Full title of project:	A feasibility study and randomised controlled trial of Acceptance and Commitment Therapy for people with motor neuron disease (COMMEND)
Short title:	A feasibility study and RCT of ACT for people with MND (Phase 1: Feasibility study)
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Chief Investigator:
Dr Rebecca Gould
Senior Research Associate
University College London
Division of Psychiatry
Wing A, 6th Floor Maple House
149 Tottenham Court Road
London WT1 7NF

Telephone: 020 7679 9225
Fax: 020 7679 9426
Email: r.gould@ucl.ac.uk

Sponsor Representative:
Tabitha Kavoi
Joint Research Office
University College London
1st Floor Maple House
149 Tottenham Court Road
London W1T 7NF

Postal address:
Joint Research Office, UCL
Gower Street,
London WC1E 6BT
Email: Rand.D@uclh.nhs.uk

National Institute for Health Research

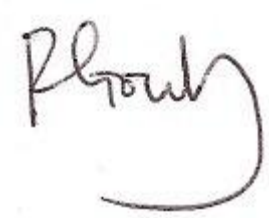
Protocol version history

Version number	Date	Protocol update finalised by (insert name of person):	Reasons for update
2	3rd Mar 2018	Rebecca Gould	Feedback from Research Ethics Committee
3	31 July 2018	Rebecca Gould	Feedback from independent oversight committee and Funder.

Signatures

The Chief Investigator and the JRO have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief Investigator Dr Rebecca Gould UCL		15/12/17
Sponsor representative **Tabitha Kavoi** **Research Management & Governance Manager**		
Sponsor representative	Signature	Date 15/01/18

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List of abbreviations

ACT	Acceptance and Commitment Therapy
ALS	amyotrophic lateral sclerosis
CRF	case report form
HRA	Health Research Authority
MND	motor neuron disease
PPI	patient and public involvement
RCT	randomised controlled trial
UCL	University College London
UCLH	University College London Hospitals NHS Foundation Trust

1 Study personnel

See protocol cover page for Chief Investigator and Sponsor contact details.

Statistician	Mr Mike Bradburn e-mail: m.bradburn@sheffield.ac.uk Clinical Trials Research Unit ScHARR University of Sheffield Regent Court 30 Regent St Sheffield S1 4DA Tel: 0114 222 0706 Fax: 0114 222 0870
Central laboratories	N/A
Head of Department	Professor Glyn Lewis Professor of Psychiatric Epidemiology University College London Division of Psychiatry 6th Floor Maple House 149 Tottenham Court Road London WT1 7NF
Chief Investigator	Dr Rebecca Gould
Co-Investigators	Professor Christopher McDermott Professor Laura Goldstein Dr Christopher Graham Professor Lance McCracken Dr Marc Serfaty Professor Ammar Al-Chalabi Professor Dame Pamela Shaw Professor Robert Howard Mr David White Mr Mike Bradburn Dr Tracey Young Dr Vanessa Lawrence Professor Cindy Cooper

2 Summary

Objectives:	The primary objective of Phase 1 is to test the feasibility and acceptability of an Acceptance and Commitment Therapy (ACT) intervention that has been tailored to people with motor neuron disease (MND) in accordance with MRC guidelines for developing and evaluating complex interventions (1). The secondary objectives are to: i) use qualitative approaches to explore the intervention's acceptability and feasibility to people with MND and therapists; ii) evaluate the acceptability and feasibility of participating in a randomised controlled trial (RCT) of ACT through individual qualitative interviews with people with MND; and iii) clarify study design parameters for a future RCT (in Phase 2– for which separate HRA approval will be sought).
Study design and methods:	An open uncontrolled feasibility study assessing the acceptability and feasibility of ACT for people with MND will be conducted using both quantitative and qualitative approaches. ACT will be adapted prior to the feasibility study via a series of PPI workshops/individual qualitative interviews with people with MND and MND healthcare professionals (approved by University College London Research Ethics Committee [12213/001]). Co-primary outcome measures will be indicators of the acceptability of the intervention: uptake and initial engagement with/deliverability of the intervention. Secondary outcome measures will be additional measures of acceptability and feasibility of the intervention, as well as patient- and caregiver-reported outcome measures. Individual qualitative interviews with a sample of participants and all therapists following completion of the intervention will further assess acceptability and feasibility.
Study duration per participant:	7 months
Estimated total study duration:	19 months for Phase 1; feasibility study start date: 01/06/2018.
Planned study sites:	Multi-site
Total number of participants planned:	28
Main inclusion/exclusion criteria:	Inclusion criteria: 1. Aged 18 and over; 2. Diagnosis of definite, laboratory-supported probable or probable familial or sporadic ALS using the World Federation of Neurology's El Escorial criteria; 3. 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. 4. For caregivers: Primary caregiver of a person with MND. Exclusion criteria: i) Need for gastrostomy feeding or non-invasive ventilation (i.e. those in stages 4A or 4B of the King's College London clinical staging system [4]); ii) Diagnosis of dementia; iii) Currently receiving ongoing formal psychological therapy delivered by a formally trained psychologist or psychotherapist or unwilling to refrain from engaging in such formal psychological therapy during the receipt of ACT; iv) Insufficient understanding of English to enable engagement in ACT and completion of screening measures and patient-reported outcome measures; v) 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; vi) Need for treatment for severe psychiatric disorder such as schizophrenia or bipolar disorder, or those expressing suicidal ideation with active plans/suicidal behaviours and intent; vii) Other medical factors that could compromise full study participation such as intellectual disabilities or severe sensory deficits (e.g. visual blindness).

Statistical methodology and analysis:	Participant recruitment, intervention uptake, data completeness and other binary or categorical measures will be summarised using frequencies and percentages, and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). No formal analysis will be conducted on the data, as recommended in pilot/feasibility studies (5-6). Qualitative data will be transcribed verbatim and anonymised to maintain confidentiality. Data will then be analysed iteratively using a focussed thematic analysis (7).

3 Background and rationale

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 (8-10). There is no cure, and riluzole, the sole disease-modifying UK-licensed drug, prolongs median survival for only 2-3 months at 1 year (11). 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 (12-14). Although shorter survival times, poorer quality of life and increased risks of suicide and mortality have been reported in those experiencing psychological distress (15-19), 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 (20). People with MND may be able to access formal psychological therapies such as Cognitive Behavioural Therapy through Improving Access to Psychological Therapy services (21). 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 (22) will be developed specifically for people with MND through a series of qualitative workshops and individual interviews (approved by 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 will then be assessed in an open uncontrolled feasibility study.

Why ACT is being proposed: ACT is an acceptance-based behaviour therapy (22) with a strong evidence base for improving outcomes (such as functioning, quality of life and mood) in chronic pain (23), and a growing evidence base in chronic disease (24) and mental health (25) 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 (26). 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 (21). 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 (27-31). 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 (27-31). 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 (32-33), predicts quality of life, mood and adjustment in MND and other progressive and incurable conditions (34-35). Third, there is emerging preliminary evidence that ACT might have advantages over conventional Cognitive Behavioural Therapy through improved engagement, retention and durability of effects (36-39). 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 (40-41). 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 (42) identified four studies that have been conducted to date (43-47): 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; 48) and a protocol and qualitative study of meditation training (40-41) - 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 (23-25, 31, 49-50). 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 (23-24). 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 (34) and other progressive, incurable, life-limiting conditions: muscle disorders (35, 51-52), Duchenne muscular dystrophy (53), and palliative care populations (54). 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 (35, 51-52).

3.1 Assessment and management of risk

Information sheets will provide participants with information about the possible benefits and risks of taking part in the study. 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 1. Risk of harm to self (including assisted and non-assisted suicide) or others will be monitored throughout the study. If suicidal ideation without 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 suicidal ideation with active 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 in full discussion with the participant and clinical team.

Inadequate treatment response: If a participant remains moderately to severely anxious or depressed at the end of the study (as indicated by a score of ≥9 on the Hospital Anxiety and Depression Scale [99] excluding data from questions which overlap physical symptoms of MND [55]) then this will be discussed with the participant and their MND care team/GP. Treatment (e.g. referral for psychological therapy, antidepressant) will be recommended, if necessary.

Potential distress: Evidence of any adverse effects from the ACT intervention will be monitored throughout the study. Reasons for withdrawing participants from the ACT intervention will be clarified with the Trial Management Group prior to the commencement of the open uncontrolled feasibility study. Anyone experiencing an increase in distress will be assessed for risk, and standard operating procedures will ensure safety is respected. New reports of suicidal behaviour during the ACT intervention will be reported as Serious Adverse Events. Any distress experienced during individual qualitative interviews will be identified and responded to by the researcher, under the supervision of the Chief Investigator.

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.

4 Study objectives

Primary: The primary object of Phase 1 of the study is to test the feasibility and acceptability of an Acceptance and Commitment Therapy (ACT) intervention that has been tailored to people with motor neuron disease (MND) in accordance with MRC guideline for developing and evaluating complex interventions.

Secondary: The secondary objectives are to:
i) Use qualitative approaches to explore the intervention's acceptability and feasibility to people with MND and therapists;
ii) Evaluate the acceptability and feasibility of participating in a future RCT of ACT through individual qualitative interviews with people with MND;
iii) Clarify study design parameters for a future RCT (in Phase 2 - HRA approval to be obtained separately for this).

5 Study design

A series of PPI workshops and individual qualitative interviews with people with MND, caregivers of people with MND and MND healthcare professionals will be conducted in order to develop the intervention. This part of the study ('manual development') has been reviewed and approved by UCL's Research Ethics Committee (ref no. 12213/001). The manual development will be followed

by an open uncontrolled feasibility study (Phase 1) assessing the acceptability and feasibility of ACT for people with MND using both quantitative and qualitative approaches.

6 Selection of participants

6.1 Inclusion criteria

i) Aged 18 and over;
ii) Diagnosis of definite, laboratory-supported probable or probable familial or sporadic ALS (which is diagnostically synonymous with MND [2]) using the World Federation of Neurology's El Escorial criteria (3);
iii) For caregivers: Primary caregiver of a person with MND.

6.2 Exclusion criteria

i) Need for gastrostomy feeding or non-invasive ventilation (i.e. those in stages 4A or 4B of the King's College London clinical staging system [4]), as 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);
ii) Diagnosis of dementia using standard diagnostic guidelines (e.g. 56-57), as this would impede engagement with the intervention;
iii) Currently receiving ongoing formal psychological therapy delivered by a formally trained psychologist or psychotherapist or unwilling to refrain from engaging in such formal psychological therapy during the receipt of ACT, due to the fact that concurrent engagement may lead to conflicts in therapeutic approaches and goals;
iv) 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;
v) 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;
vi) Need for treatment for severe psychiatric disorder such as schizophrenia or bipolar disorder, or those expressing suicidal ideation with active plans/suicidal behaviours and intent, as other forms of treatment would be indicated;
vii) Other medical factors that could compromise full study participation such as intellectual disabilities or severe sensory deficits (e.g. visual blindness).
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 study 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.

6.3 Recruitment

Potential participants will be recruited from a minimum of 10 sites in Phase 1. Potentially eligible participants with MND and their caregivers will be identified and approached about the study in one of four ways. First, clinicians will approach potentially eligible participants with MND and their caregivers attending routine clinic appointments at the MND Care Centres/ clinics about the study using the patient and caregiver information sheets (which will also be sent to them prior to their appointment by the clinicians). They will then seek verbal consent or consent with the use of a communication aid for a member of the local research team or a research nurse from the Clinical Research Network identified to work with the local site to contact the patient and caregiver to discuss the study further. Second, clinicians from MND Care Centres/clinics will identify potentially eligible participants with MND from clinic databases, and a study invitation letter and patient and caregiver information sheets will be sent to them. This will include details of how patients and caregivers can discuss the study further with a member of the local research team or a research nurse from the local Clinical Research Network. Third, 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. 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, Build-UK 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 have been identified and consent for contact has been obtained (either verbally or with the use of a communication aid), a member of the local research team or a research nurse from the Clinical Research Network will contact them to discuss the study further (either in the clinic or patient's home, or via telephone, depending on patient preference). The study 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 study then they will be given a patient or caregiver information sheet, if they do not already have one. They will then be contacted a minimum of 24 hours later 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 study. If they are 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 the clinic or patient's home, depending on patient preference). Eligibility for inclusion in the study will be determined during the screening appointment, and fully informed consent will be sought from eligible participants. Consent will be obtained as either fully informed written consent, verbal consent (for those who cannot provide written consent), 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 verbal consent or consent without the use of a communication aid is obtained. Fully informed written consent to participate in the study will also be sought from the caregiver of the person with MND.

Therapists participating in individual qualitative interviews will be recruited from the pool of therapists who have already been identified and approached about the study and have agreed to deliver ACT to people with MND. All study therapists will be invited to participate in the qualitative interviews by a member of the research team. This part of the study will be described to them and therapists will be given the opportunity to ask any questions or discuss any concerns. Those who express an interest in participating in the qualitative interviews will be sent the therapist information sheet by a member of the research team. They will then be contacted a minimum of 24 hours later by a member of the research team to determine whether they are still interested in participating in the study. If they are then they will be invited to attend an interview with a member of the research team. Fully informed written consent to participate in this part of the study will be obtained prior to completing the interview.

Participant recruitment at a site will only commence when the study has:
i) Been confirmed by the Sponsor (or its delegated representative);
ii) Received Health Research Authority (HRA) approval;
iii) Received confirmation of capability and capacity from the participating NHS Trust.

6.4 Informed consent

All potential participants will be given patient information sheets and will have the opportunity to discuss the study, ask questions and request further information at least 24 hours before being asked to provide fully informed written consent, verbal consent (for those who cannot provide written consent), 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. A copy of the signed informed consent form will be given to the participant and the original signed form will be retained in the study files at the co-ordinating site.

Participants 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 study and that they can withdraw at any time, without having to give a reason and without their subsequent care being affected. It will be made clear to participants that no disadvantage will accrue if they choose not to participate in the study. It is not expected that participants will lose the capacity to provide informed consent during the course of the study. If they do, then they will be withdrawn from the study. The initial giving of informed consent provides a clear indication of the person's likely perspective on continuing at this point. 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 study.

It will be the responsibility of the Principal Investigator, or a person delegated by the Principal Investigator to obtain written informed consent from each participant prior to participation in the study, 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 Staff Signature and Delegation of Tasks. Capacity to provide consent will be determined at the screening and baseline assessment. No study procedures will be conducted prior to the participant giving consent to participate in the study. Consent will not denote enrolment into the study. Screening and baseline assessments will only be completed after fully informed consent is given by the participant (either via written consent, verbal consent for those who cannot provide written consent, or consent via the use of a communication aid).

7 Interventions

7.1 Name and description of intervention under investigation

7.1.1 ACT

In ACT, psychological inflexibility, or the psychological suffering that emerges from experiential avoidance, cognitive fusion, loss of contact with the present moment, and failure to connect and act in accordance with one's values, is thought to underlie psychopathology (22). There are six core clinical processes aimed at increasing psychological flexibility in ACT: i) acceptance - accepting or opening up to difficult or unpleasant emotional experiences rather than avoiding them; ii) cognitive defusion - stepping back or detaching from unhelpful thoughts, images and memories as opposed to being fused with them; iii) contact with the present moment - being in the here and now in contrast to ruminating about the past or worrying about the future; iv) self-as-context - observing oneself as distinct from the content of one's experiences; v) values - re-engaging with one's personal values and what matters rather than losing contact with them; and vi) committed action - committing to doing what matters in contrast to avoidance or inaction. Research has supported the applicability of these processes in a variety of clinical populations, including MND (34) and other progressive, incurable, life-limiting conditions: muscle disorders (35, 51-52), Duchenne muscular dystrophy (53), and palliative care populations (54). Further details about the intervention and its development are provided below.

7.1.2 Usual care

All participants with MND will receive all aspects of usual multidisciplinary care in Phase 1, with the exception of formal psychological therapies such as Cognitive Behavioural Therapy. Treatment as usual will comprise standard care as outlined in NICE Clinical Guideline NG42 for MND (20). 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 (20). 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 (58). 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 study for ethical reasons, but all such interventions will be recorded as part of the modified Client Service Receipt Inventory.

8 Study procedures

8.1 Pre-intervention assessments

All pre-intervention procedures will be carried out as specified in the schedule of assessments (Appendix 1). Socio-demographic and clinical data collected at screening will include: age, ALS diagnosis using El Escorial criteria (3), 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 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 open uncontrolled feasibility study, and need for translators. Additional socio-demographic and clinical data collected at baseline for all those people with MND who meet eligibility criteria will include: i) sex, ethnicity, marital status, years of education, 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) and MND Behavioural Instrument (59-61). Where an ECAS assessment has been completed within 12 weeks (of baseline), and data are recorded in full in the patient notes, this can be added to the case report form and used for the study.

8.2 Intervention procedures

8.2.1 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 are envisaged for the open uncontrolled feasibility study. The intervention procedures described are subject to change based on patient and clinical input during manual development.

Previously successful strategies for adapting ACT to clinical populations relevant to people with MND (e.g. CanACT [29, 62] and ACTMuS [63]) will be used to create a manualised intervention for people with MND. This will be 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 will be developed through a combination of 4 PPI workshops comprising people with MND, caregivers of people with MND and MND healthcare professionals (one each for the Patient/Caregiver Advisory Group, PPI groups in London and Sheffield and MND healthcare professionals) and individual qualitative interviews via telephone with up to 10 people with MND, caregivers of people with MND or MND healthcare professionals who are unable to physically attend workshops or engage via videoconferencing. Discussions will explore: 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 will inform development of a manualised intervention based on existing ACT approaches (22), comprising a patient workbook, videos, manual and training for therapists.

The intervention will be developed so that it will be tailored to the psychological, physical, communication and cognitive needs of people with MND. Modules will 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 will 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 will be 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 will also incorporate 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 will be adjusted to accommodate physical and communication difficulties by drawing on theoretical principles of 'Selective Optimisation with Compensation' (64). 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 (65). 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 will also address mild cognitive difficulties (predominantly involving executive or language dysfunction) as these have been reported in approximately 50% of people with MND (66). Standard therapeutic strategies will be 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 will be 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.

It is anticipated (subject to change based on patient and clinical input) that the intervention will comprise up to eight 1:1 sessions, each lasting up to 1 hour, over the course of three months, with a minimum of four being face-to-face (delivered within the MND clinic, GP surgery or participant's home, or via videoconferencing, depending on patient preference and therapist availability) and up to four being delivered via online videos/DVDs (followed by therapist support via videoconferencing, instant messaging, telephone or email, depending on patient preference). Hard copies of video-based sessions will be used for those unable to operate or access equipment, or where there are compatibility issues between communication platforms and videos. A phased ending to the sessions will be incorporated such that they will be weekly for the first six sessions and then fortnightly and monthly for the last two sessions in order to avoid participants perceiving that they have been abandoned due to therapy ending abruptly. The stipulation of three months to complete the intervention allows for this phased ending, as well as breaks in sessions due to ill-health or hospital appointments.

The flexible delivery of the intervention will ensure the following issues can be accommodated: i) physical and communication deficits, fatigue and other symptoms, as video-based sessions can be completed at a time most convenient to people with MND; ii) mild cognitive difficulties, as video 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 video-based sessions 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 videoconferencing, 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 (67-72). Indeed, a recent RCT of online Cognitive Behavioural Therapy for depression observed poor uptake and no impact on outcomes compared to usual care (73). Thus, a blended approach of face-to-face sessions supplemented by video-based sessions 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.

The intervention will be 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 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 developed and 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 be developed and 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 study starting (in the pre-orientation phase). 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. As for previous and ongoing trials of ACT (38, 66), training will be developed and 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. 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 (39, 74-75).

All therapy sessions will be recorded using encrypted digital voice recorders in order to monitor adherence to the treatment manual. Therapists will be asked to complete a checklist of ACT components, ACT techniques, and themes discussed after each session, together with any deviations from the manual, in order to monitor treatment adherence during supervision. This will also be completed for 10% of sessions by an independent ACT therapist so that ratings can be compared with therapists' self-reports. 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 a deviation from the manual is identified from the ACT checklist 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 (76). 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 (77). 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 Project Development Group prior to sessions being rated.

Following assessment of the feasibility and acceptability of the intervention, individual qualitative interviews will be conducted with an estimated 15 people with MND who have received ACT and all therapists. These will examine: i) the acceptability and perceived value of the different components of the intervention; ii) the relevance of ACT to people with MND; iii) the suitability of its format to people with MND (e.g. number and frequency of sessions, use of videos); iv) ways of optimising engagement; v) the perceived benefits and limitations of the intervention, together with any recommendations for improving it; vi) how acceptable and feasible a more intense and briefer therapy format would be for people with MND to engage in and therapists to deliver, as well as what they would prefer; vii) therapists' experiences of the ACT training and delivering ACT in the context of MND; and viii) therapists' perceptions of the deliverability of the intervention within the NHS. The acceptability and feasibility of participating in a future RCT of ACT will also be assessed in individual qualitative interviews with people with MND through examining attitudes towards randomisation, recruitment practices, informed consent procedures, choice of outcomes measures and mode of outcome assessment. Interviews with people with MND and study therapists will be audio recorded on a encrypted digital voice recorder, and then transferred and stored onto University College London's password-protected secure electronic network. All data on encrypted digital voice recorders will be deleted after the data have been transferred. Transcriptions of interviews will be completed as soon as possible after interview completion either by a member of the research team or by a transcription service that has been approved by UCL (Way with Words). All data will be anonymised (and so the recordings will not include personally-identifiable data), will only be used for analysis, and will only be viewed by members of the research team.

The intervention will then be refined based on information gathered in Phase 1 from participants and therapists, in partnership with the Patient/Caregiver Advisory Group and PPI groups. Specifically, they will be invited to comment on themes arising from the qualitative interviews, and review the intervention and any proposed revisions before it is implemented in a future RCT (Phase 2). Data from the qualitative interviews, as well as data on mortality rates at 6 months in the uncontrolled feasibility study, will be used to consider whether the format of the intervention needs to be modified in light of the findings (e.g. more intense and briefer).

8.3 Subsequent assessments and procedures

This section describes all proposed patient- and caregiver-reported measures during the open uncontrolled feasibility study, which will be completed at baseline (0 months), following confirmation of eligibility, and 6-month follow-up, with one exception. The Satisfaction with Therapy and Therapist Scale-Revised will only be collected at 6-month follow-up. Data collection will be conducted via telephone, post, 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 measures:

i) McGill Quality of Life Questionnaire - Revised (78): A 14-item self-report global measure of quality of life, based on the original MQOL that has been validated in people with MND (79-81), which is being used as the main measure of psychological health;

ii) Hospital Anxiety and Depression Scale (99): 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 (55), a subset of data will also 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;

iii) Acceptance and Action Questionnaire-II (82): A 7-item self-report measure of psychological flexibility (an ACT-specific coping measure), which is commonly used in ACT studies;

iv) EQ-5D-5L (83): 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;

v) Non-physical adverse events other than physical self-harm, as people with MND will experience many physical adverse events that will be unrelated to the intervention;

vi) ALS Functional Rating Scale-Revised (84): 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;

vii) Satisfaction with Therapy and Therapist Scale-Revised (85): 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). There is no set definition of what constitutes "satisfactory" and so this will be defined as a total score of 21 or more on the Satisfaction with Therapy subscale.

Caregiver-reported measures (absence of a caregiver to complete these measures will not negate a person with MND's participation in the study):
i) EQ-5D-5L (83);
ii) Zarit Burden Interview (86): 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:
i) Modified Client Service Receipt Inventory (58): A measure of service utilisation used to calculate patient costs, which will be modified for use in people with MND. The acceptability and feasibility of this modified version will be assessed and key items of resource use for cost-effectiveness analyses in a full RCT will be identified.

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 study are all potential sources of bias that can affect treatment outcomes. Consequently, the following measures will be included, which will also allow further assessment of the acceptability and feasibility of the intervention:
i) Credibility/Expectancy Questionnaire (87): 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 will be adapted for people with MND and measured immediately after the first therapy session. 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;
ii) ACT Treatment Integrity Coding Manual (76): 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. 88). 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;
iii) ACT Adherence Checklist: A checklist of ACT components, techniques, and themes discussed in each session, which will be adapted from that which is currently being used in CanACT (29). This will be completed by therapists at the end of each session, and will also be completed for 10% of sessions by the independent ACT therapist, at the same time as the ACT Treatment Integrity Coding Manual, so that ratings can be compared with therapists' self-reports;
iv) Modified Client Service Receipt Inventory (58): This measure of service utilisation, modified for people with MND, will be used to record other forms of psychological therapy and pharmacotherapy received outside of the study. As a drug stabilisation period will not be included in the open uncontrolled feasibility study, the name, dose and frequency of all psychotropic medication prescribed, and any changes to this, will be recorded during the course of the study. This information will be extracted from GP medical records, with participants' consent. Participants 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, along with any interventions that participants are referred for after receiving the intervention.

Qualitative interviews:
Individual qualitative interviews with an estimated 15 people with MND (or until saturation is reached) and all therapists will also be conducted after participants have received ACT to explore the acceptability and feasibility of the intervention and study design. These will examine a range of issues including the acceptability, relevance and suitability of the intervention to people with MND and therapists, as well as ways of improving it. Interviews will also examine attitudes towards randomisation, consent, choice of outcome measures and mode of outcome assessment (via telephone, post, online or face-to-face interview), and any suggestions for improvement. Purposive sampling will be conducted on the basis of gender, ethnicity, time since diagnosis of ALS (which is diagnostically synonymous with MND [2]), and session attendance to explore a range of perspectives. Individual qualitative interviews with all therapists will also examine how ACT was delivered in practice, including treatment fidelity and ease of delivering ACT for people with MND, and suitability of its format.

Monitoring measures:
Evidence of any adverse effects from the intervention will be monitored and recorded throughout the study.

8.4 Discontinuation/withdrawal of participants

In consenting to participate in the study, participants are consenting to receive the intervention, screening and outcome assessments at baseline and follow-up, and data collection in the open uncontrolled feasibility study. A participant may be withdrawn from the study 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 study may include:
i) Active suicidal ideation with intent and plans;
ii) Illness that may exclude the possibility of engagement in the intervention;
iii) A person withdrawing consent or losing the capacity to consent to participate in the study.

The decision to withdraw a participant from treatment will be recorded in the Case Report Form (CRF) and Investigator Site Files. If a participant explicitly states they do not wish to contribute further data to the study their decision must be respected and recorded in the CRF.

8.5 Strategies to optimise study retention

Loss to follow-up will be minimised in a number of ways. People with MND will be encouraged to discuss any difficulties they are having regarding attendance or engagement in the sessions with their therapists. Support from therapists via videoconferencing, instant messaging, telephone or email, depending on patient preference, will be provided to supplement face-to-face sessions. Study participants will have regular contact with their MND care team. Participation in the study will be assisted by the provision of funds towards travel, either for participants to travel to clinic to receive therapy, or for therapists to travel to participants' homes. Participants will be provided with appointment reminders and flexible means of participating in outcome assessments (e.g. via telephone, post, online or face-to-face interview at home or in clinic). Study appointments will be scheduled with routine clinical follow-up appointments, where possible. Finally, 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, maintaining contact through study newsletters [89]).

8.6 Definition of end of study

The expected duration of Phase 1 of COMMEND is 19 months. The beginning of the study is defined as the date of recruitment of the first participant to the open uncontrolled feasibility study. The end of the study is defined as the date of the last follow up visit of the last participant in the open uncontrolled feasibility study.

9 Recording and reporting of adverse events

9.1 Unblinding

This is not applicable to the current study as it is an open uncontrolled feasibility study.

9.2 Notification of reportable protocol violations

A reportable protocol violation is a breach which is likely to effect to a significant degree:
(a) The safety or physical or mental integrity of the participants of the study; or
(b) The scientific value of the study.
The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The Chief Investigator or designated individual will notify the sponsor of any protocol violation.

9.3 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. A reportable incident 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 of loss or damage.

10 Data management

10.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act (1998). The CRFs will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and study identification number, will be used for identification and this will be clearly explained to the patient in the patient information sheet. Patient consent for this will be sought. All participant information will be stored in accordance with the UK Data Protection Act (1998) guidance, with all personally identifiable information, stored in locked cabinets and stored separately from study data, which will be pseudonymised and saved on password-protected computers at UCL. 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. After completion of the study all personal details will be deleted.

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's GP/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). Participants' GPs will also be informed of their participation in the study, with participants' consent.

10.2 Data collection tools and source document identification

Data will be collected from sites on study-specific CRFs or data collection tools such as electronic CRFs. Source data contained in source documents will be accurately transcribed onto the CRFs by the local research team or Clinical Research Network research nurse. Methods to maximise completeness of data will be applied when necessary. The Chief Investigator will have the primary responsibility of ensuring all data entered in the CRFs are accurate. A delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the study database (Chief Investigator, statistician, research assistant).

10.3 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 Data Protection Policy, study documentation and anonymous data will be securely kept for a period of 10 years following completion of the study. All data from all sites taking part in this project will be kept and monitored at UCL. The Chief Investigator and or a designated individual will be responsible for any data queries.

10.4 Data handling

All data will be collected in accordance with the patient consent form, patient information sheet 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 UK Data Protection Act (1998). All data will be pseudonymised using unique identification numbers and stored without contact details (names or addresses). Associations between participants' contact details and identification numbers will be stored in a separate electronic password-protected database. Access to this document will be restricted to the Chief Investigator and the research assistant. All data will be held on a secure database on a password-protected computer, and access to it will be restricted to the research team. Study consent forms will be kept in a locked cabinet at UCL for 10 years. Access to data will be restricted to the research team. Audio files of workshops, individual qualitative interviews and therapy sessions recorded on encrypted digital voice recorders will be uploaded to a secure server using a 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 using a UCL password-protected computer. Transcriptions of workshops and individual qualitative interviews will be completed as soon as possible after collection and anonymised. Data will not be transferred to any party not identified in this protocol and will not to be processed and/or transferred other than in accordance with the patients' consent.

Quality control

Accurate records will be kept, in line with the research protocol, in relation to recruitment and data collection. Data will be collected and managed in a systematic way, and researchers will be trained, supervised and supported. Quality control will be monitored in the beginning monthly and every three months subsequently. The Chief Investigator will ensure that all records are maintained and participant confidentiality is assured. Quality control to a sample of data will be performed during the first weeks of data collection. Investigator Site Files and a Master file will also be kept that will source all documents of the study.

11 Statistical considerations

11.1 Primary outcome measure(s)

The co-primary measures will be indicators of the acceptability of the intervention: uptake and initial engagement with/deliverability of the intervention (≥80% of the target sample recruited in 4 months, with ≥70% completing at least 2 sessions). These will be used as Stop/Go criteria for progression to Phase 2 of the study (RCT).

11.2 Secondary outcome measure(s)

The secondary outcome measures will be additional measures of acceptability and feasibility of the intervention, as well as patient- and caregiver-reported outcome measures. The acceptability of completing the battery of patient and caregiver measures will be assessed through completion rates and rates of missing items. No formal statistical analysis of patient and caregiver measures will be conducted as recommended for feasibility studies.

i) Acceptability:
a) Satisfaction with Therapy and Therapist Scale-Revised (85) at 6 months;
b) Failure to recruit due to lack of acceptability of the intervention;
c) Attrition due to lack of acceptability of the intervention.
ii) Feasibility:
a) Referral rate;
b) Failure to recruit for reasons other than lack of acceptability of the intervention;
c) Attrition for reasons other than lack of acceptability of the intervention;
d) Sessions offered over the course of three months (as opposed to completed).

iii) Patient-reported outcome measures at 0 and 6 months:
a) McGill Quality of Life Questionnaire - Revised (78);

b) Hospital Anxiety and Depression Scale (99, 55);
c) Acceptance and Action Questionnaire-II (82);
d) EQ-5D-5L (83);
e) Non-physical adverse events other than physical self-harm;
f) ALS Functional Rating Scale-Revised (84).

iv) Caregiver-reported outcome measures at 0 and 6 months (absence of a caregiver to complete these measures will not negate a person with MND's participation in the study):
a) EQ-5D-5L (83);
b) Zarit Burden Interview (86).

v) Cost-effectiveness-related measures at 0 and 6 months:
a) Client Service Receipt Inventory (58) modified for people with MND.

11.3 Sample size calculation

The key parameters of interest are uptake (defined as the percentage of participants screened who are eligible and consent) and initial engagement with the intervention (defined as the proportion of participants completing at least 2 sessions). Estimating that 50-56 people with MND will be assessed will allow the estimation of uptake to within a standard error of 7.5%. A sample size of 28 people with MND in the open uncontrolled feasibility study from a minimum of 10 sites, assuming 20% attrition at 6 months (90), will allow engagement with the intervention to be estimated to within a standard error of 10%. A sample size of 28 is consistent with sample sizes of 24-35 participants recommended for pilot and feasibility studies in order to provide sufficient data and precision of means and variances (91-93).

11.4 Planned recruitment rate

It is estimated that 112 people with MND will need to be identified in 4 months across a minimum of 10 sites in order for 28 people with MND to be eligible and agree to participate in the open uncontrolled feasibility study (see Appendix 2). This figure assumes that approximately 50% of participants will be ineligible (based on eligibility rates reported by participating MND Care Centres/clinics), and 50% of eligible patients will decline participation (based on 39% of respondents in a national survey conducted by the study team of people with MND who were not interested in accessing psychological therapies). In order to meet the target recruitment rate of 28 people with MND within 4 months across a minimum of 10 sites, the identification rate will need to be approximately 28 potential participants per month (2.8 people with MND per site per month), of whom it is estimated that 7 will be eligible and will agree to participate per month (0.7 people with MND per site per month). The participating MND Care Centres/clinics have reported that, on average, 89 new people with MND and 175 existing people with MND in follow-up are seen in each Centre/clinic per year. Of these, they have estimated that, on average, 52% of all people with MND would be eligible for the study. If uptake is slower than anticipated then recruitment will be expanded to other MND Care Centres/clinics.

11.5 Statistical analysis

11.5.1 Summary of baseline data and flow of participants

Essential socio-demographic and clinical data recorded at screening and baseline will be as follows:
i) Age, sex, ethnicity, marital status, years of education, highest level of educational qualification, current occupation, and highest level of occupational attainment;
ii) Diagnosis of definite, laboratory-supported probable or probable familial or sporadic ALS, ongoing medication use (dose and frequency), time since ALS diagnosis and time since symptom onset;
iii) Cognitive and behavioural difficulties using the Edinburgh Cognitive Behavioural ALS Screen and MND Behavioural Instrument (59-61);
iv) Comorbid psychiatric diagnoses and suicidal ideation.

The open uncontrolled feasibility study will produce a consort flow diagram in order to inform Phase 2 (RCT).

11.5.2 Primary outcome analysis

Data will be summarised descriptively: Participant recruitment, intervention uptake, data completeness and other binary or categorical measures will be summarised using frequencies and percentages, and continuous measures using means and standard deviations (or medians and interquartile ranges for very skewed distributions). No formal analysis will be conducted on the data, as recommended in pilot/feasibility studies (5-6).

11.5.3 Secondary outcome analysis

As above.

11.5.4 Qualitative data analysis

Qualitative data from PPI workshops and individual interviews will be transcribed verbatim and anonymised to maintain confidentiality. Data will then be analysed iteratively using a focussed thematic analysis (7). Three members of the research team will independently code initial data before constructing an analytical framework around: i) facilitators/barriers to engagement, previous experiences of psychotherapy for MND, adaptations to ACT for people with MND, ways of optimising engagement and ways of promoting the intervention to all 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, Project Steering Group and PPI groups. The computer programme QSR N-VIVO will be used to process the transcripts, enabling us to code and retrieve a large volume of narrative data.

Qualitative data from post-intervention interviews will be analysed as above. An analytical framework will be constructed around the acceptability, relevance, perceived value and feasibility of delivering ACT to people with MND.

11.5.5 Economic evaluation

Although a cost effectiveness analysis will not be conducted in the open uncontrolled feasibility study, the overall cost of service use per participant will be calculated. This will be achieved by calculating the mean cost of: i) health and social care resource use during the 6 months of the intervention using the Client Service Receipt Inventory which will be adapted for people with MND (58); and ii) delivering the intervention based on the number of sessions attended per participant, session duration, therapists' pay grade, training, supervision and overhead costs. Nationally published costs including NHS reference costs and Personal Social Service Research Unit costs (94-95) will be used to calculate the total cost of resource use per participant. The acceptability of the modified Client Service Receipt Inventory will be assessed and key items of resource use for a future RCT will be identified. Responses to the EQ-5D-5L will be examined and quality adjusted life years will be calculated. The overall mean cost per participant and incremental costs of ACT will be calculated and bootstrapping will be used to estimate 95% confidence intervals.

12 Record keeping and archiving

UCLH and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. At the end of the study, all essential documentation will be archived securely by the Chief Investigator for a minimum of 10 years from the declaration of end of study. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and show whether each site complied with all applicable regulatory requirements. The sponsor will notify the coordinating site (where all data will be stored) when study documentation can be archived. All archived documents will continue to be available for inspection by appropriate authorities upon request.

13 Oversight Committees

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.

13.1 Project Development Group and Trial Management Group

The multi-professional study team comprises:
i) Dr Rebecca Gould (RG, Senior Research Associate, University College London);
ii) Professor Christopher McDermott (CM, Professor of Translational Neurology, University of Sheffield and Chair of the NIHR UK MND Clinical Study Group);
iii) Professor Laura Goldstein (LG, Professor of Clinical Neuropsychology, King's College London);
iv) Dr Christopher Graham (GC, Academic Fellow in Behavioural Medicine, University of Leeds; and Clinical Psychologist, Clinical Neuropsychology, Leeds Teaching Hospitals NHS Trust);
v) Professor Lance McCracken (LM, Professor of Behavioural Medicine, King's College London);
vi) Dr Marc Serfaty (MS, Reader in Psychiatry, University College London);
vii) Professor Ammar Al-Chalabi (AAC, Professor of Neurology & Complex Disease Genetics, King's College London & Director of King's MND Care and Research Centre);
viii) Professor Dame Pamela Shaw (PS, Professor of Neurology, University of Sheffield & Director of Sheffield Care and Research Centre for MND);
ix) Professor Robert Howard (RH, Professor of Old Age Psychiatry, University College London);
x) Mr David White (DW, Research Associate, SCTRU);
xi) Mr Mike Bradburn (MB, Senior Statistician, SCTRU);
xii) Dr Tracey Young (TY, Senior Health Economist, School of Health and Related Research [ScHARR], University of Sheffield);
xiii) Dr Vanessa Lawrence (VL, Lecturer in Qualitative Social Sciences, King's College London);
xiv) Professor Cindy Cooper (CC, Director of the University of SCTRU & Professor of Health Services Research and Clinical Trials).

In addition, the study's collaborators comprise:
i) Two PPI representatives with lived experience of MND (JD and ST);
ii) A representative from the MND Association (Brian Dickie, BD);
iii) Clinicians from MND Care Centres/clinics: 1) Christopher McDermott (Sheffield); 2) Ammar Al-Chalabi (KCH); 3) Richard Orrell (UCLH and Royal Free); 4) Rhys Roberts (Cambridge); 5) Carolyn Young (Liverpool); 6) Tim Williams (Newcastle); 7) Idris Baker (South Wales Network); 8) Andria Merrison (Bristol); 9) Suresh Chhetri (Preston); 10) Agam Jung (Leeds); 11) David Dick (Norwich); 12) Aleksandar Radunovic (Royal London); 13) Richard Davenport, Sharon Abrahams, David Gillespie (Edinburgh); 14) Rupert Noad (Plymouth); and 15) Nigel Lyttle and Colette Donaghy (Belfast);
iv) Francesco Pagnini (FP, Catholic University of Milan & Harvard University).

A Project Development Group comprising the Chief Investigator, co-investigators with expertise in MND and ACT (CM, LG, AAC, PS, CG, LM, MS and DW), PPI collaborators and relevant study staff will meet at the beginning of the study in person/via

teleconference to outline the development of the intervention, tasks involved, and target deadlines in Phase 1. Thereafter the group will meet monthly throughout Phase 1 to monitor progress and address issues and attainment of milestones. In conjunction with this, a Patient/Caregiver Advisory Group comprising 5 people with MND/caregivers will meet bi-annually. Once the intervention has been developed, a Trial Management Group comprising the Chief Investigator, co-investigators, PPI collaborators, an interested member of the Patient/Caregiver Advisory Group and relevant study staff will meet in person/via teleconference every 3 months throughout the remainder of the study. This group will set target deadlines, monitor the conduct and progress of the study, 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 Trial Management Group will send updates to the Trial Steering Committee and Data Monitoring and Ethics Committee. 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. "Study champions" will be identified at each of the sites so that knowledge and processes about the study are disseminated to all clinicians likely to be involved, and not just the senior PIs at each site.

13.2 Trial Steering Committee and Data Monitoring and Ethics Committee

A Trial Steering Committee will be set-up and 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 Trial Steering Committee will be to provide advice on all aspects of the study and overall supervision with respect to progress, relevant approvals, protocol adherence, patient safety, as well as agree proposals for substantial amendments.

A Data Monitoring and Ethics Committee will also be set-up and 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.

13.3 Expertise of research team

The multi-professional team comprises experts in the fields of MND, development and evaluation of manual-based complex psychological interventions, mental health, and clinical trials. It has considerable expertise in conducting clinical trials and observational studies in MND (AAC, CC, CM, LG, MB, PS). It also has extensive experience of successfully developing and evaluating psychological interventions within clinical trials, including ACT for chronic pain, advanced cancer and muscle disorders (CG, LM, MS), face-to-face, computerised and telephone-supported Cognitive Behavioural Therapy for depression (CC, DW, MS), Cognitive Behavioural Therapy for dissociative (non-epileptic) seizures (LG), computerised Cognitive Behavioural Therapy for multiple sclerosis (CC), and transdiagnostic Cognitive Behavioural Therapy for comorbid anxiety and depression in older people (RG). CG and LM have led in designing and supervising an ACT intervention for people with muscle disorders. MS has clinical expertise in designing and delivering ACT for people with advanced cancer, and is currently Chief Investigator of a study of ACT in palliative care (CanACT). RG has clinical expertise in delivering mindfulness-based interventions to older people with and without dementia, has recently completed training in ACT, and is currently Chief Investigator of an NIHR-funded study of ACT for older people with generalised anxiety disorder. CG, LM and RG also work as clinical psychologists in the NHS, delivering ACT to working age and older people with progressive neurological and neuromuscular conditions, chronic pain and mental health disorders, respectively. MB, VL, DW and CC will provide expertise in collecting and analysing quantitative and qualitative data, respectively. TY will provide expertise in designing, collecting, analysing and reporting the health economic analysis. RG will be mentored by RH and CM, who have extensive experience of successfully conducting clinical trials. FP has expertise and experience in adapting mindfulness-based approaches to people with MND (40-41), which will be invaluable when adapting ACT to the needs of this population (as mindfulness is one of the components of ACT). The team has considerable previous experience of successfully working together and of leading/delivering NIHR-funded multicentre studies. All of the recruiting sites have experience in recruiting people with MND to clinical trials.

13.4 Project timetable and milestones

The project timetable and milestones are listed in Appendix 3.

14 Ethical requirements and PPI

14.1 Ethical requirements

Ethical and research governance approvals through the HRA will be obtained prior to the study commencing. The sponsor will ensure that the study protocol, participant information sheet, consent form, and submitted supporting documents have been approved by the appropriate Research Ethics Committee, prior to any participant recruitment. The protocol, 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 study will be reviewed by the Trial Steering Committee and Data Monitoring and Ethics Committee. The study has been registered as an open uncontrolled feasibility study and has been allocated an International Standard Randomised Controlled Trial ID Number (ISRCTN12655391). As the intervention is psychological, the study is not covered by the Medicines for Human Use (Clinical Trials) Regulations 2004.

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 study is declared ended. The Chief Investigator will prepare the annual progress report. Within 90 days after the end of the study, the Chief Investigator/Sponsor will ensure that the main Research Ethics Committee is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study. The Chief Investigator will supply the Sponsor with a summary report of the study, which will then be submitted to the Research Ethics Committee within 1 year after the end of the study.

14.2 PPI

The proposal was devised and developed through consultation, review and feedback from: i) people with MND and caregivers including the PPI collaborators and the Sheffield MND Research Advisory Group; ii) the Motor Neurone Disease Association, who have agreed to support the proposed study; and iii) a national survey conducted by the study team with people with MND/caregivers (N = 83) and MND Care Centres/clinics (N = 14) about access to and perception of psychological therapies. This has informed the design of the study, choice of therapy format and use of technology, outcome measures, and sample size calculation. The clinical meaningfulness of the outcome measures and how the study could be explained to potential participants has been discussed with the PPI collaborators and the Sheffield MND Research Advisory Group. The feasibility of the intervention has been discussed with clinicians from MND Care Centres/clinics and the NIHR UK MND Clinical Study Group, as well as clinical psychologists from clinical psychology, neuropsychology and Improving Access to Psychological Therapies services.

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: As noted in section 8.2.1, the intervention will be initially developed through a combination of 4 PPI workshops comprising people with MND, caregivers of people with MND and MND healthcare professionals (one each for the Patient/Caregiver Advisory Group, PPI groups in London and Sheffield and MND healthcare professionals). Individual qualitative interviews via telephone will also be conducted with up to 10 people with MND, caregivers of people with MND or MND healthcare professionals who are unable to physically attend workshops or engage via videoconferencing. Discussions will explore: 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. All PPI participants will be given a copy of the topic guide for the workshops/interviews prior to participating in them;

ii) Patient/Caregiver Advisory Group: Five interested people with MND/caregivers will be invited to be members of the Patient/Caregiver Advisory Group. The intervention will be 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 will also advise 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: An interested member of the Patient/Caregiver Advisory Group will be invited to be part of the Trial Management Group;

iv) Therapist training: Two interested people with MND/caregivers from the Patient/Caregiver Advisory Group will be invited to participate in training therapists in how to apply ACT skills to people with MND (with training and support from the Chief Investigator);

v) Dissemination: An interested service user 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);

vi) PPI collaborators: Two PPI collaborators will be invited to be members of the Project Development Group, Patient/Caregiver Advisory Group and the Trial Management Group.

15 Monitoring

The sponsor will determine the appropriate level and nature of monitoring required for the study. Standard Operating Procedures of the Sponsor 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 study. A study specific oversight and monitoring plan will be established prior to the commencement of the study. The study will be monitored in accordance with the agreed plan. Participants will be monitored for suicide risk throughout the duration of the study and in all contact with participants. Participants will remain under the care of their GP/MND Care Centre/Clinic for the duration of the study. Risk of harm to self (including assisted and non-assisted suicide) or others will be monitored throughout the study. If suicidal ideation without 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 suicidal ideation with active 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 in full discussion with the participant and clinical team. Incidents will be recorded and reported to the Trial Steering Committee, Data Monitoring and Ethics Committee, sponsor of the study and Research Ethics Committee, and if serious (and unexpected) or life threatening will be reported within 15 days of knowledge.

Expected (serious) adverse events
Due to the nature and impact of MND, physical (serious) adverse events other than physical self-harm (refer to section 3.1) are expected in this patient population.

16 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 Trial Steering Committee or Data Monitoring and Ethics Committee. The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network. Excess treatment costs arising from training therapists in ACT and delivering ACT to people with MND in the feasibility study will be supported via 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). There are no financial interests for the Chief Investigator, Co-Investigators, or collaborators. The study including the uncontrolled feasibility study and the RCT will be overseen by independent members of a Trial Steering Committee and Data Monitoring and Ethics Committee.

17 Insurance

In the event of a complaint about the conduct of the study, the complaint should be reported immediately to the Joint Research Officer (research-incidents@ucl.ac.uk) who will decide which complaints policy applies and who will be the lead organisation. The NHS complaints policy can only apply where the research subject is recruited through an NHS Trust. In other circumstances the ICL complaints policy will apply.

UCL holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study 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.

18 Dissemination and publication policy

18.1 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 combined protocol for Phases 1 and 2 will be published, and findings of Phase 1 will be reported in accordance with reporting guidelines for quantitative cohort studies (STROBE; 96) and qualitative research (COREQ; 97), as well as guidelines relevant to non-pharmacological treatment interventions such as CONSORT guidelines for non-pharmacological treatment interventions (98);
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.

18.2 Publication policy

A publication dissemination policy will be developed as part of this project. Publications arising directly or indirectly from the study 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.

19 Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, 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 study 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-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCLIPR.

20 Declaration of interests

None declared.

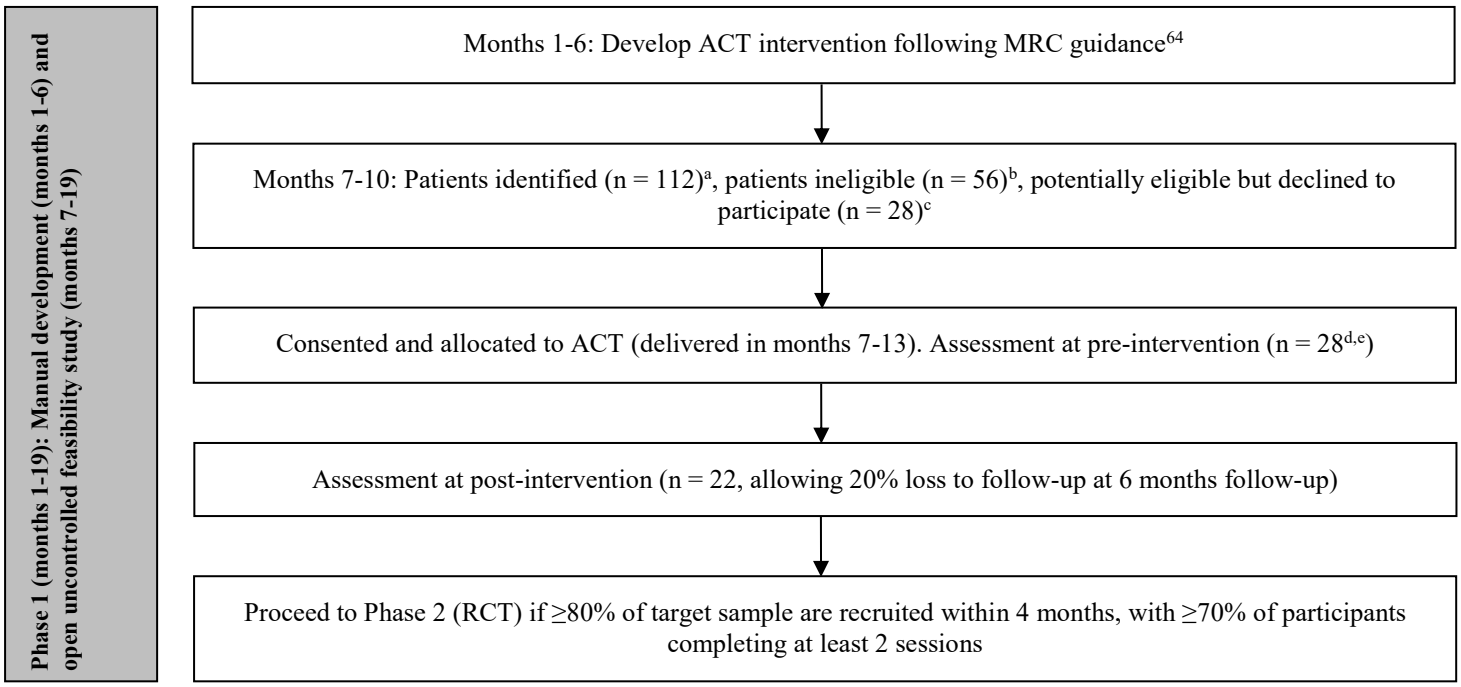
Appendix 1 – Schedule of assessments: Open uncontrolled feasibility study

	Screening & baseline Ax (0 months)	**ACT intervention (up to 8 sessions)**								**Post-Tx**	**Follow-up Ax (6 months)**
People with MND:											
Visit No	1	2	3	4	5	6	7	8	9	10	11
Day(s)	1	2	3	4	5	6	7	8	9	10	11
Window of flexibility for visits	N/A	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks	+/- 2 weeks
Informed consent	X										
ECAS*	X										
MiND-B	X										
Eligibility confirmation	X										
CEQ		X									
MQOL-R	X										X
HADS	X										X
ALS-FRS	X										X
EQ-5D-5L	X										X
AAQ-II	X										X
CSRI	X										X
STTS-R											X
Intervention		ACT+	ACT+	ACT+	ACT+	ACT+	ACT+	ACT+	ACT+		
AE review	X	X	X	X	X	X	X	X	X	X	X
Qualitative interview										X	
Caregivers:											
Visit No	1										2
Day(s)	1										2
Window of flexibility for visits	N/A										+/- 2 weeks
Informed consent	X										
EQ-5D-5L	X										X
ZBI	X										X

Note: AAQ-II = Acceptance and Action Questionnaire-II; ACT+ = Acceptance and Commitment Therapy plus usual care; AE = adverse events; ALS-FRS = ALS Functional Rating Scale-Revised; Ax = assessment; CEQ = Credibility/Expectancy Questionnaire (administered immediately after first ACT session); CSRI = modified Client Service Receipt Inventory; ECAS = Edinburgh Cognitive Behavioural ALS Screen; HADS = Hospital Anxiety and Depression Scale (99); MiND-B = MND Behavioural Instrument; MQOL-R = McGill Quality of Life Questionnaire; STTS-R = Satisfaction with Therapy and Therapist Scale-Revised; Tx = treatment; ZBI = Zarit Burden Interview.

* Where an ECAS assessment has been completed within 12 weeks (of baseline), and is recorded in full in the patient notes, this can be added to the case report form and used for the study.

Appendix 2 – Flowchart of Phase 1 in the COMMEND study.



[a] Feasibility of the identification rate is supported by figures provided by the MND Care Centres/clinics which indicated that, on average, 89 new people with MND and 175 existing people with MND are seen in each Centre/clinic per year.
[b] Based on a 50% eligibility rate (as the MND Care Centres/clinics reported that 52% would be eligible for the study).
[c] Based on a conservative 50% rate of declining as 39% of respondents in a national survey conducted by the study team were not interested in this type of therapy.
[d] Recruited and consented at a rate of 0.7 people with MND per site per month across a minimum of 10 UK-wide sites.
[e] Based on a recommended sample size of 24-35 participants in pilot and feasibility studies.

Appendix 3 – Project timetable and milestones

Date	Phase	Milestones
Months -6-0: Jun 2017-Nov 2017	Pre-orientation (prior to start date)	Place advert for research staff with date of interview. Identify therapists at feasibility sites. Apply for Phase 1 manual development approval (via UCL REC - approved on 01.12.17). Begin site set up.
Months 1-3: Dec 2017-Feb 2018	Orientation	Apply for HRA approval for Phase 1 feasibility study. Shortlist, interview and appoint research staff. Purchase equipment. Develop procedures and policies for the conduct of the study. Set up Project Development Group, Patient/Caregiver Advisory Group, Trial Management Group, Trial Steering Committee and Data Monitoring and Ethics Committee. Conduct workshops/interviews with people with MND, caregivers of people with MND and MND healthcare professionals. Continue site set up.
Months 4-6: Mar 2018-May 2018	Phase 1: Manual Development (approved by UCL REC)	Develop intervention. Produce videos. Devise and conduct 4-day training workshop on ACT for people with MND with therapists. Continue site set up.
Months 7-16: Jun 2018-Mar 2019	Phase 1: Feasibility study	Recruit participants from approximately 10 sites at a rate of 0.7 people with MND per month per site (start 1 June 2018; finish by end of Sep 2018). Deliver ACT (Jun 18-Dec 18). Collect quantitative outcome data and conduct qualitative interviews with participants and therapists. Apply for Phase 2 (RCT) HRA approval. Begin Phase 2 preparation (separate HRA approval): RCT set up (develop essential documentation, set up online database and randomisation system, contracting). Publish protocol paper and develop statistical analysis plan.
Months 17-19: Apr 2019-Jun 2019	Phase 1: Feasibility study	Clean and analyse quantitative and qualitative data. Rate ACT sessions. Make modifications to the intervention, in partnership with Patient/Caregiver Advisory and PPI groups. Phase 2 preparation (separate HRA approval): Continue RCT set up (site set-up visits). Progression to Phase 2 (RCT) if the intervention is deemed acceptable to people with MND as indicated by uptake and initial engagement (≥80% of the target sample recruited in 4 months, with ≥70% completing at least 2 sessions).

	Dates	**Jun-Nov 2017**	**Dec 2017-Feb 2018**	**Mar-May 2018**	**Jun-Aug 2018**	**Sep-Nov 2018**	**Dec 2018-Feb 2019**	**Mar-May 2019**	**Jun-Aug 2019**
	Months	**-6-0**	**1-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**
Phase	**Activity**								
0	Apply for UCL REC (manual development)								
0	Apply for HRA approvals								
0	Set up recruiting sites								
1	Orientation								
1	Develop intervention through workshops & individual interviews								
1	Train therapists								
1	Recruitment for feasibility study								
1	Deliver ACT								
1	Collect data								
1	Phase 2 (RCT) set-up								
1	Data analysis								
1	Modify intervention								

Notes: Phase 0 = pre-orientation (prior to start date). All activity relates to Phase 1 feasibility study unless otherwise stated.
The project timeline is the planned schedule of activity, and timing of tasks is subject to change.

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