

# Acceptance and Commitment Therapy plus usual care for improving quality of life in people with motor neuron disease (COMMEND): a multicentre, parallel, randomised controlled trial in the UK



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## Summary

**Background** Motor neuron disease is a progressive, fatal neurodegenerative disease for which there is no cure. Acceptance and Commitment Therapy (ACT) is a psychological therapy incorporating acceptance, mindfulness, and behaviour change techniques. We aimed to evaluate the effectiveness of ACT plus usual care, compared with usual care alone, for improving quality of life in people with motor neuron disease.

**Methods** We conducted a parallel, multicentre, two-arm randomised controlled trial in 16 UK motor neuron disease care centres or clinics. Eligible participants were aged 18 years or older with a diagnosis of definite or laboratory-supported probable, clinically probable, or possible familial or sporadic amyotrophic lateral sclerosis; progressive muscular atrophy; or primary lateral sclerosis; which met the World Federation of Neurology's El Escorial diagnostic criteria. Participants were randomly assigned (1:1) to receive up to eight sessions of ACT adapted for people with motor neuron disease plus usual care or usual care alone by a web-based system, stratified by site. Participants were followed up at 6 months and 9 months post-randomisation. Outcome assessors and trial statisticians were masked to treatment allocation. The primary outcome was quality of life using the McGill Quality of Life Questionnaire-Revised (MQOL-R) at 6 months post-randomisation. Primary analyses were multi-level modelling and modified intention to treat among participants with available data. This trial was pre-registered with the ISRCTN Registry (ISRCTN12655391).

**Findings** Between Sept 18, 2019, and Aug 31, 2022, 435 people with motor neuron disease were approached for the study, of whom 206 (47%) were assessed for eligibility, and 191 were recruited. 97 (51%) participants were randomly assigned to ACT plus usual care and 94 (49%) were assigned to usual care alone. 80 (42%) of 191 participants were female and 111 (58%) were male, and the mean age was 63.1 years (SD 11.0). 155 (81%) participants had primary outcome data at 6 months post-randomisation. After controlling for baseline scores, age, sex, and therapist clustering, ACT plus usual care was superior to usual care alone for quality of life at 6 months (adjusted mean difference on the MQOL-R of 0.66 [95% CI 0.22–1.10];  $d=0.46$  [0.16–0.77];  $p=0.0031$ ). Moderate effect sizes were clinically meaningful. 75 adverse events were reported, 38 of which were serious, but no adverse events were deemed to be associated with the intervention.

**Interpretation** ACT plus usual care is clinically effective for maintaining or improving quality of life in people with motor neuron disease. As further evidence emerges confirming these findings, health-care providers should consider how access to ACT, adapted for the specific needs of people with motor neuron disease, could be provided within motor neuron disease clinical services.

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## Introduction

Motor neuron disease is a fatal neurological disease characterised by progressive degeneration of motor neurons in the motor cortex and spinal cord, resulting in limb paralysis, dysarthria, dysphagia, and respiratory failure. It affects approximately 4.5 individuals per

100 000 worldwide,<sup>1</sup> and life expectancy is 2–4 years following diagnosis.<sup>2</sup> There is no cure, and riluzole, the sole UK-licensed, disease-modifying drug, extends median survival by about 30%.<sup>3</sup>

Because there is no therapy that significantly prolongs survival, helping people with motor neuron disease

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## Research in context

### Evidence before this study

There is a paucity of high-quality research on psychological interventions for people with motor neuron disease. We published a systematic review of psychotherapy and pharmacotherapy interventions for reducing distress or improving wellbeing in people with motor neuron disease in 2015. We searched MEDLINE, Embase, PsycINFO, and Cumulative Index to Nursing and Allied Health Literature, in addition to the Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform, and Open Grey, from database inception to Nov 20, 2014, using the keywords “amyotrophic lateral sclerosis”, “motor neuron disease”, “motor neurone disease” or “Lou Gehrig’s disease” in combination with variants of: (1) “psychotherapy”, “psychological therapy” or “counselling”; (2) “depression”, “anxiety”, “psychological distress” or “psychological wellbeing”; or (3) “antidepressant” or “anxiolytic”. The Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform, and Open Grey were searched using the following terms: “amyotrophic lateral sclerosis” OR “motor neuron disease” OR “motor neurone disease” OR “Lou Gehrig’s disease”. References of included studies and relevant systematic reviews were also manually searched. No language restrictions were applied to the search. This search was only able to identify four studies of psychological interventions and none that examined pharmacotherapy interventions. Of the studies that had been conducted, all were limited by poor methodological quality (for example, two studies did not include a control group, and three studies did not include a follow-up outcome assessment) or small sample sizes, with the combined number of participants across all studies totalling 145. We concluded that there was insufficient evidence to recommend specific psychological interventions for people with motor neuron disease at that time; a finding that was supported by a subsequent scoping review of psychological interventions for people with motor neuron disease published in 2021. A few studies have been conducted since this scoping review was published, but again these were limited by small sample sizes, high attrition rates, or poor methodological quality. We previously showed that Acceptance and Commitment Therapy (ACT), adapted for the specific needs of people with motor neuron disease, might be an appropriate psychological intervention for this population in an uncontrolled feasibility

study. However, no conclusions could be drawn about its effectiveness given the lack of control group and small sample size. We conducted an informal search of PubMed and ISRCTN every 2–3 months during the trial in order to report on any new and emerging literature to the study oversight groups.

### Added value of this study

We conducted a fully powered, multicentre randomised controlled trial to evaluate the effectiveness of ACT plus usual care in comparison to usual care alone for improving quality of life in people with motor neuron disease. This study is the first adequately powered randomised controlled trial of a psychological intervention for people with motor neuron disease conducted to date, and also the first to examine ACT in this population. After controlling for baseline scores, age, sex, and therapist clustering, we found that ACT plus usual care was superior to usual care alone for maintaining or improving quality of life at both 6 months and 9 months post-randomisation. Furthermore, this treatment effect was clinically meaningful at both timepoints. We also showed beneficial effects on symptoms of depression at 6 months and 9 months post-randomisation, brief health status at 6 months post-randomisation, and psychological flexibility at 9 months post-randomisation. Additionally, we demonstrated good evidence of the intervention’s acceptability to people with motor neuron disease (in terms of session attendance and satisfaction), feasibility of its delivery (including via remote means), and safety.

### Implications of all the available evidence

In the absence of a cure or treatment that significantly prolongs survival, helping people with motor neuron disease to improve or maintain their quality of life is vital. To date, UK Motor Neuron Disease National Institute for Health and Care Excellence clinical guidelines have not been able to recommend specific evidenced psychological interventions to help achieve improvement or maintenance of quality of life due to a paucity of high-quality research. Our findings support the use of ACT, adapted for the specific needs of these patients, for improving or maintaining quality of life in this population. As further evidence emerges confirming our findings, health-care providers should consider how access to ACT that is adapted for people with motor neuron disease could be provided within motor neuron disease services.

manage their condition, quality of life, and psychological wellbeing, is crucial. This is particularly important, as poor quality of life and psychological distress are associated with negative outcomes, including shorter survival time and increased risk of suicide.<sup>4–6</sup> However, a paucity of adequately powered randomised controlled trials means there is little clear evidence-based guidance on what psychological support should be provided.

As noted previously, studies of psychological interventions for people with motor neuron disease have been limited by small sample sizes, high attrition

rates, and variable methodological quality (such as a lack of control group or follow-up assessment).<sup>7,8</sup> For example, a randomised controlled trial of cognitive behavioural therapy (CBT) plus usual care versus usual care alone was prematurely stopped, resulting in a sample size of 15 people with motor neuron disease.<sup>9</sup> A randomised controlled trial of mindfulness meditation compared with usual care in 100 people with motor neuron disease was limited by high attrition rates (57% at the 6-month follow-up and 71% at the 12-month follow-up).<sup>10</sup> Small sample size (47 people with motor

neuron disease) and high attrition rate (47% at the 6-month follow-up) limited a randomised controlled trial of an online non-meditative mindfulness intervention versus waiting list control.<sup>11</sup> As expected, UK clinical guidelines<sup>12</sup> have not been able to recommend evidenced psychological interventions for people with motor neuron disease.

Acceptance and Commitment Therapy (ACT) is a psychological therapy<sup>13</sup> that uses a combination of acceptance, mindfulness, motivation, and behaviour change techniques to assist engagement in life-enriching activities in the presence of distressing thoughts and feelings. This approach has been shown to be beneficial for improving quality of life and psychological wellbeing in other long-term health conditions, including muscle disorders and chronic pain.<sup>14,15</sup> We have previously argued that ACT, as opposed to psychological therapies such as conventional CBT, might be particularly appropriate for people with motor neuron disease.<sup>16</sup> This is due to its more pragmatic approach of helping people to live their lives in meaningful ways alongside the condition rather than focusing primarily on alleviating distress or symptoms, or thinking more realistically; strategies which might offer less scope for improvement given the context of motor neuron disease. We showed that ACT, adapted for the specific needs of people with motor neuron disease,<sup>17</sup> was both acceptable to patients and feasible to deliver in an uncontrolled feasibility study.<sup>18</sup> We also demonstrated potential signals of efficacy, with respect to small improvements in psychological quality of life and anxiety. However, the lack of control group and small sample size meant that no conclusions could be drawn with respect to effectiveness.

There have been no adequately powered randomised controlled trials of psychological interventions for people with motor neuron disease, and none of ACT. Consequently, we aimed to assess whether ACT plus usual care was effective for improving quality of life in people with motor neuron disease, compared with usual care alone, at 6 months and 9 months post-randomisation in a fully powered randomised controlled trial. Secondary aims included examining effects on depression and anxiety in people with motor neuron disease, and indirect effects on quality of life and caregiver burden in caregivers of people with motor neuron disease.

## Methods

### Study design and participants

We conducted a multicentre, parallel group randomised controlled trial of ACT plus usual care versus usual care alone. Potential participants (people with motor neuron disease and caregivers) were recruited through 16 UK motor neuron disease care centres or clinics (14 in England, one in Wales, and one in Scotland) and via self-referral (people with motor neuron disease were referred to a recruiting site if not in geographical proximity to one). Care centres or clinics (listed from north to south) in Glasgow,

Newcastle, Middlesbrough, Preston, North Lincolnshire and Goole, Salford, Sheffield, Stoke, Leicester, Cambridge, Swansea, London, Dorset, and Plymouth were selected in order to ensure as wide a geographic spread as possible. People with motor neuron disease were eligible to participate if aged 18 years and older and they met the World Federation of Neurology's El Escorial diagnostic criteria<sup>19</sup> for familial or sporadic amyotrophic lateral sclerosis (ALS; which is diagnostically synonymous with motor neuron disease<sup>20</sup>), or motor neuron disease variants (progressive muscular atrophy or primary lateral sclerosis). Individuals were ineligible if they had clinical need for gastrostomy feeding or non-invasive ventilation (ie, King's Stage 4 motor neuron disease<sup>21</sup>); lacked capacity to provide fully informed consent; had a diagnosis of dementia;<sup>22,23</sup> required treatment for severe psychiatric disorder (eg, schizophrenia); expressed suicidal ideation with active plans or suicidal behaviours and imminent intent (ie, within the next 2 weeks); had other medical diagnoses that could compromise full study participation (eg, intellectual disabilities); were currently receiving psychological therapy and unwilling to withdraw from this if allocated to ACT; had previously participated in our feasibility study;<sup>18</sup> or had an insufficient understanding of English. Caregivers of people with motor neuron disease were eligible to participate if they were aged 18 years and older and were the primary informal caregiver of a person with motor neuron disease participating in the trial.

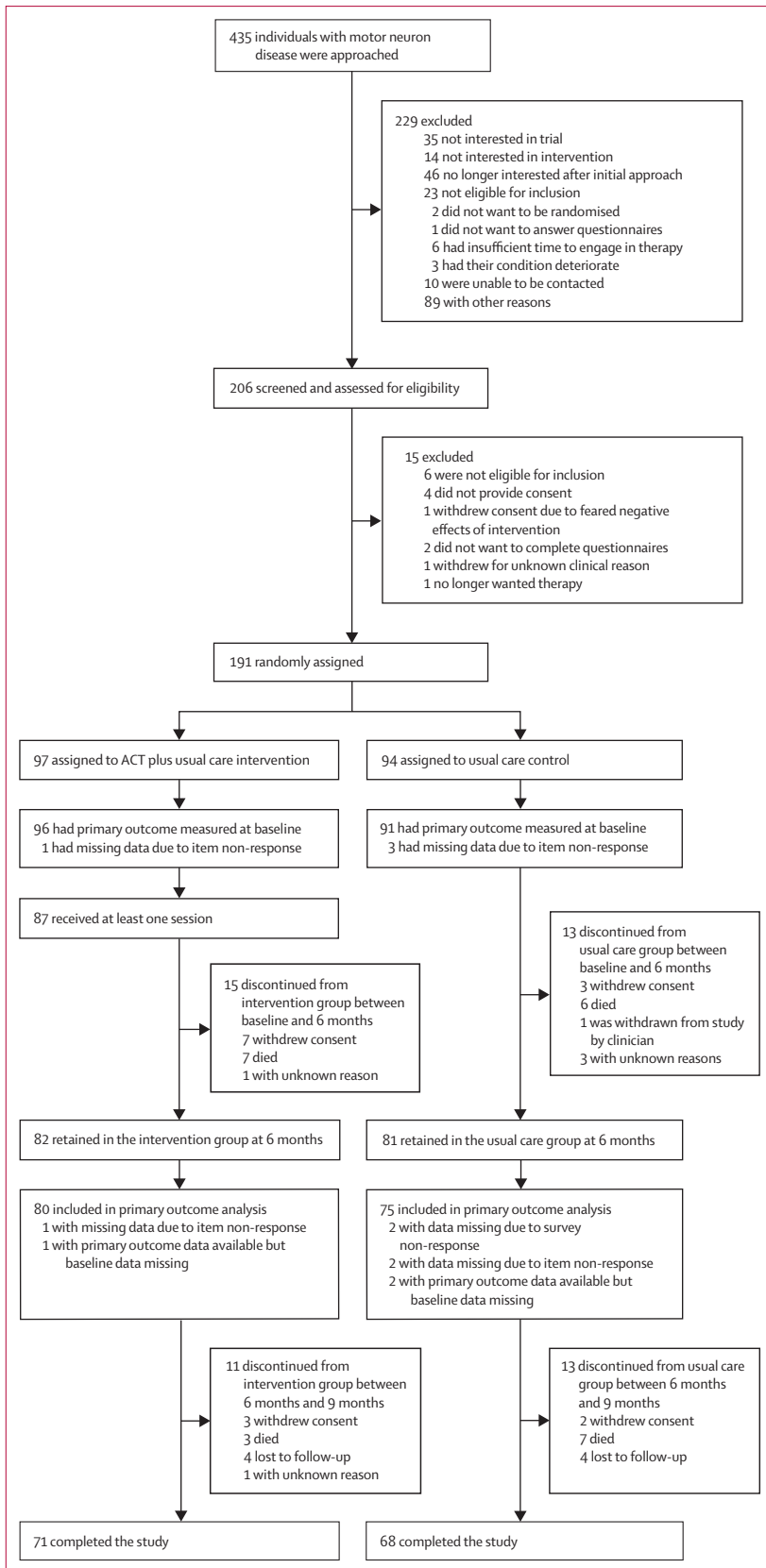
The study was pre-registered with the ISRCTN Registry on July 17, 2017 (ISRCTN12655391), and the trial protocol was published.<sup>16</sup> Ethical approval was granted by the London Dulwich Research Ethics Committee, Health Research Authority and Health and Care Research Wales on June 13, 2019 (REC: 19/LO/0272; IRAS: 255069). Oversight of the trial was provided by a Trial Management Group, Trial Steering Committee, Data Monitoring and Ethics Committee, and a Patient Caregiver Advisory Group.

### Randomisation and masking

People with motor neuron disease were randomly assigned in a 1:1 ratio to ACT plus usual care or usual care alone by a computer generated pseudo-random list within Sheffield Clinical Trials Research Unit (CTRU)'s online randomisation system. Randomisation used blocks of varying length, stratified by recruitment site. Only those with CTRU authorisation had access to the allocation sequence, and baseline data collection occurred before randomisation. Outcome assessors and trial statisticians were masked to allocation. It was not possible to mask the participants with motor neuron disease, caregivers, therapists, or treating clinicians due to the nature of the intervention.

### Procedures

People with motor neuron disease were approached first; if they consented to participate, then their primary caregiver was also invited to participate (for cases in which this was



possible). All participants gave fully informed written consent, verbal consent, or consent using a communication aid to participate in the trial. In the latter two cases, an independent witness verified this (if in person), or consent was audio recorded, with the participant's agreement.

People with motor neuron disease allocated to the treatment group received up to eight one-to-one sessions of ACT, each lasting up to 1 h, over 4 months. Sessions were delivered in person, via video call or, in exceptional circumstances, via telephone (depending on participant preference and therapist availability). Sessions were weekly for the first six sessions and fortnightly for the last two sessions and were supplemented by online audio material or CDs. As specified in the UK clinical guideline for motor neuron disease,<sup>12</sup> usual care comprised of medication for motor neuron disease and related symptoms; treatments such as non-invasive ventilation, physiotherapy and gastrostomy; and access to other hospital-based and community-based services (such as equipment and adaptations, orthotics, respiratory, gastroenterology, clinical psychology, neuropsychology and counselling, and social care services). Usual care was anticipated to be similar across sites given that UK motor neuron disease care centres and clinics are audited against the standard of care outlined in the UK clinical guideline for motor neuron disease.<sup>12</sup>

Therapists were clinical or counselling psychologists, accredited CBT therapists, or counsellors or psychotherapists with training in CBT, with a minimum of 1 years' experience in delivering psychological interventions. All therapists attended a 4-day training workshop, developed and delivered by members of the research team with expertise in ACT and motor neuron disease. Therapists also attended a 1-day top-up training course, approximately 12 months later, to review and consolidate ACT skills. Fortnightly group supervision of the therapists via telephone or video call was delivered by clinical psychologists and a psychiatrist with expertise in ACT.

To assess treatment fidelity, all sessions were recorded using encrypted digital voice recorders, with participants' consent. 10% of sessions were randomly selected (stratified by therapist and phase of intervention and recruitment) and assessed for treatment fidelity by two independent ACT-trained clinical psychologists. An adapted form of the ACT Treatment Integrity Coding Manual (ACT-TICM)<sup>24</sup> was used to assess treatment fidelity. This examined the degree to which therapy was consistent with ACT principles, adherence to the manual, and therapist competence.

**Figure 1: Trial profile**

Some participants dropped out of therapy but agreed to complete outcome measures at 6 months post-randomisation. Participants were offered up to eight sessions but were not required to attend all eight sessions to be categorised as completing the study. ACT=Acceptance and Commitment Therapy.

## Outcomes

Socio-demographic and clinical data were collected at screening and baseline, before randomisation. Assessments occurred at baseline (0 months) and 6 months and 9 months post-randomisation, and were conducted online or in person, via telephone, video call, post, or email by a masked outcome assessor. The primary outcome was quality of life in people with motor neuron disease, as measured by the total score on the McGill Quality of Life Questionnaire-Revised (MQOL-R),<sup>25</sup> at 6 months post-randomisation. The primary outcome was assessed in a modified intention-to-treat population (participants with available data). Secondary outcomes at 6 months and 9 months post-randomisation included: Existential and Psychological subscales of the MQOL-R; Hospital Anxiety and Depression Scale (HADS)<sup>26</sup> to assess symptoms of depression and anxiety, modified for people with motor neuron disease following previous guidance (modified-HADS);<sup>27</sup> Acceptance and Action Questionnaire-II (AAQ-II)<sup>28</sup> for psychological flexibility; EQ-5D-5L and Visual Analogue Scale (EQ-VAS)<sup>29</sup> using mapped tariffs from EQ-5D-5L to EQ-5D-3L<sup>30</sup> for health status, following national Institute for Health and Care Excellence recommendations; self-administered ALS Functional Rating Scale-Revised (ALS-FRS-R)<sup>31</sup> to assess disease progression; and non-physical adverse events and physical self-harm. MQOL-R total score and survival at 9 months post-randomisation and the Satisfaction with Therapy and Therapist Scale-Revised (STTS-R)<sup>32</sup> at 6 months post-randomisation in those allocated to ACT plus usual care were also secondary outcomes. Survival data at 9 months were collected from both groups and STTS-R data were only collected in the ACT plus usual care group. Secondary outcomes were assessed for all participants with available data retained in the study at the time of outcome measurement.

Secondary outcomes for caregivers at 6 months and 9 months post-randomisation were the EQ-5D-5L, EQ-VAS, and the Zarit Burden Interview (ZBI).<sup>33</sup> The ZBI assessed whether supporting people with motor neuron disease to engage in ACT placed additional burden on caregivers. These outcomes were assessed in all caregivers with available data for participants with motor neuron disease retained in the study.

Measures of bias included: Credibility/Expectancy Questionnaire,<sup>34</sup> adapted for people with motor neuron disease to assess the credibility of the rationale for therapy and treatment expectations; treatment allocation preferences before randomisation; assessment of blindness at 6 months and 9 months post-randomisation in outcome assessors; ACT-TICM; and use of psychological and pharmacological therapies at follow-up. The trial protocol also included secondary outcomes in relation to a health economic evaluation (Client Service Receipt Inventory<sup>35</sup> modified for participants with motor neuron disease, quality-adjusted life-years and resource use, and an informal process evaluation (qualitative

	ACT plus usual care (n=97)	Usual care alone (n=94)	Total (n=191)
<b>Gender</b>			
Female	40 (41%)	40 (43%)	80 (42%)
Male	57 (59%)	54 (57%)	111 (58%)
<b>Age, years</b>			
Mean (SD)	61.9 (11.4)	64.3 (10.4)	63.1 (11.0)
Median (IQR, range)	63 (54–71, 28–85)	64 (58–72, 33–92)	63 (56–71, 28–92)
<b>Ethnicity</b>			
Asian or Asian British	1 (1%)	4 (4%)	5 (3%)
Black or Black British	0	0	0
Mixed or multiple ethnic groups	0	0	0
White or White British	96 (99%)	89 (95%)	185 (97%)
Prefer not to say	0	1 (1%)	1 (<1%)
<b>Relationship status</b>			
Married, civil partnership, or co-habiting	77 (79%)	73 (78%)	150 (79%)
Single, divorced, separated, or widowed	20 (21%)	21 (22%)	41 (21%)
<b>Employment status</b>			
In paid employment (full or part time)	29 (30%)	24 (26%)	53 (28%)
Unemployed or unable to work	11 (11%)	7 (7%)	18 (9%)
Retired	53 (55%)	61 (65%)	114 (60%)
Other	4 (4%)	2 (2%)	6 (3%)
<b>Highest educational qualification*</b>			
No formal qualifications	13 (13%)	5 (5%)	18 (9%)
GCSE or equivalent	20 (21%)	22 (23%)	42 (22%)
A-level or equivalent	10 (10%)	12 (13%)	22 (12%)
Higher National Diploma	13 (13%)	13 (14%)	26 (14%)
Bachelor's degree	27 (28%)	24 (26%)	51 (27%)
Higher degree	13 (13%)	16 (17%)	29 (15%)
Missing data	1 (1%)	2 (2%)	3 (2%)
<b>Motor neuron disease type</b>			
Amyotrophic lateral sclerosis	78 (80%)	79 (84%)	157 (82%)
Progressive muscular atrophy	9 (9%)	6 (6%)	15 (8%)
Primary lateral sclerosis	10 (10%)	9 (10%)	19 (10%)
<b>Months since motor neuron disease diagnosis</b>			
Mean (SD)	21.5 (35.8)	17.1 (27.3)	19.3 (31.9)
Median (IQR, range)	9 (3–26, 1–221)	7 (3–17, 1–141)	8 (3–22, 1–221)
<b>Years since motor neuron disease diagnosis</b>			
<1	55 (57%)	65 (69%)	120 (63%)
1	13 (13%)	13 (14%)	26 (14%)
2–3	20 (21%)	8 (9%)	28 (15%)
4–6	6 (6%)	4 (4%)	10 (5%)
7–20	3 (3%)	4 (4%)	7 (4%)
<b>Months since motor neuron disease symptom onset</b>			
Mean (SD)	40.4 (45.2)	36.4 (35.7)	38.4 (40.8)
Median (IQR, range)	28 (15–49, 3–262)	24 (15–39, 4–183)	25 (15–41, 3–262)
<b>Years since motor neuron disease symptoms onset</b>			
<1	15 (15%)	13 (14%)	28 (15%)
1	30 (31%)	34 (36%)	64 (34%)
2–3	26 (27%)	29 (31%)	55 (29%)
4–6	20 (21%)	8 (9%)	28 (15%)
7–9	3 (3%)	6 (6%)	9 (5%)
10–25	3 (3%)	4 (4%)	7 (4%)

(Table 1 continues on next page)

	ACT plus usual care (N=97)	Usual care alone (N=94)	Total (N=191)
(Continued from previous page)			
<b>Rate (aggressiveness) of deterioration between symptom onset and baseline†</b>			
Lowest	35 (36%)	29 (31%)	64 (34%)
Medium	33 (34%)	31 (33%)	64 (34%)
Highest	29 (30%)	34 (36%)	63 (33%)
<b>Level (tertile) of deterioration between symptom onset and baseline</b>			
Mean (SD)	0.5 (0.5)	0.6 (0.5)	0.6 (0.5)
Median (IQR, range)	0 (0–1, 0–3)	0 (0–1, 0–4)	0 (0–1, 0–4)
<b>Concomitant disease-modifying and psychotropic medication</b>			
Riluzole	62 (64%)	58 (62%)	120 (63%)
Antidepressants	48 (49%)	31 (33%)	79 (41%)
Benzodiazepines	8 (8%)	6 (6%)	14 (7%)
Hypnotics	3 (3%)	4 (4%)	7 (4%)
Anxiolytics	6 (6%)	4 (4%)	10 (5%)
<b>Case levels of depression and anxiety on modified-HADS‡</b>			
Depression (score of ≥8)	10 (10%)	8 (9%)	18 (9%)
Anxiety (score of ≥9)	23 (24%)	18 (19%)	41 (21%)

Data are n (%) unless otherwise indicated. ACT=Acceptance and Commitment Therapy. HADS=Hospital Anxiety and Depression Scale (higher scores indicate greater depression or anxiety). \*Qualifications based on the UK educational system. †Rate of deterioration pre-randomisation using an estimate of the average deterioration in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score per month between motor neuron disease symptom onset and baseline. ‡Scored using motor neuron disease specific cutoffs.<sup>27</sup>

**Table 1: Baseline characteristics of participants with motor neuron disease**

satisfaction questionnaires from people with motor neuron disease and therapists). These data will be reported elsewhere.

### Statistical analysis

We aimed to recruit 188 people with motor neuron disease (94 per group) to have 90% power to detect an effect size of 0.44 SD, with a two-sided alpha of 5%, allowing for 20% attrition at 6 months post-randomisation,<sup>36</sup> an intra-class correlation coefficient of 0.01 among therapists (as used previously<sup>37</sup>), and a correlation of 0.58 between baseline and 6 months post-randomisation for the primary outcome.<sup>36</sup> No minimal clinically important difference has been reported for the MQOL-R and so the effect size was based on a clinically meaningful pooled effect size of 0.44 SD reported in a meta-analysis of ACT for mental and physical health conditions versus controls.<sup>38</sup>

Statistical analyses were pre-specified in the Statistical Analysis Plan (appendix pp 2–29) before the end of data collection, which was reviewed and approved, along with the trial protocol, by the Trial Steering Committee and the Data Monitoring and Ethics Committee. Continuous outcomes were analysed using a multi-level mixed-effects model, which included a random effect for therapist (to account for potential therapist clustering) and fixed effects for age, sex, and baseline scores. Self-reported biological sex (male or female) data were reported by participants with motor neuron disease or caregivers. Primary and secondary outcomes were assessed in the

modified intention-to-treat population (all participants with data available at 6 months post-randomisation), and analyses were conducted separately at 6 months and 9 months post-randomisation. Survival at 9 months post-randomisation was analysed using Kaplan–Meier curves of overall survival and Cox proportional hazards model, both with and without a random effect for therapist. Measures of bias and the STTS-R were reported descriptively.

Several sensitivity analyses were performed on the primary outcome. First, a per-protocol analysis in the subset of the intention-to-treat population who received at least four sessions within a 4-month period, before 6 months post-randomisation. Second, a complier average causal effect analysis in the intention-to-treat population, using modelling to account for compliance, with compliance (yes or no) defined as for the per-protocol population. Third, an analysis in the intention-to-treat population using different multiple imputations to reduce potential bias due to missing responses. 100 multiple imputation datasets were created using chained equations, which included baseline data, treatment group, and predictors of missing data, to make the missing at random assumption as plausible as possible.

Planned exploratory analyses using multi-level mixed-effects models examined whether the treatment effect, as measured by the MQOL-R at 6 months post-randomisation, was moderated by: (1) baseline disease severity using the ALS-FRS-R; (2) baseline depression and anxiety severity using the modified-HADS; (3) rate of deterioration pre-randomisation using an estimate of the average deterioration in ALS-FRS-R score per month between motor neuron disease symptom onset and baseline; (4) highest level of education at baseline; (5) marital status; (6) baseline psychological flexibility using the AAQ-II; and (7) COVID-19-related restrictions in place at randomisation.

Additional exploratory analyses used structural equation modelling to examine whether the treatment effect, as measured by the MQOL-R at 6 months and 9 months post-randomisation, was moderated by rate of deterioration on the ALS-FRS-R from 0 to 6 months post-randomisation, or mediated by change in psychological flexibility on the AAQ-II from 0 to 6 months post-randomisation. The effect of treatment on preventing progression to case levels of depression or anxiety on the modified-HADS was examined using logistic regression. Stata 18 was used for all analyses.

### Role of the funding source

One of the funders of the study (National Institute for Health and Care Research) specified brief details about the study design, as part of their commissioned call. Other than this, the funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

See Online for appendix

## Results

Participants were recruited between Sept 18, 2019, and Aug 31, 2022, with recruitment temporarily halted from March 17 to June 23, 2020, due to the COVID-19 pandemic. 435 people with motor neuron disease were approached, of whom 206 (47%) were assessed for eligibility. Of these, 191 (93%) were eligible and consented to participate, with 97 (51%) being randomly allocated to ACT plus usual care and 94 (49%) to usual care alone (figure 1). There were similar numbers of discontinuations by 6 months and 9 months post-randomisation across groups. Data for the primary outcome analysis were available for 81% (155 of 191) of participants at 6 months post-randomisation. Of the 155 recruited participants with analysable data, 99 (64%) were recruited during COVID-19-related restrictions, with only 17 (11%) being recruited before these restrictions were put in place. 93 caregivers were recruited, with 44 (47%) being a caregiver of a participant in the ACT plus usual care arm and 49 (53%) being a caregiver of a participant in the usual care alone group.

Baseline demographic and clinical characteristics for people with motor neuron disease and caregivers are shown in tables 1 and 2. Characteristics appeared balanced across groups, with no evidence of systematic differences. 80 (42%) of 191 participants were female and 111 (58%) were male. The mean age was 63.1 years (SD 11.0) and 185 (97%) of 191 participants were White or White British. The number of sessions attended by people with motor neuron disease allocated to ACT plus usual care is shown in the appendix (p 30). 87 (90%) of 97 participants in the ACT plus usual care group attended at least one session, with 68 (70%) attending all eight sessions. 72 (74%) of 97 participants randomly assigned to the ACT plus usual care group were compliant according to our per-protocol criterion, with nine of 14 withdrawing for therapy-related reasons. Most ACT sessions were delivered by video call (547 [86%] of 635).

Primary and secondary outcomes at all timepoints are shown in table 2 and data completeness is presented in the appendix (pp 32–34). The primary outcome analysis showed that ACT plus usual care was superior to usual care alone at 6 months and 9 months post-randomisation, with an adjusted mean difference on the MQOL-R of 0.66 (95% CI 0.22–1.10) at 6 months ( $d=0.46$  [95% CI 0.16–0.77];  $p=0.0031$ ) and 0.76 (95% CI 0.30–1.22) at 9 months ( $d=0.53$  [95% CI 0.21–0.85];  $p=0.0011$ ). The trend between baseline and 6 months post-randomisation was a small increase in MQOL-R in the ACT plus usual care group combined with a decline in the usual care alone group. Importantly, the result at 6 months post-randomisation was robust to sensitivity analyses using different assumptions for missing responses, supporting ACT plus usual care being superior to usual care alone (appendix p 35).

Significant adjusted mean differences in favour of ACT plus usual care compared with usual care alone were also found for the MQOL-R Psychological and

	ACT plus usual care (N=44)	Usual care alone (N=49)	Total (N=93)
<b>Gender</b>			
Female	32 (73%)	32 (65%)	64 (69%)
Male	12 (27%)	16 (33%)	28 (30%)
Missing data	0	1 (2%)	1 (1%)
<b>Age, years</b>			
Mean (SD)	58.2 (11.7)	60.2 (14.2)	59.2 (13.1)
Median (IQR, range)	62 (49–67, 37–80)	61 (54–68, 21–92)	61 (52–67, 21–92)
<b>Ethnicity</b>			
Asian or Asian British	1 (2%)	1 (2%)	2 (2%)
Black or Black British	0	0	0
Mixed or multiple ethnic groups	0	0	0
White or White British	43 (98%)	47 (96%)	90 (97%)
Missing data	0	1 (2%)	1 (1%)
<b>Relationship status</b>			
Married, civil partnership, co-habiting	43 (98%)	43 (88%)	86 (92%)
Single, divorced, separated, widowed	1 (2%)	5 (10%)	6 (6%)
Missing data	0	1 (2%)	1 (1%)
<b>Employment status</b>			
In paid employment (full or part time)	23 (52%)	23 (47%)	46 (49%)
Unemployed or unable to work	0	0	0
Not working due to being a carer	0	3 (6%)	3 (3%)
Retired	19 (43%)	22 (45%)	41 (44%)
Other	1 (2%)	0	1 (1%)
Missing data	1 (2%)	1 (2%)	2 (2%)
<b>Highest educational qualification*</b>			
No formal qualifications	2 (5%)	5 (10%)	7 (8%)
GCSE or equivalent	6 (14%)	7 (14%)	13 (14%)
A-level or equivalent	5 (11%)	10 (20%)	15 (16%)
Higher National Diploma	12 (27%)	9 (18%)	21 (23%)
Bachelor's degree	11 (25%)	10 (20%)	21 (23%)
Higher degree	7 (16%)	7 (14%)	14 (15%)
Missing data	1 (2%)	1 (2%)	2 (2%)
<b>Relationship with person with motor neuron disease</b>			
Spouse or partner	34 (77%)	40 (82%)	74 (80%)
Parent	2 (5%)	0	2 (2%)
Sibling	0	1 (2%)	1 (1%)
Child or grandchild	7 (16%)	5 (10%)	12 (13%)
Friend	1 (2%)	2 (4%)	3 (3%)
Missing data	0	1 (2%)	1 (1%)
<b>Length of time spent as primary caregiver (months)</b>			
Mean (SD)	17.2 (23.1)	21.8 (35.9)	19.6 (30.4)
Median (IQR, range)	10 (4–24, 0–120)	10 (4–24, 0–168)	10 (4–24, 0–168)
<b>Average number of h per week involved in caring</b>			
Mean (SD)	49.2 (64.0)	56.0 (64.7)	52.8 (64.1)
Median (IQR, range)	14 (5–70, 0–168)	21 (5–105, 0–189)	20 (5–98, 0–189)

Data are n (%), unless otherwise indicated. ACT=Acceptance and Commitment Therapy. \*Qualifications based on the UK educational system.

**Table 2: Baseline characteristics of caregivers of people with motor neuron disease**

Existential subscales and modified-HADS Depression at 6 months and 9 months post-randomisation, AAQ-II at 9 months post-randomisation, and EQ-VAS at 6 months post-randomisation (table 3; figure 2). No other significant between-group differences were observed,

including for survival (appendix p 36) or caregiver outcomes (table 3).

All subgroup interaction terms were non-significant in moderation analyses, except for baseline depression (appendix pp 37–38). Participants who did not meet the

	ACT plus usual care		Usual care alone		Mean difference (95% CI)	Adjusted mean difference (95% CI)*	Effect size (Cohen's d, 95% CI)	p value
	n/N (%)	Mean (SD)	n/N (%)	Mean (SD)				
<b>People with motor neuron disease</b>								
MQOL-R (possible range 0–10)								
Baseline	96/97 (99%)	6.67 (1.47)	91/94 (97%)	6.85 (1.39)	-0.18 (-0.59 to 0.23)	..	..	..
6 months	81/97 (84%)	6.88 (1.68)	77/94 (82%)	6.34 (1.63)	0.54 (0.02 to 1.06)	0.66 (0.22 to 1.10)	0.46 (0.16 to 0.77)	0.0031
9 months	70/97 (72%)	6.86 (1.61)	68/94 (72%)	6.34 (1.67)	0.52 (-0.03 to 1.07)	0.76 (0.30 to 1.22)	0.53 (0.21 to 0.85)	0.0011
MQOL-R Psychological subscale (possible range 0–10)								
Baseline	96/97 (99%)	6.59 (2.42)	91/94 (97%)	6.81 (2.21)	-0.22 (-0.88 to 0.44)	..	..	..
6 months	81/97 (84%)	7.24 (2.29)	78/94 (83%)	6.63 (2.42)	0.61 (-0.12 to 1.34)	0.71 (0.02 to 1.39)	0.30 (0.01 to 0.60)	0.043
9 months	70/97 (72%)	7.29 (2.18)	68/94 (72%)	6.50 (2.49)	0.79 (0.01 to 1.57)	1.10 (0.40 to 1.80)	0.47 (0.17 to 0.78)	0.0020
MQOL-R Existential subscale (possible range 0–10)								
Baseline	97/97 (100%)	6.70 (1.73)	94/94 (100%)	6.71 (1.57)	-0.02 (-0.49 to 0.45)	..	..	..
6 months	82/97 (85%)	6.92 (1.94)	79/94 (84%)	6.18 (1.64)	0.74 (0.18 to 1.30)	0.72 (0.23 to 1.20)	0.43 (0.14 to 0.73)	0.0042
9 months	70/97 (72%)	6.86 (1.83)	68/94 (72%)	6.24 (1.83)	0.63 (0.02 to 1.24)	0.65 (0.09 to 1.21)	0.39 (0.05 to 0.73)	0.023
Modified-HADS Depression (possible range 0–18)†								
Baseline	97/97 (100%)	3.99 (3.00)	94/94 (100%)	3.80 (2.89)	0.19 (-0.65 to 1.03)	..	..	..
6 months	81/97 (84%)	3.54 (3.23)	78/94 (83%)	4.45 (3.46)	-0.91 (-1.95 to 0.13)	-1.13 (-1.81 to -0.45)	-0.38 (-0.61 to -0.15)	0.0012
9 months	69/97 (71%)	3.71 (3.06)	67/94 (71%)	4.90 (3.40)	-1.19 (-2.28 to -0.10)	-1.12 (-2.06 to -0.19)	-0.38 (-0.70 to -0.06)	0.018
Modified-HADS Anxiety (possible range 0–18)†								
Baseline	97/97 (100%)	5.73 (3.89)	94/94 (100%)	5.30 (3.71)	0.43 (-0.65 to 1.51)	..	..	..
6 months	81/97 (84%)	4.68 (3.46)	78/94 (83%)	5.15 (3.47)	-0.47 (-1.55 to 0.61)	-0.79 (-1.64 to 0.05)	-0.21 (-0.43 to 0.01)	0.064
9 months	69/97 (71%)	4.59 (3.42)	67/94 (71%)	5.33 (3.94)	-0.73 (-1.97 to 0.51)	-0.78 (-1.73 to 0.17)	-0.21 (-0.46 to 0.04)	0.11
AAQ-II (possible range 7–49)								
Baseline	97/97 (100%)	16.8 (9.9)	94/94 (100%)	15.8 (8.0)	0.96 (-1.59 to 3.51)	..	..	..
6 months	79/97 (81%)	15.5 (8.5)	77/94 (82%)	17.0 (9.3)	-1.48 (-4.28 to 1.32)	-1.73 (-3.69 to 0.23)	-0.19 (-0.41 to 0.03)	0.083
9 months	67/97 (69%)	15.2 (7.8)	67/94 (71%)	17.6 (9.2)	-2.39 (-5.28 to 0.50)	-2.54 (-4.52 to -0.55)	-0.28 (-0.50 to -0.06)	0.012
ALS-FRS-R (possible range 0–48)								
Baseline	97/97 (100%)	35.6 (6.8)	94/94 (100%)	35.5 (6.2)	0.11 (-1.73 to 1.95)	..	..	..
6 months	81/97 (84%)	32.5 (8.9)	77/94 (82%)	31.7 (8.3)	0.78 (-1.91 to 3.47)	0.85 (-0.71 to 2.40)	0.13 (-0.11 to 0.37)	0.29
9 months	69/97 (71%)	32.3 (8.9)	66/94 (70%)	30.9 (8.5)	1.47 (-1.47 to 4.41)	1.62 (-0.36 to 3.59)	0.25 (-0.06 to 0.55)	0.11
EQ-5D-5L (possible range -0.59 to 1.0)								
Baseline	97/97 (100%)	0.51 (0.29)	93/94 (99%)	0.53 (0.27)	-0.02 (-0.10 to 0.06)	..	..	..
6 months	81/97 (84%)	0.45 (0.33)	78/94 (83%)	0.45 (0.31)	-0.00 (-0.10 to 0.10)	0.03 (-0.03 to 0.09)	0.10 (-0.11 to 0.31)	0.35
9 months	69/97 (71%)	0.44 (0.31)	67/94 (71%)	0.42 (0.32)	0.01 (-0.09 to 0.11)	0.04 (-0.04 to 0.11)	0.13 (-0.13 to 0.39)	0.34
EQ-VAS (possible range 0–100)								
Baseline	96/97 (99%)	61.9 (21.3)	93/94 (99%)	60.3 (22.3)	1.57 (-4.64 to 7.78)	..	..	..
6 months	81/97 (84%)	63.4 (21.6)	78/94 (83%)	55.9 (20.8)	7.49 (0.88 to 14.10)	6.49 (1.28 to 11.7)	0.30 (0.06 to 0.54)	0.015
9 months	69/97 (71%)	62.5 (23.1)	67/94 (71%)	55.6 (21.1)	6.88 (-0.56 to 14.32)	6.38 (-0.04 to 12.8)	0.29 (-0.00 to 0.59)	0.051
STTS-R Satisfaction with therapy (possible range 6–30)‡								
Baseline	..	..	..	..	..	..	..	..
6 months	71/87 (82%)	24.6 (3.6)	..	..	..	..	..	..
9 months	..	..	..	..	..	..	..	..
STTS-R Satisfaction with therapist (possible range 6–30)								
Baseline	..	..	..	..	..	..	..	..
6 months	71/87 (82%)	28.0 (2.8)	..	..	..	..	..	..
9 months	..	..	..	..	..	..	..	..

(Table 3 continues on next page)



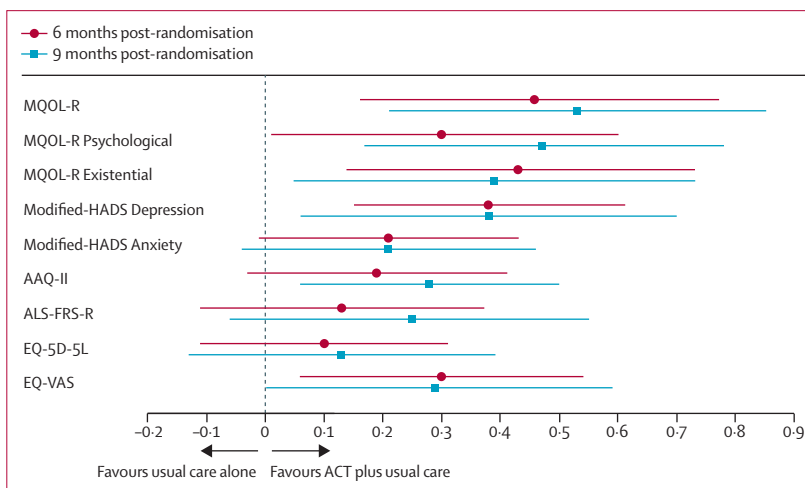
	ACT plus usual care		Usual care alone		Mean difference (95% CI)	Adjusted mean difference (95% CI)*	Effect size (Cohen's d, 95% CI)	p value
	n/N (%)	Mean (SD)	n/N (%)	Mean (SD)				
(Continued from previous page)								
<b>Caregivers</b>								
EQ-5D-5L (possible range -0.59 to 1.0)								
Baseline	41/44 (93%)	0.81 (0.16)	44/49 (90%)	0.81 (0.22)	-0.01 (-0.09 to 0.07)	..	..	..
6 months	35/44 (80%)	0.85 (0.15)	35/49 (71%)	0.83 (0.13)	0.02 (-0.05 to 0.09)	0.04 (-0.02 to 0.09)	0.20 (-0.08 to 0.48)	0.17
9 months	33/44 (75%)	0.83 (0.16)	34/49 (69%)	0.80 (0.13)	0.03 (-0.04 to 0.10)	0.01 (-0.05 to 0.07)	0.05 (-0.27 to 0.38)	0.75
EQ-VAS (possible range 0-100)								
Baseline	42/44 (95%)	78.3 (18.4)	44/49 (90%)	82.1 (17.6)	-3.83 (-11.4 to 3.78)	..	..	..
6 months	35/44 (80%)	79.9 (10.6)	35/49 (71%)	83.5 (10.0)	-3.54 (-8.37 to 1.29)	-1.65 (-5.84 to 2.55)	-0.09 (-0.32 to 0.14)	0.44
9 months	33/44 (75%)	79.6 (17.7)	34/49 (69%)	80.8 (15.4)	-1.19 (-9.13 to 6.75)	-1.17 (-10.3 to 8.01)	-0.06 (-0.58 to 0.45)	0.80
ZBI (possible range 0-88)								
Baseline	42/44 (95%)	22.6 (11.4)	44/49 (90%)	19.4 (12.7)	3.17 (-1.95 to 8.29)	..	..	..
6 months	34/44 (77%)	27.9 (15.8)	35/49 (71%)	23.8 (12.7)	4.08 (-2.65 to 10.8)	-0.36 (-4.19 to 3.47)	-0.03 (-0.35 to 0.29)	0.86
9 months	33/44 (75%)	27.2 (16.4)	33/49 (67%)	24.6 (15.2)	2.52 (-5.10 to 10.1)	-1.13 (-7.40 to 5.14)	-0.09 (-0.61 to 0.42)	0.72

AAQ-II=Acceptance and Action Questionnaire-II (higher scores indicate greater psychological inflexibility). ACT=Acceptance and Commitment Therapy. ALS-FRS-R= Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (higher scores indicate better disease-related functioning). EQ-VAS=EuroQoL Visual Analogue Scale (higher scores indicate better health status). HADS=Hospital Anxiety and Depression Scale (higher scores indicate greater depression or anxiety). MQOL-R=McGill Quality of Life Questionnaire-Revised (higher scores indicate better quality of life). STTS-R=Satisfaction with Therapy and Therapist Scale-Revised (higher scores indicate greater satisfaction with therapy or the therapist). ZBI=Zarit Burden Interview (higher scores indicate greater caregiver burden). For the EQ-5D-5L higher scores indicate better health status. \*Adjusted for age, sex, baseline scores, and therapist clustering (intracluster correlation coefficient 0.11); 31 therapists saw, on average, 2.81 participants each (SD 1.64, minimum 1, maximum 6). †One depression item and one anxiety item were not scored on the HADS, as recommended for people with motor neuron disease.<sup>27</sup> ‡For both subscales of the STTS-R, percentages were calculated from 87 participants in the ACT group who attended at least one session.

**Table 3: Primary and secondary outcome measures at 6 months and 9 months post-randomisation for ACT plus usual care and usual care alone groups**

case threshold for depression on the modified-HADS at baseline (ie, scoring ≥8), appeared to respond better to treatment, as measured by the MQOL-R at 6 months post-randomisation, than those who did meet the threshold (adjusted mean difference 0.85 [95% CI 0.38 to 1.32] vs -0.46 [95% CI -1.80 to 0.88]; p=0.0057). Additionally, logistic regression analyses showed a beneficial effect of treatment on preventing progression to case levels of depression on the modified-HADS, whereby the chance of transitioning from non-case to case level at 6 months post-randomisation was 11% lower in the ACT plus usual care group compared with the usual care alone group (risk difference -0.11 [95% CI -0.22 to -0.01]; p=0.044). However, these analyses were limited by the small number of participants within depression subgroups of interest (n=15 and n=11, respectively; appendix p 41). Finally, as an adjusted mean difference in favour of ACT plus usual care versus usual care alone was found for the AAQ-II at 9 months but not 6 months post-randomisation, a post-hoc structural equation modelling analysis that included the AAQ-II at 9 months post-randomisation was conducted. This showed that change in the MQOL-R at 9 months post-randomisation was mediated by change in the AAQ-II from 0 to 9 months post-randomisation, with the indirect (mediated) effect being significant at the 5% level (appendix p 42). All other analyses were non-significant.

With respect to acceptability from a safety and satisfaction perspective, there were 75 adverse events, 38 of which were serious (table 4). 31% of participants in



**Figure 2: Standardised mean differences for primary and secondary outcomes at 6 months and 9 months post-randomisation**

Mean differences are presented with 95% CIs. AAQ-II=Acceptance and Action Questionnaire-II (higher scores indicate greater psychological inflexibility). ACT=Acceptance and Commitment Therapy. ALS-FRS-R=ALS Functional Rating Scale-Revised (higher scores indicate better disease-related functioning). EQ-VAS=EuroQoL Visual Analogue Scale (higher scores indicate better health status). HADS=Hospital Anxiety and Depression Scale (higher scores indicate greater depression or anxiety). MQOL-R=McGill Quality of Life Questionnaire-Revised (higher scores indicate better quality of life). For the EQ-5D-5L, higher scores indicate better health status.

both arms reported at least one event (ACT plus usual care: 30 of 97; usual care alone: 29 of 94). No serious adverse events were deemed to be associated with ACT plus usual care. There were no significant between-group differences in adverse events, apart from social stressors

	Total number of events	ACT plus usual care	Usual care alone	Risk difference (95% CI)	Risk ratio (95% CI)
Suicidal ideation with imminent intent	1	0	1/94 (1%)	-1.1 (-3.1 to 1.0)	..
Suicide attempt	1	0	1/94 (1%)	-1.1 (-3.1 to 1.0)	..
Related to motor neuron disease					
Death	21	9/97 (9%)	12/94 (13%)	-3.5 (-12.4 to 5.4)	0.73 (0.3 to 1.7)
Unplanned admission to hospital	3	2/97 (2%)	1/94 (1%)	1.0 (-2.5 to 4.5)	1.94 (0.2 to 21.0)
Prolonged hospital stay	2	2/97 (2%)	0	2.1 (-0.8 to 4.9)	..
Not related to motor neuron disease					
Death	1	1/97 (1%)	0	1.0 (-1.0 to 3.0)	..
Unplanned hospital admission	4	1/97 (1%)	3/94 (3%)	-2.2 (-6.2 to 1.9)	0.32 (0.0 to 3.0)
Unknown cause					
Death	1	0	1/94 (1%)	-1.1 (-3.1 to 1.0)	..
Unplanned hospital admission*	5	2/97 (2%)	2/94 (2%)	-0.1 (-4.1 to 4.0)	0.97 (0.1 to 6.7)
Participants with at least 1 event	..	16/97 (16%)	18 (19%)	..	..
Overall number of events	38	..	..	..	..

Data are absolute values or n/N (%), unless otherwise specified. ACT=Acceptance and Commitment Therapy. \*There were five unplanned hospital admissions from four participants; one participant in the usual care alone group had two unplanned hospital admissions of unknown cause.

**Table 4: Serious adverse events**

(eg, bereavement), where more of these events were reported for ACT plus usual care (n=8) than usual care alone (n=1), although none were related to the intervention (appendix p 43). Mean scores on the STTS-R Satisfaction with Therapy (24.6/30.0 [SD 3.6]) and Satisfaction with Therapist subscales (28.0/30.0 [SD 2.8]) were high. 79% (69 of 87) of participants who attended at least one session rated therapy as “satisfactory” (ie, scoring  $\geq 18/30$  on the Satisfaction with therapy subscale), with only 2% (two of 87) rating therapy as “unsatisfactory”. Only minor protocol deviations were reported (appendix pp 44–46).

Turning to measures of bias, ratings for credibility and expectancy were similar across groups, as were the proportions of participants who “completely” hoped to receive ACT plus usual care or usual care alone before randomisation (appendix pp 47–48). Cases of accidental unmasking of assessors were very low (n=3). Most outcome datasets were completed online (226 [72%] of 313) and so were at minimal risk of researcher bias affecting data collection. 11% of ACT sessions (71 of 635) were rated using the ACT-TICM. High rates of overall adherence to the manual (mean 4.7/5.0 [SD 0.5]) and overall ACT competence of therapists (mean 4.7/5.0 [SD 0.5]) were observed. Furthermore, there was no

evidence of ACT-inconsistent responses in any rated sessions.

Finally, use of psychological and pharmacological therapies were similar across groups and therefore no additional exploratory data analyses were deemed necessary (appendix p 49).

## Discussion

This is the first adequately powered randomised controlled trial of a psychological intervention for people with motor neuron disease, and the first to compare the effectiveness of ACT plus usual care for improving quality of life in people with motor neuron disease compared with usual care alone. We found that ACT plus usual care was superior to usual care alone for maintaining or improving quality of life in people with motor neuron disease at 6 months post-randomisation, and this treatment effect was maintained at 9 months post-randomisation. Treatment effect sizes of 0.46 and 0.53 at 6 months and 9 months post-randomisation, respectively, were consistent with the predefined clinically meaningful effect size of 0.44<sup>38</sup> and a universally reported minimal clinically important difference of approximately 0.5 for quality of life in clinical populations.<sup>39</sup> We also found significant between-group differences in favour of ACT plus usual care for psychological and existential quality of life and depression at both 6 months and 9 months post-randomisation, psychological flexibility at 9 months post-randomisation, and brief health status at 6 months post-randomisation. There was also suggestive evidence that: (1) baseline depression moderated changes in quality of life at 6 months post-randomisation; (2) ACT plus usual care had a protective effect in preventing progression to case levels of depression compared with usual care alone; and (3) change in quality of life at 9 months post-randomisation was mediated by change in psychological flexibility from 0 to 9 months post-randomisation. These latter results should be interpreted with caution given the small number of participants within depression subgroups, and as the mediation analysis assumed that changes in psychological flexibility preceded changes in quality of life (which cannot be verified since they were assessed at the same time).

We showed good acceptability in terms of session attendance, as 70% (68 of 97) of participants allocated to ACT plus usual care opted to attend all eight sessions. This was supported by high satisfaction ratings: 79% (69 of 87) of participants attending at least one session rated therapy as “satisfactory”. No serious adverse events were deemed associated with ACT plus usual care, highlighting the safety of the intervention. Although more adverse events in the form of social stressors were reported for ACT plus usual care than for usual care alone, these were unrelated to the intervention. There was no evidence of additional burden of ACT plus usual care on caregivers, but this was limited by small sample sizes. Ratings of overall manual adherence and ACT competence were

high, with no evidence of ACT-inconsistent responding, indicating the intervention was feasible to deliver. Finally, the fact that 86% (547 of 635) of sessions were delivered by video call demonstrates the feasibility of remote intervention delivery, making this a clinically effective, accessible option for people with motor neuron disease who live in remote areas or are unable to travel to clinic.

Our findings extend those of previously underpowered studies<sup>10,11</sup> in providing crucial high-quality evidence of the clinical effectiveness of a psychological intervention for people with motor neuron disease. The lack of such evidence to date has meant that UK clinical guidelines have not been able to recommend evidenced psychological interventions for this population. Our findings represent the first steps in rectifying this and build on previous results<sup>10</sup> by suggesting that treatment response within the context of a progressive, neurodegenerative condition might be reflected by a pattern of stabilisation in quality of life rather than improvement. Future adequately powered studies should seek to replicate this pattern of results, as well as examining potentially protective effects of ACT in preventing progression to clinical levels of depression given preliminary evidence presented here.

Real-world evidence, together with evidence of clinical effectiveness, is increasingly being used to inform clinical guidance and provide timely access to innovative treatments. Consequently, the next steps to translating results presented here into patient benefit could be to conduct a real-world evaluation. This could involve creating a digital version of training for therapists; setting up a peer supervision network for therapists; creating a process of fidelity checks to ensure that levels of ACT competency and treatment fidelity remain high once translated into real-world clinical settings; and establishing a process of routine, continuous outcome data collection to support a real-world evaluation following the National Institute for Health and Care Excellence Real-World Evidence Framework.<sup>40</sup>

It has been hypothesised that ACT operates via psychological flexibility,<sup>13</sup> and that changes in psychological flexibility partially or fully mediate treatment effects.<sup>41</sup> In the current trial, adjusted mean differences in favour of ACT plus usual care compared with usual care alone were found for psychological flexibility at 9 months but not 6 months post-randomisation. Although the lack of between-group differences at 6 months post-randomisation might appear surprising, one possible explanation for this is an incubation effect, whereby treatment effects become stronger over time.<sup>42</sup> Supporting this explanation, effect sizes for psychological flexibility increased from  $-0.19$  at 6 months post-randomisation to  $-0.28$  at 9 months post-randomisation. This is noteworthy given expected deterioration in disease-related functioning. Furthermore, there was suggestive evidence that change in quality of life at 9 months post-randomisation was mediated by change in psychological flexibility. A similar pattern of results has been previously

reported.<sup>43</sup> A possible explanation for this incubation effect is that it takes time for psychological flexibility skills to develop and be practised, and to influence behavioural change.<sup>43</sup> This explanation might be particularly relevant in the current trial given that approximately two-thirds of participants (63%, 120 of 191) had been diagnosed with motor neuron disease within a year of the baseline assessment. ACT might have been particularly beneficial in allowing people with motor neuron disease to see and act on opportunities for better quality of life, without being exclusively focused on motor neuron disease or symptoms; a process we might otherwise call adjusting to or coming to terms with their diagnosis. It might also be that these skills took time to develop, and so between-group differences in psychological flexibility were only observed at 9 months but not 6 months post-randomisation. Alternatively, psychological flexibility skills might have been put into practice more at 9 months than at 6 months to cope with disease progression, and so further clarification is needed.

The negative impact of the COVID-19 pandemic and related restrictions on people with motor neuron disease in the UK has been previously documented.<sup>44</sup> Pre-planned subgroup analyses examined whether the treatment effect, as measured by the MQOL-R, was moderated by COVID-19 related restrictions. Three subgroups were defined based on when participants were randomly assigned: before, during, and after COVID-19-related restrictions. Unfortunately, as only 11% (17 of 155) of participants with analysable data were recruited before these restrictions were put in place, no conclusions can be drawn with respect to whether COVID-19-related restrictions moderated the treatment effect.

There were some limitations in the current trial. First, ACT was compared to a non-active rather than active control condition. This means that observed between-group differences in outcomes might have been partly attributable to expectancy or non-specific therapeutic factors such as provision of attention or social support rather than the intervention itself. Future studies might consider comparing ACT with a talking placebo control, such as that used previously.<sup>45</sup> Second, participants from ethnic minorities were under-represented, with most participants self-identifying as White or White British, so our findings cannot be generalised to the broader population. Similarly, our findings might not generalise to all people with motor neuron disease seen in clinics given that, at baseline, two-thirds of participants had been diagnosed with motor neuron disease less than a year previously; ALS functional impairment was fairly mild, on average; and low numbers of participants scored at case levels for depression (9%, 18 of 191) and anxiety (21%, 41 of 191) on the modified-HADS. Furthermore, whether ACT is beneficial for those in a more advanced disease stage is unknown as people with motor neuron disease in King's Stage 4 (the most advanced motor neuron disease stage before death<sup>21</sup>) were excluded to reduce

attrition rates. Consequently, future studies should examine the effectiveness of ACT in broader populations of people with motor neuron disease. Another limitation was that we were not able to examine whether cognitive status at baseline moderated treatment response, as the use of the Edinburgh Cognitive and Behavioural ALS Screen was ceased when COVID-19 related restrictions commenced (because its remote administration had not yet been validated). Additionally, we did not collect data on accommodation status at baseline. Future studies should seek to explore these possible moderating factors further. The lack of follow-up assessment beyond 9 months post-randomisation also means it is uncertain whether treatment effects are maintained beyond this point. Future studies should consider how participant retention can be optimised and attrition minimised to permit a broader examination of psychological interventions across the disease course. Finally, it is important to note that most people with motor neuron disease who were not included in this randomised controlled trial declined participation due to lack of interest rather than because they were ineligible. This is unsurprising given that participants were not approached based on the presence of anxiety or depression symptoms, and so many might not have appreciated the value of a psychological intervention at that time or might have preferred to participate in motor neuron disease drug trials. Although these figures are consistent with previous research,<sup>46,47</sup> they limit the external validity of the study and hence generalisability of results, as noted by other research groups.<sup>48</sup> It is worth noting that being offered an experimental intervention in a randomised controlled trial is not the same as being offered an evidence-based intervention as part of routine clinical practice. Although it is anticipated that more people would be interested in receiving ACT as part of motor neuron disease care now that clinical effectiveness has been demonstrated, uptake within clinics should be examined further as part of a real-world evaluation.

In conclusion, ACT plus usual care is effective at maintaining or improving quality of life in people with motor neuron disease at 6 months and 9 months post-randomisation compared with usual care alone. In the absence of a therapy that significantly prolongs survival, interventions aimed at maintaining or improving quality of life in these patients are vital given the progressive nature of the condition—this trial provides definitive evidence for one such intervention.

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#### Contributors

RLG, CJM, LHG, CDG, LMM, MAS, AA-C, PJS, RJH, VL, CC, TY, DAW, and MBr contributed to trial conceptualisation and funding acquisition. RLG, CJM, LHG, CDG, LMM, MAS, AA-C, PJS, RJH, VL, CC, TY, DAW, MBr, MBu, BJT, CVR, and PK contributed to methodology development. RLG, CJM, DAW, BJT, CVR, and PK contributed to project administration. RLG, CJM, LHG, CDG, LMM, MAS, AA-C, PJS, RJH, VL, CC, TY, DAW, MBr, and MBu contributed to supervision. RLG, CJM, BJT, CVR, PK, AA-C, IB, CF, SKC, JE, NG, RWO, TW, TL, AH, AR, GM, GHG, and RN contributed to investigation and provision of resources. EJT and RLG contributed to data curation. EJT contributed to programming of software. MBu and MBr contributed to formal analysis and verified the underlying data. RLG and MBu contributed to writing of the original manuscript and visualisation of data. All authors contributed to manuscript review and editing. All authors confirm they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

#### Declaration of interests

RLG, CJM, BJT, CVR, MBu, MBr, PK, EJT, DAW, MAS, CDG, LMM, LHG, AA-C, TY, VL, CC, PJS, and RJH declare institutional financial support from the grant for the submitted work (National Institute for Health and Care Research Health Technology Assessment 16/81/01). RLG, MAS, RJH, MBr, CC, TY, PJS, CJM, AA-C, VL, and LHG are supported by a public research body (National Institute for Health and Care Research Biomedical Research Centres). LHG has received royalties for books on psychology and neuropsychology and fees for lectures on neurology. AA-C and PJS receive payment for consultancy and advisory board participation from commercial organisations (Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, Sano, Sanofi, and Wave Pharmaceuticals), none of which are related to the content of this submitted work. RWO, LMM, and CF have received grants for research from public bodies. RWO has received grants for research and trials from commercial organisations (Amylyx Pharmaceuticals, Biogen, Orphazyme) and received payment for neurological medicolegal work. RWO and CF sit on safety monitoring or advisory boards for motor neuron disease. RWO, JE, and AH sit on boards in organisations associated with motor neuron disease. AH receives grant funding for his clinical role at Motor Neurone Disease Association. All other authors declare no competing interests.

#### Data sharing

De-identified datasets and statistical code will be available upon request, following publication of the study results. Emails should be sent to the corresponding author, stating the fields required and purpose of the request (ideally with a protocol but, at a minimum, with a research plan). The data dictionary can also be made available. The statistical analysis plan is provided in the appendix (pp 2–29). Requests will be considered on a case-by-case basis and requestors will be asked to complete a data sharing agreement with the sponsor before data transfer. Data will be retained for 10 years following close of the study, before being destroyed.

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