number of years practicing ACT.

7.5 Subsequent assessments and procedures

Following the consent visit, participants with MND and caregivers will complete further follow-up visits at 6 and 9 months post-randomisation. Data collection will be conducted via telephone, videoconference, post, online or via face-to-face interview at 0 months, 6 months (+/- 4 weeks) and 9 months (+/- 4 weeks) by a blind outcome assessor from the research site or central research team, with the exception of the question about psychological therapies received on the adapted Client Service Receipt Inventory. In order to prevent any potential unblinding of outcome assessors, the question about psychological therapies received on the adapted Client Service Receipt Inventory will be administered in one of four ways: i) via post and then returned to the central study team at 6 months; ii) by online methods; iii) by telephone by the non-blind assessor arranging the follow-up visit; and iv)at the end of the outcome assessment session at 9 months, after the outcome assessor has completed the unblinding question (where data are collected via telephone, videoconference or face-to-face interview).

The mode of administration will be recorded at each time point. Table 1 provides details of the data to be collected at each visit. The primary outcome measure for participants with MND will be the McGill Quality of Life Questionnaire-R[1,2], with the primary endpoint being at 6 months post-randomisation. This relatively short duration accounts for the reduced life expectancy in people with MND, and will be able

to accommodate variability in the disease course that participants may present at and their differing prognoses. Further assessment at 9 months will examine whether potential gains are maintained at short-term follow-up. A summary of the participant timeline is outlined in Figure 1.

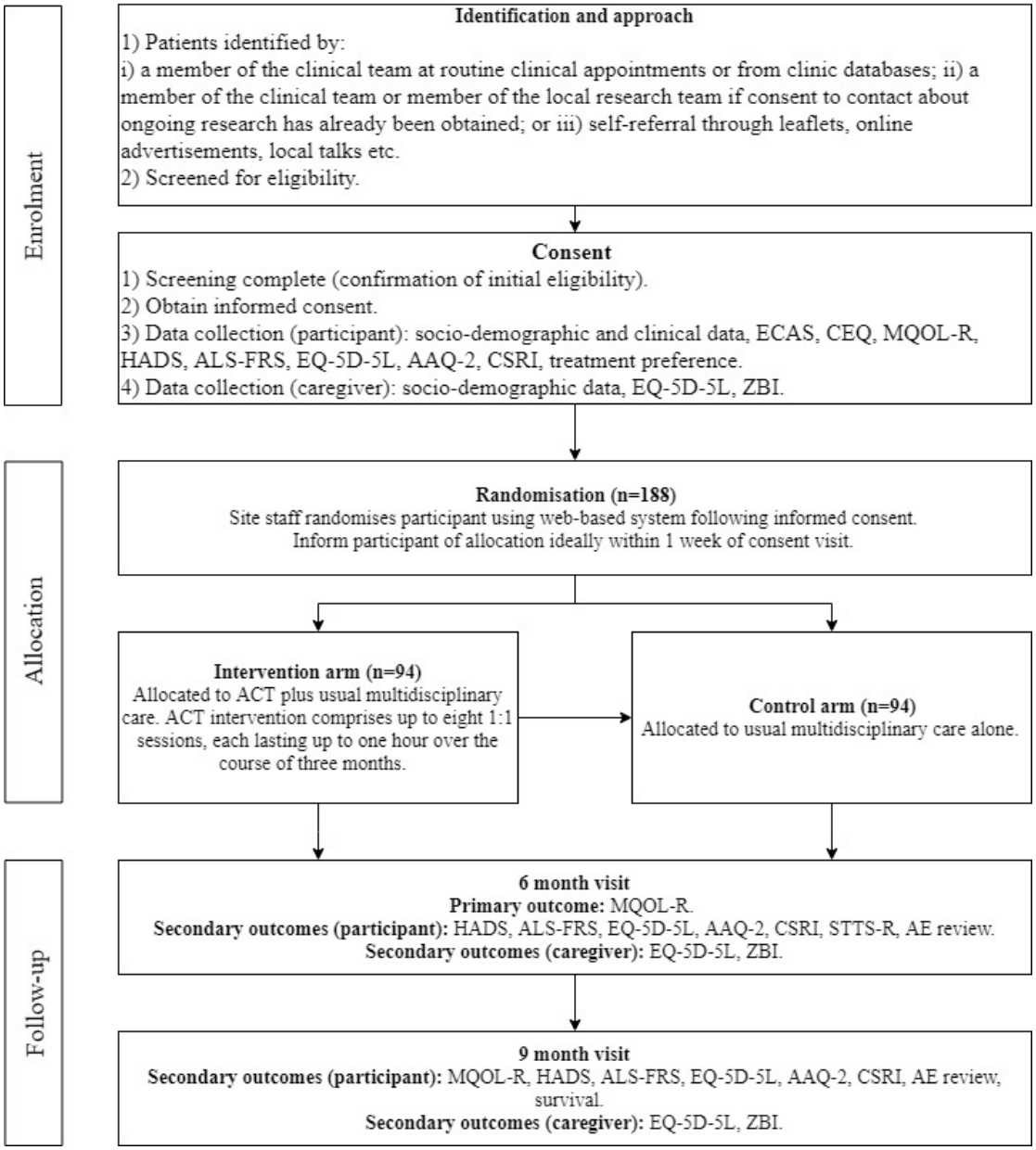
Table 1. Assessment intervals for measures used in the RCT.

Primary and secondary outcome measures and measures of bias (for participants with MND unless otherwise indicated)	**0 months**	**6 months**	**9 months**
Primary outcome measure			
McGill Quality of Life Questionnaire-R	✓	✓	✓
Secondary outcome measures			
Existential & Psychological subscales of McGill Quality of Life Questionnaire-R	✓	✓	✓
Hospital Anxiety and Depression Scale	✓	✓	✓
Acceptance and Action Questionnaire-II	✓	✓	✓
EQ-5D-5L	✓	✓	✓
Quality-adjusted life years	✓	✓	✓
ALS Functional Rating Scale-Revised	✓	✓	✓
Non-physical adverse events and physical self-harm		✓	✓
Survival at 9-months			✓
Satisfaction with Therapy and Therapist Scale-Revised (intervention arm only)		✓	
Zarit Burden Interview (caregivers only)	✓	✓	✓
EQ-5D-5L (caregivers only)	✓	✓	✓
Cost-effectiveness-related measures			
Modified version of the Client Service Receipt Inventory	✓	✓	✓
Measures of bias			
Credibility/Expectancy Questionnaire*	✓		
Treatment preference*	✓		
Assessment of blindness (for outcome assessors only)			✓
ACT Treatment Integrity Coding Manual (for ACT independent rater - intervention arm only)**	On a regular basis throughout the duration of intervention delivery		

* This will be completed after consent, but prior to randomisation, after participants are given a rationale for ACT.

** Sessions will be rated on a regular basis throughout the duration of intervention delivery, as stipulated by the random order of sessions to be rated, so that therapists can receive ongoing feedback on their intervention delivery.

Figure 1. Timeline for participants with MND in the RCT



7.6 Qualitative component

Participants with MND and study therapists will be asked to anonymously complete a written qualitative satisfaction questionnaire at the end of intervention delivery to further examine the acceptability and feasibility of the intervention for those in the intervention arm (or usual multidisciplinary care for both intervention and control arms). This will comprise a combination of open and closed questions. The participant version of the satisfaction questionnaire will examine satisfaction with ACT and its suitability and relevance to people with MND, perceived benefits and limitations of the intervention, difficulties in implementing the intervention in their everyday lives, and any recommendations for revising the intervention. The therapist version will additionally explore how ACT was delivered in practice (e.g. treatment fidelity, ease of delivering ACT for people with MND, difficulty of skills for participants to learn, etc).

Participants with MND in the TAU arm will be asked to specifically comment on the acceptability and feasibility of the psychological aspects of their management rather than all aspects of their management. Questions will focus on what kind of psychological support participants felt they needed and what they

actually received, what was helpful and what was not, and what other psychological support would have been helpful.

If participants are unable to complete the written questionnaire (either via post, email or online) due to MND-related difficulties, they will be invited to complete the questionnaire verbally via telephone, videoconference, or face-to-face interview. An independent member of the research team will complete satisfaction questionnaires verbally with all those who cannot complete the written questionnaire. This will ensure that independent blind outcome assessors remain masked as much as possible. The independent member of the research team will audio record any satisfaction questionnaires completed verbally using an encrypted digital voice recorder. Audio files will be uploaded to a secure server using a system called Data Safe Haven, which satisfies the highest level of security requirements of NHS trusts. The audio recordings will then be transferred and stored onto UCL's password protected secure electronic network. All data on encrypted digital voice recorders will be deleted after the data have been transferred. Data will not be transferred to any party not identified in this protocol and will not be processed and/or transferred other than in accordance with patients' consent.

7.7 Discontinuation/withdrawal of participants with MND

Discontinuation/withdrawal of participants will be managed in accordance with the Sheffield CTRU Participant Discontinuation and Withdrawal of Consent SOP (SSU003). In consenting to participate in the trial, participants with MND are consenting to receive the intervention (if allocated), screening and outcome assessments at baseline and follow-up, and data collection. Participants will be made aware that their participation is voluntary and that they may discontinue from the trial, should they wish, at any time.

Participants will have the following options if they wish to withdraw:

1. Withdrawal from the trial intervention, but not subsequent data collection (i.e. the participant would be withdrawn from therapy sessions only but would remain in the trial).
2. Withdrawal from the trial entirely (i.e. the participant would be withdrawn from both therapy sessions and subsequent data collection). Any data collected up to this point would be retained and used in the analysis. No further contact with regard to the trial would be made. If the participant specifically requests for all their data to be removed, information regarding the participant would be retained at site, as part of the patient notes, along with their withdrawal form and request to delete the data. If this occurs, the Sheffield CTRU SOP ST003 Data Evaluation would be followed. The Statistical Analysis Plan (SAP) will provide details on how data are to be included/excluded from the statistical analyses.

If a participant requests to withdraw, they will be able to speak to a member of the research team. This will be documented on a participant withdrawal form, within the Case Report Form. A participant may be withdrawn from the trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so will be recorded (whenever possible). Reasons for discontinuing the trial may include:

- Major escalation of mental health service support;
- Suicidal ideation with active suicidal behaviours/plans and imminent intent, where the intervention is believed to be contributing to further distress;
- Illness that may exclude the possibility of engagement in the intervention;
- A person withdrawing consent or losing the capacity to consent to participate in the trial.

A participant will be classed as complete if they have continued in the trial until the last protocol defined visit, however, there may be missing visits and/or data.

Loss to follow-up

A participant would be classed as lost to follow-up if the participant has not completed the trial, despite attempts for further contact having been made.

7.8 Discontinuation/withdrawal of caregivers

Discontinuation/withdrawal of caregivers will be managed in accordance with the Sheffield CTRU Participant Discontinuation and Withdrawal of Consent SOP (SSU003). In consenting to participate in the trial, caregivers are consenting to screening and outcome assessments at baseline and follow-up, and data collection. Caregivers will be made aware that their participation is voluntary and that they may discontinue from the trial, should they wish, at any time. Should the person with MND they are providing care for withdraw from the study, caregivers will be given the option as to whether they would like to continue in the trial or similarly withdraw.

Caregivers will have the following options if they wish to withdraw:

1. Withdrawal from the trial entirely (i.e. the caregiver would be withdrawn from subsequent data collection). Any data collected up to this point would be retained and used in the analysis. No further contact with regard to the trial would be made. If the caregiver specifically requests for all their data to be removed, information regarding the caregiver would be retained at site along with their withdrawal form and request to delete the data. If this occurs, the Sheffield CTRU SOP ST003 Data Evaluation would be followed. The Statistical Analysis Plan (SAP) will provide details on how data are to be included/excluded from the statistical analyses.

If a caregiver requests to withdraw, they will be able to speak to a member of the research team. This will be documented on a participant withdrawal form, within the Case Report Form. A caregiver may be withdrawn from the trial whenever continued participation is no longer in the caregiver's best interests, but the reasons for doing so will be recorded (whenever possible). Reasons for discontinuing the trial may include:

- Unwilling or unable to complete follow-up questionnaires (e.g. due to illness, lack of time or personal/family issues);
- A person withdrawing consent or losing the capacity to consent to participate in the trial.

A caregiver will be classed as complete if they have continued in the trial until the last protocol defined visit, however, there may be missing visits and/or data.

Loss to follow-up
A caregiver would be classed as lost to follow-up if the caregiver has not completed the trial, despite attempts for further contact having been made.

7.9 Definition of end of study

The expected duration of Phase 2 of COMMEND is 29 months. The start of the study is defined as the date of recruitment of the first participant with MND to the trial. The end of the study is defined as the date of the last follow-up visit of the last participant with MND in the trial.

8. Recording and reporting of adverse events

Trial sites are to report Adverse Events (AEs) and Serious Adverse Events (SAEs) in conjunction with the Sheffield CTRU Adverse Events and Serious Adverse Events SOP (PM004).

8.1 Adverse events

An AE is any untoward medical occurrence in a trial participant with MND. Physical AEs other than physical self-harm are expected in this population and will not be collected and recorded within the Case Report Form (CRF). Incidents of non-physical AEs and physical self-harm will be collected and recorded within the CRF. The assessor (e.g. PI or Research Nurse) will make a judgement as to whether an AE is deemed to be physical or non-physical. Incidents of physical self-harm will be recorded as serious adverse events (SAEs). If suicidal ideation without active suicidal behaviours/plans and imminent intent is identified, this will be recorded as an AE and the participant's GP and/or MND care Centre/clinic will be informed and the participant will be monitored weekly during therapy sessions (if in the ACT arm). Local standard clinical procedures will be followed for those in the TAU arm.

AEs will be categorised as follows:

- Any new co-morbid psychiatric condition reported;

- Any event that has significantly affected the psychological health status of the participant (e.g. a stressful life event such as a bereavement);
- New reports of suicidal ideation (with or without active suicidal behaviour/plans, but without imminent intent) during the study (i.e. not reported at baseline);
- Other.

8.2 Serious adverse events (SAEs)

The definition of an SAE in relation to participants with MND is as follows:

- New reports of suicidal ideation with active suicidal behaviour/plans and imminent intent;
- Reports of physical self-harm;
- Requires unplanned in-patient hospitalisation*;
- Requires prolongation of existing hospitalisation*;
- Is life-threatening**;
- Results in persistent or significant disability or incapacity;
- Results in death;
- Considered medically significant by the investigator.

* Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.
** A 'life-threatening' event refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

New reports of suicidal ideation with active suicidal behaviours/plans and imminent intent, reports of physical self-harm, and death from actual or suspected suicide will be classified as unexpected, with all other events being classified as expected. For SAEs that report death, if there is any indication of suicide then the event will be classed as unexpected for the purposes of reporting.

Intensity

The following categories will be used to define the intensity of an SAE:

Category	Definition
Mild	The event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort.
Moderate	The event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort.
Severe	The event results in alteration, discomfort or disability which is clearly damaging to health.

Relationship to trial intervention

The relationship to the trial intervention will be categorised as follows: i) reasonable possibility of being related; ii) no reasonable possibility of being related; or iii) not assessable. The assessment of causality must be made by a trained clinician (usually the Principal Investigator (PI) or a Co-Investigator). If a causality assessment is not provided by the site or causality is recorded as 'not assessable', the event should be deemed to be related until the investigator confirms otherwise. If there is disagreement between the PI and CI over the causality assessment, the CI's decision is final. Advice may be sought from the TSC if applicable.

8.3 Reporting

AEs and SAEs can be reported for participants with MND at any stage of their trial participation. A member of the site team will complete a review of the MND care centre records at the 6-month and 9-month visit. A member of the site team or central research team will also ask participants to self-report any AEs/SAEs at both follow-up visits. Therapists or MND clinicians will notify the local Principal Investigator in the site team and/or un-blind members of research team if they become aware of any AEs/SAEs during the study. AEs will be recorded on the AE section of the paper CRF, and must be entered onto the electronic trial database within 1 week of completing the paper form. The events will be assessed by the local Principal Investigator and the form will be stored within the CRF.

All SAEs must be reported to CTRU and the sponsor within 24 hours of discovery at site. The following steps must be taken:

1. The event details need to be completed on the SAE form within the CRF;
2. The completed form needs to be downloaded and emailed to the following groups:
   - research-incidents@ucl.ac.uk;
   - commend-centralteam-group@sheffield.ac.uk;
   - ctru-saes-group@sheffield.ac.uk.

All SAEs that are deemed both "unexpected" and "related" to the intervention (ACT) or trial require expedited reporting. These must be reported to the REC within 15 days of being reported to the study team; this is the responsibility of the Sheffield CTRU. All SAEs will be reported in the periodic safety reports to the Research Ethics Committee, Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC).

8.4 Risks

Information sheets will provide all participants with information about the possible benefits and risks of taking part in the study. All participants will be given the opportunity to discuss this with the researcher prior to consenting to the study.

Risk: Participants with MND will remain under the care of their GP/MND Care Centre/clinic for the duration of Phase 2. Risk of harm to self (including assisted and non-assisted suicide) or others will be monitored throughout the study. If suicidal ideation without active suicidal behaviours/plans and imminent intent is expressed at any point then the participant's GP/MND Care Centre/clinic will be contacted and the participant will continue to be monitored weekly (if in the ACT arm). Local standard clinical procedures will be followed for those in the TAU arm. If suicidal ideation with active suicidal behaviours/plans and imminent intent is expressed at any point then the participant's GP/MND Care Centre/clinic will be contacted and the participant will be referred for urgent psychiatric assessment. The decision as to whether the participant should be withdrawn from the study will depend on the outcome of this assessment, and will be made in full discussion with the participant, clinical team, and Trial Management Group/DMEC (where necessary). If there are any unexpected disclosures of actual or potentially illegal behaviour at any point during the trial then this will be discussed with the person disclosing the information, and the MND Care Team will be contacted (if necessary) and/or relevant authorities notified (if necessary). Local standard clinical procedures will be followed for safeguarding participants.

Inadequate treatment response: If a participant with MND remains moderately to severely anxious or depressed at the end of the follow up period (as indicated by a score of ≥9 on the anxiety subscale of the Hospital Anxiety and Depression Scale[75], or a score of ≥8 on the depression subscale, excluding data from two questions which overlap with physical symptoms of MND[76]) then this will be discussed with the participant and their MND care team/GP. We will recommend treatment (e.g. referral for psychological therapy, antidepressant) at the end of the 9-month follow-up period, if necessary.

Potential distress: Evidence of any adverse effects from the ACT intervention will be monitored throughout the trial. Reasons for withdrawing participants with MND from the ACT intervention are listed in section 7.7. Reasons for withdrawing participants will be monitored by the Trial Management Group and DMEC throughout the duration of the study. Anyone experiencing an increase in distress will be assessed for risk, and local standard operating procedures will ensure safety is respected. New reports of suicidal ideation with active suicidal behaviours/plans and imminent intent during the ACT intervention will be reported as Serious Adverse Events.

Lone working: All staff seeing participants in their own homes (e.g. therapists, members of the research team) will follow local procedures for lone working in the community, including ensuring that a diary system is implemented to monitor movements and 'checking in' with a central administrator after sessions to confirm one's safety.

8.5 Notifications of reportable protocol non-compliance

A non-compliance is a departure from the protocol or GCP that has been identified retrospectively.

A “serious breach” is a breach, of either the conditions and principles of GCP in connection with the trial; or the protocol relating to the trial, which is likely to affect to a significant degree –
(a) The safety or physical or mental integrity of the subjects in the trial; or
(b) The scientific value of the trial.

A very serious non-compliance significantly affecting either of the above may alone constitute a serious breach. Less serious but persistent, systematic or deliberate non-compliances might also be considered a serious breach. The sponsor will be notified immediately of any case where the above serious breach definition applies during the trial conduct phase. The Chief Investigator or designated individual will notify the sponsor of any protocol non-compliance, within one week of becoming aware of the event.

8.6 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:
i) It is an accident or other incident which results in injury or ill health.
ii) It is contrary to specified or expected standard of patient care or service.
iii) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
iv) It puts the relevant Trust in an adverse position with potential loss of reputation.
v) It puts relevant Trust property or assets in an adverse position or at risk.

Incidents and near misses will be reported to the relevant Trust through DATIX as soon as the individual becomes aware of them.

8.7 Auditing

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The Principal Investigators will also allow monitoring and audits by these bodies and the sponsor, and they will provide direct access to source data and documents.

9. Statistics

9.1 Planned recruitment rate

We estimate that we will need to identify 752 people with MND in 20 months across approximately 14 sites, in order for 188 people with MND to be eligible and agree to participate in the trial. In order to meet this target recruitment rate, our identification rate will need to be approximately 37.6 potential participants per month (2.69 people with MND per site per month), of whom it is estimated that 9.4 will be eligible and will agree to participate per month (0.67 people with MND per site per month).

We will include an internal pilot in the first 10 months of the RCT to assess the feasibility of recruitment rates and acceptability of randomisation. We will complete the full RCT if we have recruited 71 people with MND (or 0.51 people with MND per site per month), with ≥70%+ in the ACT arm completing at least 2 sessions, by then.

9.2 Sample size calculation

We plan to recruit 188 people with MND from approximately 14 sites. This will allow detection of an effect size of 0.44 standard deviations, with a two-sided alpha of 5% and 90% power. This assumes 20% attrition at 6 months post-randomisation[87], an intra-class correlation coefficient of 0.01 among therapists (as used in other psychotherapy trials;[88] in the intervention arm, assuming 1 therapist per site and a correlation of 0.58 between 0 and 6 months post-randomisation for the McGill Quality of Life questionnaire in people with MND[87]. Our sample size is based on a clinically-meaningful pooled effect size of 0.44 standard deviations reported in a meta-analysis of ACT for mental and physical health conditions vs. controls[20], which falls within the range found for quality of life in studies of ACT in long-term conditions[19]. There are no published data with respect to what a clinically important difference is on the McGill Quality of Life Questionnaire-R in people with MND. However, our effect size is consistent with the minimal clinically important difference of 0.5 standard deviations that has been consistently reported for quality of life across different clinical populations[89].

9.3 Quantitative analysis

Our primary outcome measure will be analysed using multi-level modelling in which treatment group and baseline score will be included as fixed effect covariates and site/therapist will be included as a random effect to account for potential clustering. Analyses will be conducted separately at 6 months (the primary analysis time point) and 9 months. The difference between groups in mean quality of life will be quantified by the model coefficient, along with its 95% confidence interval. Primary analyses will be by intention to treat, but additional sensitivity analyses will be used to assess whether outcomes vary across sites/therapists, and by disease severity at baseline, psychotropic medication use, number of weeks taken to complete the therapy sessions and participants' engagement in the intervention (as determined by the number of sessions completed within 4 months, and if applicable, whether the sessions were ongoing beyond 6 months post-randomisation).

Secondary outcome measures (for patients and caregivers) will be analysed in a similar fashion to the primary outcome measure. Adverse events will be summarised as the number and percentage of patients experiencing each event and the number of events by treatment arm. Patient deaths are expected to be relatively uncommon at 9 months (<10%) and will be summarised descriptively as an adverse event. It is expected that some participants will have missing outcome data either due to death, loss to follow up or withdrawal from trial. The number of missing values will be summarised by treatment group, time point and reason. Multiple imputation using Rubin's rules[90] will be implemented for the primary and other key endpoints if the level of missing data exceeds 5% for reasons other than participant death.

We will also undertake additional exploratory analysis to assess the consistency of treatment effect across the following subgroups: i) severity of depression and/or anxiety at baseline, according to clinical cut-offs on the Modified Hospital Anxiety and Depression Scale for MND[76]; ii) patient preference for treatment; iii) use of pharmacological therapy for mood disorder; and iv) disease severity as measured using the ALS Functional Rating Scale-Revised. We will also undertake exploratory analyses in those who score below clinical cut-offs for anxiety or depression at baseline on the HADS to see whether ACT is beneficial in preventing progression to clinical levels of these symptoms at follow-up.

The impact of non-adherence (i.e. non-uptake of ACT in the intervention group) and contamination (i.e. delivery of psychological therapy in the control group) will be assessed using complier-average causal effect (CACE) analysis and a per-protocol analysis. Average Causal Response (ACR) Analysis will be used to assess any incremental impacts of the number of ACT sessions received[91].

9.4 Qualitative analysis

Data from open-ended questions in the Satisfaction questionnaire will be transcribed and anonymised to maintain confidentiality. Data will then be analysed iteratively using focussed thematic analysis[92]. Three members of the research team will independently code initial data before constructing an analytic framework around: i) facilitators/barriers to engagement, previous experiences of psychotherapy, and adaptations to ACT for people with MND; and ii) the acceptability, relevance, perceived value and feasibility of delivering ACT to people with MND. The analytical framework will be applied to the remaining transcripts, with themes and subthemes refined as necessary. Ideas about themes and their relationships will be recorded in theoretical memos and discussed among our Patient/Caregiver Advisory Group, Trial Steering Committee and PPI groups. The computer programme QSR N-VIVO will be used to process data, enabling us to code the information.

9.5 Economic evaluation

A cost-utility analysis will present the incremental costs per quality-adjusted life years from an NHS and social care perspective of people with MND receiving ACT plus usual multidisciplinary care compared to those receiving usual multidisciplinary care. Costs will be estimated for each participant with MND and will include costs for delivering the intervention (training and staff time for delivering the intervention, cost of materials)) and primary and secondary health care usage. Data on health care resource use will be collected using the modified Client Service Receipt Inventory and will collect information on hospital, nursing home and hospice services, out-patient visits and day care, primary and community care services, and equipment obtained. Unit costs will be derived from appropriate national sources and will include NHS reference costs and Personal Social Service Research Unit costs[93,94]. The standard version of the EQ-5D-5L will be used to collect utility values, which will be used to estimate quality-adjusted life years. These will be calculated using the area under the curve method. Where data on the EQ-5D-5L or resource use are missing, multiple imputation techniques will be implemented.

Differences between costs and quality-adjusted life years in the two groups will be described and the incremental cost effectiveness ratio will be calculated. A trial-based analysis will be supplemented by an analysis using a simple decision analytic model (a Markov model), which will be used to estimate the cost effectiveness of the intervention over the lifetime of people with MND. The model will use transition states related to the severity of MND (mild, moderate, severe, terminal and death) and will use a two-month cycle. It will be based on previous models published in the literature. This will be populated using the trial data plus information from the literature where required. This analysis will allow the estimation of lifetime cost-effectiveness and associated cost-effectiveness acceptability curves through the use of probabilistic sensitivity analysis. Caregiver costs will be included in a secondary analysis which will take a wider perspective to include patient and caregiver burden. Sensitivity analysis will explore assumptions made around transition probabilities, costs and long-term survival estimates. Bootstrapping will be used to capture uncertainty around cost-effectiveness estimates.

10. Trial supervision

10.1 Oversight

The study will be conducted in line with the Helsinki Declaration. UCL is the nominated sponsor. Research governance will be led by the Joint Research Office UCL/UCLH, the Research and Development Organisation of the lead trust. The local Principal Investigator (PI) will be responsible for the trial at each participating site and it will be registered and approved with each local R&D department. The study will be conducted in accordance with the protocol, GCP and Sheffield CTRU SOPs. The three committees which will govern the conduct of the trial are:

- Trial Management Group (TMG)
- Trial Steering Committee (TSC)
- Data Monitoring and Ethics Committee (DMEC)

The TMG will comprise of the Chief Investigator, co-applicants, collaborators, an interested member of the Patient/Caregiver Advisory Group, and relevant trial staff. The TMG will meet in person/via teleconference every month initially until recruitment is well established and then every 3 months throughout the remainder of the trial. This group will set target deadlines, monitor the conduct and progress of the trial, and troubleshoot any issues that arise. It will also review recruitment figures, incidents and substantial amendments to the protocol prior to submission to the Research Ethics Committee. In addition, it will ensure adherence to Mental Capacity and Data Protection Acts, ethical guidelines, Information Governance procedures, and the British Psychological Society's Code of Conduct for Research. The TMG will send updates to the TSC and DMEC. The Chief Investigator, the trial manager and research assistant will maintain monthly contact with recruiting sites via site visits and telephone to ensure that recruitment targets are met and any issues with recruitment are managed promptly. "Trial champions" will be identified at each of the sites so that knowledge and processes about the trial are disseminated to all clinicians likely to be involved, and not just the senior PIs at each site.

The TSC will include an independent Chair, an independent statistician, an independent health economist, an independent clinician, and a non-independent PPI collaborator. The group will meet every 6 months to review progress and address any issues as necessary. Representatives of the sponsor and research network will also be invited to attend meetings. The role of the TSC will be to provide advice on all aspects of the trial and overall supervision with respect to progress, relevant approvals, protocol adherence, patient safety, as well as agree proposals for substantial amendments.

The DMEC will include an independent Chair, an independent statistician, and an independent clinician. The group will meet every 12 months and will discuss issues related to data collection, ethical issues and other incidents, and will provide recommendations in relation to data monitoring and ethical or safety issues, as necessary. It will be able to recommend premature closure of the study, if necessary.

10.2 Description of any interim analyses and stopping guidelines

There are no planned interim analyses or stopping rules based on efficacy. The trial may terminate prematurely if it fails to meet progression criteria following an internal pilot in the first 10 months of the RCT (as described in section 9.1) or on the basis of safety concerns (as described in section 10.1).

11. Data handling and record keeping

11.1 Data management

The Sheffield CTRU will oversee data collection, management and analysis and ensure the trial is undertaken according to Good Clinical Practice Guidelines and CTRU SOPs. Data will be collected and retained in accordance with The General Data Protection Regulation 2016/679.

Trial data will be entered on a study database hosted on CTRU's web based data management system (Prospect). Prospect stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to Prospect is controlled by usernames and passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks.

The research staff at sites will be responsible for data entry locally. The Sheffield CTRU trial manager, research assistant and the data management team will work with sites to ensure the quality of data provided. The trial manager, research assistant, data manager, PIs, any research nurses and site staff will be able to access the database via a web browser through the use of usernames and encrypted passwords. The system has a full electronic audit trail and is regularly backed up. The study database will incorporate quality control procedures to validate the trial data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator.

11.2 Completing CRFs

All CRFs will be completed and signed by staff that are listed on the site staff delegation log and authorised by the Chief Investigator/Principal Investigator to perform this duty. The Chief Investigator will be responsible for the accuracy of all data reported in the CRF. In line with UCL's (Sponsor) Data Protection Policy, study documentation and anonymous data will be securely kept for a period of 10 years following completion of the study.

11.3 Data handling

All data will be collected in accordance with the consent forms and information sheets for participants with MND, their caregivers and study therapists and this protocol. UCL, as the study sponsor, will act as the data controller for the study. All data will be handled in accordance with The General Data Protection Regulation 2016/679. Participants will be assigned unique identification numbers. Prospect will store a participant's (person with MND and caregiver) name, address, phone number and email address. Prospect's permissions system will be used to ensure that access to names and contact details will be restricted to those members of the study team who need to contact participants. All data will be held on a secure server with access restricted to the research team.

Audio files of therapy sessions and any Satisfaction questionnaires recorded on encrypted digital voice recorders will be uploaded to a secure server using UCL's system called Data Safe Haven, which satisfies the highest level security requirements of NHS trusts. Treatment integrity ratings will be completed by an independent ACT therapist who will review audio files stored on the secure server via Data Safe Haven. Data will not be transferred to any party not identified in this protocol and will not be processed and/or transferred other than in accordance with the patients' consent.

Sheffield CTRU will receive copies of participant, caregiver and therapist consent forms for monitoring purposes. Consent forms will be sent securely to Sheffield CTRU, and the documents will be stored on the University of Sheffield secure, access-restricted server. Digitally received consent forms will be stored in the same location. Audio recordings of verbal consent obtained by telephone or videoconference will be uploaded to Data Safe Haven. Any photocopies will be destroyed once scanned, and participant, caregiver and therapist consent will be sought for sending copies of the consent forms and making audio recordings of verbal consent.

11.4 Confidentiality

Participant confidentiality will be respected at all times. All data will be handled in accordance with The General Data Protection Regulation 2016/679. The CRFs will not bear the participant's name or other personal identifiable data, apart from their date of birth. The contact details form for participants with MND and their caregivers will be removed from the CRF once complete and stored in the investigator site file with the consent form. The participant's trial identification number will be used for identification and this will be clearly explained in the information sheets. All participant information will be stored in accordance with The General Data Protection Regulation 2016/679, with any personally identifiable information, stored in locked cabinets. Each participant will be assigned an identification code, which will be used in all data storage, and will not contain any names or other personally identifiable information.

Participants will be assured that confidentiality will be kept unless there is evidence of risk of harm to self or others. This will be specified in the information sheet. If the screening assessment reveals undiagnosed disorders such as cognitive impairment suggestive of dementia, or other undiagnosed psychiatric conditions (e.g. clinically significant depression or anxiety), then the participant with MND's GP and/or MND Care Centre/clinic will be informed with the participant's consent (or without their consent if there are concerns about risk of harm to self). The GPs of participants with MND will also be informed of their participation in the trial, with participants' consent.

11.5 Plans to promote participant retention and complete follow-up

Loss to follow-up and participant withdrawal will be minimised in a number of ways:

1. People with MND will be encouraged to discuss any difficulties they are having regarding attendance or engagement in the sessions with their therapists.
2. Support from therapists via videoconference, instant messaging, telephone or email, depending on patient preference, will be provided to supplement face-to-face sessions.
3. Participants with MND will have regular contact with their MND care team.
4. Participation in the trial will be assisted by the provision of funds towards travel, either for participants with MND and their caregivers to travel to clinic to receive therapy, or for therapists to travel to the homes of participants with MND.
5. Participants with MND will be provided with appointment reminders and flexible means of participating in therapy sessions, wherever possible (e.g., face-to-face at home or in the clinic, or via videoconference or telephone).
6. Participants with MND and their caregivers will be provided with appointment reminders and flexible means of participating in outcome assessments, wherever possible (e.g. via telephone, videoconference, post, online, email, or face-to-face interview at home or in the clinic).
7. Trial appointments will be scheduled with routine clinical follow-up appointments, where possible.
8. Evidence-based procedures for recruiting and maintaining study participation and encouraging people with MND to complete outcome measures will be adopted (e.g. the use of incentives such as non-contingent vouchers for completion of follow-up measures, sending greetings cards, personalizing letters, and maintaining contact through study newsletters[95]).
9. An online peer support forum will be available to provide participants with MND with the opportunity to receive additional support from those who are currently undergoing or have completed the intervention. The online forum will be set up on Google Groups and membership will be by invitation only.
10. An online therapist peer support forum will be available to provide study therapists with the opportunity to receive additional support from those who are currently delivering the intervention. This will be in addition to telephone group supervision that therapists will receive on a fortnightly basis. The online forum will be set up on Google Groups and membership will be by invitation only.
11. People with MND randomised to the control arm will have the option of accessing the interventional online materials and patient workbook (including handouts and worksheets) after the 9-month follow-up period (for the duration of the trial), thereby reducing the potential for withdrawal due to resentful demoralisation among people in the control group[96].

12. Data access and quality assurance

12.1 Data quality assurance

Prospect provides a full electronic audit trail, as well as validation features which will be used to monitor trial data quality, in line with CTRU SOPs and the Data Management Plan (DMP). Error reports will be generated where data clarification is required. Rates of missing data and data points which are out of the expected or allowed range will be presented to the team at monthly management group meetings.

12.2 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the trial. The Sheffield CTRU SOPs will be followed. Risk will be assessed on an ongoing basis and adjustments will be made accordingly. The degree of monitoring will be proportionate to the risks associated with the trial. A trial specific site monitoring plan will be established prior to the commencement of the trial. The trial will be monitored in accordance with the agreed plan.

12.3 Record keeping and archiving

Trial documents will be retained in a secure location during and after the trial has finished. Participating sites recognise that there is an obligation to archive trial-related documents at the end of the trial (as such end is defined within this protocol). All trial documents held in the CTRU will be archived and retained for 10 years from the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether each site complied with all applicable regulatory requirements. All archived documents will continue to be available for inspection by appropriate authorities upon request.

13. PPI

Service user involvement will continue in a number of ways in order to provide partnership and enhance the relevance, appropriateness and practicality of the intervention:
i) Manual development: The intervention was initially developed through a combination of interviews and workshops comprising people with MND, caregivers of people with MND and MND healthcare professionals. Discussions explored: a) facilitators/barriers to engagement in a psychological intervention for people with MND (including potential ways of overcoming barriers); b) positive and negative experiences of psychotherapy for MND (for those who have previously engaged in these approaches); c) how best to adapt ACT for people with MND (for example, which components of ACT interventions are considered suitable or most relevant for people with MND, which will require adaptation, and which general adaptations to therapy would be most helpful for people with MND); d) ways of optimising engagement (e.g. using peer mentors to provide support during therapy); and e) how best to promote the intervention to people with MND not currently experiencing distress, as they may perceive less of a need for such an intervention;
ii) Patient/Caregiver Advisory Group: Five interested people with MND/caregivers were invited to be members of the Patient/Caregiver Advisory Group. The intervention has been developed and refined in close collaboration with them, getting advice from them on how best to adapt the intervention for people with MND and the appropriateness of the materials. They have also advised on research management, trial literature preparation and dissemination of the findings, in conjunction with established PPI groups in London and Sheffield and the MND Association;
iii) Trial Management Group: Two people with MND have been invited to be part of the Trial Management Group;
iv) Trial Steering Committee: Two people with MND have been invited to be part of the Trial Steering Committee;
v) Therapist training: Two interested people with MND/caregivers from the Patient/Caregiver Advisory Group were invited to participate in training therapists in how to apply ACT skills to people with MND (with training and support from the Chief Investigator);
vi) Dissemination: An interested person with MND/caregiver from the Patient/Caregiver Advisory Group will be invited to participate in local and national presentations of the findings (with training and support from the Chief Investigator).

14. Publication

14.1 Dissemination

Dissemination to the academic and clinical community, service users and the broader public will occur through:
i) Peer-reviewed, international open-access academic journals. The protocol for Phase 2 will be published, and findings will be reported in accordance with reporting guidelines for quantitative cohort studies (STROBE;[97]) and qualitative research (COREQ;[98]), as well as guidelines relevant to non-pharmacological treatment interventions such as CONSORT guidelines for non-pharmacological treatment interventions[99];
ii) National and international academic conferences (e.g. International Symposium on ALS/MND, Association of Contextual Behavioural Sciences Conference);
iii) Local clinical conferences and meetings;
iv) Talks to local MND groups, the MND Association, and other organisations following guidance from our Patient/Caregiver Advisory Group, and including an interested member of this group;
v) University media releases, Twitter feeds and the University website;
vi) Training and seminars delivered via ACT special interest groups and professional bodies (such as the Association of Contextual Behavioural Sciences and the British Psychological Society's ACT and clinical health special interest groups), associated conferences and UK regional ACT clinician groups.

14.2 Publication policy

A publication and dissemination policy will be developed as part of this project. Publications arising directly or indirectly from the trial will adhere to UCL and BMJ (2009) guidelines on authorship and contributorship. These state that 'authorship credit should reflect substantial contribution to:
i) Conception and design, or analysis and interpretation of data;
ii) Drafting the article or revising it critically for important intellectual content;
iii) Final approval of the version to be published.
All these conditions must be met. All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing, other than those presented at scientific forums/meetings.

14.3 Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the trial, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the trial at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL, with the understanding that they may use know-how gained during the trial in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCLIPR.

15. Finance

There are no financial interests for the Chief Investigator, Co-Investigators, or collaborators. It will also be ensured that there are no financial interests for the TSC or DMEC. The trial funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the trial. Research costs and service support costs will be supported via UCL and the Local Clinical Research Network, respectively. Excess treatment costs arising from training therapists in ACT and delivering ACT to people with MND in the feasibility study will be supported via the NHS and funding from the MND Association. The research costs for the study have been funded by the NIHR HTA programme (HTA 16/81/01; £1,373,735; 12 June 2017).

16. Ethics approval

16. 1 Ethical requirements

Ethical and research governance approvals through the HRA will be obtained prior to the trial commencing. The sponsor will ensure that the trial protocol, information sheets, consent forms, and submitted supporting documents have been approved by the appropriate Research Ethics Committee, prior to any participant recruitment. The protocol, and all other supporting documents including any agreed amendments, will be documented and submitted for ethical and regulatory approval in line with Governance Arrangements for NHS Research Ethics and Quality Assurance guidelines. Ethical concerns

arising from the trial will be reviewed by the TSC and DMEC. The trial has been registered as an RCT and has been allocated an International Standard Randomised Controlled Trial ID Number (ISRCTN12655391).

Amendments will not be implemented prior to receipt of the required approvals. Before any NHS site may be opened to recruit participants, the Chief Investigator or designee must receive confirmation of capability and capacity in writing from the relevant Trust's Research & Development department. It is the responsibility of the Chief Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants. An annual progress report will be submitted to the Research Ethics Committee within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will prepare the annual progress report. Within 90 days after the end of the trial, the Chief Investigator/Sponsor will ensure that the main Research Ethics Committee is notified that the study has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. The Chief Investigator will supply the Sponsor with a summary report of the trial, which will then be submitted to the Research Ethics Committee within 1 year after the end of the trial. As the intervention is psychological, the study is not covered by the Medicines for Human Use (Clinical Trials) Regulations 2004.

17. Indemnity, compensation and insurance

All participants will be recruited through an NHS trust, and will be eligible to exercise their rights under the NHS complaint policy. In addition, participants are able to contact the Chief Investigator regarding a complaint. In the event of a complaint about the conduct of the trial, the complaint should be reported immediately to the Joint Research Office (research-incidents@ucl.ac.uk) who will decide which complaints policy applies and who will be the lead organisation.

UCL holds insurance against claims from participants for harm caused by their participation in this trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

The trial has been financed by the NIHR and details have been drawn up in a separate agreement. This is an NHS sponsored trial. If there is negligent harm during the trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

18. Declaration of interests

None declared.

19. References

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