BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028525
Article Type:	Research
Date Submitted by the Author:	19-Dec-2018
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Keywords:	Neurology < INTERNAL MEDICINE, PALLIATIVE CARE, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

Telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a pilot, feasibility study

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Key words
Telehealth, telemedicine, motor neuron disease, amyotrophic lateral sclerosis

Word count
5262

ABSTRACT

Objectives
Care of patients with motor neuron disease (MND) in a specialist, multidisciplinary clinic is associated with improved survival but access is not universal. We wanted to pilot and establish the feasibility of a definitive trial of a novel telehealth system (TiM: Telehealth in Motor neuron disease) in patients with MND.

Design
An 18-month, single-centre, mixed methods, randomised, controlled pilot and feasibility study.

Intervention
TiM telehealth plus usual care vs. usual care.

Setting
A specialist MND care centre in the UK

Participants
Patients with MND and their primary informal carers.

Primary and secondary outcome measures
Recruitment, retention and data collection rates, clinical outcomes including participant quality of life and anxiety and depression.

Results
Recruitment achieved the target of 40 patients and 37 carers. Participant characteristics reflected those attending the specialist clinic an included those with severe disability or with limited experience of technology. Retention and data collection was good. 80% of patient and 82% of carer participant reported outcome measures were completed at six months. Using a longitudinal analysis with repeated measures of quality of life, a sample size of 131 per arm is recommended in a definitive trial.

The methods and intervention were acceptable to participants who were highly motivated to participate to research. The low burden of participation and accessibility of the intervention meant barriers to participation were minimal. However, the study highlighted difficulties assessing the associated costs of the intervention, the challenge of recruitment in such a rare disease and the difficulties of producing rigorous evidence of impact in such a complex intervention.

Conclusion
A definitive trial of TiM is feasible but challenging. The complexity of the intervention and heterogeneity of the patient population means that a randomised controlled trial may not be the best way to evaluate the further development and implementation of the TIM.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a study of the feasibility of a digitally-enabled care system for patients and carers living with motor neuron disease.
- The acceptability and low burden of the methods and intervention resulted in successful recruitment and retention of patients who were a good reflection of those attending an MND clinic including those facing barriers to participation such as severe disability.
- The qualitative data collection enabled identification of key barriers and enablers to participation in clinical trials in motor neuron disease from the perspective of patients, carers and nurses.
- This was a study with a small number of patients in a single centre.
- It was not possible to fully assess the impact of the intervention on the clinical service.

BACKGROUND

Motor neuron disease (MND) is an incurable, neurodegenerative disease that causes progressive muscle paralysis, limb weakness, breathing, speech and swallowing difficulties leading to death after, on average, two to four years from symptom onset (1). Riluzole, non-invasive ventilation (NIV) and possibly edaravone only offer small survival benefits (2-4). Attendance at a multidisciplinary specialist MND clinic (MDC) is associated with improved survival and increased use of proven therapies (5-10). The aim of specialist MND care is to maximise survival and quality of life by providing coordinated, patient-centred care to address the biopsychosocial needs of patients and their families (11). It is recommended that the MDC should monitor patients regularly to detect and treat complications quickly (12,13). However, patients become progressively more disabled and travelling to clinic becomes difficult or impossible. Even in developed, countries attendance at MDCs varies (between 43% to 85%) and many of those who do see a specialist are unable to return (14). The disease is rare (a worldwide prevalence of 5.40 per 100 000 (15)) meaning there are few specialist centres and general clinicians have limited experience of caring for patients with MND. This makes accessing the right care at the right time difficult leading to significant distress (16-21). There is therefore a great need to improve access to specialist MND care.

We developed the TiM system: a digitally-enabled care system using telehealth to enable patients and their informal carers to report their progress and symptoms from their homes (22). We hypothesised that improving access to specialist care may result in earlier identification and management of complications thus improving quality of life and survival. We thought the TiM system could improve care coordination and result in better prioritisation of health-resource use, thereby reducing costs or increasing service capacity. The TiM was developed using a process of user-centred co-design (22) but further piloting of such a complex intervention was required (23).

Telehealth is a complex intervention that consists of different component parts (such as the software, the context, and behaviours of those who use it) whose success depends on these interacting factors (23). Clinical trials of telehealth face various challenges including difficulties with recruitment, staff engagement and difficulties capturing the important impacts of the intervention (24-26). Furthermore, MND trials tend to recruit an unrepresentative sample of patients (on average younger, male patients with longer survival) (27). This may be explained, in part, due to the many barriers to participation including the need to travel to study centres, and the small number of geographically dispersed patients who may be frail or deteriorating rapidly. The Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions highlights the importance of feasibility and piloting of the study methods to ensure the definitive trial will overcome these barriers (23).

Aims of the study

We wanted to pilot the methods and evaluate the feasibility of conducting a definitive randomised controlled trial of the TiM in patients and carers versus usual care. We aimed to use low-burden, pragmatic study methods that could recruit and retain a representative sample of all patients with MND. The feasibility outcomes examine recruitment, retention and data collection. The study also aimed to provide an understanding of the resources required to conduct a definitive trial including staff burden and an estimation of variation in outcomes in order to provide a more accurate predictor of sample size. A supplementary data table describes the feasibility questions using the ADePT framework (28). We also explored factors that may influence these outcomes and also whether the outcomes measures effectively assessed aspects of life with MND and the impact of the TiM.

We also conducted a process evaluation of the TiM to understand how the system was used and to identify some of the potential impacts of the TiM on participants, carers and the MND service. This is reported in a parallel publication.

METHODS

Study design

This was a single-centre, unblinded, randomised, controlled, pilot, feasibility trial of usual MND care vs. the TiM plus usual care. The protocol and statistical analysis plan are available as supplementary data. Approval was gained from Leeds Bradford Research Ethics Committee (REC reference 14/YH/1068) and the sponsor (Sheffield Teaching Hospitals NHS Foundation Trust Clinical Research Office). Trial identifier ISRCTN26675465.

Patient and public involvement

In addition to the user-centred design process used to develop the TiM ((22)) during development of the intervention and the protocol we consulted patients, carers and the Sheffield MND Research Advisory group (a patient and public involvement group). They reviewed the intervention, principles of the trial, trial design, outcome measures and participant information leaflets and provided

comments on their feasibility and accessibility. They were not involved in recruitment. Results of the study have been communicated at various public meetings, through the Sheffield MND Research Advisory group and local branch of the MND Association and a lay summary will be circulated. Members of this group attended the trial steering and trial management groups. AQ was a member of the trial management group, provided advice on the research methods, interpretation of the data and dissemination and is a co-author on this paper.

Recruitment

We pre-screened patients using a clinical database of patients attending the Sheffield MDC. We determined the order of invitation using a list of random numbers generated using Excel. When the pool of prevalent patients was exhausted, we invited all newly diagnosed patients. We invited patients and their primary informal carer to participate by letter including a prepaid return slip. Eligibility was confirmed and written/witnessed verbal consent was obtained All research visits and data collection were conducted in participants' homes. . This approach meant patients who were not currently attending the MDC (due to frailty or geography) were able to participate.

Eligibility criteria

We included adult patients receiving care from the Sheffield MDC, living within two hours drive from Sheffield. Initially the diagnostic inclusion criteria was those with a diagnosis of clinically definite or probable amyotrophic lateral sclerosis (ALS) according to the El Escorial criteria (29). However, prior to recruitment commencing, a review of 200 patients on the MDC database found that 58% of patients would be excluded based on these criteria: 38% of patients had ALS but did not fulfill the El Escorial Criteria at their last assessment (29) and 21% of patients had atypical MND (primary lateral sclerosis: PLS, progressive muscular atrophy: PMA, or an uncategorised progressive ALS/MND illness). We felt many of these patients not fulfilling the strict criteria would benefit from better MDC care and so we modified the criteria to include all patients with ALS with symptom onset within the last three years. We also included all patients diagnosed with any type of MND (ALS, PLS, PMA) who had evidence of progression in their condition (an indicator that they may require MDC monitoring and care) as evidenced by a deterioration in the ALS functional rating score (ALS-FRS-R) (30) of at least two points during the previous 18 months (a small but meaningful change).

We excluded patients attending another MDC, those unwilling to allow their carer to operate the TiM on their behalf if they could not do it themselves and those with no form of telephone or internet access. Patients had the option of identifying their primary informal carer who was then invited to participate as a carer and consented. Eligible informal carers were adults who were the patients' main provider of unpaid care. Initially, patients could participate only if their carer consented to be involved. Later we changed the criteria to allow patients to participate without a carer.

Randomisation

Patients were randomised 1:1 to receive usual care or TiM using www.sealedenvelope.com which employs permuted block randomisation with a mixture of block sizes. Stratification was not employed.

Intervention

A detailed description of the TiM has been published (22). The use of the TiM in this trial is described in detail in the parallel publication describing the process evaluation. In brief patients and carers were asked to complete weekly sessions answering questions about their condition (such as functional ability, symptoms, depression and anxiety symptoms, carer strain) and patients recorded their weight and balance. The results could be viewed on a website by the MND nurse at the specialist care centre. She could take actions including telephoning the patient/carer, expediting clinic appointments or liaising with the MDT. She could not delay appointments or make clinical decisions without checking the accuracy of the information with the patient, carer or clinical team.

Data collection

Patient/carer-reported outcome measures (PROMs) were completed at home during the baseline study visit and at 3, 6, 12 and 18 months using postal questionnaires. Generic and MND specific PROMs captured quality of life, MND clinical outcomes, survival and health resource use. Adverse events were recorded using PROMs and during MDC visits. We created a "Shadow Monitoring Protocol" whereby the MND physician would review the TiM data and complete a questionnaire two weeks prior to MDC appointments and again at each appointment. Physicians were asked to respond to agree/disagree statements assessing their opinion on the accuracy and acceptability of the TiM answers and whether it may be possible to use the information to make decisions without seeing the patient (see online supplementary data file). Telehealth Nurse activity was also collected using a two week diary, twice in the trial. After the trial we downloaded all data in TiM system into Excel.

We conducted 56 semi-structured participant interviews (characteristics are described in full in the supplementary data file). Control participants were interviewd at baseline (17 interviews) and intervention participants were interviewed at one and six months (20 at one month and 19 interviews at six months). Most interviews were face-to-face at home with patients and carers together, but telephone and email were also used. Interviews were also conducted with the Telehealth Nurse (at month 4 and month 14) and a community nurse (month 18). Topic guides were used (see trial protocol in supplementary material) and field notes taken during and after the interview. Interviews were audio-recorded and transcribed verbatim. Early results and observations during the trial informed later interviews. As new themes were being identified later in the research study, we attempted to interview all participants and by the end of the study no new themes were identified. To evaluate the feasibility of the study, participants were asked about their attitudes towards research. To evaluate the validity and acceptability of the PROMs, control participants also performed a "*think-aloud*" task during which they were asked to complete the baseline PROMs and describe their reactions. To explore

the feasibility and acceptability of digitally-enabled care, participants and clinicians were asked about their attitudes towards technology, the TiM system and MND care.

Blinding, bias and study conduct

It was not possible to blind the patients or investigators to treatment allocation and EH had involvement in some patients' clinical MDC visits. Measures to reduce bias were used. The role of EH as an investigator and her involvement in the TiM development was explained at each visit and any clinical queries were passed onto the Telehealth Nurse. Follow-up PROMs were completed by participants independently at home and entered by an independent study nurse. Quantitative analysis was overseen by the study statistician using a pre-specified analysis plan. Data triangulation (qualitative, TiM use, trial data) and methodological triangulation (patients, carers, staff) were employed. EVH conducted all the interviews except the 14 month interview with the telehealth nurse which was conducted by co-author WOB (an experienced qualitative researcher independent of the clinical team) who also oversaw the interview planning, conduct and analysis.

Analysis

Quantitative data was analysed using descriptive statistics and qualitative data was organised using NVivo (31) and analysed using thematic analysis (32). A triangulation process compared the quantitative and qualitative data to further understand and explain important, incongruent and unexpected observed phenomenon. Early results provided some insight into how the TiM was being used and informed changes to the intervention and study methods.

Sample size

A target of 40 patients and 40 carers was selected to enable an estimation of the standard deviation of potential outcome measures to within a precision of ±20% of its true underlying value with 90% confidence (33). The sample size was also based on guidance that a minimum of 12 evaluable patients per trial arm is required (i.e. after allowing for death, withdrawal or drop-out) in order to inform a sample size calculation for a definitive trial (33,34).

Role of the funding sources

The study design, conduct, analysis, and interpretation of data, writing of the report, and the decision to submit the paper for publication were conducted by the authors independently of the funders with the exception of a requirement to report adverse events the investigator deemed to be related to Abbott Pharmaceuticals. Mylan provided technical expertise to support improvements to the software.

RESULTS

A summary of the feasibility questions, using the ADePT framework (28) are presented in supplementary data files. Qualitative data is reported within each section to explain the findings. A supplementary data file contains the results of each outcome measure and supporting qualitative quotes.

Screening and eligibility

306 patients were pre-screened (Figure 1). 123 patients (40%) were excluded because the Sheffield MDC was not their main or current care centre. Of the remaining 183, 88 patients were excluded on clinical grounds, mainly due to lack of disease progression or cognitive impairment. This left 95 eligible patients (52% of the patients attending the MDC).

Recruitment

42 patients (44%) expressed an interest in participating. 40 (42%) were eligible: 28 prevalent and 12 incident cases. All 40 were consented, randomised and received the intervention between October 2014 and November 2015. 37 eligible carers were recruited. Three patients were recruited who did not have a primary carer.

Participant characteristics

Age, gender, phenotype and site of onset were similar to a much larger cohort of patients at the Sheffield MDC (7) (Table 1). Age ranged from 30 to 78 years and participants had disabilities ranging from mild to severe, including 13 (33%) who used either NIV or a gastrostomy tube (King's stage 4 (35)).

Table 1 Participant characteristics

	Telehealth n=20	Control n=20
Gender Male	14 (70%)	14 (70%)
Age (years) Mean (SD), range	60.4 (11.7), 30-78	60.0 (10.0), 39-73
Phenotype		
Amyotrophic lateral sclerosis	17 (85%)	18 (90%)
Primary lateral sclerosis	2 (10%)	2 (10%)
Progressive muscular atrophy	1 (5%)	0 (0%)
Disease duration (months)		
Mean (SD), range	53 (48), 12-197	46 (35), 7-123
Duration since diagnosis (months)		
Mean (SD), range	32 (34), 3-137	21 (19), 1-58
King's ALS clinical stage[a]		
1	3 (15%)	2 (10%)
2	4 (20%)	5 (25%)
3	5 (25%)	8 (40%)
4	8 (40%)	5 (25%)
Use of the TiM App		
Independently	17 (85%)	17 (85%)
Assistance from carer	1 (5%)	1 (5%)
Patient instructs carer	2 (10%)	2 (10%)
Technology use[b]		
Daily	14 (70%)	18 (90%)
A few times per week	3 (15%)	1 (5%)
Once a week	1 (5%)	1 (5%)
Every few weeks	0 (0%)	0 (0%)
Never	2 (10%)	0 (0%)
Home technology		
Broadband	18 (90%)	20 (100%)
3G mobile reception	18 (90%)	15 (75%)
	Telehealth n=18	**Control n=19**
Carer gender Male	4 (21%)	5 (28%)
Carer age (years) Mean (SD), range	59 (12, 42-84)	60.8 (11,38-73)
Relationship to patient		
Partner	18 (95%)	16 (89%)
Child	0 (0%)	1 (6%)
Parent	1 (5%)	1 (6%)
Carer technology use[b]		
Daily	12 (67%)	16 (84%)
A few times per week	1 (6%)	1 (5%)
Once a week	1 (6%)	1 (5%)
Every few weeks	0 (0%)	0 (0%)
Never	4 (22%)	0 (0%)

[a]King's stage 1 refers to patients with functional deficit in 1 domain, stage 2: 2 domains, stage 3: 3 domains and stage 4: patients requiring NIV and/or gastrostomy (35). King's stage was calculated using the ALSFRS-R scale at baseline. [b] Technology: computer, smart phone, tablet. SD: standard deviation.

Barriers and enablers to recruitment

Interviews indicated that recruitment and randomisation were acceptable and participants understood the principles of the study and were willing to be randomised. Some participants thought that the TiM would simply function to collect research data, rather than to facilitate MDC care. Participants wanted to participate because they liked the concept of telehealth and because they were highly motivated to participate in research. They expressed a strong altruistic desire to help others and to help the clinical team. Participation made patients feel they still had a valuable contribution to make, even when severely disabled:

"I love being part of something worthwhile." Patient 229

Participants thought that they might gain benefit by learning more about the condition, to improve their chances of taking part in a treatment trial and to have increased contact with the MND team. Some kept up to date with information on the internet and many expressed frustration about the speed of research and felt time was running out for them to be cured. They all wanted to see treatments that had tangible benefits.

"…it doesn't have to cure you it just has to make things better." Carer 232

Participants wanted to learn about research as this provided hope. Patients thought trials would be "*safe*" if they involved a doctor whom they trusted but also recognised that information could be unreliable and offer "*false hope*". A small number were willing to use unproven therapies or take part in trials even if they had to potential for significant harm in order to gain an opportunity to be cured as they felt they had "*have nothing to lose".*

Retention

To maximise the experience gained using the TiM, all participants remained in the study until they died or the study finished in April 2016. Follow-up ranged from six to 18 months. Two patients (5%) who were severely disabled at recruitment felt too ill to continue. No carers withdrew and no participants were lost to follow-up.

The factors that facilitated study participation were the low burden of the study and the intervention (completed at home, minimal visits and a clear understanding of what would be expected of them). Participants identified barriers posed by other clinical trials such as fatigue, burden or disruption of family life but stated these were not experienced in this study. Carers did not want research that required them to be removed from their caring duties.

"My care's here. I can't have anything that takes it away from what I'm doing with P. It's got to be very simple things. I can sit with my iPad and I can fill in a questionnaire." Carer 184

Adherence to the intervention

Detailed description of the acceptability, use of and adherence to the intervention is described in the parallel publication. In brief: compliance was high with 14 (70%) patients completing a TiM session, on average, fortnightly and 13 (70%) carers completing at least three weekly sessions.

Feasibility and validity of the participant reported outcome measures.

Adherence to the postal questionnaires was good. At 6/12 months 80%/71% of patient and 82%/67% of carer questionnaires were returned. Both treatment groups had similar completion rates. Participants felt the PROMs were accessible and not burdensome. They welcomed a thorough assessment of all aspects of life with MND and identified PROMs examining their emotional health and carer strain as the best assessment of their experiences of MND.

"To be quite frank, doctor, I wouldn't care a monkey's what you ask ...I have no hang-ups about any questions, however personal, the team think it's necessary to ask." Carer 229

Most PROMs were returned complete but 2% of the RAND-36 questionnaires were incomplete and participants felt the statements posed in the RAND-36 were too subjective and did not reflect the experiences of life as a carer or patient with MND. Patients and carers found it difficult to answer questions referring to "*health*": some thought they were entirely healthy or did not perceive MND to be a "*health*" problem. Participants favoured the MND specific quality of life questionnaire (ALSAQ-40), preferring the format and content. It was observed that the language used in the ALSAQ-40 closely reflected the language patients used to describe their experiences. Patients found it difficult to report the number of informal hours of care they received per week. 9% of these questions were blank. There was a large variation in informal carer hours required (0 to 168 hours per week) with no clear relationship between a patient's disability and hours of care. Couples' roles had gradually changed as carers took over many of the domestic jobs that were usually shared. This made it difficult to quantify how much of their role was "*caregiving".* Some carers explained that even if they weren't directly providing care they always had to be alert to the needs of their loved one and so many patients wrote that they required care "*24x7*". In addition, the questionnaire did not record multiple carers or where professional carers took over the role of an informal carer.

Feasibility of other data collection methods

The telehealth nurse diaries were returned incomplete. The nurse reported that it was difficult to assess her time using the TiM because she was often doing multiple tasks making it difficult to determine whether the time spent on an activity was part of "*usual care"* or triggered by a TiM session. The Shadow Monitoring Protocol planned for clinicians to review information on the TiM and provide feedback prior to clinic. This was found to be infeasible because clinic appointments were frequently rescheduled or not booked sufficiently far in advance. There were administrative difficulties accessing the paper records (electronic records were not used during the trial). However, after the MDC clinic, physicians completed 38 Shadow Monitoring feedback forms about the

TiM, although total clinic numbers were not collected so compliance with this form could not be measured.

Outcome assessment

All clinical outcomes are reported in the online supplement. Adverse events were low and none directly caused by the TiM system. We did not compare treatment arms in this feasibility study. However, we examined the data to determine whether it was possible to capture the impact of the TiM on MND outcomes. It is expected that over 6-12 months most patients with MND deteriorate in a meaningful way and therefore this change should be captured by our outcome measures. The ALSFRS-R confirms this as scores declined at a similar rate to the MDC population indicating disease progression (0.39 points per month compared to 0.34 pre month recorded in the Sheffield MDC clinic (7)). Physical QoL showed a trend towards deterioration in both the RAND-36 and the physical sub-scores of the participants' preferred QoL measure the ALSAQ-40. The incidence of severe anxiety in carers also increased. Mostly these changes were small and did not reach significance but the sample sizes were too small to draw firm conclusions. Measuring health economic data identified a number of difficulties: only four hospital admissions were reported during the whole trial and other health resource use was highly variable. For example, between the third and sixth month of the trial health care visits ranged from 0 to 121 visits (intervention: median 8, range 0-121, control: median 4, range 2-17). The number of encounters did not appear to be related to patient satisfaction or access to MND services: some patients who reported to receive excellent, coordinated care had very few appointments whereas other patients reporting good care had many appointments.

Sample size for a full RCT

The sample size for a full-scale trial depends on the type I and II errors, the level of missing data due either to death or withdrawal, and the anticipated size of effect. Assuming a 5% level of statistical significance, 90% power and 75% follow-up (based on the number completing 12 month follow-up in this study) and an effect size of 0.3 standard deviations, a standard sample size calculation requires a prohibitive 312 patients per trial arm. This number can be reduced by employing a longitudinal approach to the analysis which the repeated measures (in this study the baseline, 3, 6 and 12 months) are used in a repeated measures regression (36). Adopting this approach to the above scenario and assuming a correlation of 0.5 between measures leads to a more achievable sample size of 131 per arm. The sample size could be reduced further if a larger effect size was used (a 0.4 standard deviation effect size requires 74 patients per arm), although larger effect sizes seem unlikely for a non-disease modifying intervention. On the other hand, smaller effect sizes would be unjustified given the cost and service redesign requirements associated with implementation. We also note the present study is limited by its size, thus precluding a reliable estimate of whether the postulated effect sizes are reasonable.

DISCUSSION

The aim of the study was to determine the feasibility and acceptability of conducting an RCT of TiM. Recruitment and retention were successful and rates similar to those in trials of disease modifying treatments in MND (such as diaphragmatic pacing (37)). In addition, it was retain typical patients compared to other clinical trials in MND where patients characteristics are less representative (27,38,39). This included patients with severe disability and those living at a distance from hospital. Involvement of patient groups in the trial design, the low burden of the study and the participants motivations to participate in research were the key facilitators of study success. The potential barriers to research participation identified (time, fatigue and the impact on research on day-to-day life) were not a problem in this trials. We recommend that our methods and findings be adopted in other trials in MND in order to improve recruitment and equality of access. Future clinical trials could even use the TiM as a cost-effective, low burden research tool to collect outcome measures.

The main challenges to a larger study will be a recruiting a sufficient sample size. Problems with recruitment are not unique to MND: less than a third of trials manage to meet recruitment targets and half require an extension (40). A sample size of 260 is feasible but challenging. The Sheffield MND clinic is one of the largest in the UK, and even using very broad inclusion criteria, only approximately half of patients recently attending the MDC were eligible to participate. Of these, only approximately half responded to an invitation. Therefore, for a sample size of 260 and a realistic estimate of recruiting 10-25% of all the patients under the care of MND centre, the involvement of MND centres with a total caseload of between 1000 and 2500 patients would be required (this accounts for one quarter and half of UK centres). Recruitment might be improved with face-to-face invitations, advertising and the use of national MND registries (e.g. (41)) that could even allow patients to identify themselves for research even when they cannot travel to a research centre.

A further challenge of a larger evaluation would be assessing the impacts of the TiM. Like other trials of telehealth (e.g. (42)) it would be challenging to demonstrate a reduction in health resource use. In this case it is the low levels of the most costly encounters (hospital admissions) and the complexity of MDC care with highly variable levels of health resource use which do not appear to be directly linked to quality of care that pose challenges. In addition, our parallel paper suggests that any potential impact of the TiM on individual patients may vary depending on the stage and severity of the disease meaning single outcome measures may fail to capture all relevant impacts (for example improved communication may improve emotional quality of life for patients early in the disease whereas earlier identification of physical complications that may prolong survival in the later stages).

Whilst it may be feasible to conduct a larger trial of telehealth in MND, a traditional RCT may not always be the best way to evaluate such a complex intervention (43). An RCT aims to determine whether, all other factors being equal, a specific intervention works at the population level. However, a

multicenter study would involve different MND services and whilst all MND care centres do adhere to the same guidelines (12,13). Their structures differ meaning the impact of the TiM may differ with results from one site unlikely to fully predict whether it would work in other services. Service-level evaluations using non-randomised studies are inevitably less costly, quicker and able to recruit in larger cohorts than RCTs (all important factors in rare, terminal diseases such as MND). However, the limitations of such studies have been extensively documented with several published examples reminding us of the need to undertake assessments of both benefits and risks of new interventions. These including in MND where apparently beneficial therapies subsequently were reported as ineffective or even harmful (e.g. (37)). However, there is conflicting evidence on the extent by which RCTs and well-designed controlled studies differ in this regard (44-47).

Whilst the role of non-RCTs in evidence-based medicine remains controversial, they are appealing in this type of situation where the intervention is perceived as being low risk and having modest clinical impact. In terms of efficacy, given MDC has been demonstrated to improve outcomes, it may be preferable to simply determine whether the TiM system can deliver an equivalent service to the current usual care, and/or widen access to MDC services that are already proven to be beneficial. In addition, the MRC framework recommends that developing and implementing technology is an iterative processes (23). An RCT would not provide sufficient opportunity to change the intervention substantially during the trial in response to feedback from centres, advances in technology and changes to the way MND care is delivered. Implementation studies may be better placed to demonstrate this whilst also providing the opportunity to demonstrate some of the complex clinical, professional and institutional factors that influence the success or failure of such an intervention (43,48). These also enable clinical services to test and modify the TiM to increase the likelihood of local buy-in, promoting local "champions" who witness the successes of new services can deliver persuasive arguments to support commissioning of services (49). In the case of digitally-enabled technology, at both a methodological and health service level it remains uncertain what represents a good trial and what evidence is need would persuade interventions to be funded and adopted.

CONCLUSION

The study suggests that a large-scale evaluation of the TiM system would be possible but challenging. This study suggests that it could be possible to overcome some challenges seen in other MND trials (such as recruitment and retention). With such diverse clinical settings with complex groups of patients, alternative methods of evaluating may be more appropriate in generating practical and generalisable data and support TiM development and implementation.

Funding and acknowledgements
The TiM was developed within a collaboration between the University of Sheffield, Sheffield Teaching Hospitals NHS Trust, Mylan Ltd and Abbott Healthcare. This trial was funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship grant to EH (DRF-2013-06-076) and the Motor Neuron Disease Association. The trial was supported by the Sheffield Teaching Hospitals NHS Trust NIHR Clinical Research Facility and the University of Sheffield Clinical Trials Unit. Mylan Ltd supplied the software and hardware required for the trial. EH is also funded by an NIHR Clinical Lecturer award. PJS is supported by NIHR Senior Investigator award NF-SI-0512-10082 and PJS and CMD by the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience) IS-BRC-1215-20017.

This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest
The TiM intellectual property is owned by Mylan and the University of Sheffield. There are no individual conflicts of interest.

Author contributions
The following were involved: intervention development (CMD, EH, TW, PJS), trial design and management (EH, MB, WO, CC, AQ, CMD), clinical oversight (CMD and PJS), recruitment and intervention delivery (EH and TW) data collection (EH, WB), data analysis (EH, MB, WB) and manuscript preparation. (EH). All authors reviewed and commented on the manuscript. The authors are grateful to Sheffield MND Research Advisory Group for their guidance on the research methods.

Data statement
Supplementary data is available in the online appendices of this paper and the parallel publication. Additional data is available from the corresponding author on request.

Figures
Figure 1: CONSORT flow diagram. Follow up varied depending on when patients entered the study ranging from 18 months (for those recruited at the start of recruitment period) to 6 months for those recruited at the end of the recruitment period. At each time-point patients are either reported as reached the time-point (analysed) or had died, withdrawn, or did not reach that time-point due to being recruited later in the study.

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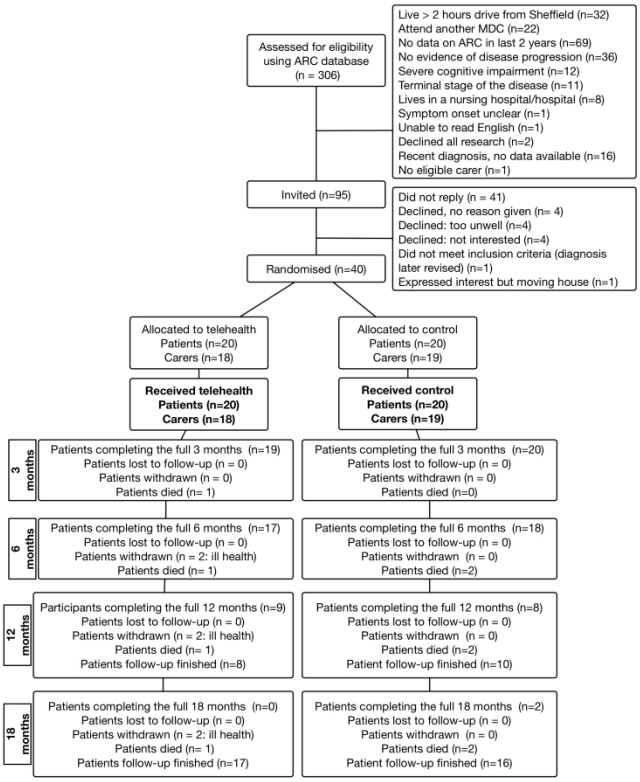

CONSORT flow diagram. Follow up varied depending on when patients entered the study ranging from 18 months (for those recruited at the start of recruitment period) to 6 months for those recruited at the end of the recruitment period. At each time-point patients are either reported as reached the time-point (analysed) or had died, withdrawn, or did not reach that time-point due to being recruited later in the study.

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Question	Findings	Evidence	Suggestions for improvement
1. Did the feasibility/pilot study allow a sample size calculation for the main trial?	Sample size of 131 patients per group indicated for main trial.	See Sample Size for main trial	Use longitudinal data for primary outcome.
2. What factors influenced eligibility and what proportion of those approached were eligible?	Clear eligibility criteria enabled prescreening using clinical records. Large number of patients were excluded because they were not currently receiving MDC care. Fewer patients excluded on clinical grounds. Including atypical MND and patients without their carer increased eligibility.	CONSORT diagram and Table 1.	Maintain low burden intervention and study methods and continue to use a broad and pragmatic inclusion criteria that can be applied at pre-screening using notes/clinical database.
3. Was recruitment successful?	Achieved target but took longer than expected due initially to study resources and later due to availability of eligible patients. Patient response rates to invitation good. Participants reflected a published cohort of Sheffield MDC patients, those with severe disabilities and those with little experience using technology.	Target of 40 patients and 37 carers achieved in 13 months. 28 existing patients and 12 newly diagnosed patients were recruited. 42/90 patients interested in participating. See Table 1.	Use face-to-face invitations and use registries to identify more eligible patients in other participating centres.
4. Did eligible participants consent?	Good conversion to consent facilitated by good participant motivation and low study burden.	All eligible participants indicating an interest in the trial were recruited	Maintain good information in the patient invitation processes and participant literature.
5. Were participants successfully randomized and did randomization yield equality in groups?	All patients randomised on the day of recruitment and all received the allocated treatment on the same day except one patient who received it three days later.	Characteristics of groups appeared broadly similar.	
6. Were blinding procedures adequate?	Blinding not possible but follow-up data was collected without the involvement of the study team.	Patient interviews.	
7. Did participants adhere to the intervention?	Good participant adherence. Fewer actions taken by telehealth nurse than expected. See parallel publication.	14 (70%) patients completed a TiM session, on average, fortnightly. 13 (70%) carers completed a TiM session at least three weekly.	Further research to promote the use of the TiM system by staff in different clinical settings.
8. Was the intervention acceptable to the participants?	Intervention acceptable to patients, carers and staff. Main findings described parallel publication. Withdrawal rate low.	See parallel publication. Two patients withdrew.	Further research is required to assess the acceptability of the TiM system by staff in different clinical settings.
9. Was it possible to calculate intervention costs?	Telehealth nurse time was not assessed: diaries unfeasible. Assessment of health economic data limited, see text.	Telehealth nurse time was not assessed: diaries unfeasible.	Automatic assessment of TiM system use collected by the TiM software.

10. Were outcome assessments completed?	PROMs return was good in both treatment arms. Pre-clinic shadow monitoring was not feasible (see text for reasons). Some clinic shadow monitoring forms completed, but it was not clear how many were missed due to lack of records.	Participant questionnaires completed: 6 months 80% patient and 82% carer, 12 months 71% patient, 67% carer. 0 pre-clinic shadow monitoring forms and 38 clinic shadow monitoring forms collected.	Fund administration and clinician time to collect clinical outcomes.
11. Were outcomes measured those that were the most appropriate outcomes?	The MND specific ALSAQ-40 was the preferred QoL measure and captured a trend towards deterioration in the physical QoL of patients during the trial. RAND-36 was less acceptable with more missing data. Collecting informal carer hour requirements using patient estimation was not successful. Health and social care resource use varied widely and did not appear to be related to quality of care. Hospital admissions rates low.	Incomplete questionnaires: RAND-36 2%, ALSAQ-40 0%, HADS 0%, ZBI 0% number of carer hours required 9%. Interview data highlighting participants' preference for the ALSAQ-40, ZBI, HADS. Range of healthcare episodes was very high: 0-120 in three months. 4 emergency MND related admissions.	Continue postal questionnaires and offer participant support to complete outcomes at baseline. Use outcome measures that best reflect participant experiences (ALSAQ-40, ZBI, HADS) and do not measure carer hours using simple recall. Examine whether TiM delivered non-inferior care and/or improves access to MDC care, which is known to improve outcomes.
12. Was retention to the study good?	Dropout was low.	2/40 patients withdrew due to ill health. No loss to follow-up.	
13. Were the logistics of running a multicenter trial assessed?	N/A	N/A	N/A
14. Did all components of the protocol work together?	Components had strong synergy except the components using quantitative outcomes to capture clinician experiences and activities due to lack of administrative time and potential burden on clinical staff.	All those recruited were randomised, received the allocated treatment arm and a good level of data completion. Completion of the Shadow Monitoring forms & Telehealth Nurse diaries was poor.	Use automated systems and qualitative methodologies to capture clinician data.

Telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a pilot, feasibility study.

Supplementary data tables

Table of Contents

Table 1 Patient outcome measures collected.[1]

	Baseline	3 months	6 months	12 months	18 months	Clinic visits
Patient characteristics						
Age, gender	X					
Frequency of technology use	X					
Broadband/mobile internet access	X					
Difficulties using TiM	X					
Need for help using TiM	X					
Medical history						
Diagnosis	X					
Disease duration	X					
Comorbidities	X					
Drug history	X					
Quality of life						
ALSAQ-40 (218)	X	X	X	X	X	
SF-36 v1 (219)	X	X	X	X	X	
EQ-5D+D	X	X	X	X	X	
Clinical measures						
ALS-FRS-R (205)	X	X	X	X	X	
Pain score (current and worst)**	X	X	X	X	X	
CSS-MND saliva scale (220)	X	X	X	X	X	
Hospital Anxiety and Depression score (221)	X	X	X	X	X	
Survival						X
Adverse events		X	X	X	X	X
Health resource use						
Clinician encounters**	X	X	X	X	X	X
Hospital admissions**	X	X	X	X	X	X
Informal care use**	X	X	X	X	X	
Formal care use**	X	X	X	X	X	
Satisfaction						
MND care satisfaction**	X	X	X	X	X	
TiM satisfaction**		X*	X*	X*	X*	

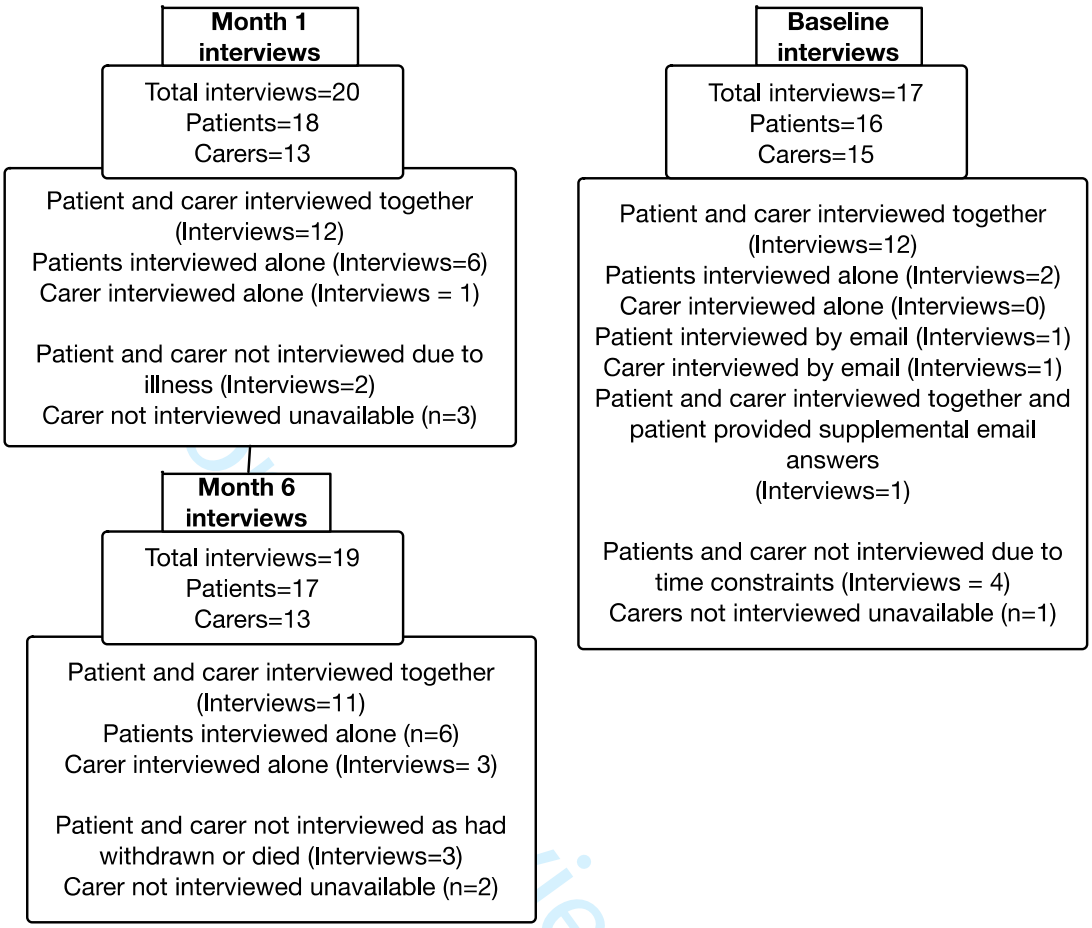
[1] *intervention arm only ** questionnaires designed for the trial

Table 2 Carer outcome measures collected.

	Baseline	3 months	6 months	12 months	18 months	Clinic visits
Carer characteristics						
Age, gender	X					
Relationship to patient	X					
Frequency of technology use	X					
Difficulties using TiM	X					
Quality of life						
SF-36 v1 (219)	X	X	X	X	X	
Clinical measures						
Hospital Anxiety and Depression score (221)	X	X	X	X	X	
Zarit Burden Interview (222)	X	X	X	X	X	
Adverse events		X	X	X	X	X
Satisfaction						
MND care satisfaction**	X	X	X	X	X	
TiM satisfaction**		X*	X*	X*	X*	

*intervention arm only, ** questionnaires designed for the trial

Figure 1 Detailed description of the semi-structured interviews.



In one case a patient was interviewed with his carer, who was not participating in the study. In one case a community nurse was present during the interview. She later was interviewed as part of the study. Telephone interviews were conducted when the patient lived at a distance from the study centre and email interviews were used when the patient had significant dysarthria. All interviews took place in the patients' home except one which took place in a café at the request of the carer. The transcripts were not returned to participants to avoid over burdening them but they were checked by EH who transcribed interviews where participants had speech disturbance. The results were presented to the trial management group which included a member of the Sheffield MND Research Advisory Group who was an experienced volunteer visitor to families with MND and she provided context and confirmed validity of the findings.

Figure 2 Mean ALSAQ-40 sub-scores and standard errors at baseline, three, six, and twelve months.

Scores range from 0 (best possible QoL) to 100 (worse possible QoL). An * indicates scores where the mean change from baseline differs significantly from baseline ($p<0.05$).

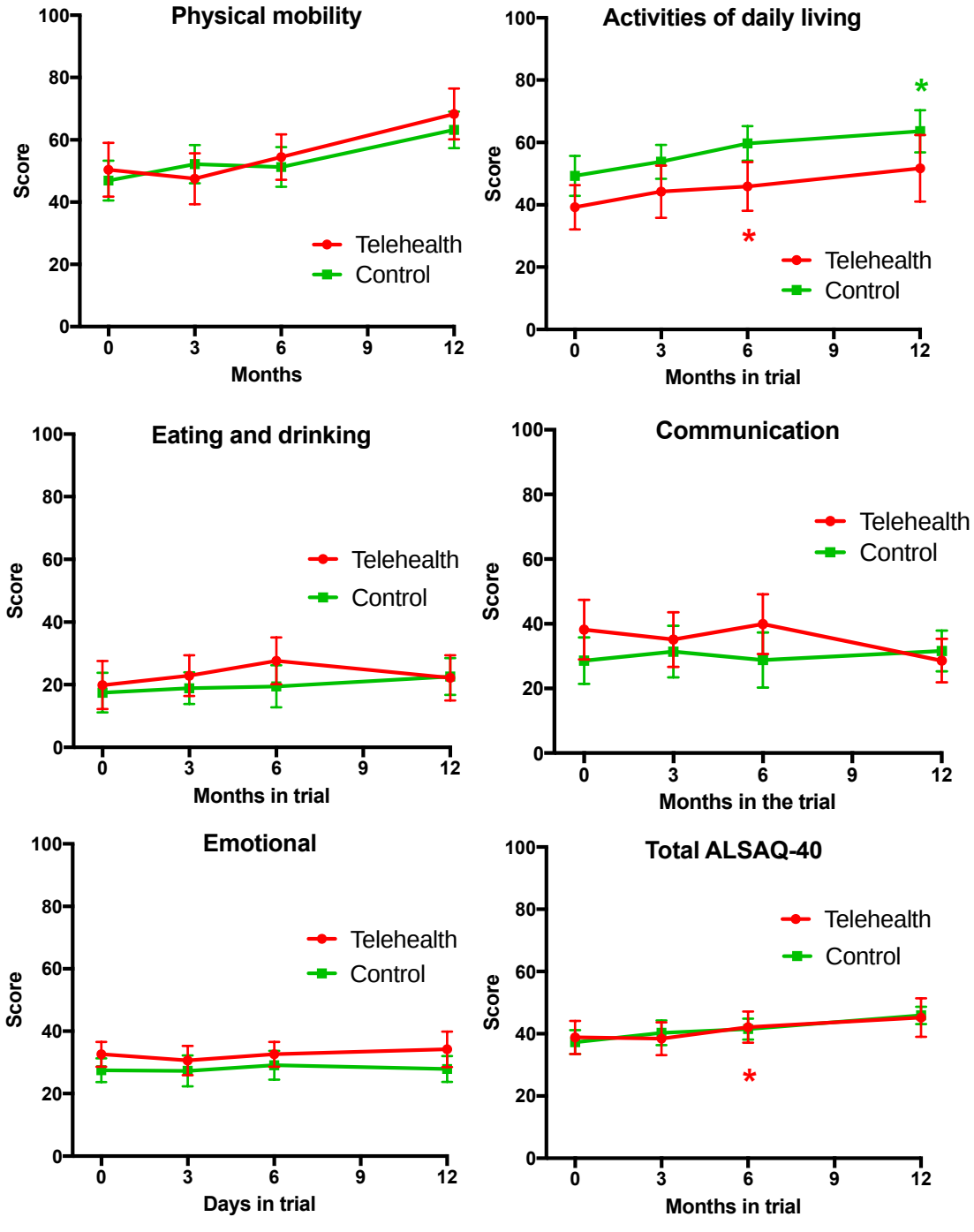


Table 3 Patient ALSAQ-40 index scores

Mean, standard deviation (SD), mean change from the baseline and 95% confidence intervals. Scores range from 0 (best possible QoL) to 100 (worse possible QoL). Cells highlighted in bold indicate where scores are significantly different to baseline.

	Base-line	3 months		6 months		12 months	
Patient ALSAQ-40	**ALSAQ -40 Mean (SD)**	**ALSAQ -40 Mean (SD)**	**Mean change from baseline (CI)**	**ALSAQ -40 Mean (SD)**	**Mean change from baseline (CI)**	**ALSAQ-40 Mean (SD)**	**Mean change from baseline (CI)**
Telehealth	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Physical mobility	50.4 (36.6)	47.5 (34.6)	-4.7 (-15.4, 6.1)	54.5 (30.9)	5.8 (-3.8, 15.4)	68.3 (26.8)	10.4 (-3.6, 24.4)
Activities of daily living	39.2 (30.2)	44.2 (35.6)	5.8 (-0.1, 11.8)	45.9 (33.1)	**8.4 (1.6, 15.3)**	51.7 (45.2)	15.8 (-1.5, 33.1)
Eating and drinking	19.9 (32.5)	22.9 (27.6)	6.1 (-1.4, 13.6)	27.6 (31.7)	**11.5 (2.6, 20.3)**	22.2 (30.6)	13.9 (-16.7, 44.5)
Communic-ation	38.3 (39.0)	35.1 (35.9)	0.5 (-5.0, 5.9)	39.9 (39.1)	3.6 (-2.1, 9.3)	28.6 (45.2)	13.1 (-12.1, 38.3)
Emotional	32.6 (16.8)	30.6 (20.0)	0 (-6.4, 6.4)	32.6 (16.9)	1.4 (-4.6, 7.5)	34.2 (24.3)	3.8 (-13.0, 20.5)
Total	38.8 (22.5)	38.4 (22.2)	0.83 (-2.6, 4.3)	42.1 (21.2)	**5.4 (0.2, 10.6)**	45.2 (26.3)	10.8 (-1.5, 23.2)
Control	n=20	n=15	n=15	n=12	n=12	n=7	n=6
Physical mobility	46.9 (28.7)	52.2 (27.6)	1.6 (-12.9, 16.1)	51.3 (28.6)	8.3 (-8.2, 24.9)	63.2 (26.1)	15.0 (-17.6, 47.6)
Activities of daily living	49.3 (28.7)	53.8 (24.2)	2.3 (-7.0, 11.6)	59.7 (24.6)	9.0 (-9.6, 18.9)	63.6 (30.4)	**15.8 (1.9, 30.0)**
Eating and drinking	17.5 (28.2)	18.9 (22.6)	0.6 (-7.1, 8.3)	19.5 (30.1)	8.3 (-10.7, 27.4)	22.6 (26.2)	2.8 (-6.3, 11.8)
Communic-ation	28.6 (32.2)	31.4 (35.8)	1.5 (-5.9, 8.9)	28.8 (38.1)	8.0 (-20.5, 36.6)	31.6 (28.2)	9.5 (-9.8, 28.9)
Emotional	27.5 (17.0)	27.3 (22.0)	-1.4 (-9.2, 6.3)	29.1 (20.5)	-2.3 (-16.4, 11.8)	27.9 (18.6)	-3.8 (-23.6, 16.1)
Total	37.3 (17.2)	40.3 (17.7)	0.8 (-2.6, 4.3)	41.5 (14.9)	5.8 (-3.7, 15.3)	45.9 (12.5)	10.8 (-1.5, 23.2)
Total	n=38	n=31	n=30	n=28	n=28	n=13	n=12
Physical mobility	48.6 (32.3)	49.8 (31.0)	0.9 (-6.7, 8.6)	53.1 (29.4)	6.9 (-1.4, 15.2)	65.6 (25.5)	12.7 (-1.8, 27.3)
Activities of daily living	44.5 (29.5)	48.9 (30.5)	1.6 (-12,9, 16.1)	51.8 (30.0)	**8.7 (3.3, 14.0)**	58.1 (29.0)	**15.8 (6.8, 24.9)**
Eating and drinking	18.6 (28.4)	21.0 (25.0)	2.3 (-7.0, 8.3)	24.1 (30.8)	**10.1 (1.3, 19.0)**	22.4 (27.1)	8.3 (-5.2, 21.9)
Communic-ation	33.3 (35.4)	33.3 (35.3)	01.5 (-5.9, 8.9)	35.2 (38.3)	5.5 (-6.1, 17.1)	30.2 (35.3)	11.3 (-1.7, 24.3)
Emotional	29.9 (16.9)	29.0 (20.7)	-1.4 (-9.2, 6.3)	31.1 (18.2)	-0.2 (-6.6, 6.3)	30.8 (20.8)	0 (-10.9, 10.9)
Total	38.0 (19.6)	39.3 (19.9)	0.88 (-2.9, 4.7)	41.8 (18.5)	**5.6 (0.9, 10.2)**	45.6 (19.1)	8.6 (-0.4, 17.6)

Table 4 RAND-36 physical (PCS) and mental (MCS) sub-scores.

The mean and standard deviation (SD) of the mean scores, the mean change from baseline and the 95% confidence interval of the mean change from baseline. These are standardised to a normative reference population in which the mean is 50 and Standard deviation is 10.

Patient SF-36	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
PCS	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean (SD/CI)	30.1 (9.1)	30.7 (7.7)	-0.7 (-3.3, 1.9)	28.2 (8.6)	-3.1 (-7.1, 0.9)	22.6 (4.1)	-5.8 (-15.0, 3.4)
MCS	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean (SD/CI)	52.3 (10.0)	50.7 (11.7)	-1.4 (-5.4, 2.6)	52.3 (12.3)	-0.2 (-4.2, 3.8)	48.8 (15.8)	-5.7 (-18.8, 7.2)
Control							
PCS	n=20	n=14	n=14	n=12	n=12	n=6	n=6
Mean (SD/CI)	28.0 (8.7)	26.6 (5.8)	-0.6 (-5.4, 4.3)	27.0 (7.9)	-0.1 (-7.8, 7.6)	23.7 (3.0)	-6.6 (-13.8, 0.5)
MCS	n=20	n=14	n=14	n=12	n=12	n=6	n=6
Mean (SD/CI)	54.3 (9.5)	55.1 (13.5)	0.9 (-5.4, 7.3)	50.8 (12.1)	-3.6 (-10.7,3.6)	54.7 (9.2)	-1.3 (-17.8,15.3)
Total							
PCS	n=38	n=30	n=29	n=28	n=28	n=12	n=12
Mean (SD/CI)	29.0 (8.8)	28.3 (7.2)	-0.7 (-3.2, 1.9)	27.7 (8.2)	-1.8 (-5.5, 1.9)	23.2 (3.5)	**-6.2 (-11.0,-1.4)**
MCS	n=38	n=30	n=29	n=28	n=28	n=12	n=12
Mean (SD/CI)	53.3 (9.7)	52.7 (12.6)	-0.3 (-3.8, 3.2)	51.7 (12.0)	-1.7 (-5.2, 1.9)	51.8 (12.7)	-3.5 (-12.2, 5.2)

Figure 3 RAND-36 scores

Physical component scores (PCS) and mental component scores (MCS) mean and standard errors. RAND-36 scores are standardised to a normative reference population (mean is 50 and SD is 10.) An * indicates scores where the mean change from baseline differs significantly different from baseline ($p<0.05$).

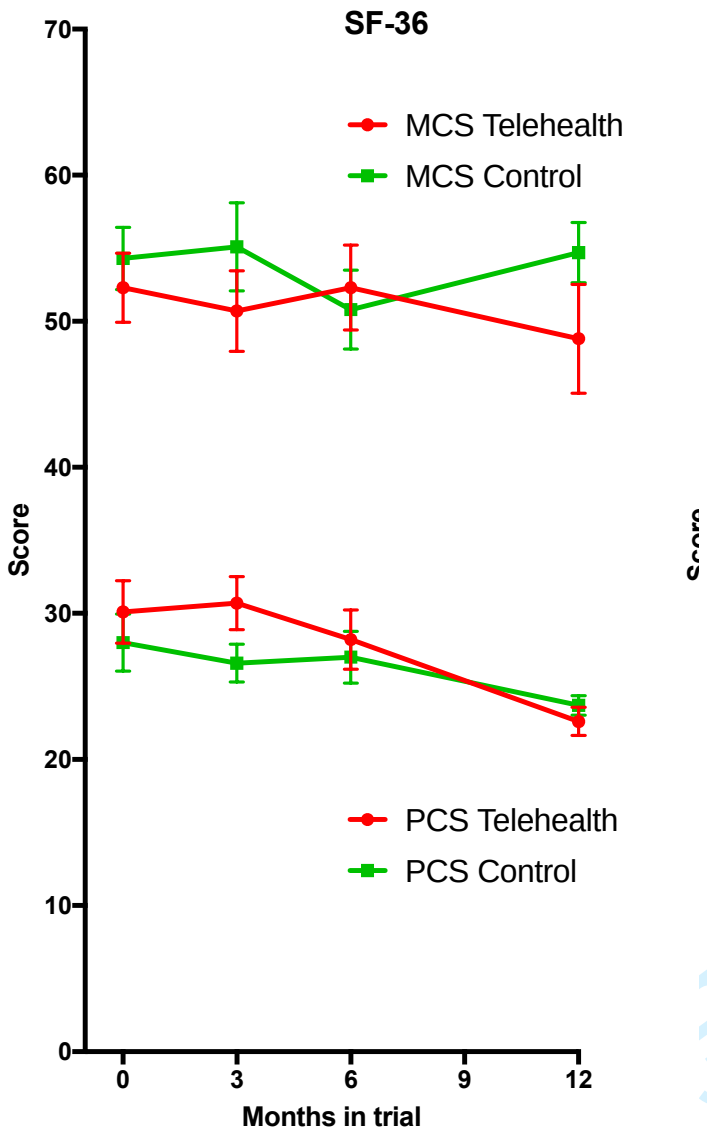


Table 5 EQ-5D-3L and EQ-5D plus dignity bolt-on and the EQ5D thermometer.

	Baseline	3 months		6 months		12 months	
Patient EQ-5D	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth	n=17	n=16	n=14	n=16	n=15	n=6	n=6
EQ5D-3L	0.52 (0.31)	0.49 (0.27)	-0.04 (-0.13, 0.05)	0.49 (0.30)	-0.07 (-0.20, 0.06)	0.39 (0.36)	-0.09 (-0.38, 0.21)
EQ5D-3L+D	0.46 (0.40)	0.48 (0.30)	-0.02 (-0.18, 0.14)	0.47 (0.35)	-0.04 (-0.24, 0.16)	0.26 (0.54)	-0.15 (-0.63, 0.33)
Thermometer	61.1 (22.5)	63.8 (25.0)	-2.1 (-8.7, 4.6)	61.6 (20.5)	-3.7 (-9.6, 2.3)	57.5 (22.3)	-5.8 (-12.8, 1,1)
Control	n=20	n=15	n=15	n=12	n=12	n=6[2]	n=6[3]
EQ5D-3L	0.53 (0.27)	0.50 (0.29)	0.02 (-0.10, 0.14)	0.46 (0.25)	-0.11 (-0.22, 0.01)	0.37 (0.33)	-0.25 (-0.50, 0.0)
EQ5D-3L+D	0.49 (0.37)	0.44 (0.41)	0.01 (-0.10, 0.14)	0.44 (0.29)	-0.10 (-0.21, 0.01)	0.26 (0.48)	-0.27 (-0.59, 0.04)
Thermometer	64.5 (20.6)	64.6 (26.8)	0.9 (-13.5, 15.4)	61.7 (25.3)	-6.7 (-19.8, 6.5)	60.9 (21.6)	-7.0 (-37.2, 23.2)
Total	n= 37	n=31	n=29	n=28	n=27	n=12[3]	n=12[3]
EQ5D-3L	0.53 (0.29)	0.50 (0.27)	-0.01 (-0.01, 0.06)	0.47 (0.27)	**-0.09 (-0.17, -0.01)**	0.38 (0.33)	-0.17 (-0.33, 0.00)
EQ5D-3L+D	0.48 (0.37)	0.46 (0.35)	-0.01 (-0.10, 0.08)	0.46 (0.32)	-0.07 (-0.18, 0.05)	0.26 (0.49)	-0.21 (-0.45, 0.03)
Thermometer	63.0 (21.3)	64.2 (25.5)	-0.5 (-8.2, 7.1)	61.6 (23.0)	-5.0 (-11.2, 1.2)	59.3 (21.1)	-6.4 (-20.7, 7.7)

[2] Control group n=6 in EQ5D calculations and n=7 in thermometer calculations at both 6 and 12 months.

Table 6 EQ-5D-3L and EQ-5D plus dignity bolt-on and the EQ5D thermometer.
In these calculations, patients who had died were included in the scoring and were assigned a score of 0. Thermometer scores are unchanged.

Patient EQ-5D	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
n= *	17	17	15	17	16	8	8
EQ5D-3L Mean (SD/CI)	0.52 (0.31)	0.46 (0.29)	-0.05 (-0.14, 0.03)	0.46 (0.31)	-0.08 (-0.20, 0.04)	0.35 (0.37)	-0.12 (-0.33, 0.08)
EQ5D-3L+D Mean (SD/CI)	0.46 (0.40)	0.44 (0.41)	-0.03 (-0.18, 0.12)	0.44 (0.35)	-0.05 (-0.23,0.14)	0.20 (0.47)	-0.17 (-0.50, 0.15)
Thermometer n=	17	16	14	16	15	6	6
Mean (SD/CI)	61.1 (22.5)	63.8 (25.0)	-2.1 (-8.7, 4.6)	61.6 (20.5)	-3.7 (-9.6, 2.3)	57.5 (22.3)	-5.8 (-12.8, 1,1)
Control							
n=*	20	15	15	14	14	8	7
EQ5D-3L Mean (SD/CI)	0.53 (0.28)	0.50 (0.28)	0.02 (-0.10, 0.14)	0.39 (0.28)	-0.12 (-0.26, 0.01)	0.28 (0.33)	-0.28 (-0.48, -0.08)
EQ5D-3L+D Mean (SD/CI)	0.49 (0.37)	0.44 (0.41)	0.00 (-0.12, 0.12)	0.38 (0.31)	-0.08 (-0.23, 0.07)	0.19 (0.43)	-0.28 (-0.51, 0.10)
Thermometer n=	20	15	15	12	12	7	7
Mean (SD/CI)	64.5 (20.6)	64.6 (26.8)	0.9 (-13.5, 15.4)	61.7 (25.3)	-6.7 (-19.8, 6.5)	60.9 (21.6)	-7.0 (32.6)
Total							
n= *	37	32	30	31	30	16	15
EQ5D-3L Mean (SD/CI)	0.53 (0.29)	0.49 (0.28)	-0.02 (-0.09, 0.05)	0.43 (0.29)	-0.10 (-0.19, -0.02)	0.29 (0.33)	-0.20 (-0.33, 0.08)
EQ5D-3L+D Mean (SD/CI)	0.48 (0.37)	0.44 (0.41)	-0.02 (-0.10, 0.07)	0.41 (0.33)	-0.06 (-0.18, 0.05)	0.20 (0.43)	-0.23 (-0.40, -0.05)
Thermometer n=	37	31	29	28	27	13	13
Mean (SD/CI)	63.0 (21.3)	64.2 (25.5)	-0.5 (-8.2, 7.1)	61.6 (53.0)	-5.0 (-11.2, 1.2)	59.3 (21.1)	-6.4 (-20.7, 7.7)

Table 7 Patient ALSFRS-R scores.

Scores range from 0 (severe disability) to 48 (no disability). Scores highlighted in bold indicate scores that have changed significantly from baseline.

	Baseline	3 months		6 months		12 months	
ALSFRS-R	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean	31.9 (9.7)	32.1 (10.4)	-0.06 (-2.6, 3.4)	31.1 (9.0)	-0.3 (-2.6, 1.9)	28.7 (7.6)	**-4.7 (-8.5, -0.91)**
Control							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean	32.1 (8.0)	29.8 (8.7)	-1.5 (-4.1, 1.0)	29.4 (9.0)	-3.7 (-6.8, -0.5)	25.9 (6.0)	-5.1 (-12, 1.8)
Total							
	n=38	n=31	n=30	n=28	n=28	n=13	n=13
Mean	32.0 (8.7)	30.9 (9.5)	-0.6 (-2.2, 1.0)	31.1 (8.9)	-1.6 (-3.6 – 0.4)	27.9 (9.6)	**-4.9 (-8.4, -1.4)**

Figure 4 Mean ALS-FRS-R and standard error .

Scores range from 0 (severe disability) to 48 (no disability). An * indicates scores where the mean change from baseline differs significantly from baseline ($p<0.05$).

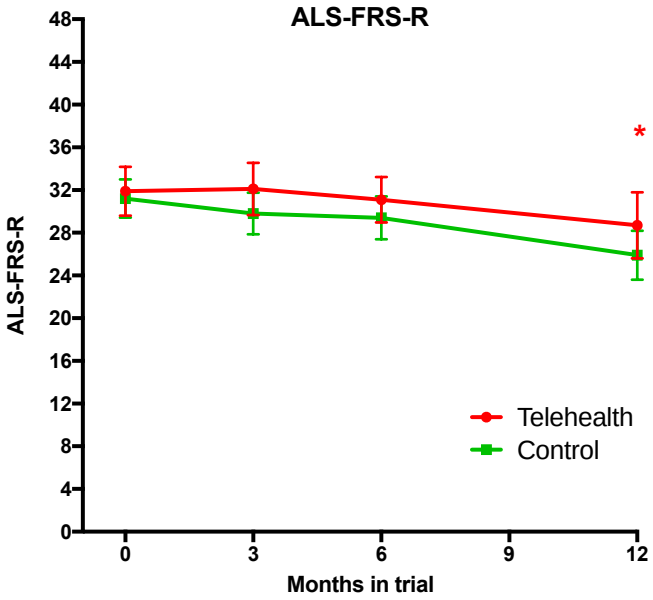


Table 8 Patient HADS Anxiety sub-scores and the number (%) of patients with borderline scores and abnormal scores.
0-7 normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe.

	Baseline	3 months		6 months		12 months	
HADS	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth Anxiety							
	n=17	n=16	n=16	n=16	n=15	n=7	n=6
Mean (SD/CI)	6.0 (4.0)	5.7 (4.3)	-0.2 (-2.3, 1.9)	4.7 (3.7)	-0.9 (-2.1, 0.4)	5.0 (2.6)	-.0.7 (-3.3, 2.0)
Score ≥8	8 (47%)	4 (25%)	-	3 (19%)	-	1 (6%)	-
Score ≥11	1 (6%)	2 (13%)	-	1 (6%)	-	0 (0%)	-
Control Anxiety							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean (SD/CI)	4.9 (3.9)	4.6 (4.4)	-0.5 (-2.1, 1.2)	5.1 (5.1)	-.3 (-1.8, 1.3)	6.0 (4.3)	0.9 (4.7)
Score ≥8	3 (15%)	4 (27%)	-	3 (20%)	-	2 (14%)	-
Score ≥11	2 (10%)	3 (20%)	-	2 (13%)	-	1 (7%)	-
Total Anxiety							
	n=37	n=31	n=31	n=28	n=27	n=13	n=13
Mean (SD/CI)	5.4 (4.0)	5.2 (4.3)	-0.3 (-1.6, 0.9)	4.9 (4.3)	-0.6 (-1.5, 0.3)	5.5 (3.3)	0.2 (-2.1, 2.4)
Score ≥8	11 (30%)	8 (26%)	-	6 (19%)	-	3 (10%)	-
Score ≥	3 (8%)	5 (16%)	-	3 (10%)	-	1 (3%)	-

Table 9 Patient HADS Depression sub-scores and the number (%) of patients with borderline scores and abnormal scores.
0-7 normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe.

	Baseline	3 months		6 months		12 months	
HADS	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth Depression							
	n=20	n=16	n=16	n=16	n=15	n=6	n=6
Mean (SD/CI)	5.9 (2.9)	5.6 (2.7)	-0.3 (-2.1, 1.6)	5.8 (3.0)	0.3 (-1.0, 1.6)	7.5 (4.3)	1.7 (-1.0, 4.4)
Score ≥8	5 (29%)	6 (38%)	-	6 (38%)	-	3 (19%)	-
Score ≥11	0 (0%)	0 (0%)	-	0 (0%)	-	3 (19%)	-
Control Depression							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean (SD/CI)	3.9 (3.0)	6.1 (3.8)	1.5 (-0.4, 3.3)	5.8 (3.3)	0.8 (-1.7, 3.3)	6.4 (3.6)	0.9 (-3.4, 5.1)
Score ≥8	3 (15%)	4 (27%)	-	3 (20%)	-	3 (20%)	-
Score ≥11	1 (5%)	3 (20%)	-	1 (7%)	-	1 (7%)	-
Total Depression							
	n=37	n=31	n=31	n=28	n=27	n=13	n=13
Mean (SD/CI)	4.8 (3.1)	5.8 (3.2)	0.6 (-0.7, 1.9)	5.8 (3.1)	0.5 (-0.7, 1.7)	6.9 (4.6, 9.2)	1.2 (-1.0, 3.5)
Score ≥8	8 (22%)	10(32%)	-	9 (29%)	-	6 (19%)	-
Score ≥11	1 (3%)	3 (10%)	-	1 (3%)	-	4 (13%)	-

Table 10 "Current" and "worst" pain scores over previous week.
Rated on a modified Likert score from 0-10.

Pain scores	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Current pain (0-10)							
Control	20	15	15	13	13	7	7
Mean (SD/CI)	1.4 (1.4)	1.6 (2.0)	0.33 (-0.5, 1.2)	1.4 (2.0)	0.2 (-1.1, 1.4)	2.6 (2.5)	-0.9 (-2.6, 0.9)
Telehealth	17	16	15	15	15	6	6
Mean (SD/CI)	1.7 (1.9)	2.1 (2.4)	0.1 (-1.3, 1.4)	1.8 (2.3)	1.8 (0.7, 2.9)	1.8 (1.6)	0.8 (-1.2, 2.9)
Total	37	31	30	28	28	13	13
Mean (SD/CI)	1.5 (1.7)	1.9 (2.2)	0.2 (-0.5, 0.9)	1.6 (2.2)	1.0 (0.2, 1.9)	2.2 (2.1)	-0.1 (-1.3, 1.1)
Worst pain (0-10)							
Control	20	15	15	13	13	7	7
Mean (SD/CI)	3.2 (2.7)	3.4 (3.1)	-0.1 (-1.3, 1.0)	2.6 (2.7)	-0.2 (-0.8, 0.4)	3.9 (3.1)	0.3 (-1.0, 1.6)
Telehealth	17	16	15	15	15	6	6
Mean (SD/CI)	2.9 (2.8)	3.4 (3.1)	0.1 (-1.2, 1.5)	3.0 (2.8)	3.1 (1.6, 4.7)	3.5 (2.2)	0.3 (-2.4, 2.1)
Total	37	31	30	28	28	13	13
Mean (SD/CI)	3.0 (2.7)	3.2 (2.9)	0.0 (-0.8, 0.8)	2.8 (2.7)	1.6 (0.5, 2.6)	3.7 (2.7)	0.1 (-1.0, 1.1)

Table 11 CSS-MND saliva severity scores.

Mean, standard deviation and change from baseline (mean, 95% confidence interval). Scores range from 0 (no problems with orophrayngeal secretions) to 36 (severe secretions).

	Baseline	3 months		6 months		12 months	
CSS MND	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth	n=17	n=16	n=14	n=16	n=16	n=6	n=6
Mean (SD)	4.2 (6.0)	4.8 (6.4)	1.9 (0.2, 3.5)	2.6 (1.2)	0.0 (-2.8, 2.8)	2.3 (3.2)	0.2 (-1.4, 1.9)
Control	n=20	n=15	n=14	n=12	n=12	n=7	n=6
Mean (SD)	4.1 (5.2)	5.5 (6.2)	1.0 (-1.5, 3.5)	2.8 (1.1)	0.1 (-1.56, 1.7)	3.4 (4.5)	-0.7 (-0.7, 3.4)
Total	n=37	n=31	n=29	n=28	n=28	n=13	n=12
Mean (SD)	4.1 (5.5)	5.1 (6.2)	1.4 (0-2.9)	2.6 (1.1)	0.0 (-1.6, 1.6)	3.4 (4.5)	0.2 (-1.4, 1.9)

Table 12 Carer SF-36 physical and mental sub-scores.

These scores are standardised to a normative reference population in which the mean is 50 and standard deviation is 10.

Carer SF-36	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
Physical	n=16	n=14	n=13	n=15	n=14	n=4	n=4
Mean (SD/CI)	52.4 (11.1)	49.0 (9.6)	-1.9 (-8.0, 4.2)	51.6 (9.7)	0.10 (-4.9, 5.2)	51.0 (3.1)	-3.6 (-13.8,6.6)
Mental	16	14	13	15	14	4	4
Mean (SD/CI)	47.9 (13.1)	50.5 (14.5)	3.3 (-1.1, 7.7)	48.6 (14.4)	1.2 (-2.8, 5.2)	45.3 (14.5)	-2.9 (-9.6, 3.8)
Control							
Physical	n=18	n=13	n=13	n=11	n=11	n=7	n=7
Mean (SD/CI)	52.9 (7.7)	51.9 (7.0)	-3.2 (-8.1, 1.8)	49.1 (8.8)	-4.7 (-8.9, -0.4)	52.2 (9.6)	-3.0 (-10.2,4.2)
Mental	n=18	n=13	n=13	n=11	n=11	n=7	n=7
Mean (SD/CI)	50.6 (10.3)	51.2 (8.7)	1.7 (-2.2, 5.5)	51.8 (10.5)	0.70 (-6.8, 8.1)	51.7 (10.3)	2.4 (-4.5, 9.3)
Total							
Physical	n=34	n=27	n=26	n=26	n=25	n=11	n=11
Mean (SD/CI)	52.7 (9.3)	50.4 (8.4)	-2.5 (-6.1, 1.1)	50.1 (9.2)	-2.0 (-5.3, 1.3)	51.8 (7.6)	-3.2 (-7.9, 1.5)
Mental	n=34	n=27	n=26	n=26	n=25	n=11	n=11
Mean (SD/CI)	49.3 (11.6)	50.8 (11.8)	2.5 (-0.3, 5.2)	49.9 (12.8)	1.0 (-2.7, 4.6)	49.4 (11.7)	0.4 (-4.1, 5.0)

Figure 5 Carer RAND physical component scores (PCS) and mental component scores (MCS).

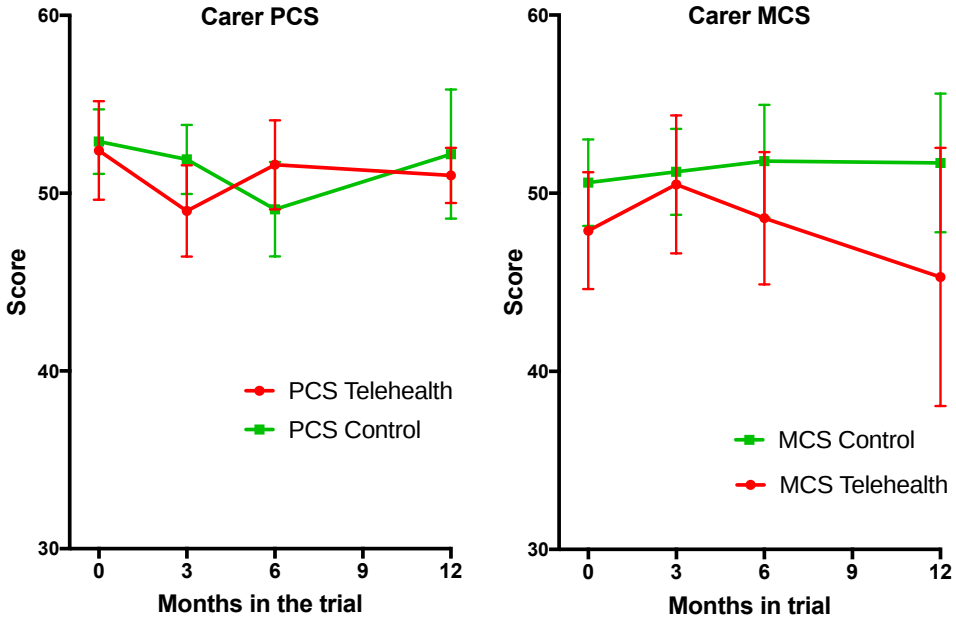


Table 13 Carer HADS depression sub scores and the number (%) of patients with borderline scores or abnormal scores.
Scores 0-7 are normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe).

	Baseline	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth Depression							
	n=16	n=14	n=13	n=15	n=14	n=6	n=6
Mean (SD/CI)	4.0 (3.2)	4.6 (4.1)	0.1 (-1.0, 1,2)	4.3 (3.9)	0.1 (-0.9, 1.0)	4.8 (3.5)	1.3 (-1.5, 4.1)
Score ≥8	1 (6%)	3 (21%)	-	3 (20%)	-	1 (14%)	-
Score ≥11	1 (6%)	1 (7%)	-	1 (7%)	-	0 (0%)	-
Control Depression							
	n=18	n=14	n=14	n=11	n=11	n=7	n=7
Mean (SD/CI)	3.3 (2.8)	4.8 (4.2)	1.4 (0.0, 2.8)	4.3 (4.5)	2.1 (0.4, 4.6)	3.4 (3.4)	1.3 (-0.8, 3.4)
Score ≥8	2 (11%)	3 (21%)	-	3 (27%)	-	1 (14%)	-
Score ≥11	1 (6%)	1 (7%)	-	1 (9%)	-	0 (0%)	-
Total Depression							
	n=34	n=28	n=27	n=26	n=25	n=13	n=13
Mean (SD/CI)	3.6 (3.0)	4.7 (4.0)	0.8 (-0.1, 1.7)	4.3 (4.0)	1.0 (-0.2, 2.1)	4.1 (3.4)	1.3 (-0.2, 2.7)
Score ≥8	2 (6%)	6 (21%)	-	6 (21%)	-	2 (15%)	-
Score ≥11	1 (3%)	2 (7%)	-	2 (7%)	-	0 (0%)	-

Table 14 Carer HADS anxiety sub scores and the number (%) of patients with borderline scores or abnormal scores. Scores 0-7 are normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe).

	Baseline	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth Anxiety							
	n=16	n=14	n=13	n=15	n=14	n=6	n=6
Mean (SD/CI)	6.3 (4.6)	7.1 (4.6)	0.0 (-1.8, 1.7)	6.0 (5.1)	-0.8 (-2.9, 1.3)	7.3 (5.0)	0.3 (-1.4, 1.9)
Score ≥8	7 (44%)	3 (21%)	-	5 (33%)	-	3 (43%)	-
Score ≥11	2 (13%)	1 (7%)	-	3 (20%)	-	3 (43%)	-
Control Anxiety							
	n=18	n=14	n=14	n=11	n=11	n=7	n=7
Mean (SD/CI)	5.9 (3.5)	6.2 (4.4)	-0.2 (-1.8, 1.4)	6.4 (4.8)	0.3 (-2.1, 2.7)	5.6 (4.0)	-0.6 (-1.6, 0.5)
Score ≥8	6 (33%)	6 (43%)	-	4 (36%)	-	2 (29%)	-
Score ≥11	2 (11%)	2 (14%)	-	3 (27%)	-	1 (14%)	-
Total Anxiety							
	n=34	n=28	n=27	n=26	n=25	n=13	n=13
Mean (SD/CI)	6.1 (4.0)	7.1 (4.6)	-0.1 (-1.2, 1.0)	6.2 (4.8)	-0.3 (-1.8, 1.1)	6.4 (4.4)	-0.2 (-1.4, 1.9)
Score ≥8	13 (35%)	3 (11%)	-	**9 (31%)**	**-**	**5 (38%)**	-
Score ≥11	4 (11%)	5 (18%)	-	**6 (21%)**	**-**	**4 (31%)**	**-**

Table 15 The 12-item Zarit Burden Interview scores.
Scores range from 0 (no burden) to 48 (severe burden). A cut-off of scores ≥17 suggests high burden (222).

	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
	n=18	n=14	n=14	n=15	n=15	n=6	n=6
Mean (SD/CI)	11.5 (9.9)	12.7 (11.2)	1.6 (-1.6, 4.8)	13.7 (10.7)	2.4 (-1.3, 6.1)	13.8 (12.6)	4.3 (-1.2, 9.9)
Score ≥17	3 (19%)	4 (29%)		4 (27%)		2 (33%)	
Control							
	n=16	n=13	n=13	n=10	n=10	n=6	n=6
Mean (SD/CI)	12.9 (7.9)	15.9 (8.9)	3.0 (-0.6, 6.6)	12.4 (9.5)	2.6 (-0.5, 5.7)	13.5 (9.6)	-0.3 (-7.9, 6.2)
Score ≥17	6 (33%)	4 (31%)	-	2 (20%)		2 (33%)	
Total							
	n=34	n=27	n=27	n=25	n=25	n=12	n=12
Mean (SD/CI)	12.3 (8.8)	14.2 (10.1)	2.6 (0.0-4.5)	13.2 (9.0)	2.5 (0.1, 4.8)	13.7 (10.7)	1.8 (-2.3, 5.8)
Score ≥17	9 (27%)	8 (30%)		6 (24%)		4 (33%)	

Figure 6 The number of patient-reported MND related healthcare encounters in the three months prior to the study (baseline) and during the study

Mean and range, n=38.

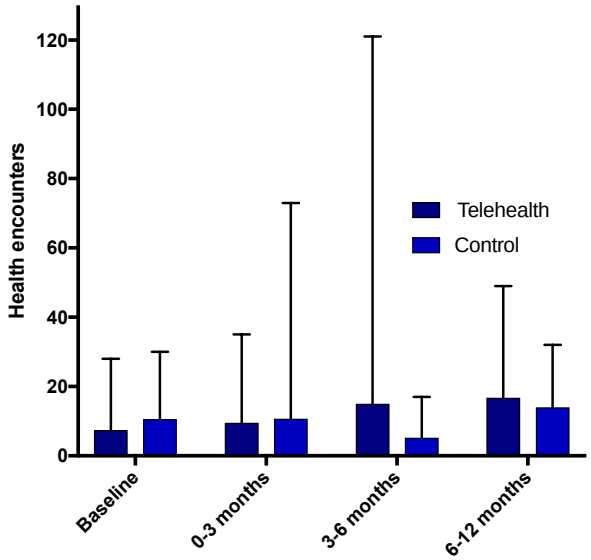


Figure 7 Patient encounters with healthcare professionals due to MND in the three months prior to the study commencement

Mean and range, n=38.

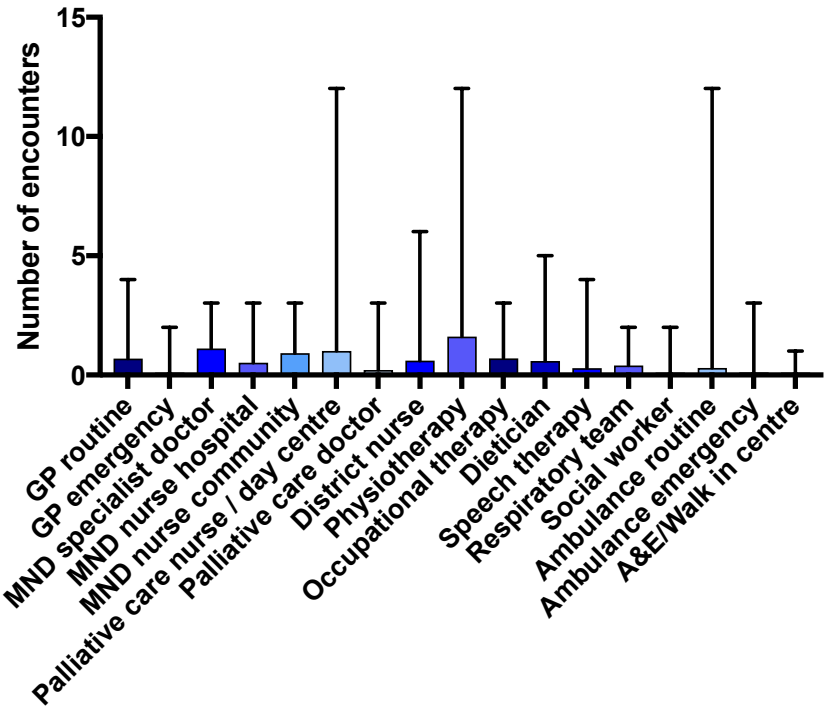


Figure 8 Patient estimated hours of informal (unpaid) and formal (paid) care received per week.
Mean and interquartile range.

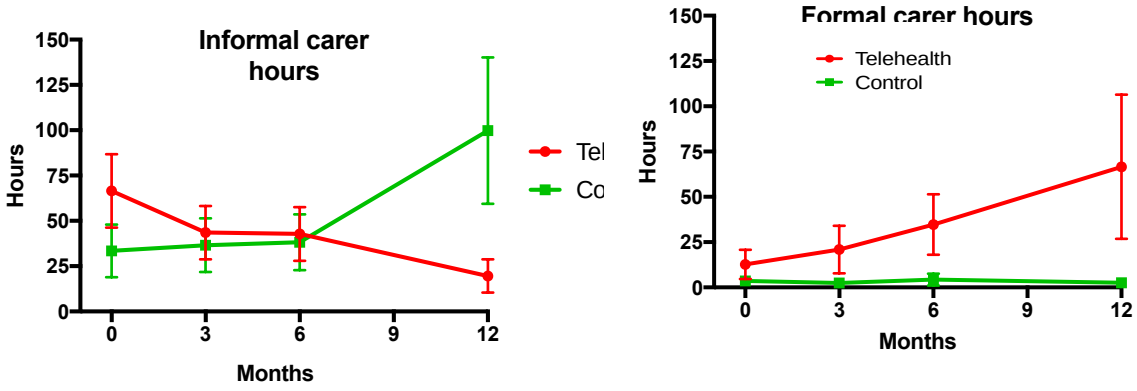


Figure 8 Individual patient estimated median hours of informal (unpaid) and formal (paid) care received per week
Mean and the interquartile range.

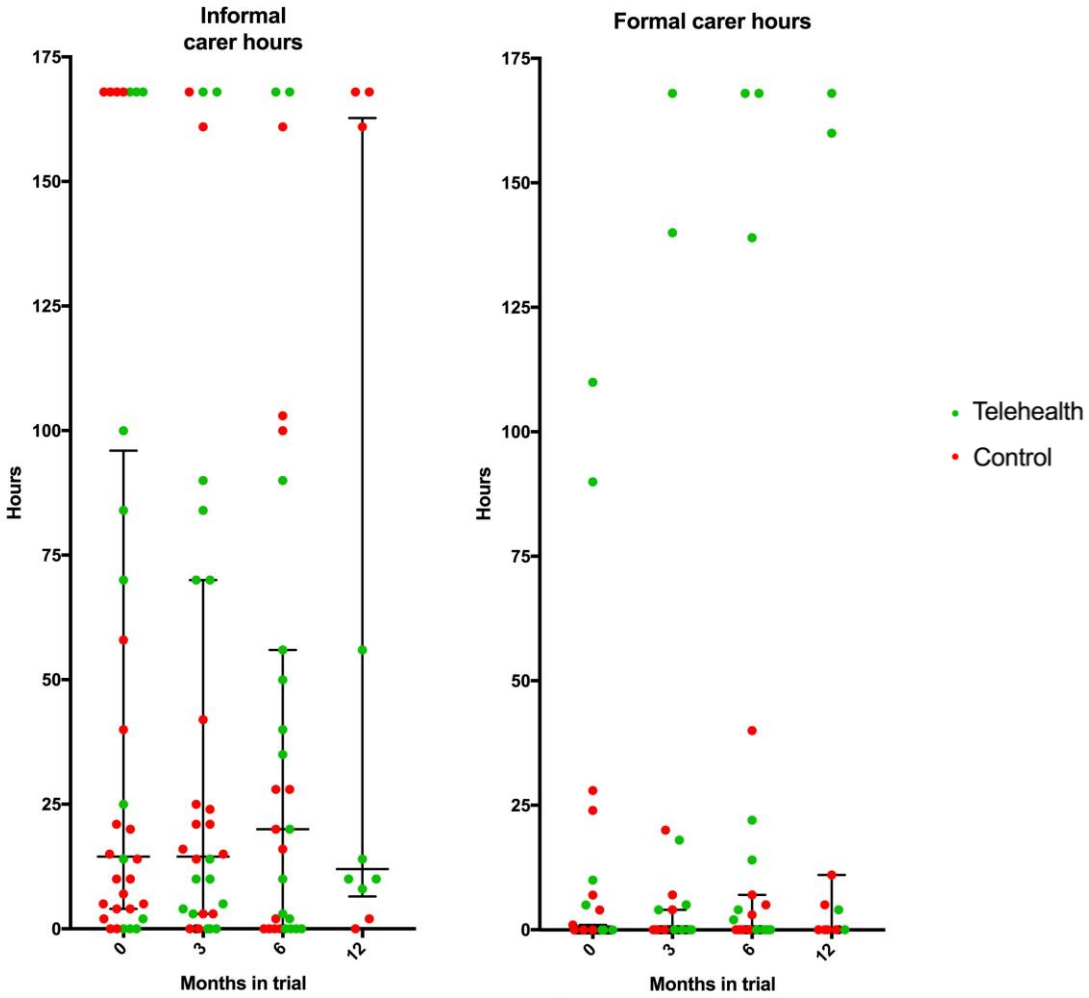


Table 16 Patient estimated hours of paid and unpaid care received per week.

	Baseline	3 month	6 months	12 months
Telehealth				
Paid carer hours	n=17	n=16	n=15	n=5
Mean (SD)	12.7 (33.2)	20.9 (52.4)	34.7 (64.6)	66.6 (89.0)
Median (Range)	0 (0-110)	0 (0-168)	0 (0-168)	5 (0-168)
Unpaid carer hours	n=12	n=16	n=15	n=5
Mean (SD)	66.6 (70.2)	43.5 (58.6)	42.8 (57.4)	19.6 (20.5)
Median (Range)	47.5 (0-168)	10 (0-168)	20 (0-168)	10 (0-168)
Control				
Paid carer hours	n=18	n=13	n=12	n=6
Mean (SD)	3.6 (8.4)	2.4 (5.7)	4.3 (11.4)	2.5 (4.5)
Median (Range)	0 (0-28)	0 (0-20)	0 (0-40)	0 (0-11)
Unpaid carer hours	n=20	n=14	n=12	n=5
Mean (SD)	33.4 (64.9)	36.6 (55.4)	38.2 (53.3)	99.8 (90.2)
Median (Range)	12.0 (0-168)	18.5 (0-168)	18 (0-161)	161 (0-168)
Total				
Paid carer hours	n=35	n=29	n=27	n=11
Mean (SD)	8.0 (24.0)	12.6 (39.7)	21.2 (50.4)	31.6 (65.6)
Median (Range)	0 (0-110)	0 (0-168)	0 (0-168)	0 (0-168)
Unpaid carer hours	n=32	n=30	n=27	n=10
Mean (SD)	52.7 (66.7)	40.3 (56.3)	40.7 (54.6)	59.7 (74.8)
Median (Range)	14.5 (0-168)	14.5 (0-168)	20 (0-168)	12 (0-168)

Table 17 The adverse events recorded during the trial.

	Telehealth		Control		Total	
	Number of events	Number of patients/carers (%)	Number of events	Number of patients/ carers (%)	Number of events	Number of patients /carers (%)
MND related						
Chest infection/ respiratory symptoms	7	7 (35%)	4	4 (20%)	11	11 (55%)
Falls	8	7 (35%)	3	3 (15%)	11	10 (50%)
Musculoskeletal symptoms	3	3 (15%)	0	0 (0%)	3	3 (15%)
Excessive saliva / choking	2	1 (5%)	0	0 (0%)	2	1 (5%)
Elective PEG insertion	2	2 (10%)	1	1 (5%)	3	3 (15%)
PEG site problem	0	0 (0%)	1	1 (5%)	1	1 (5%)
Patient psychological distress	0	0 (0%)	1	1 (5%)	1	1 (3%)
Carer psychological distress	11	5 (29%)	6	5 (26%)	17	10 (27%)
Other adverse events						
Other medical	7	3 (15%)	5	5 (25%)	12	8 (40%)
Other surgical	0	0 (0%)	2	1 (5%)	2	1 (5%)

Table 18 Summary of health encounters for the three months prior to baseline

	Total in 3 months[3]	Total physicians[4]	Total nurses[5]	Total therapists[6]
Telehealth				
Total (n=18)	133	38	43	52
Mean (SD)	7.4 (6.3)	2.1 (2.3)	2.4 (2.6)	2.9 (3.1)
Median	5.5	1	1.5	2
Range	0-28	0-8	0-10	0-11
Control				
Total (n=20)	211	45	72	88
Mean (SD)	10.6 (8.5)	2.3 (2.1)	3.6 (5.1)	4.4 (4.3)
Median	8	2	1	4
Range	1-30	0-10	0-19	0-13
Total				
Total (n=38)	344	83	115	140
Mean (SD)	9.1 (7.7)	2.2 (2.2)	3.0 (4.1)	3.7 (3.8)
Median	7	2	1	2.5
Range	0-30	0-10	0-19	0-13

[3] Total excluded ambulance journey and unrelated/non-NHS services
[4] Physicians included were MND neurologists, palliative care physicians and general practitioners.
[5] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[6] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 19 Summary of patient reported MND related health-care encounters between months 0-3 of the study.

	Total[7]	Total physicians[8]	Total nurses[9]	Total therapists[10]
Telehealth				
Total (n=16)	152	40	51	61
Mean (SD)	9.5 (9.1)	2.5 (2.3)	3.2 (3.6)	3.8 (4.7)
Median	8	2	2	3
Range	2-35	0-8	0-13	0-18
Control				
Total (n=15)	160	38	55	59
Mean (SD)	10.7 (17.6)	2.5 (4.2)	3.7 (9.6)	3.9 (3.7)
Median	8	1	1	3
Range	0-73	0-17	0-38	0-11
Total				
Total (n=31)	312	78	106	120
Mean (SD)	10.1 (13.6)	2.5 (3.3)	3.4 (7.0)	3.9 (4.2)
Median	6	2	1	3
Range	0-73	0-17	0-38	0-18

[7] Total excluded ambulance journey and unrelated/non-NHS services
[8] Physicians included MND neurologists, palliative care physicians and general practitioners.
[9] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[10] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 20 Summary of patient reported MND related health-care encounters between months 3-6 of the study.

	Total[11]	Total physicians[12]	Total nurses[13]	Total therapists[14]
Telehealth				
Total (n=16)	241	45	143	53
Mean (SD)	15.1 (29.3)	2.8 (3.0)	8.9 (28.3)	3.3 (4.9)
Median	8	2	1	1.5
Range	0-121	0-12	0-115	0-17
Control				
Total (n=12)	83	16	41	26
Mean (SD)	5.2 (1.5)	1.3 (0.9)	3.4 (4.0)	2.2 (1.6)
Median	4	1	2	2.5
Range	2-17	0-3	0-12	0-4
Total				
Total (n=28)	310	61	184	79
Mean (SD)	11.3 (22.2)	2.1 (2.4)	6.8	2.8 (3.9)
Median	4	2	1	2
Range	0-121	0-12	0-115	0-79

[11] Total excluded ambulance journey and unrelated/non-NHS services
[12] Physicians included MND neurologists, palliative care physicians and general practitioners.
[13] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[14] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 21 Summary of patient reported MND related health-care encounters for the six months between months 6-12 of the study.

	Total in 6 months[15]	Total physicians[16]	Total nurses[17]	Total therapists[18]
Telehealth				
Total (n=6)	101	18	52	30
Mean (SD)	16.8 (17.2)	3.0 (1.4)	8.8 (13)	5.0 (3.9)
Median	9.5	3	3	4
Range	3-49	1-5	1-35	1-10
Control				
Total (n=7)	98	26	32	40
Mean (SD)	14.0 (10.7)	3.7 (1.8)	4.6 (8.0)	5.7 (6.3)
Median	8	4	1	5
Range	5-32	1-6	0-22	1-19
Total				
Total (n=13)	199	44	87	70
Mean (SD)	15.3 (13.5)	3.4 (1.6)	6.5 (10.5)	5.4 (5.1)
Median	8	4	2	5
Range	3-49	1-6	0-35	1-19

[15] Total excluded ambulance journey and unrelated/non-NHS services
[16] Physicians included MND neurologists, palliative care physicians and general practitioners.
[17] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[18] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 22 The number of admissions (and number of patients) and days in hospital reported by patients in the three months prior to recruitment.

	Telehealth (n=18)		Control (n=20)		Total (n=38)	
	Number of admissions (number of patients)	Nights in hospital	Number of admissions (number of patients)	Nights in hospital	Number of admissions (number of patients)	Nights in hospital
Elective						
PEG insertion	0	0	4 (3)	15	4 (3)	15
Diagnosis	1 (1)	1	0	0	1 (1)	1
Total elective	1 (1)	1	4 (3)	15	5 (5)	16
Emergency						
Fall	0	0	1 (1)	9	1 (1)	9
Choking	3 (1)	16	0	0	3 (1)	16
Gastrostomy site infection	0	0	1 (1)	2	1 (1)	2
Total emergency	3 (1)	16	2 (2)	11	5 (3)	27
Unrelated to MND						
Total unrelated admissions	0	0	0	0	0	0

Table 23 The total number and reason for hospital admissions reported by all participants during the first 12 months of the study and the number of overnights stayed in hospital.

	Telehealth		Control		Total	
	Admissions (patients)	**Nights**	**Admissions (patients)**	**Nights**	**Admissions (patients)**	**Nights**
Elective						
PEG insertion	2 (2)	21	1 (1)	6	3 (3)	27
Symptom control	2 (2)	14*	0	0	2 (2)	14*
Total elective	4 (4)	72*	1 (1)	6	5 (5)	41*
Emergency						
Respiratory symptoms	1 (1)	6	2 (2)	15	3 (3)	21
Collapse, poor oral intake	1 (1)	2	0	0	1 (1)	2
Total emergency	2 (2)	8	2 (2)	15	4 (4)	23
Unrelated to MND						
Elective: hip replacement	2 (1)	6	0	0	2 (1)	6
Emergency: lung cancer	0	0	4 (1)	50	4 (1)	50
Emergency: postural hypotension	0	0	1 (1)	3	1 (1)	3
Total unrelated	2 (1)	6	5 (2)	53	7 (3)	59

*It was not possible to establish the number of nights from one patients' admission so these nights are not included.

Table 24 Participants' motivations to participation in research.

Incentives to participating in trials	
Low burden of the intervention	*" Oh I was interested in that because it's so easy to do; it literally takes five minutes from home." Patient 317*
Able to participate in trials without leaving home	*"My care's here. I can't have anything that takes it away from what I'm doing with P. It's got to be very simple things. I can sit with my iPad and I can fill in a questionnaire. Done, dusted, finished." Carer 184*
Clear information about what is involved	*"If it was local and we were going anywhere or people were coming here and; I could always look at each one individually but I think I wouldn't want to spend a lot of time away from home. So that would be my main criteria. Patient 408*
Motivations to participating in research	
To help find a cure	*"If I can be of any help to any research, you know, which'll help try and find a cure." Patient 056*
To help other people with MND	*"It might come along too later to help me but it will help people who come after me." Patient 122* *"Just trying to help other people; if me pressing a few buttons …can help in the future, it's not a problem" Patient 354*
In gratitude to the clinicians	*"I think that the people at the Hallamshire are just about the best in the, in the, in the game" Patient 062*
To do something positive	*"… it's that feeling of doing something positive." Carer 402* *"I like that idea that moving forward" Patient 423*
To learn about research	*"I've always been interested in medical science…so I said any research that they're doing I want to get involved in." Patient 423*
To help their family, who may be at risk	*"Carer: I gave blood as well.. because …we've got the boys … I think that's quite a big thing for me" Carer 381*
To have better contact with MND team	*"It was good because, it meant, in the first year I was going to the clinic every month." Patient 122*
To receive better treatment	*"I'm offering my services … but in return … I'm getting a repeating MOT." Patient 313*
To find out more about their condition	*"That led to the, the obvious question "Well if you find anything wrong will you tell me?"." Patient 313*
To increase the chances of them being involved in a treatment trial	*"I do believe that if you're not in the loop then if something comes along then you're on the wrong side of the fence. If you're involved with different … then you're more likely to be selected for possible hopeful cures…" Patient 232*

Table 25 Participants' attitudes towards recruitment and randomisation in the TiM trial.

Recruitment and randomisation to the TiM trial	
Recruitment process provided sufficient information	*"I think it were all pretty much straight forward, in the letter that you sent out, plus when you came, I think it were all pretty straight forward, yeah." Patient 145*
Patients were willing to be randomised as they understood the research question	*"Q: Was there a particular arm of the study that you wanted..?* *Patient : No, because it's a subject that not very much seems to be known about, so if I can help in any area of it, I will." Patient 166*
Patients would prefer to be in the intervention arm	*"Q: And how did you feel about being assigned to the Telehealth side?* *Patient : Well I've preferred that side of it." Patient 381*
Patients were not demoralized if they were assigned the control arm	*"I should think most people would probably want to have tablet. I think, they'd think "this is alright." But quite frankly it doesn't bother me." Patient 070*
Involving the control arm in interviews avoided resentful demoralization	*"I read the notes. Some would get the interview, some would get the tablet" Carer 070*
Researchers could influence the randomisation process	*"Patient : We thought: they'll put [my sister] on the real drug because they can monitor her for longer.* *Q: Do you think that the study researchers can have an influence on which arm of the study you go in?* *Patient : Probably not, no. Probably it's the drug company who are pulling the strings. They are paying the money aren't they?" Patient 184*

Table 26 Participants' attitudes towards and knowledge of research.

Participants' attitudes towards and knowledge of research	
Patients gain information about research and new treatments through…	
Clinic	*" I like having a chat with you and finding out what's happened, what's new, because all we have is hope, we don't have a lot more"." Patient 134*
Friends and fellow patients	*"It's really just through word of mouth. " Patient 122*
MND Association	*"The MNDA puts posts on about research" Patient 145*
Internet	*"I mean we have found, for instance, a website; you can actually see it on YouTube, called Deanna Protocol" Patient 317*
Social media/ peer networks	*"There's also a long term ALS survivors' website where people, have been diagnosed with it… and been told that you've only got a year left to live, but they've done radical changes, ….and those people have halted it" Patient 317*
Patient seek out, evaluate and use unproven treatments	*"I don't follow regimes as strict as the Deanna protocol but I just pick out certain things that I think would help me, hence the reference to moringa and coconut oil." Patient 232*
Frustration with the speed of drug development	*"I just feel like, after 30 years with millions … of pounds spent we've still got a tablet that [has little evidence]" Patient 184* *"We need to be getting a move on… Some day, we've got to stop messing around with mice." Patient 184* *"I don't hold out too much confidence about the UK system of getting drugs to market and funding them with the likes of NICE posing usual financial constraints." Patient 232*
Time is running out for a cure	*"Once you get to what I always call "frank" stage …I don't think there's any drug that would bring you out of that." Patient 184*
Patients have little to lose	*"We being the patients with MND, have nothing to lose… There's always risk in life." Patient 232*
Learning about research makes patients hopeful	*"[you think] There's got to be things that we can do, come on, we're gonna really give this a hundred percent; and the more we looked the more intrigued we became…. you can see people that have had really good benefits from it." Patient 317* *"We're all kind of pinning our hopes …on GM604" Patient 232*
Patients recognize information may be giving false hope	*"Too much information could fill people with a false hope and you've gotta manage people's expectations" Patient 122*
Putting trust in the doctors to run safe trials in the best interests of the patient	*"Q: Did you consider the downsides, the risks of having a lumbar puncture when you came?* *Patient: No. I just thought, well if that's all I've got to put up with. But if a doctor can't do a lumbar it's a bad job." Patient 184* *"I would have complete faith in [consultants] team saying "Right, lets get some people in now and let's do it" Patient 184*
Wanting to see tangible benefits of treatments which reverse the disease	*"No one will ever convince me that they know [riluzole] works. …How do they know I've had three months more life?…Who would know? .. I can't walk any better, I can't speak any better, I can't do anything any better." Patient 184* *"…it doesn't have to cure you it just has to make things better." Carer 232* *"If there was a magic bullet and I had to sell everything to purchase that bullet, I would." Patient 232*

Table 27 Barriers to participation in research.

Barriers to participation in research	
Additional burden	*" Well, just another job…. To remember" Carer 217*
Research is time consuming	*"Initially it is a bit overwhelming … we do seem to have signed-up for absolutely everything…" Carer 402* *"It's difficult, … sometimes you get to the stage where you think: you know what? I just don't feel like this, I've just had enough" Carer 402*
Intrusion or disruption of family life	*"Carer: I just don't think; … we, we just try to keep ourself and look after him, look after him and that's it.* *Q: …Have any of those worries been the case during the study?* *Carer: No." Carer 228* *"I don't want the family life to be disrupted, that's really important to us." Patient 408*
Time spent away from home	*"I'd need to know about the, the time that would be needed to be spent, if I needed to spend time away from here, from home" Patient 408*
Research can be tiring	*"On Thursday I went for my research, had the lumbar puncture, the tissue sample, blood samples I think. So then I came home. For two days after that I was more or less housebound." Patient 184*
Travel to hospital is expensive	*"…the train tickets are a bit expensive, so we've driven the last few times. But … we got the free parking and things like that…" Carer 392*
Travel difficult	*"It's gonna be a lot more difficult with a wheelchair" Carer 392*

Table 28 Participant reaction to the TiM research questionnaires.

Were questions acceptable?	
Questions posed in the questionnaire were acceptable	*"No. To be quite frank, doctor, I wouldn't care a monkey's what you ask …I have no hang-ups about any questions, however personal, the team think it's necessary to ask; I've seen it all, done it all and got the t-shirt." Carer 229* *"Patient : I was fine about doing them." Patient 116*
There was a limit to the number of questions participants were willing to answer	*"Patient : You don't want another one of them hundred and fifty page things to fill out, that were, whatever it was last year." Carer 248*
Questions on emotions were acceptable to those experiencing emotional distress	*"It's more the emotional ones that I have trouble filling in cos I've been depressed for quite a …and it's, it's just hard admitting that yes, maybe some days it's not great and I know that I'm not great at the moment but. But no, they seemed good. They were really clear, and it wasn't too, too much to do." Patient 408*
Participants wanted questions to cover all potential aspects of MND	*"At the moment I've not got a lot of problems with my legs, but in 18 months I might need a wheelchair, or I might be having to use a breathing machine. So every question is relevant." Patient 070*
Questions about future complications were acceptable because patients were aware of what may occur	*"When you read things about these questions: it brings things home to you. Well yeah, I have deteriorated…. It doesn't really significantly affect me at all because, I like to think I'm a reasonably intelligent man and I know things are deteriorating." Patient 184*
Which questions best reflected the experiences of patients and carers?	
Questions about mood/emotions best reflected their experiences	*"I think the best ones are the ones about how it makes you feel and how it affects your mood etc. That's very important …." Patient 122*
The carer burden accurately captured the experience of carers	*"It was a strange one cos [the ZBI] was asking you what I feel about spending the time with him, that I don't have time for meself…. Yeah, it is quite a thing cos you're always thinking… "Has he got enough drinks? … then anything to eat?"… I don't like to be too far away from him, even though I'm in the house … in case summat happened and he needs me." Carer 091*
Carer strain is linked to patient and carer wellbeing	*"…obviously if strains exist, become too much for the carer, then the patient, to a degree, suffers.." Carer 229*
Mood/emotions affected patients health and functional abilities	*"Feelings of anxiousness can affect my legs, and I know that. I try not to control, try not to get anxious about situations but sometimes it's hard when you know, your are going to move from A to B, you're going to get anxious about it." Patient 076*

Table 29 Weaknesses with the questionnaires identified.

SF-36 questionnaires failed to reflect the experience of life with MND	
SF-36 questions were too subjective	*"That's sort of looking at question [SF-36], and putting down, you're limited and then you sort of realise; I can't really do that; and you don't think about it all the time do you? Some of them I wanted to put "sometimes", you know… sometimes I have but I've just gone for on the whole" Patient 408*
Patients found it difficult to assess their global health and were unsure whether to include MND in the assessment	*"Patient : It's slightly confusing when they ask about health because it's hard to take the MND out of the equation, I think. Apart from that I would be very healthy." Patient 116* *"Patient : My health other than the illness? (Pause) Taking the illness into account I would say poor, but if I ignore the, the illness I would say very good." Patient 137 [referring to SF-36]*
Patients felt "healthy" despite having MND	*" To be honest, I feel great. So does that say I'm excellent. But you know that you're not, so you can't be excellent." Patient 175 [referring to SF-36]*
Carers felt they had no health problems and felt the QoL questions were not relevant	*"I mean this: [reads] "I feel as if I'm slowed down"; it's not because of caring for you but because I'm getting older… I can't do a forward roll over a gatepost anymore!" Carer 137 [referring to SF-36]*
Those with severe disability had few "daily activities" on which to assess the impact of MND	*"Patient : It doesn't affect my work because I don't do any! Q: It's housework as well. Patient : No. I don't do any! I do a little bit." Patient 070 [referring to SF-36]*
Other weaknesses	
Participants found it difficult to quantify the time taken by domestic jobs that are usually shared	*" But there are things now… I'll say "its time for a cup of tea". It will always be me that makes it. I'm not saying I resent it, because P can't do it… But I don't class that as care… Carer 175 [referring to informal care question]*
Questions should better reflect patients' functional abilities and coping strategies	*"It's about monitoring really, and with these questionnaires you are not able to say how you manage. If we know we are going out for a full day, then P knows not to plan anything for the next day because he's gonna be tired." Carer 076*
Answering questions may be difficult if they not want to admit they have problems	*"….It's like C was saying, you've just got to be honest and sometimes that's really hard cos you don't want to admit that maybe you're not as good as you were". Patient 408*

Table 30 The calculated total sample sizes for the two approaches to calculating the endpoint at different effect sizes.

These were calculated by the trial statistician and based on the parameters stated above.

	Single time point		Longitudinal[19]	
	Unadjusted	**+30% drop-out**	**Unadjusted**	**+30% drop-out**
Effect size				
0.2 SD	n=1052	n=1503	n=396	n=566
0.3 SD	n= 468	n= 669	n=176	n=251
0.4 SD	n= 264	n= 377	n=100	n=143
0.5 SD	n= 170	n= 243	n=64	n=91

[19] Assuming one baseline and four follow-ups with a common correlation of 0.5.

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported in section
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Page 1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	Background
	2b	Specific objectives or research questions for pilot trial	Aims of the study
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	Study design
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	Eligibility criteria
Participants	4a	Eligibility criteria for participants	Eligibility criteria
	4b	Settings and locations where the data were collected	Eligibility criteria
	4c	How participants were identified and consented	Recruitment
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Intervention, parallel paper and publication
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	Data collection, Table 1
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	Sample size
Sample size	7a	Rationale for numbers in the pilot trial	Sample size
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Randomisation
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	Randomisation
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Randomisation

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Randomisation
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding, bias and study conduct
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	Data collection
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	CONSORT diagram
	13b	For each group, losses and exclusions after randomisation, together with reasons	CONSORT diagram
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Recruitment
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Supplementary data file
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplementary data file
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Supplementary data file
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Adverse events
	19a	If relevant, other important unintended consequences	Parallel publication
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	Discussion
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	Discussion
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	Discussion
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	Discussion
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	Study design
Protocol	24	Where the pilot trial protocol can be accessed, if available	Supplementary file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Acknowledgements and funding
	26	Ethical approval or approval by research review committee, confirmed with reference number	Study design

BMJ Open

Telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a UK-based pilot, feasibility study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028525.R1
Article Type:	Research
Date Submitted by the Author:	23-May-2019
Complete List of Authors:	Hobson, Esther; University of Sheffield, Sheffield Institute for Translational Neuroscience; Sheffield Teaching Hospitals NHS Foundation Trust, Academic Department of Neurology Baird, Wendy; University of Sheffield, School of Health and Related Research Bradburn, Mike; University of Sheffield, ScHARR; University of Sheffield, Clinical Trials Research Unit Cooper, Cindy; University of Sheffield, Clinical Trials Research Unit Mawson, Susan; University of Sheffield, School of Health and Related Research Quinn, Ann; Sheffield Motor Neurone Disease Association Research Advisory Group, SITraN Shaw, Pamela; University of Sheffield, Sheffield Institute for Translational Neuroscience; Sheffield Teaching Hospitals NHS Foundation Trust, Academic Department of Neurology Walsh, Theresa; University of Sheffield, Sheffield Institute for Translational Neuroscience; Sheffield Teaching Hospitals NHS Foundation Trust, Academic Department of Neurology McDermott, Christopher; University of Sheffield, Sheffield Institute for Translational Neuroscience; Sheffield Teaching Hospitals NHS Foundation Trust, Academic Department of Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Health services research, Qualitative research
Keywords:	Neurology < INTERNAL MEDICINE, PALLIATIVE CARE, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Motor neurone disease < NEUROLOGY, Information technology < BIOTECHNOLOGY & BIOINFORMATICS

Telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a UK-based pilot, feasibility study

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Key words
Telehealth, telemedicine, motor neuron disease, amyotrophic lateral sclerosis

Word count
5603

ABSTRACT

Objectives
Care of patients with motor neuron disease (MND) in a specialist, multidisciplinary clinic is associated with improved survival but access is not universal. We wanted to pilot and establish the feasibility of a definitive trial of a novel telehealth system (TiM: Telehealth in Motor neuron disease) in patients with MND.

Design
An 18-month, single-centre, mixed methods, randomised, controlled pilot and feasibility study.

Intervention
TiM telehealth plus usual care vs. usual care.

Setting
A specialist MND care centre in the UK

Participants
Patients with MND and their primary informal carers.

Primary and secondary outcome measures
Recruitment, retention and data collection rates, clinical outcomes including participant quality of life and anxiety and depression.

Results
Recruitment achieved the target of 40 patients and 37 carers. Participant characteristics reflected those attending the specialist clinic and included those with severe disability or with limited experience of technology. Retention and data collection was good. 80% of patient and 82% of carer participant reported outcome measures were completed at six months. Using a longitudinal analysis with repeated measures of quality of life, a sample size of 131 per arm is recommended in a definitive trial.

The methods and intervention were acceptable to participants who were highly motivated to participate to research. The low burden of participation and accessibility of the intervention meant barriers to participation were minimal. However, the study highlighted difficulties assessing the associated costs of the intervention, the challenge of recruitment in such a rare disease and the difficulties of producing rigorous evidence of impact in such a complex intervention.

Conclusion
A definitive trial of TiM is feasible but challenging. The complexity of the intervention and heterogeneity of the patient population means that a randomised controlled trial may not be the best way to evaluate the further development and implementation of the TIM.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study of the feasibility of a digitally-enabled care system for patients and carers living with motor neuron disease.
- The trial methods and intervention enabled patients with significant disabilities to participate.
- The qualitative data collection aimed to identify key barriers and enablers to participation in clinical trials of telehealth and motor neuron disease from the perspective of patients, carers and nurses.
- This was a study with a small number of patients in a single centre.
- It was not possible to fully assess the impact of the intervention on the clinical service's staffing or healthcare resource use.

BACKGROUND

Motor neuron disease (MND) is an incurable, neurodegenerative disease that causes progressive muscle paralysis, limb weakness, breathing, speech and swallowing difficulties leading to death after, on average, two to four years from symptom onset (1). Riluzole, non-invasive ventilation (NIV) and possibly edaravone only offer small survival benefits (2-4). Attendance at a multidisciplinary specialist MND clinic (MDC) is associated with improved survival and increased use of proven therapies (5-10). The aim of specialist MND care is to maximise survival and quality of life by providing coordinated, patient-centred care to address the biopsychosocial needs of patients and their families (11). It is recommended that the MDC should monitor patients regularly to detect and treat complications quickly (12,13). However, patients become progressively more disabled and travelling to clinic becomes difficult or impossible. Even in developed, countries attendance at MDCs varies (between 43% to 85%) and many of those who do see a specialist are unable to return (14). The disease is rare (a worldwide prevalence of 5.40 per 100 000 (15)) meaning there are few specialist centres and general clinicians have limited experience of caring for patients with MND. This makes accessing the right care at the right time difficult leading to significant distress (16-21). There is therefore a great need to improve access to specialist MND care.

We developed the TiM system (Telehealth In Motor neuron disease): a digitally-enabled care system using telehealth to enable patients and their informal carers to report their progress and symptoms from their homes (22). We hypothesised that improving access to specialist care may result in earlier identification and management of complications thus improving quality of life and survival. We thought the TiM system could improve care coordination and result in better prioritisation of health-resource use, thereby reducing costs or increasing service capacity. The TiM was developed using a process of user-centred co-design (22) but further piloting of such a complex intervention was required (23).

Telehealth is a complex intervention that consists of different component parts

(such as the software, the context, and behaviours of those who use it) whose success depends on these interacting factors (23). Clinical trials of telehealth face various challenges including difficulties with recruitment, staff engagement and difficulties capturing the important impacts of the intervention (24-26). Furthermore, MND trials tend to recruit an unrepresentative sample of patients (on average younger, male patients with longer survival) (27). This may be explained, in part, due to the many barriers to participation including the need to travel to study centres, and the small number of geographically dispersed patients who may be frail or deteriorating rapidly. The Medical Research Council (MRC) Framework for Developing and Evaluating Complex Interventions highlights the importance of feasibility and piloting of the study methods to ensure the definitive trial will overcome these barriers (23).

Aims of the study

We wanted to pilot the methods and evaluate the feasibility of conducting a definitive randomised controlled trial of the TiM in patients and carers versus usual care. We aimed to use low-burden, pragmatic study methods that could recruit and retain a representative sample of all patients with MND. The feasibility outcomes examine recruitment, retention and data collection. The study also aimed to provide an understanding of the resources required to conduct a definitive trial including staff burden and an estimation of variation in outcomes in order to provide a more accurate predictor of sample size. A supplementary data table describes the feasibility questions using the ADePT framework (28) [ADePT Table April 2018]. We also explored factors that may influence these outcomes and also whether the outcomes measures effectively assessed aspects of life with MND and the impact of the TiM.

We also conducted a process evaluation of the TiM to understand how the system was used and to identify some of the potential impacts of the TiM on participants, carers and the MND service. This is reported in a parallel publication.

METHODS

Study design

This was a single-centre, unblinded, randomised, controlled, pilot, feasibility trial of usual MND care vs. the TiM plus usual care. Usual care involves invitations to the MDC clinic every two to six months and access to the MDC between times via the specialist nurse. The protocol and statistical analysis plan are available as an online supplementary file [Online supplementary file Methods TiM protocol and Statistics analysis plan Feasibility 2019]. Approval was gained from Leeds Bradford Research Ethics Committee (REC reference 14/YH/1068) and the sponsor (Sheffield Teaching Hospitals NHS Foundation Trust Clinical Research Office). Trial identifier ISRCTN26675465.

Patient and public involvement

In addition to the user-centred design process used to develop the TiM (22) during development of the intervention and the protocol we consulted patients, carers and the Sheffield MND Research Advisory group (a patient and public

involvement group). They reviewed the intervention, principles of the trial, trial design, outcome measures and participant information leaflets and provided comments on their feasibility and accessibility. They were not involved in recruitment. Results of the study have been communicated at various public meetings, through the Sheffield MND Research Advisory group and local branch of the MND Association and a lay summary will be circulated. Members of this group attended the trial steering and trial management groups. AQ was a member of the trial management group, provided advice on the research methods, interpretation of the data and dissemination and is a co-author on this paper.

Recruitment

We pre-screened patients using a clinical database of patients attending the Sheffield MDC. We determined the order of invitation using a list of random numbers generated using Excel. When the pool of prevalent patients was exhausted, we invited all newly diagnosed patients. We invited patients and their primary informal carer to participate by letter including a prepaid return slip. Eligibility was confirmed and written/witnessed verbal consent was obtained at all research visits and data collection were conducted in participants' homes. This approach meant patients who were not currently attending the MDC (due to frailty or geography) were able to participate.

Eligibility criteria

We included adult patients receiving care from the Sheffield MDC, living within two hours drive from Sheffield. Initially the diagnostic inclusion criteria was those with a diagnosis of clinically definite or probable amyotrophic lateral sclerosis (ALS) according to the El Escorial criteria (29). However, prior to recruitment commencing, a review of 200 patients on the MDC database found that 58% of patients would be excluded based on these criteria: 38% of patients had ALS but did not fulfill the El Escorial Criteria at their last assessment (29) and 21% of patients had atypical MND (primary lateral sclerosis: PLS, progressive muscular atrophy: PMA, or an uncategorised progressive ALS/MND illness). We felt many of these patients not fulfilling the strict criteria would benefit from better MDC care and so we modified the criteria to include all patients with ALS with symptom onset within the last three years. We also included all patients diagnosed with any type of MND (ALS, PLS, PMA) who had evidence of progression in their condition (an indicator that they may require MDC monitoring and care) as evidenced by a deterioration in the ALS functional rating score (ALS-FRS-R) (30) of at least two points during the previous 18 months (a small but meaningful change).

We excluded patients attending another MDC, those unwilling to allow their carer to operate the TiM on their behalf if they could not do it themselves and those with no form of telephone or internet access. Patients had the option of identifying their primary informal carer who was then invited to participate as a carer and consented. Eligible informal carers were adults who were the patients' main provider of unpaid care. Initially, patients could participate only if their carer consented to be involved. Later we changed the criteria to allow patients to participate without a carer.

Randomisation
Patients were randomised 1:1 after recruitment to receive usual care or TiM using www.sealedenvelope.com which employs permuted block randomisation with a mixture of block sizes (block size concealed). Stratification was not employed.

Intervention
A detailed description of the TiM has been published (22). The use of the TiM in this trial is described in detail in the parallel publication describing the process evaluation. In brief patients and carers were asked to complete weekly sessions answering questions about their condition (such as functional ability, symptoms, depression and anxiety symptoms, carer strain) and patients recorded their weight and balance. The results could be viewed on a website by the MND nurse at the specialist care centre. She could take actions including telephoning the patient/carer, expediting clinic appointments or liaising with the MDT. She could not delay appointments or make clinical decisions without checking the accuracy of the information with the patient, carer or clinical team. All participants were shown how to use the TiM app during recruitment and the presence of any difficulties using the system was recorded.

Data collection
Patient/carer-reported outcome measures (PROMs) were completed at home during the baseline study visit and at 3, 6, 12 and 18 months using postal questionnaires. Generic and MND specific PROMs captured quality of life, MND clinical outcomes, survival and health resource use. Adverse events were recorded using PROMs and during MDC visits. We created a "Shadow Monitoring Protocol" whereby the MND physician would review the TiM data and complete a questionnaire two weeks prior to MDC appointments and again at each appointment. Physicians were asked to respond to agree/disagree statements assessing their opinion on the accuracy and acceptability of the TiM answers and whether it may be possible to use the information to make decisions without seeing the patient (see online supplementary data file [Online supplementary file Methods TiM protocol and Statistics analysis plan Feasibility 2019] page 71). Telehealth Nurse activity was also collected using a two week diary, twice in the trial. After the trial we downloaded all data in TiM system into Excel.

We conducted 56 semi-structured participant interviews (characteristics are described in full in [Online supplementary Results file April 2019 feasibility]). Control participants were interviewd at baseline (17 interviews) and intervention participants were interviewed at one and six months (20 at one month and 19 interviews at six months). Most interviews were face-to-face at home with patients and carers together, but telephone and email were also used. Interviews were also conducted with the Telehealth Nurse (at month 4 and month 14) and a community nurse (month 18). Topic guides were used (see [Online supplementary file Methods TiM protocol and Statistics analysis plan Feasibility 2019] pages 41-44) and field notes taken during and after the interview. Interviews were audio-recorded and transcribed verbatim. Early

results and observations during the trial informed later interviews. As new themes were being identified later in the research study, we attempted to interview all participants and by the end of the study no new themes were identified. To evaluate the feasibility of the study, participants were asked about their attitudes towards research. To evaluate the validity and acceptability of the PROMs, control participants also performed a "*think-aloud*" task during which they were asked to complete the baseline PROMs and describe their reactions. To explore the feasibility and acceptability of digitally-enabled care, participants and clinicians were asked about their attitudes towards technology, the TiM system and MND care.

Outcomes

The trial assessed the following feasibility outcomes:

- Trial processes: rates of eligibility, recruitment, retention and completion of postal questionnaires.
- Use of the intervention: frequency of use of TiM by participants (collected automatically by the TiM system), participant satisfaction with TiM (questionnaires) and telehealth nurse time using TiM using two fortnight diaries (see parallel paper for additional results).

In addition, clinical outcomes (listed in tables 1 and 2) were collected to test trial procedures and as indicative parameters to inform the sample size of a full-scale trial.

Table 1 Patient outcome measures collected.

	Baseline ***	Postal questionnaires					Clinic visits
		Baseline	3 months	6 months	12 months	18 months	
Patient characteristics							
Age, gender	X						
Frequency of technology use	X						
Broadband/mobile internet access	X						
Presence of difficulties using TiM	X						
Need for help using TiM	X						
Medical history							
Diagnosis		X					
Disease duration		X					
Comorbidities		X					
Drug history		X					
Quality of life							
ALSAQ-40		X	X	X	X	X	
RAND-36		X	X	X	X	X	
EQ-5D+D		X	X	X	X	X	
Clinical measures							
ALS-FRS-R		X	X	X	X	X	
Pain score (current and worst)**		X	X	X	X	X	
CSS-MND saliva scale		X	X	X	X	X	
Hospital Anxiety and Depression score		X	X	X	X	X	
Survival							X
Adverse events			X	X	X	X	X
Health resource use							
Clinician encounters**		X	X	X	X	X	X
Hospital admissions**		X	X	X	X	X	X
Informal care use**		X	X	X	X	X	
Formal care use**		X	X	X	X	X	
Satisfaction							
MND care satisfaction**		X	X	X	X	X	
TiM satisfaction**			X*	X*	X*	X*	

*intervention arm only ** questionnaires designed for the trial ***collected by investigator

Table 2 Carer outcome measures collected

		Postal questionnaires					
	Baseline ***	**Baseline**	**3 months**	**6 months**	**12 months**	**18 months**	**Clinic visits**
Carer characteristics							
Age, gender	X						
Relationship to patient	X						
Frequency of technology use	X						
Presence of difficulties using TiM	X						
Quality of life							
RAND-36	X		X	X	X	X	
Clinical measures							
Hospital Anxiety and Depression score	X		X	X	X	X	
Zarit Burden Interview	X		X	X	X	X	
Adverse events			X	X	X	X	X
MND care satisfaction**	X		X	X	X	X	
TiM satisfaction**			X*	X*	X*	X*	

*intervention arm only, ** questionnaires designed for the trial ***investigator completed

Blinding, bias and study conduct

It was not possible to blind the patients or investigators to treatment allocation and EH had involvement in some patients' clinical MDC visits. Measures to reduce bias were used. The role of EH as an investigator and her involvement in the TiM development was explained at each visit and any clinical queries were passed onto the Telehealth Nurse. Follow-up PROMs were completed by participants independently at home and entered by an independent study nurse. Quantitative analysis was overseen by the study statistician using a pre-specified analysis plan. Data triangulation (qualitative, TiM use, trial data) and methodological triangulation (patients, carers, staff) were employed. EVH conducted all the interviews except the 14 month interview with the telehealth nurse which was conducted by co-author WOB (an experienced qualitative researcher independent of the clinical team) who also oversaw the interview planning, conduct and analysis.

Analysis

Quantitative data was analysed using descriptive statistics and qualitative data was organised using NVivo (31) and analysed using thematic analysis (32). A triangulation process compared the quantitative and qualitative data to further understand and explain important, incongruent and unexpected observed phenomenon. Early results provided some insight into how the TiM was being used and informed changes to the intervention and study methods.

Sample size

A target of 40 patients and 40 carers was selected to enable an estimation of the standard deviation of potential outcome measures to within a precision of ±20% of its true underlying value with 90% confidence (33). The sample size was also based on guidance that a minimum of 12 evaluable patients per trial arm is required (i.e. after allowing for death, withdrawal or drop-out) in order to inform a sample size calculation for a definitive trial (33,34).

Role of the funding sources

The TiM was developed through a collaboration between the University of Sheffield (UoS), Sheffield Teaching Hospitals NHS Trust, Mylan Ltd and Abbott Healthcare. This trial was funded the National Institute for Health Research and the Motor Neurone Disease Association. Mylan Ltd supplied software, hardware and some technical expertise. The Telehealth Nurse took on the additional duties as part of her current role. The study design, conduct, analysis, and interpretation of data, writing of the report, and the decision to submit the paper for publication were conducted by the authors independently of the funders with the exception of a requirement to report adverse events the investigator deemed to be related to Abbott Pharmaceuticals' drugs.

RESULTS

A summary of the feasibility questions, using the ADePT framework (28) is presented in an online supplementary file [ADePT Table April 2018]. Qualitative data is reported within each section to explain the findings. A supplementary data file contains the results of each outcome measure and supporting qualitative quotes [Online supplementary Results file April 2019 feasibility].

Screening and eligibility

306 patients were pre-screened (Figure 1). 123 patients (40%) were excluded because the Sheffield MDC was not their main or current care centre. Of the remaining 183, 88 patients were excluded on clinical grounds, mainly due to lack of disease progression or cognitive impairment. This left 95 eligible patients (52% of the patients attending the MDC).

Recruitment

42 patients (44%) expressed an interest in participating. 40 (42%) were eligible: 28 prevalent and 12 incident cases. All 40 were consented, randomised and received the intervention between October 2014 and November 2015. 37 eligible carers were recruited. Three patients were recruited who did not have a primary carer.

Participant characteristics

Age, gender, phenotype and site of onset were similar to a much larger cohort of patients at the Sheffield MDC (7) (Table 3). Age ranged from 30 to 78 years and participants had disabilities ranging from mild to severe, including 13 (33%) who used either NIV or a gastrostomy tube (King's stage 4 (35)).

Table 3 Participant characteristics

	Telehealth n=20	Control n=20
Gender Male	14 (70%)	14 (70%)
Age (years) Mean (SD), range	60.4 (11.7), 30-78	60.0 (10.0), 39-73
Phenotype		
Amyotrophic lateral sclerosis	17 (85%)	18 (90%)
Primary lateral sclerosis	2 (10%)	2 (10%)
Progressive muscular atrophy	1 (5%)	0 (0%)
Disease duration (months)		
Mean (SD), range	53 (48), 12-197	46 (35), 7-123
Duration since diagnosis (months)		
Mean (SD), range	32 (34), 3-137	21 (19), 1-58
King's ALS clinical stage[a]		
1	3 (15%)	2 (10%)
2	4 (20%)	5 (25%)
3	5 (25%)	8 (40%)
4	8 (40%)	5 (25%)
Use of the TiM App		
Independently	17 (85%)	17 (85%)
Assistance from carer	1 (5%)	1 (5%)
Patient instructs carer	2 (10%)	2 (10%)
Technology use[b]		
Daily	14 (70%)	18 (90%)
A few times per week	3 (15%)	1 (5%)
Once a week	1 (5%)	1 (5%)
Every few weeks	0 (0%)	0 (0%)
Never	2 (10%)	0 (0%)
Home technology		
Broadband	18 (90%)	20 (100%)
3G mobile reception	18 (90%)	15 (75%)
	Telehealth n=18	**Control n=19**
Carer gender Male	4 (21%)	5 (28%)
Carer age (years) Mean (SD), range	59 (12, 42-84)	60.8 (11,38-73)
Relationship to patient		
Partner	18 (95%)	16 (89%)
Child	0 (0%)	1 (6%)
Parent	1 (5%)	1 (6%)
Carer technology use[b]		
Daily	12 (67%)	16 (84%)
A few times per week	1 (6%)	1 (5%)
Once a week	1 (6%)	1 (5%)
Every few weeks	0 (0%)	0 (0%)
Never	4 (22%)	0 (0%)

[a]King's stage 1 refers to patients with functional deficit in 1 domain, stage 2: 2 domains, stage 3: 3 domains and stage 4: patients requiring NIV and/or gastrostomy (35). King's stage was calculated using the ALSFRS-R scale at baseline. [b] Technology: computer, smart phone, tablet. SD: standard deviation.

Barriers and enablers to recruitment

Interviews indicated that recruitment and randomisation were acceptable and participants understood the principles of the study and were willing to be randomised. Some participants thought that the TiM would simply function to collect research data, rather than to facilitate MDC care. Participants wanted to participate because they liked the concept of telehealth and because they were highly motivated to participate in research. They expressed a strong altruistic desire to help others and to help the clinical team. Participation made patients feel they still had a valuable contribution to make, even when severely disabled:

"I love being part of something worthwhile." Patient 229

Participants thought that they might gain benefit by learning more about the condition, to improve their chances of taking part in a treatment trial and to have increased contact with the MND team. Some kept up to date with information on the internet and many expressed frustration about the speed of research and felt time was running out for them to be cured. They all wanted to see treatments that had tangible benefits.

"…it doesn't have to cure you it just has to make things better." Carer 232

Participants wanted to learn about research as this provided hope. Patients thought trials would be "*safe*" if they involved a doctor whom they trusted but also recognised that information could be unreliable and offer "*false hope*". A small number were willing to use unproven therapies or take part in trials even if they had to potential for significant harm in order to gain an opportunity to be cured as they felt they had "*have nothing to lose".*

Retention

To maximise the experience gained using the TiM, all participants remained in the study until they died or the study finished in April 2016. Follow-up ranged from six to 18 months. Two patients (5%) who were severely disabled at recruitment felt too ill to continue. No carers withdrew and no participants were lost to follow-up.

The factors that facilitated study participation were the low burden of the study and the intervention (completed at home, minimal visits and a clear understanding of what would be expected of them). Participants identified barriers posed by other clinical trials such as fatigue, burden or disruption of family life but stated these were not experienced in this study. Carers did not want research that required them to be removed from their caring duties.

"My care's here. I can't have anything that takes it away from what I'm doing with P. It's got to be very simple things. I can sit with my iPad and I can fill in a questionnaire." Carer 184

Adherence to the intervention

Detailed description of the acceptability, use of and adherence to the intervention is described in the parallel publication. In brief: compliance was high with 14 (70%) patients completing a TiM session, on average, fortnightly and 13 (70%) carers completing at least three weekly sessions.

Feasibility and validity of the participant reported outcome measures.

Adherence to the postal questionnaires was good. At 6/12 months 80%/71% of patient and 82%/67% of carer questionnaires were returned. Both treatment groups had similar completion rates. Participants felt the PROMs were accessible and not burdensome. They welcomed a thorough assessment of all aspects of life with MND and identified PROMs examining their emotional health and carer strain as the best assessment of their experiences of MND.

"To be quite frank, doctor, I wouldn't care a monkey's what you ask ...I have no hang-ups about any questions, however personal, the team think it's necessary to ask." Carer 229

Most PROMs were returned complete but 2% of the RAND-36 questionnaires were incomplete and participants felt the statements posed in the RAND-36 were too subjective and did not reflect the experiences of life as a carer or patient with MND. Patients and carers found it difficult to answer questions referring to "*health*": some thought they were entirely healthy or did not perceive MND to be a "*health*" problem. Participants favoured the MND specific quality of life questionnaire (ALSAQ-40), preferring the format and content. It was observed that the language used in the ALSAQ-40 closely reflected the language patients used to describe their experiences. Patients found it difficult to report the number of informal hours of care they received per week. 9% of these questions were blank. There was a large variation in informal carer hours required (0 to 168 hours per week) with no clear relationship between a patient's disability and hours of care. Couples' roles had gradually changed as carers took over many of the domestic jobs that were usually shared. This made it difficult to quantify how much of their role was "*caregiving".* Some carers explained that even if they weren't directly providing care they always had to be alert to the needs of their loved one and so many patients wrote that they required care "*24x7*". In addition, the questionnaire did not record multiple carers or where professional carers took over the role of an informal carer.

Feasibility of other data collection methods

The telehealth nurse diaries were returned incomplete. The nurse reported that it was difficult to assess her time using the TiM because she was often doing multiple tasks making it difficult to determine whether the time spent on an activity was part of "*usual care"* or triggered by a TiM session. The Shadow Monitoring Protocol planned for clinicians to review information on the TiM and provide feedback prior to clinic. This was found to be infeasible because clinic appointments were frequently rescheduled or not booked sufficiently far in advance. There were administrative difficulties accessing the paper records (electronic records were not used during the trial). However, after the MDC clinic, physicians completed 38 Shadow Monitoring feedback forms about the

TiM, although total clinic numbers were not collected so compliance with this form could not be measured.

Outcome assessment

All clinical outcomes are reported in the online supplementary file [Online supplementary Results file April 2019 feasibility]. Adverse events were low and none directly caused by the TiM system. We did not compare treatment arms in this feasibility study. However, we examined the data to determine whether it was possible to capture the impact of the TiM on MND outcomes. It is expected that over 6-12 months most patients with MND deteriorate in a meaningful way and therefore this change should be captured by our outcome measures. The ALSFRS-R confirms this as scores declined at a similar rate to the MDC population indicating disease progression (0.39 points per month compared to 0.34 per month recorded in the Sheffield MDC clinic (7). Physical QoL showed a trend towards deterioration in both the RAND-36 and the physical sub-scores of the participants' preferred QoL measure the ALSAQ-40. The incidence of severe anxiety in carers also increased. Mostly these changes were small and did not reach significance but the sample sizes were too small to draw firm conclusions. Measuring health economic data identified a number of difficulties: only four hospital admissions were reported during the whole trial and other health resource use was highly variable. For example, between the third and sixth month of the trial health care visits ranged from 0 to 121 visits (intervention: median 8, range 0-121, control: median 4, range 2-17). The number of encounters did not appear to be related to patient satisfaction or access to MND services: some patients who reported to receive excellent, coordinated care had very few appointments whereas other patients reporting good care had many appointments.

Sample size for a full RCT

The sample size for a full-scale trial depends on the type I and II errors, the level of missing data due either to death or withdrawal, and the anticipated size of effect. Assuming a 5% level of statistical significance, 90% power and 75% follow-up (based on the number completing 12 month follow-up in this study) and an effect size of 0.3 standard deviations, a standard sample size calculation requires a prohibitive 312 patients per trial arm. This number can be reduced by employing a longitudinal approach to the analysis which the repeated measures (in this study the baseline, 3, 6 and 12 months) are used in a repeated measures regression (36). Adopting this approach to the above scenario and assuming a correlation of 0.5 between measures leads to a more achievable sample size of 131 per arm. The sample size could be reduced further if a larger effect size was used (a 0.4 standard deviation effect size requires 74 patients per arm), although larger effect sizes seem unlikely for a non-disease modifying intervention. On the other hand, smaller effect sizes would be unjustified given the cost and service redesign requirements associated with implementation. We also note the present study is limited by its size, thus precluding a reliable estimate of whether the postulated effect sizes are reasonable.

DISCUSSION

The aim of the study was to determine the feasibility and acceptability of conducting an RCT of TiM. Recruitment and retention were successful and rates similar to those in trials of disease modifying treatments in MND (such as diaphragmatic pacing (37)). In addition, we recruited patients who were more representative of the typical MND population than in other clinical trials (27,38,39). This included patients with severe disability and those living at a distance from hospital. Involvement of patient groups in the trial design, the low burden of the study and participants' motivations to participate in research were the key facilitators of study success. The potential barriers to research participation identified (time, fatigue and the impact on research on day-to-day life) were not a problem in this trials. We recommend that our methods and findings be adopted in other trials in MND in order to improve recruitment and equality of access. Future clinical trials could even use the TiM as a cost-effective, low burden research tool to collect outcome measures.

This was a small study in a single centre using motivated patients and staff involved in the development of the TiM. Larger trials at other centres may not experience the high levels of recruitment and retention seen here. Problems with recruitment are not unique to MND: less than a third of trials manage to meet recruitment targets and half require an extension (40). A sample size of 260 is feasible but challenging. The Sheffield MND clinic is one of the largest in the UK, and even using very broad inclusion criteria, only approximately half of patients recently attending the MDC were eligible to participate. Of these, only approximately half responded to an invitation. Therefore, for a sample size of 260 and a realistic estimate of recruiting 10-25% of all the patients under the care of MND centre, the involvement of MND centres with a total caseload of between 1000 and 2500 patients would be required (this accounts for one quarter and half of UK centres). Recruitment might be improved with face-to-face invitations, advertising and the use of national MND registries, e.g. (41) that could even allow patients to identify themselves for research even when they cannot travel to a research centre.

The main limitation of this study was the difficulty estimating the impact that the TiM system would have on a service and healthcare resources. Hardware costs are likely to be minimal, particularly if patients used their own devices and software costs will depend on factors such as the uptake of the service, the capability of the system and data storage costs. The nurses' time diary was not completed and it was difficult to differentiate time spent providing *usual care* from the additional work generated by the TiM system. Any additional work or time saved will vary depending on the MDC set-up and how the individual reacts to alerts (discussed in the parallel paper) but reassuringly the telehealth nurse felt the additional work was minimal and she could use the system within her current role. Many trials of telehealth employ additional staff to use the system but this fails to reflect how a new system would be used when embedded within an established service. Like other trials of telehealth, e.g. (42) it would also be challenging to demonstrate a reduction in health resource use. In this case it is the low levels of the most costly encounters (hospital admissions) and the complexity of MDC care with highly variable levels of health resource use which

do not appear to be directly linked to quality of care that pose challenges. In addition, our parallel paper suggests that any potential impact of the TiM on individual patients may vary depending on the stage and severity of the disease meaning single outcome measures may fail to capture all relevant impacts (for example improved communication may improve emotional quality of life for patients early in the disease whereas earlier identification of physical complications that may prolong survival in the later stages).

Whilst it may be feasible to conduct a larger trial of telehealth in MND, a traditional RCT may not always be the best way to evaluate such a complex intervention (43). An RCT aims to determine whether, all other factors being equal, a specific intervention works at the population level. However, a multicenter study would involve different MND services and whilst all MND care centres do adhere to the same guidelines (12,13). Their structures differ meaning the impact of the TiM may differ with results from one site unlikely to fully predict whether it would work in other services. Service-level evaluations using non-randomised studies are inevitably less costly, quicker and able to recruit in larger cohorts than RCTs (all important factors in rare, terminal diseases such as MND). However, the limitations of such studies have been extensively documented with several published examples reminding us of the need to undertake assessments of both benefits and risks of new interventions. These including in MND where apparently beneficial therapies subsequently were reported as ineffective or even harmful, e.g. (37). However, there is conflicting evidence on the extent by which RCTs and well-designed controlled studies differ in this regard (44-47).

Whilst the role of non-RCTs in evidence-based medicine remains controversial, they are appealing in this type of situation where the intervention is perceived as being low risk and having modest clinical impact. In terms of efficacy, given MDC has been demonstrated to improve outcomes, it may be preferable to simply determine whether the TiM system can deliver an equivalent service to the current usual care, and/or widen access to MDC services that are already proven to be beneficial. In addition, the MRC framework recommends that developing and implementing technology is an iterative processes (23). An RCT would not provide sufficient opportunity to change the intervention substantially during the trial in response to feedback from centres, advances in technology and changes to the way MND care is delivered. Implementation studies may be better placed to demonstrate this whilst also providing the opportunity to demonstrate some of the complex clinical, professional and institutional factors that influence the success or failure of such an intervention (43,48). These also enable clinical services to test and modify the TiM to increase the likelihood of local buy-in, promoting local "champions" who witness the successes of new services can deliver persuasive arguments to support commissioning of services (49). In the case of digitally-enabled technology, at both a methodological and health service level it remains uncertain what represents a good trial and what evidence is needed to enable interventions to be funded and adopted.

CONCLUSION

The study suggests that a large-scale evaluation of the TiM system would be possible but challenging. This study suggests that it could be possible to overcome some challenges seen in other MND trials (such as recruitment and retention). With such diverse clinical settings with complex groups of patients, alternative methods of evaluating may be more appropriate in generating practical and generalisable data and support TiM development and implementation.

Funding and acknowledgements
The TiM was developed within a collaboration between the University of Sheffield, Sheffield Teaching Hospitals NHS Trust, Mylan Ltd and Abbott Healthcare. This trial was funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship grant to EH (DRF-2013-06-076) and the Motor Neuron Disease Association. The trial was supported by the Sheffield Teaching Hospitals NHS Trust NIHR Clinical Research Facility and the University of Sheffield Clinical Trials Unit. Mylan Ltd supplied the software and hardware required for the trial. EH is also funded by an NIHR Clinical Lecturer award. PJS is supported by NIHR Senior Investigator award NF-SI-0512-10082 and PJS and CMD by the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience) IS-BRC-1215-20017.

This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest
The TiM intellectual property is owned by Mylan and the University of Sheffield. There are no individual conflicts of interest.

Author contributions
The following were involved: intervention development (CMD, EH, TW, PJS), trial design and management (EH, MB, WO, CC, AQ, CMD), clinical oversight (CMD and PJS), recruitment and intervention delivery (EH and TW) data collection (EH, WB), data analysis (EH, MB, WB, CMD, CC, SM, AQ) and manuscript preparation (All). All authors reviewed and commented on the manuscript. The authors are grateful to Sheffield MND Research Advisory Group for their guidance on the research methods.

Data statement
Supplementary data is available in the online appendices of this paper and the parallel publication. Additional data is available from the corresponding author on request.

Figures
Figure 1: CONSORT flow diagram. Follow up varied depending on when patients entered the study ranging from 18 months (for those recruited at the start of recruitment period) to 6 months for those recruited at the end of the recruitment period. At each time-point patients are either reported as reached the time-point (analysed) or had died, withdrawn, or did not reach that time-point due to being recruited later in the study.

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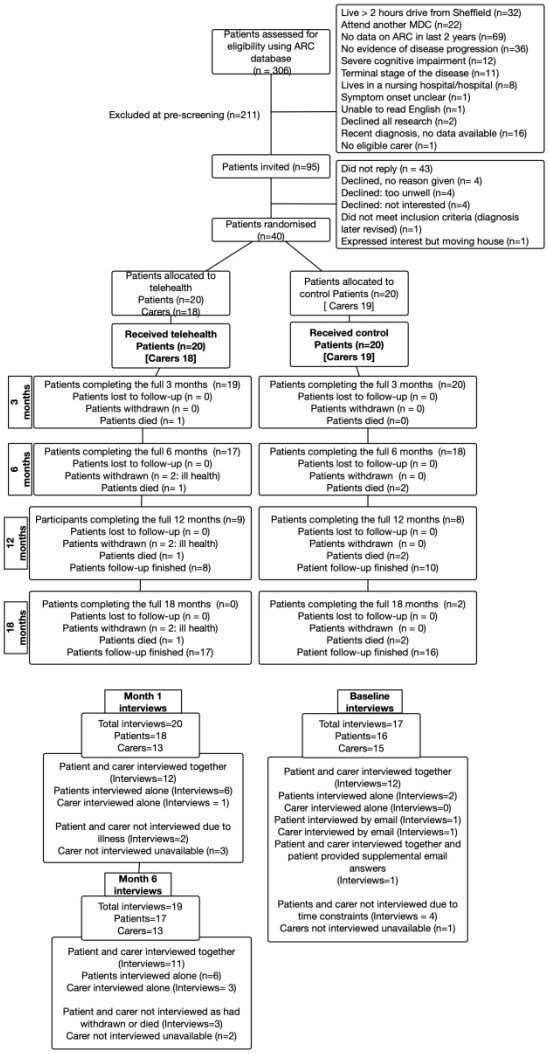


CONSORT flow diagram. Follow up varied depending on when patients entered the study ranging from 18 months (for those recruited at the start of recruitment period) to 6 months for those recruited at the end of the recruitment period. At each time-point patients are either reported as reached the time-point (analysed) or had died, withdrawn, or did not reach that time-point due to being recruited later in the study.

306x430mm (300 x 300 DPI)

Question	Findings	Evidence	Suggestions for improvement
1. Did the feasibility/pilot study allow a sample size calculation for the main trial?	Sample size of 131 patients per group indicated for main trial.	See Sample Size for main trial	Use longitudinal data for primary outcome.
2. What factors influenced eligibility and what proportion of those approached were eligible?	Clear eligibility criteria enabled prescreening using clinical records. Large number of patients were excluded because they were not currently receiving MDC care. Fewer patients excluded on clinical grounds. Including atypical MND and patients without their carer increased eligibility.	CONSORT diagram and Table 1.	Maintain low burden intervention and study methods and continue to use a broad and pragmatic inclusion criteria that can be applied at pre-screening using notes/clinical database.
3. Was recruitment successful?	Achieved target but took longer than expected due initially to study resources and later due to availability of eligible patients. Patient response rates to invitation good. Participants reflected a published cohort of Sheffield MDC patients, those with severe disabilities and those with little experience using technology.	Target of 40 patients and 37 carers achieved in 13 months. 28 existing patients and 12 newly diagnosed patients were recruited. 42/90 patients interested in participating. See Table 1.	Use face-to-face invitations and use registries to identify more eligible patients in other participating centres.
4. Did eligible participants consent?	Good conversion to consent facilitated by good participant motivation and low study burden.	All eligible participants indicating an interest in the trial were recruited	Maintain good information in the patient invitation processes and participant literature.
5. Were participants successfully randomized and did randomization yield equality in groups?	All patients randomised on the day of recruitment and all received the allocated treatment on the same day except one patient who received it three days later.	Characteristics of groups appeared broadly similar.	
6. Were blinding procedures adequate?	Blinding not possible but follow-up data was collected without the involvement of the study team.	Patient interviews.	
7. Did participants adhere to the intervention?	Good participant adherence. Fewer actions taken by telehealth nurse than expected. See parallel publication.	14 (70%) patients completed a TiM session, on average, fortnightly. 13 (70%) carers completed a TiM session at least three weekly.	Further research to promote the use of the TiM system by staff in different clinical settings.
8. Was the intervention acceptable to the participants?	Intervention acceptable to patients, carers and staff. Main findings described parallel publication. Withdrawal rate low.	See parallel publication. Two patients withdrew.	Further research is required to assess the acceptability of the TiM system by staff in different clinical settings.
9. Was it possible to calculate intervention costs?	Telehealth nurse time was not assessed: diaries unfeasible. Assessment of health economic data limited, see text.	Telehealth nurse time was not assessed: diaries unfeasible.	Automatic assessment of TiM system use collected by the TiM software.

10. Were outcome assessments completed?	PROMs return was good in both treatment arms. Pre-clinic shadow monitoring was not feasible (see text for reasons). Some clinic shadow monitoring forms completed, but it was not clear how many were missed due to lack of records.	Participant questionnaires completed: 6 months 80% patient and 82% carer, 12 months 71% patient, 67% carer. 0 pre-clinic shadow monitoring forms and 38 clinic shadow monitoring forms collected.	Fund administration and clinician time to collect clinical outcomes.
11. Were outcomes measured those that were the most appropriate outcomes?	The MND specific ALSAQ-40 was the preferred QoL measure and captured a trend towards deterioration in the physical QoL of patients during the trial. RAND-36 was less acceptable with more missing data. Collecting informal carer hour requirements using patient estimation was not successful. Health and social care resource use varied widely and did not appear to be related to quality of care. Hospital admissions rates low.	Incomplete questionnaires: RAND-36 2%, ALSAQ-40 0%, HADS 0%, ZBI 0% number of carer hours required 9%. Interview data highlighting participants' preference for the ALSAQ-40, ZBI, HADS. Range of healthcare episodes was very high: 0-120 in three months. 4 emergency MND related admissions.	Continue postal questionnaires and offer participant support to complete outcomes at baseline. Use outcome measures that best reflect participant experiences (ALSAQ-40, ZBI, HADS) and do not measure carer hours using simple recall. Examine whether TiM delivered non-inferior care and/or improves access to MDC care, which is known to improve outcomes.
12. Was retention to the study good?	Dropout was low.	2/40 patients withdrew due to ill health. No loss to follow-up.	
13. Were the logistics of running a multicenter trial assessed?	N/A	N/A	N/A
14. Did all components of the protocol work together?	Components had strong synergy except the components using quantitative outcomes to capture clinician experiences and activities due to lack of administrative time and potential burden on clinical staff.	All those recruited were randomised, received the allocated treatment arm and a good level of data completion. Completion of the Shadow Monitoring forms & Telehealth Nurse diaries was poor.	Use automated systems and qualitative methodologies to capture clinician data.

Telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a pilot, feasibility study.

Supplementary data tables

Table of Contents

Table 1 Patient outcome measures collected.[1]

	Baseline	3 months	6 months	12 months	18 months	Clinic visits
Patient characteristics						
Age, gender	X					
Frequency of technology use	X					
Broadband/mobile internet access	X					
Difficulties using TiM	X					
Need for help using TiM	X					
Medical history						
Diagnosis	X					
Disease duration	X					
Comorbidities	X					
Drug history	X					
Quality of life						
ALSAQ-40 (218)	X	X	X	X	X	
SF-36 v1 (219)	X	X	X	X	X	
EQ-5D+D	X	X	X	X	X	
Clinical measures						
ALS-FRS-R (205)	X	X	X	X	X	
Pain score (current and worst)**	X	X	X	X	X	
CSS-MND saliva scale (220)	X	X	X	X	X	
Hospital Anxiety and Depression score (221)	X	X	X	X	X	
Survival						X
Adverse events		X	X	X	X	X
Health resource use						
Clinician encounters**	X	X	X	X	X	X
Hospital admissions**	X	X	X	X	X	X
Informal care use**	X	X	X	X	X	
Formal care use**	X	X	X	X	X	
Satisfaction						
MND care satisfaction**	X	X	X	X	X	
TiM satisfaction**		X*	X*	X*	X*	

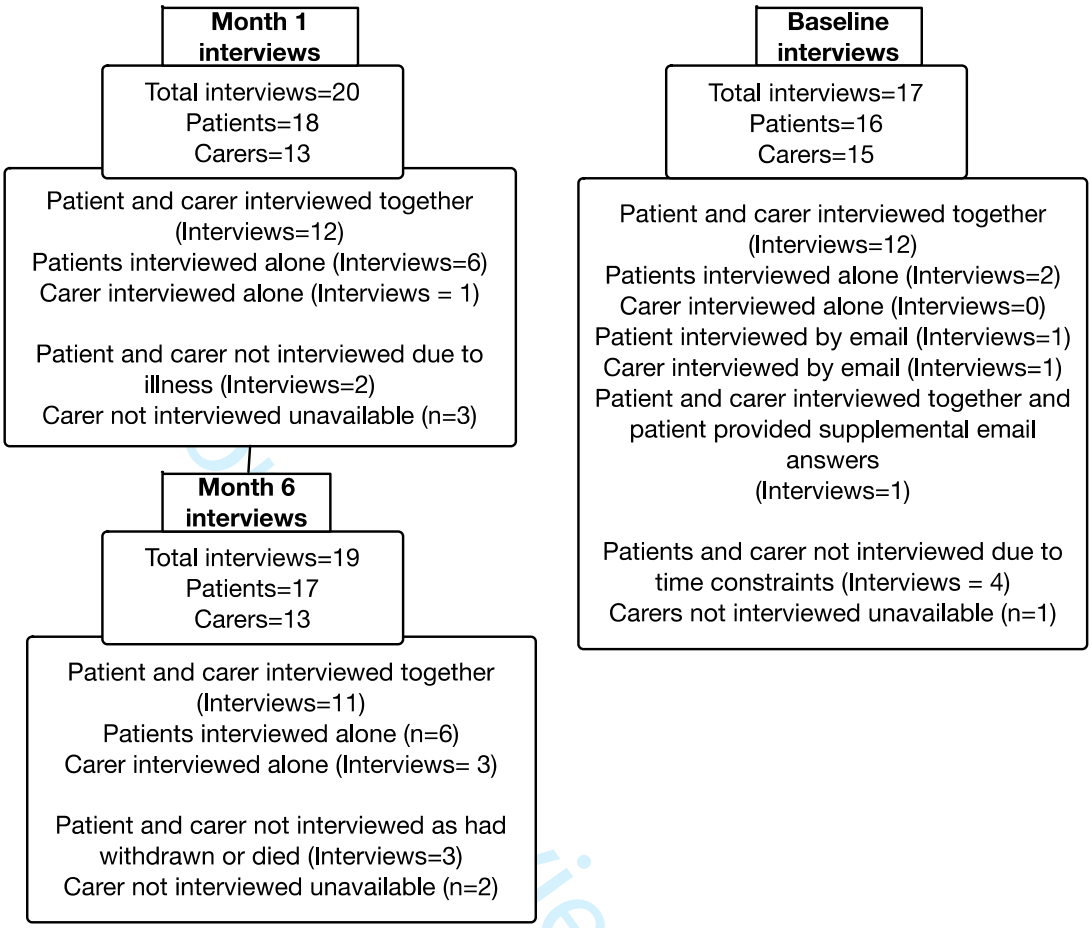
[1] *intervention arm only ** questionnaires designed for the trial

Table 2 Carer outcome measures collected.

	Baseline	3 months	6 months	12 months	18 months	Clinic visits
Carer characteristics						
Age, gender	X					
Relationship to patient	X					
Frequency of technology use	X					
Difficulties using TiM	X					
Quality of life						
SF-36 v1 (219)	X	X	X	X	X	
Clinical measures						
Hospital Anxiety and Depression score (221)	X	X	X	X	X	
Zarit Burden Interview (222)	X	X	X	X	X	
Adverse events		X	X	X	X	X
Satisfaction						
MND care satisfaction**	X	X	X	X	X	
TiM satisfaction**		X*	X*	X*	X*	

*intervention arm only, ** questionnaires designed for the trial

Figure 1 Detailed description of the semi-structured interviews.



In one case a patient was interviewed with his carer, who was not participating in the study. In one case a community nurse was present during the interview. She later was interviewed as part of the study. Telephone interviews were conducted when the patient lived at a distance from the study centre and email interviews were used when the patient had significant dysarthria. All interviews took place in the patients' home except one which took place in a café at the request of the carer. The transcripts were not returned to participants to avoid over burdening them but they were checked by EH who transcribed interviews where participants had speech disturbance. The results were presented to the trial management group which included a member of the Sheffield MND Research Advisory Group who was an experienced volunteer visitor to families with MND and she provided context and confirmed validity of the findings.

Figure 2 Mean ALSAQ-40 sub-scores and standard errors at baseline, three, six, and twelve months.

Scores range from 0 (best possible QoL) to 100 (worse possible QoL). An * indicates scores where the mean change from baseline differs significantly from baseline ($p<0.05$).

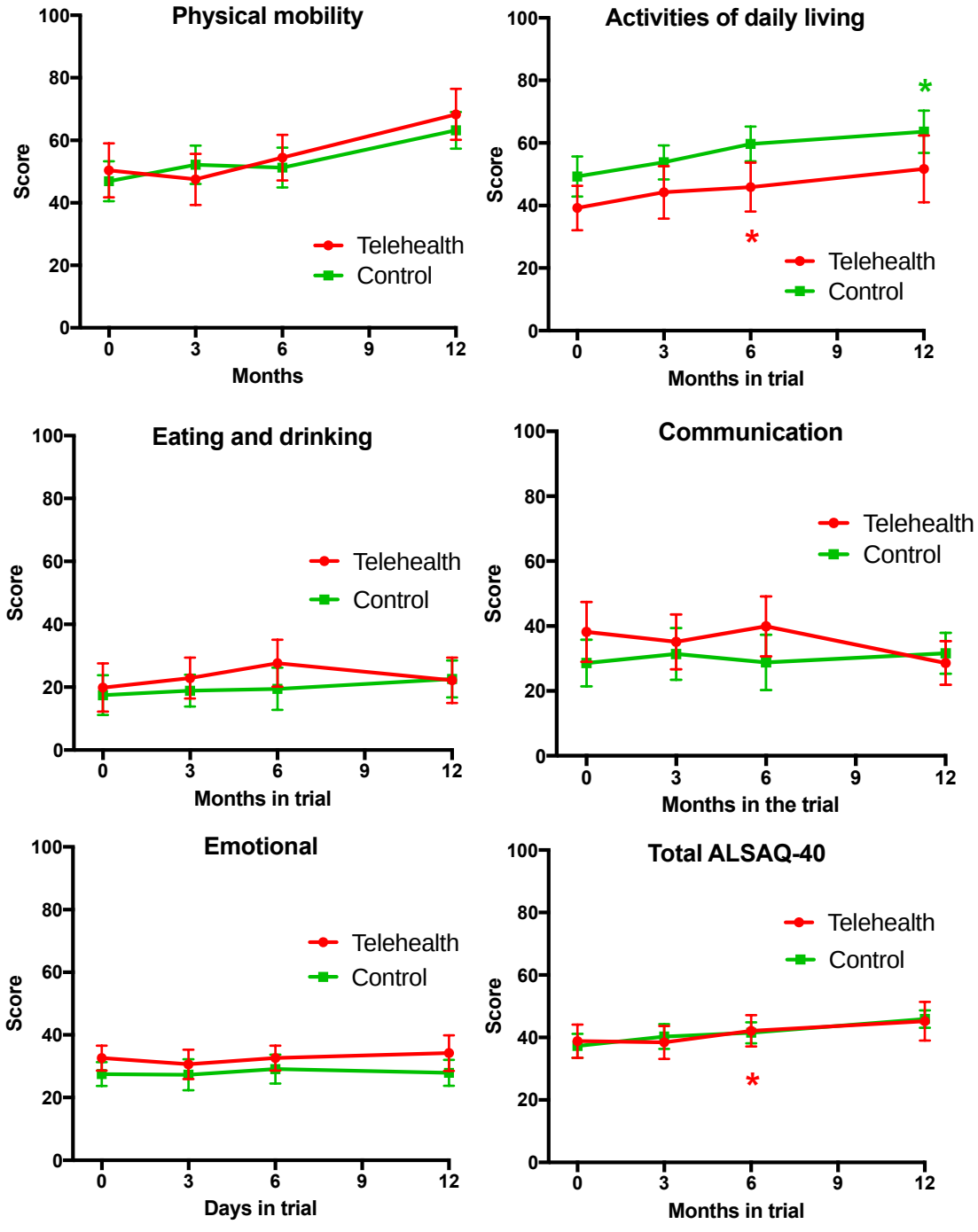


Table 3 Patient ALSAQ-40 index scores

Mean, standard deviation (SD), mean change from the baseline and 95% confidence intervals. Scores range from 0 (best possible QoL) to 100 (worse possible QoL). Cells highlighted in bold indicate where scores are significantly different to baseline.

	Base-line	3 months		6 months		12 months	
Patient ALSAQ-40	**ALSAQ -40 Mean (SD)**	**ALSAQ -40 Mean (SD)**	**Mean change from baseline (CI)**	**ALSAQ -40 Mean (SD)**	**Mean change from baseline (CI)**	**ALSAQ-40 Mean (SD)**	**Mean change from baseline (CI)**
Telehealth	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Physical mobility	50.4 (36.6)	47.5 (34.6)	-4.7 (-15.4, 6.1)	54.5 (30.9)	5.8 (-3.8, 15.4)	68.3 (26.8)	10.4 (-3.6, 24.4)
Activities of daily living	39.2 (30.2)	44.2 (35.6)	5.8 (-0.1, 11.8)	45.9 (33.1)	**8.4 (1.6, 15.3)**	51.7 (45.2)	15.8 (-1.5, 33.1)
Eating and drinking	19.9 (32.5)	22.9 (27.6)	6.1 (-1.4, 13.6)	27.6 (31.7)	**11.5 (2.6, 20.3)**	22.2 (30.6)	13.9 (-16.7, 44.5)
Communic-ation	38.3 (39.0)	35.1 (35.9)	0.5 (-5.0, 5.9)	39.9 (39.1)	3.6 (-2.1, 9.3)	28.6 (45.2)	13.1 (-12.1, 38.3)
Emotional	32.6 (16.8)	30.6 (20.0)	0 (-6.4, 6.4)	32.6 (16.9)	1.4 (-4.6, 7.5)	34.2 (24.3)	3.8 (-13.0, 20.5)
Total	38.8 (22.5)	38.4 (22.2)	0.83 (-2.6, 4.3)	42.1 (21.2)	**5.4 (0.2, 10.6)**	45.2 (26.3)	10.8 (-1.5, 23.2)
Control	n=20	n=15	n=15	n=12	n=12	n=7	n=6
Physical mobility	46.9 (28.7)	52.2 (27.6)	1.6 (-12.9, 16.1)	51.3 (28.6)	8.3 (-8.2, 24.9)	63.2 (26.1)	15.0 (-17.6, 47.6)
Activities of daily living	49.3 (28.7)	53.8 (24.2)	2.3 (-7.0, 11.6)	59.7 (24.6)	9.0 (-9.6, 18.9)	63.6 (30.4)	**15.8 (1.9, 30.0)**
Eating and drinking	17.5 (28.2)	18.9 (22.6)	0.6 (-7.1, 8.3)	19.5 (30.1)	8.3 (-10.7, 27.4)	22.6 (26.2)	2.8 (-6.3, 11.8)
Communic-ation	28.6 (32.2)	31.4 (35.8)	1.5 (-5.9, 8.9)	28.8 (38.1)	8.0 (-20.5, 36.6)	31.6 (28.2)	9.5 (-9.8, 28.9)
Emotional	27.5 (17.0)	27.3 (22.0)	-1.4 (-9.2, 6.3)	29.1 (20.5)	-2.3 (-16.4, 11.8)	27.9 (18.6)	-3.8 (-23.6, 16.1)
Total	37.3 (17.2)	40.3 (17.7)	0.8 (-2.6, 4.3)	41.5 (14.9)	5.8 (-3.7, 15.3)	45.9 (12.5)	10.8 (-1.5, 23.2)
Total	n=38	n=31	n=30	n=28	n=28	n=13	n=12
Physical mobility	48.6 (32.3)	49.8 (31.0)	0.9 (-6.7, 8.6)	53.1 (29.4)	6.9 (-1.4, 15.2)	65.6 (25.5)	12.7 (-1.8, 27.3)
Activities of daily living	44.5 (29.5)	48.9 (30.5)	1.6 (-12,9, 16.1)	51.8 (30.0)	**8.7 (3.3, 14.0)**	58.1 (29.0)	**15.8 (6.8, 24.9)**
Eating and drinking	18.6 (28.4)	21.0 (25.0)	2.3 (-7.0, 8.3)	24.1 (30.8)	**10.1 (1.3, 19.0)**	22.4 (27.1)	8.3 (-5.2, 21.9)
Communic-ation	33.3 (35.4)	33.3 (35.3)	01.5 (-5.9, 8.9)	35.2 (38.3)	5.5 (-6.1, 17.1)	30.2 (35.3)	11.3 (-1.7, 24.3)
Emotional	29.9 (16.9)	29.0 (20.7)	-1.4 (-9.2, 6.3)	31.1 (18.2)	-0.2 (-6.6, 6.3)	30.8 (20.8)	0 (-10.9, 10.9)
Total	38.0 (19.6)	39.3 (19.9)	0.88 (-2.9, 4.7)	41.8 (18.5)	**5.6 (0.9, 10.2)**	45.6 (19.1)	8.6 (-0.4, 17.6)

Table 4 RAND-36 physical (PCS) and mental (MCS) sub-scores.

The mean and standard deviation (SD) of the mean scores, the mean change from baseline and the 95% confidence interval of the mean change from baseline. These are standardised to a normative reference population in which the mean is 50 and Standard deviation is 10.

	Base-line	**3 months**		**6 months**		**12 months**	
Patient SF-36	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth							
PCS	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean (SD/CI)	30.1 (9.1)	30.7 (7.7)	-0.7 (-3.3, 1.9)	28.2 (8.6)	-3.1 (-7.1, 0.9)	22.6 (4.1)	-5.8 (-15.0, 3.4)
MCS	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean (SD/CI)	52.3 (10.0)	50.7 (11.7)	-1.4 (-5.4, 2.6)	52.3 (12.3)	-0.2 (-4.2, 3.8)	48.8 (15.8)	-5.7 (-18.8, 7.2)
Control							
PCS	n=20	n=14	n=14	n=12	n=12	n=6	n=6
Mean (SD/CI)	28.0 (8.7)	26.6 (5.8)	-0.6 (-5.4, 4.3)	27.0 (7.9)	-0.1 (-7.8, 7.6)	23.7 (3.0)	-6.6 (-13.8, 0.5)
MCS	n=20	n=14	n=14	n=12	n=12	n=6	n=6
Mean (SD/CI)	54.3 (9.5)	55.1 (13.5)	0.9 (-5.4, 7.3)	50.8 (12.1)	-3.6 (-10.7,3.6)	54.7 (9.2)	-1.3 (-17.8,15.3)
Total							
PCS	n=38	n=30	n=29	n=28	n=28	n=12	n=12
Mean (SD/CI)	29.0 (8.8)	28.3 (7.2)	-0.7 (-3.2, 1.9)	27.7 (8.2)	-1.8 (-5.5, 1.9)	23.2 (3.5)	**-6.2 (-11.0,-1.4)**
MCS	n=38	n=30	n=29	n=28	n=28	n=12	n=12
Mean (SD/CI)	53.3 (9.7)	52.7 (12.6)	-0.3 (-3.8, 3.2)	51.7 (12.0)	-1.7 (-5.2, 1.9)	51.8 (12.7)	-3.5 (-12.2, 5.2)

Figure 3 RAND-36 scores

Physical component scores (PCS) and mental component scores (MCS) mean and standard errors. RAND-36 scores are standardised to a normative reference population (mean is 50 and SD is 10.) An * indicates scores where the mean change from baseline differs significantly different from baseline ($p<0.05$).

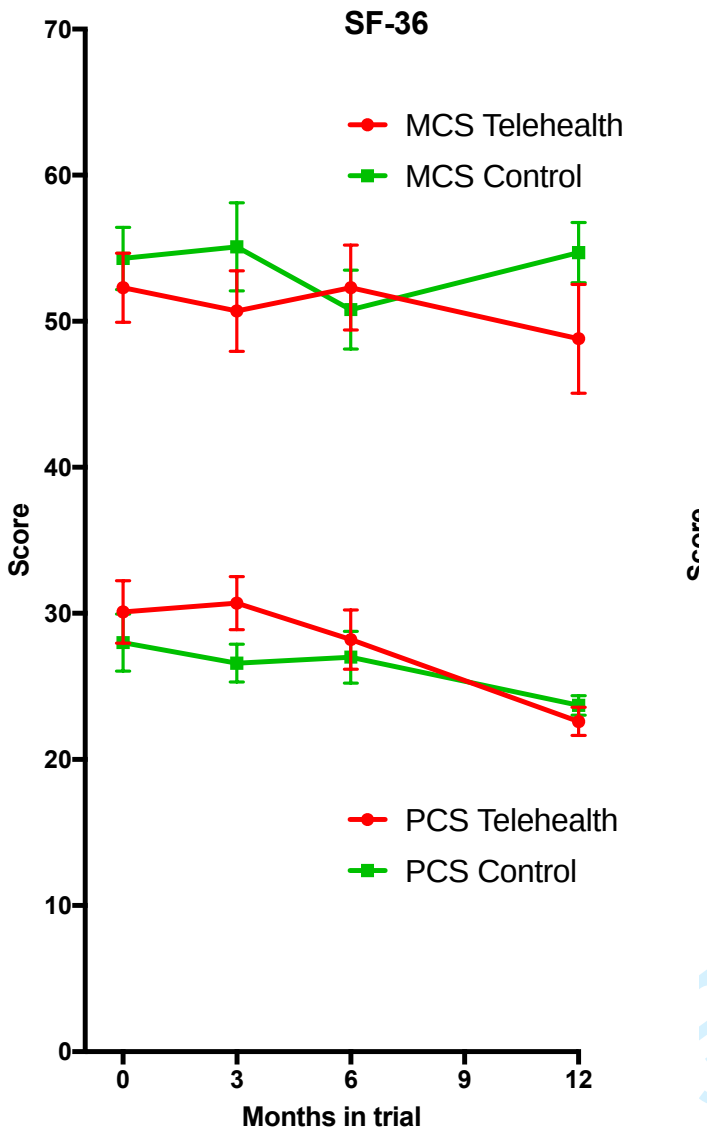


Table 5 EQ-5D-3L and EQ-5D plus dignity bolt-on and the EQ5D thermometer.

Patient EQ-5D	Baseline Mean (SD)	3 months Mean (SD)	3 months Change from baseline Mean (CI)	6 months Mean (SD)	6 months Change from baseline Mean (CI)	12 months Mean (SD)	12 months Change from baseline Mean (CI)
Telehealth	n=17	n=16	n=14	n=16	n=15	n=6	n=6
EQ5D-3L	0.52 (0.31)	0.49 (0.27)	-0.04 (-0.13, 0.05)	0.49 (0.30)	-0.07 (-0.20, 0.06)	0.39 (0.36)	-0.09 (-0.38, 0.21)
EQ5D-3L+D	0.46 (0.40)	0.48 (0.30)	-0.02 (-0.18, 0.14)	0.47 (0.35)	-0.04 (-0.24, 0.16)	0.26 (0.54)	-0.15 (-0.63, 0.33)
Thermometer	61.1 (22.5)	63.8 (25.0)	-2.1 (-8.7, 4.6)	61.6 (20.5)	-3.7 (-9.6, 2.3)	57.5 (22.3)	-5.8 (-12.8, 1,1)
Control	n=20	n=15	n=15	n=12	n=12	n=6[2]	n=6[3]
EQ5D-3L	0.53 (0.27)	0.50 (0.29)	0.02 (-0.10, 0.14)	0.46 (0.25)	-0.11 (-0.22, 0.01)	0.37 (0.33)	-0.25 (-0.50, 0.0)
EQ5D-3L+D	0.49 (0.37)	0.44 (0.41)	0.01 (-0.10, 0.14)	0.44 (0.29)	-0.10 (-0.21, 0.01)	0.26 (0.48)	-0.27 (-0.59, 0.04)
Thermometer	64.5 (20.6)	64.6 (26.8)	0.9 (-13.5, 15.4)	61.7 (25.3)	-6.7 (-19.8, 6.5)	60.9 (21.6)	-7.0 (-37.2, 23.2)
Total	n= 37	n=31	n=29	n=28	n=27	n=12[3]	n=12[3]
EQ5D-3L	0.53 (0.29)	0.50 (0.27)	-0.01 (-0.01, 0.06)	0.47 (0.27)	**-0.09 (-0.17, -0.01)**	0.38 (0.33)	-0.17 (-0.33, 0.00)
EQ5D-3L+D	0.48 (0.37)	0.46 (0.35)	-0.01 (-0.10, 0.08)	0.46 (0.32)	-0.07 (-0.18, 0.05)	0.26 (0.49)	-0.21 (-0.45, 0.03)
Thermometer	63.0 (21.3)	64.2 (25.5)	-0.5 (-8.2, 7.1)	61.6 (23.0)	-5.0 (-11.2, 1.2)	59.3 (21.1)	-6.4 (-20.7, 7.7)

[2] Control group n=6 in EQ5D calculations and n=7 in thermometer calculations at both 6 and 12 months.

Table 6 EQ-5D-3L and EQ-5D plus dignity bolt-on and the EQ5D thermometer.
In these calculations, patients who had died were included in the scoring and were assigned a score of 0. Thermometer scores are unchanged.

Patient EQ-5D	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
n= *	17	17	15	17	16	8	8
EQ5D-3L Mean (SD/CI)	0.52 (0.31)	0.46 (0.29)	-0.05 (-0.14, 0.03)	0.46 (0.31)	-0.08 (-0.20, 0.04)	0.35 (0.37)	-0.12 (-0.33, 0.08)
EQ5D-3L+D Mean (SD/CI)	0.46 (0.40)	0.44 (0.41)	-0.03 (-0.18, 0.12)	0.44 (0.35)	-0.05 (-0.23,0.14)	0.20 (0.47)	-0.17 (-0.50, 0.15)
Thermometer n=	17	16	14	16	15	6	6
Mean (SD/CI)	61.1 (22.5)	63.8 (25.0)	-2.1 (-8.7, 4.6)	61.6 (20.5)	-3.7 (-9.6, 2.3)	57.5 (22.3)	-5.8 (-12.8, 1,1)
Control							
n=*	20	15	15	14	14	8	7
EQ5D-3L Mean (SD/CI)	0.53 (0.28)	0.50 (0.28)	0.02 (-0.10, 0.14)	0.39 (0.28)	-0.12 (-0.26, 0.01)	0.28 (0.33)	-0.28 (-0.48, -0.08)
EQ5D-3L+D Mean (SD/CI)	0.49 (0.37)	0.44 (0.41)	0.00 (-0.12, 0.12)	0.38 (0.31)	-0.08 (-0.23, 0.07)	0.19 (0.43)	-0.28 (-0.51, 0.10)
Thermometer n=	20	15	15	12	12	7	7
Mean (SD/CI)	64.5 (20.6)	64.6 (26.8)	0.9 (-13.5, 15.4)	61.7 (25.3)	-6.7 (-19.8, 6.5)	60.9 (21.6)	-7.0 (32.6)
Total							
n= *	37	32	30	31	30	16	15
EQ5D-3L Mean (SD/CI)	0.53 (0.29)	0.49 (0.28)	-0.02 (-0.09, 0.05)	0.43 (0.29)	-0.10 (-0.19, -0.02)	0.29 (0.33)	-0.20 (-0.33, 0.08)
EQ5D-3L+D Mean (SD/CI)	0.48 (0.37)	0.44 (0.41)	-0.02 (-0.10, 0.07)	0.41 (0.33)	-0.06 (-0.18, 0.05)	0.20 (0.43)	-0.23 (-0.40, -0.05)
Thermometer n=	37	31	29	28	27	13	13
Mean (SD/CI)	63.0 (21.3)	64.2 (25.5)	-0.5 (-8.2, 7.1)	61.6 (53.0)	-5.0 (-11.2, 1.2)	59.3 (21.1)	-6.4 (-20.7, 7.7)

Table 7 Patient ALSFRS-R scores.

Scores range from 0 (severe disability) to 48 (no disability). Scores highlighted in bold indicate scores that have changed significantly from baseline.

	Baseline	3 months		6 months		12 months	
ALSFRS-R	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth							
	n=18	n=16	n=15	n=16	n=16	n=6	n=6
Mean	31.9 (9.7)	32.1 (10.4)	-0.06 (-2.6, 3.4)	31.1 (9.0)	-0.3 (-2.6, 1.9)	28.7 (7.6)	**-4.7 (-8.5, -0.91)**
Control							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean	32.1 (8.0)	29.8 (8.7)	-1.5 (-4.1, 1.0)	29.4 (9.0)	-3.7 (-6.8, -0.5)	25.9 (6.0)	-5.1 (-12, 1.8)
Total							
	n=38	n=31	n=30	n=28	n=28	n=13	n=13
Mean	32.0 (8.7)	30.9 (9.5)	-0.6 (-2.2, 1.0)	31.1 (8.9)	-1.6 (-3.6 – 0.4)	27.9 (9.6)	**-4.9 (-8.4, -1.4)**

Figure 4 Mean ALS-FRS-R and standard error .

Scores range from 0 (severe disability) to 48 (no disability). An * indicates scores where the mean change from baseline differs significantly from baseline ($p<0.05$).

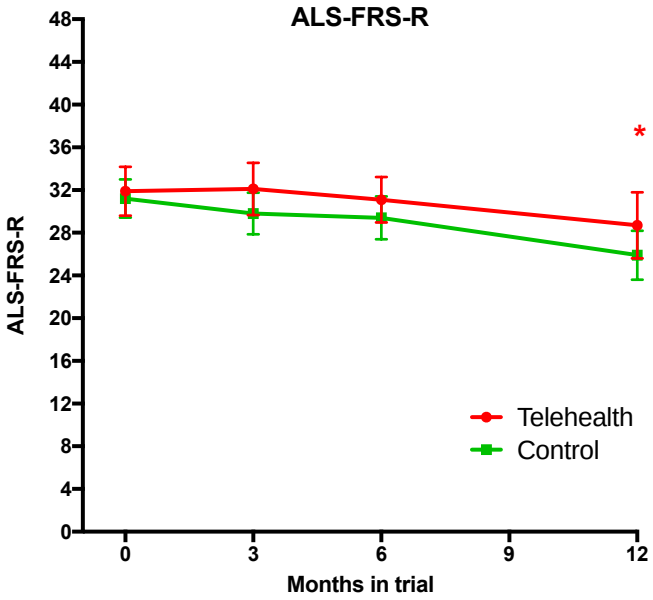


Table 8 Patient HADS Anxiety sub-scores and the number (%) of patients with borderline scores and abnormal scores.
0-7 normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe.

	Baseline	3 months		6 months		12 months	
HADS	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth Anxiety							
	n=17	n=16	n=16	n=16	n=15	n=7	n=6
Mean (SD/CI)	6.0 (4.0)	5.7 (4.3)	-0.2 (-2.3, 1.9)	4.7 (3.7)	-0.9 (-2.1, 0.4)	5.0 (2.6)	-.0.7 (-3.3, 2.0)
Score ≥8	8 (47%)	4 (25%)	-	3 (19%)	-	1 (6%)	-
Score ≥11	1 (6%)	2 (13%)	-	1 (6%)	-	0 (0%)	-
Control Anxiety							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean (SD/CI)	4.9 (3.9)	4.6 (4.4)	-0.5 (-2.1, 1.2)	5.1 (5.1)	-.3 (-1.8, 1.3)	6.9 (4.3)	0.9 (4.7)
Score ≥8	3 (15%)	4 (27%)	-	3 (20%)	-	2 (14%)	-
Score ≥11	2 (10%)	3 (20%)	-	2 (13%)	-	1 (7%)	-
Total Anxiety							
	n=37	n=31	n=31	n=28	n=27	n=13	n=13
Mean (SD/CI)	5.4 (4.0)	5.2 (4.3)	-0.3 (-1.6, 0.9)	4.9 (4.3)	-0.6 (-1.5, 0.3)	5.9 (3.3)	0.2 (-2.1, 2.4)
Score ≥8	11 (30%)	8 (26%)	-	6 (19%)	-	3 (10%)	-
Score ≥	3 (8%)	5 (16%)	-	3 (10%)	-	1 (3%)	-

Table 9 Patient HADS Depression sub-scores and the number (%) of patients with borderline scores and abnormal scores.
0-7 normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe.

	Baseline	3 months		6 months		12 months	
HADS	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth Depression							
	n=20	n=16	n=16	n=16	n=15	n=6	n=6
Mean (SD/CI)	5.9 (2.9)	5.6 (2.7)	-0.3 (-2.1, 1.6)	5.8 (3.0)	0.3 (-1.0, 1.6)	7.5 (4.3)	1.7 (-1.0, 4.4)
Score ≥8	5 (29%)	6 (38%)	-	6 (38%)	-	1 (19%)	-
Score ≥11	0 (0%)	0 (0%)	-	0 (0%)	-	1 (19%)	-
Control Depression							
	n=20	n=15	n=15	n=12	n=12	n=7	n=7
Mean (SD/CI)	3.9 (3.0)	6.1 (3.8)	1.5 (-0.4, 3.3)	5.8 (3.3)	0.8 (-1.7, 3.3)	6.4 (3.6)	0.9 (-3.4, 5.1)
Score ≥8	3 (15%)	4 (27%)	-	3 (20%)	-	1 (20%)	-
Score ≥11	1 (5%)	3 (20%)	-	1 (7%)	-	1 (7%)	-
Total Depression							
	n=37	n=31	n=31	n=28	n=27	n=13	n=13
Mean (SD/CI)	4.8 (3.1)	5.8 (3.2)	0.6 (-0.7, 1.9)	5.8 (3.1)	0.5 (-0.7, 1.7)	6.9 (4.6, 9.2)	1.2 (-1.0, 3.5)
Score ≥8	8 (22%)	10(32%)	-	9 (29%)	-	2 (19%)	-
Score ≥11	1 (3%)	3 (10%)	-	1 (3%)	-	1 (13%)	-

36/bmjopen-2018-028525 on 22 October 2019.

Table 10 "Current" and "worst" pain scores over previous week.
Rated on a modified Likert score from 0-10.

Pain scores	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Current pain (0-10)							
Control	20	15	15	13	13	7	7
Mean (SD/CI)	1.4 (1.4)	1.6 (2.0)	0.33 (-0.5, 1.2)	1.4 (2.0)	0.2 (-1.1, 1.4)	2.6 (2.5)	-0.9 (-2.6, 0.9)
Telehealth	17	16	15	15	15	6	6
Mean (SD/CI)	1.7 (1.9)	2.1 (2.4)	0.1 (-1.3, 1.4)	1.8 (2.3)	1.8 (0.7, 2.9)	1.8 (1.6)	0.8 (-1.2, 2.9)
Total	37	31	30	28	28	13	13
Mean (SD/CI)	1.5 (1.7)	1.9 (2.2)	0.2 (-0.5, 0.9)	1.6 (2.2)	1.0 (0.2, 1.9)	2.2 (2.1)	-0.1 (-1.3, 1.1)
Worst pain (0-10)							
Control	20	15	15	13	13	7	7
Mean (SD/CI)	3.2 (2.7)	3.4 (3.1)	-0.1 (-1.3, 1.0)	2.6 (2.7)	-0.2 (-0.8, 0.4)	3.9 (3.1)	0.3 (-1.0, 1.6)
Telehealth	17	16	15	15	15	6	6
Mean (SD/CI)	2.9 (2.8)	3.4 (3.1)	0.1 (-1.2, 1.5)	3.0 (2.8)	3.1 (1.6, 4.7)	3.5 (2.2)	0.3 (-2.4, 2.1)
Total	37	31	30	28	28	13	13
Mean (SD/CI)	3.0 (2.7)	3.2 (2.9)	0.0 (-0.8, 0.8)	2.8 (2.7)	1.6 (0.5, 2.6)	3.7 (2.7)	0.1 (-1.0, 1.1)

Table 11 CSS-MND saliva severity scores.

Mean, standard deviation and change from baseline (mean, 95% confidence interval). Scores range from 0 (no problems with orophrayngeal secretions) to 36 (severe secretions).

	Baseline	3 months		6 months		12 months	
CSS MND	**Mean (SD)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**	**Mean (SD)**	**Change from baseline Mean (CI)**
Telehealth	n=17	n=16	n=14	n=16	n=16	n=6	n=6
Mean (SD)	4.2 (6.0)	4.8 (6.4)	1.9 (0.2, 3.5)	2.6 (1.2)	0.0 (-2.8, 2.8)	2.3 (3.2)	0.2 (-1.4, 1.9)
Control	n=20	n=15	n=14	n=12	n=12	n=7	n=6
Mean (SD)	4.1 (5.2)	5.5 (6.2)	1.0 (-1.5, 3.5)	2.8 (1.1)	0.1 (-1.56, 1.7)	3.4 (4.5)	-0.7 (-0.7, 3.4)
Total	n=37	n=31	n=29	n=28	n=28	n=13	n=12
Mean (SD)	4.1 (5.5)	5.1 (6.2)	1.4 (0-2.9)	2.6 (1.1)	0.0 (-1.6, 1.6)	3.4 (4.5)	0.2 (-1.4, 1.9)

Table 12 Carer SF-36 physical and mental sub-scores.
These scores are standardised to a normative reference population in which the mean is 50 and standard deviation is 10.

Carer SF-36	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
Physical	n=16	n=14	n=13	n=15	n=14	n=4	n=4
Mean (SD/CI)	52.4 (11.1)	49.0 (9.6)	-1.9 (-8.0, 4.2)	51.6 (9.7)	0.10 (-4.9, 5.2)	51.0 (3.1)	-3.6 (-13.8,6.6)
Mental	16	14	13	15	14	4	4
Mean (SD/CI)	47.9 (13.1)	50.5 (14.5)	3.3 (-1.1, 7.7)	48.6 (14.4)	1.2 (-2.8, 5.2)	45.3 (14.5)	-2.9 (-9.6, 3.8)
Control							
Physical	n=18	n=13	n=13	n=11	n=11	n=7	n=7
Mean (SD/CI)	52.9 (7.7)	51.9 (7.0)	-3.2 (-8.1, 1.8)	49.1 (8.8)	-4.7 (-8.9, -0.4)	52.2 (9.6)	-3.0 (-10.2,4.2)
Mental	n=18	n=13	n=13	n=11	n=11	n=7	n=7
Mean (SD/CI)	50.6 (10.3)	51.2 (8.7)	1.7 (-2.2, 5.5)	51.8 (10.5)	0.70 (-6.8, 8.1)	51.7 (10.3)	2.4 (-4.5, 9.3)
Total							
Physical	n=34	n=27	n=26	n=26	n=25	n=11	n=11
Mean (SD/CI)	52.7 (9.3)	50.4 (8.4)	-2.5 (-6.1, 1.1)	50.1 (9.2)	-2.0 (-5.3, 1.3)	51.8 (7.6)	-3.2 (-7.9, 1.5)
Mental	n=34	n=27	n=26	n=26	n=25	n=11	n=11
Mean (SD/CI)	49.3 (11.6)	50.8 (11.8)	2.5 (-0.3, 5.2)	49.9 (12.8)	1.0 (-2.7, 4.6)	49.4 (11.7)	0.4 (-4.1, 5.0)

Figure 5 Carer RAND physical component scores (PCS) and mental component scores (MCS).

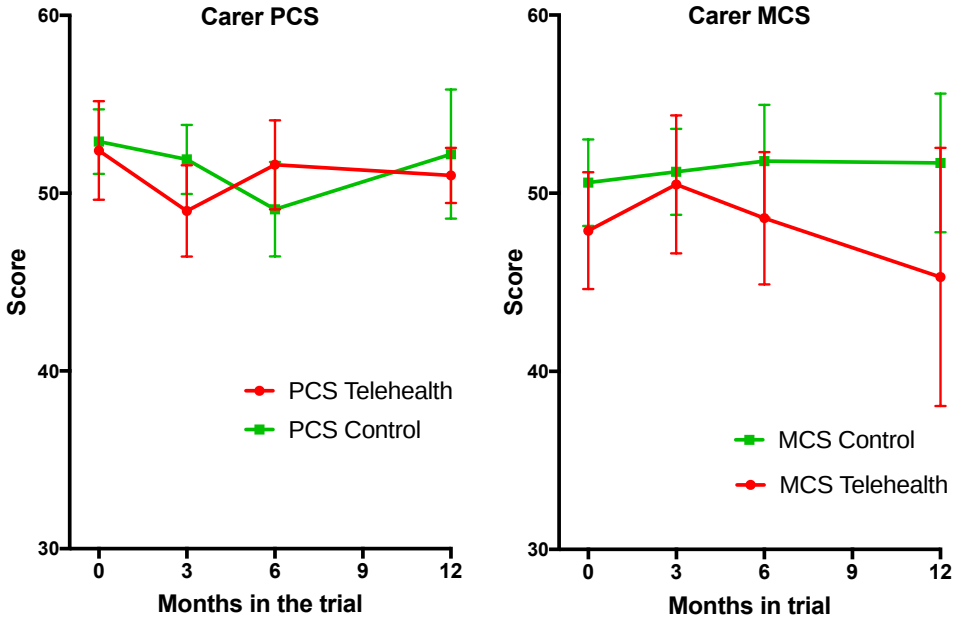


Table 13 Carer HADS depression sub scores and the number (%) of patients with borderline scores or abnormal scores.
Scores 0-7 are normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe).

	Baseline	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth Depression							
	n=16	n=14	n=13	n=15	n=14	n=6	n=6
Mean (SD/CI)	4.0 (3.2)	4.6 (4.1)	0.1 (-1.0, 1,2)	4.3 (3.9)	0.1 (-0.9, 1.0)	4.8 (3.5)	1.3 (-1.5, 4.1)
Score ≥8	1 (6%)	3 (21%)	-	3 (20%)	-	1 (14%)	-
Score ≥11	1 (6%)	1 (7%)	-	1 (7%)	-	0 (0%)	-
Control Depression							
	n=18	n=14	n=14	n=11	n=11	n=7	n=7
Mean (SD/CI)	3.3 (2.8)	4.8 (4.2)	1.4 (0.0, 2.8)	4.3 (4.5)	2.1 (0.4, 4.6)	3.4 (3.4)	1.3 (-0.8, 3.4)
Score ≥8	2 (11%)	3 (21%)	-	3 (27%)	-	1 (14%)	-
Score ≥11	1 (6%)	1 (7%)	-	1 (9%)	-	0 (0%)	-
Total Depression							
	n=34	n=28	n=27	n=26	n=25	n=13	n=13
Mean (SD/CI)	3.6 (3.0)	4.7 (4.0)	0.8 (-0.1, 1.7)	4.3 (4.0)	1.0 (-0.2, 2.1)	4.1 (3.4)	1.3 (-0.2, 2.7)
Score ≥8	2 (6%)	6 (21%)	-	6 (21%)	-	2 (15%)	-
Score ≥11	1 (3%)	2 (7%)	-	2 (7%)	-	0 (0%)	-

Table 14 Carer HADS anxiety sub scores and the number (%) of patients with borderline scores or abnormal scores. Scores 0-7 are normal, 8-10 borderline/mild symptoms, 11-21 abnormal: moderate/severe).

	Baseline	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth Anxiety							
	n=16	n=14	n=13	n=15	n=14	n=6	n=6
Mean (SD/CI)	6.3 (4.6)	7.1 (4.6)	0.0 (-1.8, 1.7)	6.0 (5.1)	-0.8 (-2.9, 1.3)	7.3 (5.0)	0.3 (-1.4, 1.9)
Score ≥8	7 (44%)	3 (21%)	-	5 (33%)	-	3 (43%)	-
Score ≥11	2 (13%)	1 (7%)	-	3 (20%)	-	3 (43%)	-
Control Anxiety							
	n=18	n=14	n=14	n=11	n=11	n=7	n=7
Mean (SD/CI)	5.9 (3.5)	6.2 (4.4)	-0.2 (-1.8, 1.4)	6.4 (4.8)	0.3 (-2.1, 2.7)	5.6 (4.0)	-0.6 (-1.6, 0.5)
Score ≥8	6 (33%)	6 (43%)	-	4 (36%)	-	2 (29%)	-
Score ≥11	2 (11%)	2 (14%)	-	3 (27%)	-	1 (14%)	-
Total Anxiety							
	n=34	n=28	n=27	n=26	n=25	n=13	n=13
Mean (SD/CI)	6.1 (4.0)	7.1 (4.6)	-0.1 (-1.2, 1.0)	6.2 (4.8)	-0.3 (-1.8, 1.1)	6.4 (4.4)	-0.2 (-1.4, 1.9)
Score ≥8	13 (35%)	3 (11%)	-	**9 (31%)**	**-**	**5 (38%)**	-
Score ≥11	4 (11%)	5 (18%)	-	**6 (21%)**	**-**	**4 (31%)**	**-**

Table 15 The 12-item Zarit Burden Interview scores.

Scores range from 0 (no burden) to 48 (severe burden). A cut-off of scores ≥17 suggests high burden (222).

	Base-line	3 months		6 months		12 months	
	Mean (SD)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)	Mean (SD)	Change from baseline Mean (CI)
Telehealth							
	n=18	n=14	n=14	n=15	n=15	n=6	n=6
Mean (SD/CI)	11.5 (9.9)	12.7 (11.2)	1.6 (-1.6, 4.8)	13.7 (10.7)	2.4 (-1.3, 6.1)	13.8 (12.6)	4.3 (-1.2, 9.9)
Score ≥17	3 (19%)	4 (29%)		4 (27%)		2 (33%)	
Control							
	n=16	n=13	n=13	n=10	n=10	n=6	n=6
Mean (SD/CI)	12.9 (7.9)	15.9 (8.9)	3.0 (-0.6, 6.6)	12.4 (9.5)	2.6 (-0.5, 5.7)	13.5 (9.6)	-0.3 (-7.9, 6.2)
Score ≥17	6 (33%)	4 (31%)	-	2 (20%)		2 (33%)	
Total							
	n=34	n=27	n=27	n=25	n=25	n=12	n=12
Mean (SD/CI)	12.3 (8.8)	14.2 (10.1)	2.6 (0.0-4.5)	13.2 (9.0)	2.5 (0.1, 4.8)	13.7 (10.7)	1.8 (-2.3, 5.8)
Score ≥17	9 (27%)	8 (30%)		6 (24%)		4 (33%)	

Figure 6 The number of patient-reported MND related healthcare encounters in the three months prior to the study (baseline) and during the study
Mean and range, n=38.

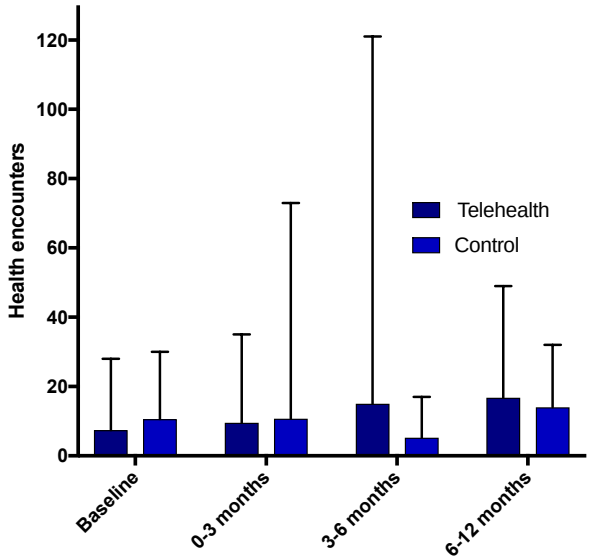


Figure 7 Patient encounters with healthcare professionals due to MND in the three months prior to the study commencement
Mean and range, n=38.

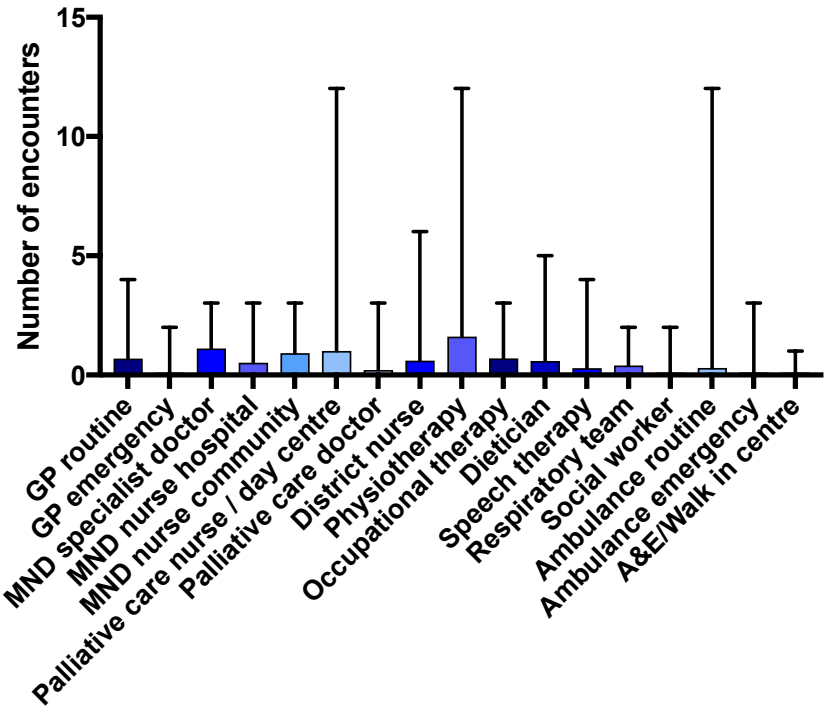


Figure 8 Patient estimated hours of informal (unpaid) and formal (paid) care received per week.

Mean and interquartile range.

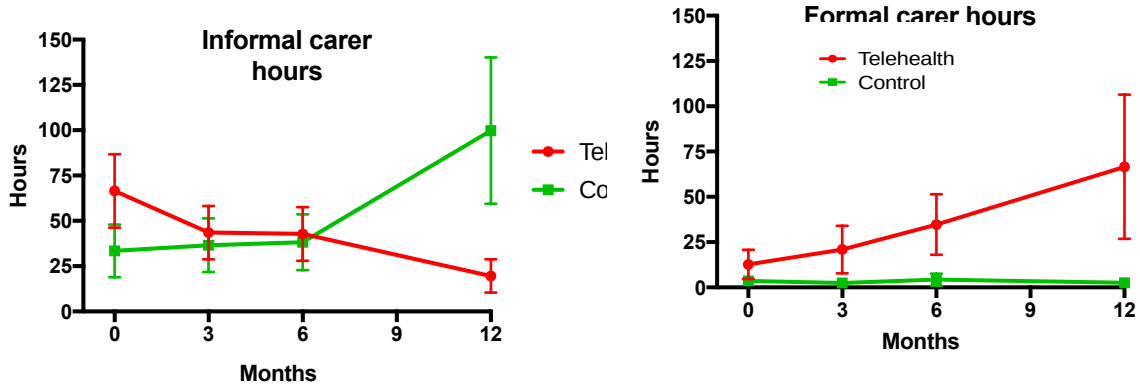


Figure 8 Individual patient estimated median hours of informal (unpaid) and formal (paid) care received per week

Mean and the interquartile range.

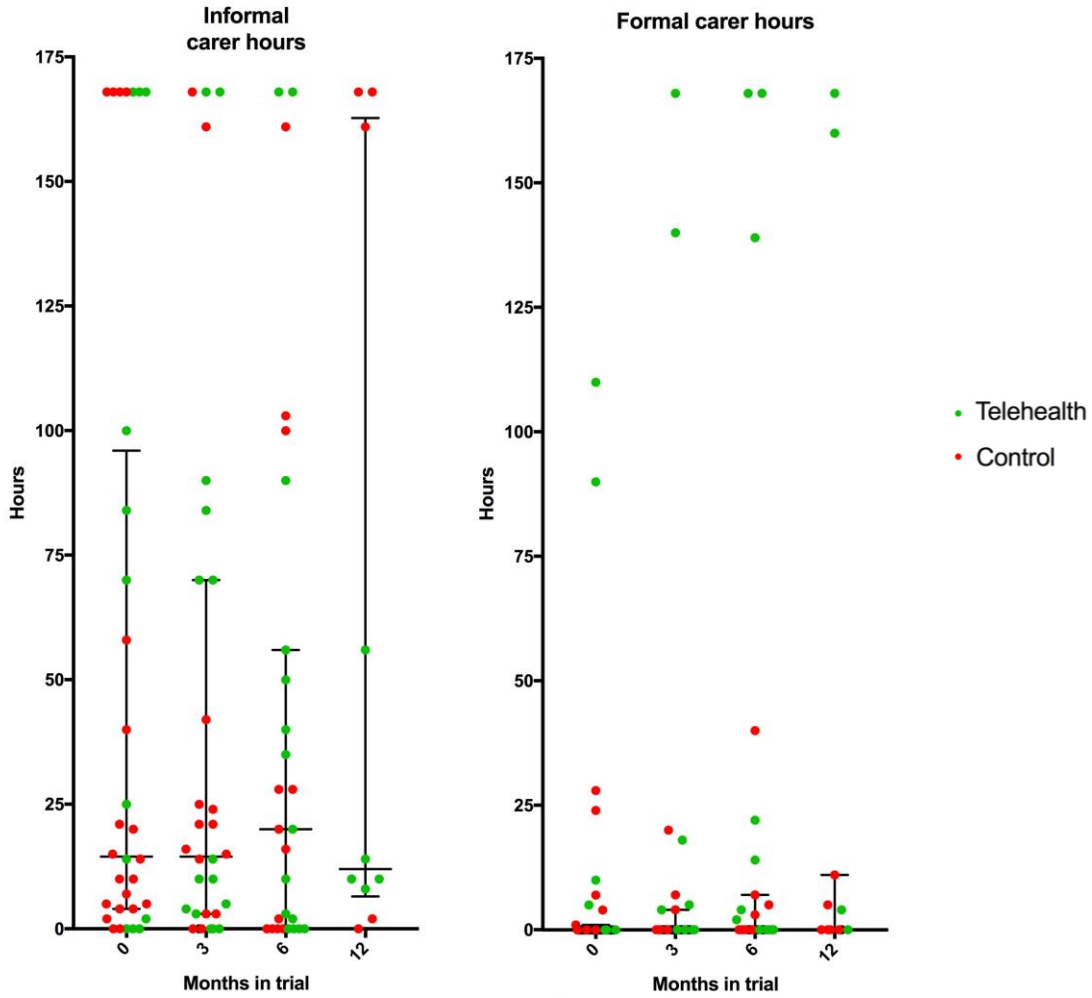


Table 16 Patient estimated hours of paid and unpaid care received per week.

	Baseline	3 month	6 months	12 months
Telehealth				
Paid carer hours	n=17	n=16	n=15	n=5
Mean (SD)	12.7 (33.2)	20.9 (52.4)	34.7 (64.6)	66.6 (89.0)
Median (Range)	0 (0-110)	0 (0-168)	0 (0-168)	5 (0-168)
Unpaid carer hours	n=12	n=16	n=15	n=5
Mean (SD)	66.6 (70.2)	43.5 (58.6)	42.8 (57.4)	19.6 (20.5)
Median (Range)	47.5 (0-168)	10 (0-168)	20 (0-168)	10 (0-168)
Control				
Paid carer hours	n=18	n=13	n=12	n=6
Mean (SD)	3.6 (8.4)	2.4 (5.7)	4.3 (11.4)	2.5 (4.5)
Median (Range)	0 (0-28)	0 (0-20)	0 (0-40)	0 (0-11)
Unpaid carer hours	n=20	n=14	n=12	n=5
Mean (SD)	33.4 (64.9)	36.6 (55.4)	38.2 (53.3)	99.8 (90.2)
Median (Range)	12.0 (0-168)	18.5 (0-168)	18 (0-161)	161 (0-168)
Total				
Paid carer hours	n=35	n=29	n=27	n=11
Mean (SD)	8.0 (24.0)	12.6 (39.7)	21.2 (50.4)	31.6 (65.6)
Median (Range)	0 (0-110)	0 (0-168)	0 (0-168)	0 (0-168)
Unpaid carer hours	n=32	n=30	n=27	n=10
Mean (SD)	52.7 (66.7)	40.3 (56.3)	40.7 (54.6)	59.7 (74.8)
Median (Range)	14.5 (0-168)	14.5 (0-168)	20 (0-168)	12 (0-168)

Table 17 The adverse events recorded during the trial.

	Telehealth		Control		Total	
	Number of events	Number of patients/carers (%)	Number of events	Number of patients/ carers (%)	Number of events	Number of patients /carers (%)
MND related						
Chest infection/ respiratory symptoms	7	7 (35%)	4	4 (20%)	11	11 (55%)
Falls	8	7 (35%)	3	3 (15%)	11	10 (50%)
Musculoskeletal symptoms	3	3 (15%)	0	0 (0%)	3	3 (15%)
Excessive saliva / choking	2	1 (5%)	0	0 (0%)	2	1 (5%)
Elective PEG insertion	2	2 (10%)	1	1 (5%)	3	3 (15%)
PEG site problem	0	0 (0%)	1	1 (5%)	1	1 (5%)
Patient psychological distress	0	0 (0%)	1	1 (5%)	1	1 (3%)
Carer psychological distress	11	5 (29%)	6	5 (26%)	17	10 (27%)
Other adverse events						
Other medical	7	3 (15%)	5	5 (25%)	12	8 (40%)
Other surgical	0	0 (0%)	2	1 (5%)	2	1 (5%)

Table 18 Summary of health encounters for the three months prior to baseline

	Total in 3 months[3]	Total physicians[4]	Total nurses[5]	Total therapists[6]
Telehealth				
Total (n=18)	133	38	43	52
Mean (SD)	7.4 (6.3)	2.1 (2.3)	2.4 (2.6)	2.9 (3.1)
Median	5.5	1	1.5	2
Range	0-28	0-8	0-10	0-11
Control				
Total (n=20)	211	45	72	88
Mean (SD)	10.6 (8.5)	2.3 (2.1)	3.6 (5.1)	4.4 (4.3)
Median	8	2	1	4
Range	1-30	0-10	0-19	0-13
Total				
Total (n=38)	344	83	115	140
Mean (SD)	9.1 (7.7)	2.2 (2.2)	3.0 (4.1)	3.7 (3.8)
Median	7	2	1	2.5
Range	0-30	0-10	0-19	0-13

[3] Total excluded ambulance journey and unrelated/non-NHS services
[4] Physicians included were MND neurologists, palliative care physicians and general practitioners.
[5] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[6] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 19 Summary of patient reported MND related health-care encounters between months 0-3 of the study.

	Total[7]	Total physicians[8]	Total nurses[9]	Total therapists[10]
Telehealth				
Total (n=16)	152	40	51	61
Mean (SD)	9.5 (9.1)	2.5 (2.3)	3.2 (3.6)	3.8 (4.7)
Median	8	2	2	3
Range	2-35	0-8	0-13	0-18
Control				
Total (n=15)	160	38	55	59
Mean (SD)	10.7 (17.6)	2.5 (4.2)	3.7 (9.6)	3.9 (3.7)
Median	8	1	1	3
Range	0-73	0-17	0-38	0-11
Total				
Total (n=31)	312	78	106	120
Mean (SD)	10.1 (13.6)	2.5 (3.3)	3.4 (7.0)	3.9 (4.2)
Median	6	2	1	3
Range	0-73	0-17	0-38	0-18

[7] Total excluded ambulance journey and unrelated/non-NHS services
[8] Physicians included MND neurologists, palliative care physicians and general practitioners.
[9] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[10] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 20 Summary of patient reported MND related health-care encounters between months 3-6 of the study.

	Total[11]	Total physicians[12]	Total nurses[13]	Total therapists[14]
Telehealth				
Total (n=16)	241	45	143	53
Mean (SD)	15.1 (29.3)	2.8 (3.0)	8.9 (28.3)	3.3 (4.9)
Median	8	2	1	1.5
Range	0-121	0-12	0-115	0-17
Control				
Total (n=12)	83	16	41	26
Mean (SD)	5.2 (1.5)	1.3 (0.9)	3.4 (4.0)	2.2 (1.6)
Median	4	1	2	2.5
Range	2-17	0-3	0-12	0-4
Total				
Total (n=28)	310	61	184	79
Mean (SD)	11.3 (22.2)	2.1 (2.4)	6.8	2.8 (3.9)
Median	4	2	1	2
Range	0-121	0-12	0-115	0-79

[11] Total excluded ambulance journey and unrelated/non-NHS services
[12] Physicians included MND neurologists, palliative care physicians and general practitioners.
[13] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[14] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 21 Summary of patient reported MND related health-care encounters for the six months between months 6-12 of the study.

	Total in 6 months[15]	Total physicians[16]	Total nurses[17]	Total therapists[18]
Telehealth				
Total (n=6)	101	18	52	30
Mean (SD)	16.8 (17.2)	3.0 (1.4)	8.8 (13)	5.0 (3.9)
Median	9.5	3	3	4
Range	3-49	1-5	1-35	1-10
Control				
Total (n=7)	98	26	32	40
Mean (SD)	14.0 (10.7)	3.7 (1.8)	4.6 (8.0)	5.7 (6.3)
Median	8	4	1	5
Range	5-32	1-6	0-22	1-19
Total				
Total (n=13)	199	44	87	70
Mean (SD)	15.3 (13.5)	3.4 (1.6)	6.5 (10.5)	5.4 (5.1)
Median	8	4	2	5
Range	3-49	1-6	0-35	1-19

[15] Total excluded ambulance journey and unrelated/non-NHS services
[16] Physicians included MND neurologists, palliative care physicians and general practitioners.
[17] Nurses included district nurses, MND specialist nurses in hospital and community and hospice nurses.
[18] Therapists included speech and language therapists, physiotherapists, occupational therapists, respiratory specialists, dieticians and PEG nurses.

Table 22 The number of admissions (and number of patients) and days in hospital reported by patients in the three months prior to recruitment.

	Telehealth (n=18)		Control (n=20)		Total (n=38)	
	Number of admissions (number of patients)	Nights in hospital	Number of admissions (number of patients)	Nights in hospital	Number of admissions (number of patients)	Nights in hospital
Elective						
PEG insertion	0	0	4 (3)	15	4 (3)	15
Diagnosis	1 (1)	1	0	0	1 (1)	1
Total elective	1 (1)	1	4 (3)	15	5 (5)	16
Emergency						
Fall	0	0	1 (1)	9	1 (1)	9
Choking	3 (1)	16	0	0	3 (1)	16
Gastrostomy site infection	0	0	1 (1)	2	1 (1)	2
Total emergency	3 (1)	16	2 (2)	11	5 (3)	27
Unrelated to MND						
Total unrelated admissions	0	0	0	0	0	0

Table 23 The total number and reason for hospital admissions reported by all participants during the first 12 months of the study and the number of overnights stayed in hospital.

	Telehealth		Control		Total	
	Admissions (patients)	**Nights**	**Admissions (patients)**	**Nights**	**Admissions (patients)**	**Nights**
Elective						
PEG insertion	2 (2)	21	1 (1)	6	3 (3)	27
Symptom control	2 (2)	14*	0	0	2 (2)	14*
Total elective	4 (4)	72*	1 (1)	6	5 (5)	41*
Emergency						
Respiratory symptoms	1 (1)	6	2 (2)	15	3 (3)	21
Collapse, poor oral intake	1 (1)	2	0	0	1 (1)	2
Total emergency	2 (2)	8	2 (2)	15	4 (4)	23
Unrelated to MND						
Elective: hip replacement	2 (1)	6	0	0	2 (1)	6
Emergency: lung cancer	0	0	4 (1)	50	4 (1)	50
Emergency: postural hypotension	0	0	1 (1)	3	1 (1)	3
Total unrelated	2 (1)	6	5 (2)	53	7 (3)	59

*It was not possible to establish the number of nights from one patients' admission so these nights are not included.

Table 24 Participants' motivations to participation in research.

Incentives to participating in trials	
Low burden of the intervention	*" Oh I was interested in that because it's so easy to do; it literally takes five minutes from home." Patient 317*
Able to participate in trials without leaving home	*"My care's here. I can't have anything that takes it away from what I'm doing with P. It's got to be very simple things. I can sit with my iPad and I can fill in a questionnaire. Done, dusted, finished." Carer 184*
Clear information about what is involved	*"If it was local and we were going anywhere or people were coming here and; I could always look at each one individually but I think I wouldn't want to spend a lot of time away from home. So that would be my main criteria. Patient 408*
Motivations to participating in research	
To help find a cure	*"If I can be of any help to any research, you know, which'll help try and find a cure." Patient 056*
To help other people with MND	*"It might come along too later to help me but it will help people who come after me." Patient 122* *"Just trying to help other people; if me pressing a few buttons …can help in the future, it's not a problem" Patient 354*
In gratitude to the clinicians	*"I think that the people at the Hallamshire are just about the best in the, in the, in the game" Patient 062*
To do something positive	*"… it's that feeling of doing something positive." Carer 402* *"I like that idea that moving forward" Patient 423*
To learn about research	*"I've always been interested in medical science…so I said any research that they're doing I want to get involved in." Patient 423*
To help their family, who may be at risk	*"Carer: I gave blood as well.. because …we've got the boys … I think that's quite a big thing for me" Carer 381*
To have better contact with MND team	*"It was good because, it meant, in the first year I was going to the clinic every month." Patient 122*
To receive better treatment	*"I'm offering my services … but in return … I'm getting a repeating MOT." Patient 313*
To find out more about their condition	*"That led to the, the obvious question "Well if you find anything wrong will you tell me?"." Patient 313*
To increase the chances of them being involved in a treatment trial	*"I do believe that if you're not in the loop then if something comes along then you're on the wrong side of the fence. If you're involved with different … then you're more likely to be selected for possible hopeful cures…" Patient 232*

Table 25 Participants' attitudes towards recruitment and randomisation in the TiM trial.

Recruitment and randomisation to the TiM trial	
Recruitment process provided sufficient information	*"I think it were all pretty much straight forward, in the letter that you sent out, plus when you came, I think it were all pretty straight forward, yeah." Patient 145*
Patients were willing to be randomised as they understood the research question	*"Q: Was there a particular arm of the study that you wanted..?* *Patient : No, because it's a subject that not very much seems to be known about, so if I can help in any area of it, I will." Patient 166*
Patients would prefer to be in the intervention arm	*"Q: And how did you feel about being assigned to the Telehealth side?* *Patient : Well I've preferred that side of it." Patient 381*
Patients were not demoralized if they were assigned the control arm	*"I should think most people would probably want to have tablet. I think, they'd think "this is alright." But quite frankly it doesn't bother me." Patient 070*
Involving the control arm in interviews avoided resentful demoralization	*"I read the notes. Some would get the interview, some would get the tablet" Carer 070*
Researchers could influence the randomisation process	*"Patient : We thought: they'll put [my sister] on the real drug because they can monitor her for longer.* *Q: Do you think that the study researchers can have an influence on which arm of the study you go in?* *Patient : Probably not, no. Probably it's the drug company who are pulling the strings. They are paying the money aren't they?" Patient 184*

Table 26 Participants' attitudes towards and knowledge of research.

Participants' attitudes towards and knowledge of research	
Patients gain information about research and new treatments through…	
Clinic	*" I like having a chat with you and finding out what's happened, what's new, because all we have is hope, we don't have a lot more"." Patient 134*
Friends and fellow patients	*"It's really just through word of mouth. " Patient 122*
MND Association	*"The MNDA puts posts on about research" Patient 145*
Internet	*"I mean we have found, for instance, a website; you can actually see it on YouTube, called Deanna Protocol" Patient 317*
Social media/ peer networks	*"There's also a long term ALS survivors' website where people, have been diagnosed with it… and been told that you've only got a year left to live, but they've done radical changes, ….and those people have halted it" Patient 317*
Patient seek out, evaluate and use unproven treatments	*"I don't follow regimes as strict as the Deanna protocol but I just pick out certain things that I think would help me, hence the reference to moringa and coconut oil." Patient 232*
Frustration with the speed of drug development	*"I just feel like, after 30 years with millions … of pounds spent we've still got a tablet that [has little evidence]" Patient 184* *"We need to be getting a move on… Some day, we've got to stop messing around with mice." Patient 184* *"I don't hold out too much confidence about the UK system of getting drugs to market and funding them with the likes of NICE posing usual financial constraints." Patient 232*
Time is running out for a cure	*"Once you get to what I always call "frank" stage …I don't think there's any drug that would bring you out of that." Patient 184*
Patients have little to lose	*"We being the patients with MND, have nothing to lose… There's always risk in life." Patient 232*
Learning about research makes patients hopeful	*"[you think] There's got to be things that we can do, come on, we're gonna really give this a hundred percent; and the more we looked the more intrigued we became…. you can see people that have had really good benefits from it." Patient 317* *"We're all kind of pinning our hopes …on GM604" Patient 232*
Patients recognize information may be giving false hope	*"Too much information could fill people with a false hope and you've gotta manage people's expectations" Patient 122*
Putting trust in the doctors to run safe trials in the best interests of the patient	*"Q: Did you consider the downsides, the risks of having a lumbar puncture when you came?* *Patient: No. I just thought, well if that's all I've got to put up with. But if a doctor can't do a lumbar it's a bad job." Patient 184* *"I would have complete faith in [consultants] team saying "Right, lets get some people in now and let's do it" Patient 184*
Wanting to see tangible benefits of treatments which reverse the disease	*"No one will ever convince me that they know [riluzole] works. …How do they know I've had three months more life?…Who would know? .. I can't walk any better, I can't speak any better, I can't do anything any better." Patient 184* *"…it doesn't have to cure you it just has to make things better." Carer 232* *"If there was a magic bullet and I had to sell everything to purchase that bullet, I would." Patient 232*

Table 27 Barriers to participation in research.

Barriers to participation in research	
Additional burden	*" Well, just another job…. To remember" Carer 217*
Research is time consuming	*"Initially it is a bit overwhelming … we do seem to have signed-up for absolutely everything…" Carer 402* *"It's difficult, … sometimes you get to the stage where you think: you know what? I just don't feel like this, I've just had enough" Carer 402*
Intrusion or disruption of family life	*"Carer: I just don't think; … we, we just try to keep ourself and look after him, look after him and that's it.* *Q: …Have any of those worries been the case during the study?* *Carer: No." Carer 228* *"I don't want the family life to be disrupted, that's really important to us." Patient 408*
Time spent away from home	*"I'd need to know about the, the time that would be needed to be spent, if I needed to spend time away from here, from home" Patient 408*
Research can be tiring	*"On Thursday I went for my research, had the lumbar puncture, the tissue sample, blood samples I think. So then I came home. For two days after that I was more or less housebound." Patient 184*
Travel to hospital is expensive	*"…the train tickets are a bit expensive, so we've driven the last few times. But … we got the free parking and things like that…" Carer 392*
Travel difficult	*"It's gonna be a lot more difficult with a wheelchair" Carer 392*

Table 28 Participant reaction to the TiM research questionnaires.

Were questions acceptable?	
Questions posed in the questionnaire were acceptable	*"No. To be quite frank, doctor, I wouldn't care a monkey's what you ask …I have no hang-ups about any questions, however personal, the team think it's necessary to ask; I've seen it all, done it all and got the t-shirt." Carer 229* *"Patient : I was fine about doing them." Patient 116*
There was a limit to the number of questions participants were willing to answer	*"Patient : You don't want another one of them hundred and fifty page things to fill out, that were, whatever it was last year." Carer 248*
Questions on emotions were acceptable to those experiencing emotional distress	*"It's more the emotional ones that I have trouble filling in cos I've been depressed for quite a …and it's, it's just hard admitting that yes, maybe some days it's not great and I know that I'm not great at the moment but. But no, they seemed good. They were really clear, and it wasn't too, too much to do." Patient 408*
Participants wanted questions to cover all potential aspects of MND	*"At the moment I've not got a lot of problems with my legs, but in 18 months I might need a wheelchair, or I might be having to use a breathing machine. So every question is relevant." Patient 070*
Questions about future complications were acceptable because patients were aware of what may occur	*"When you read things about these questions: it brings things home to you. Well yeah, I have deteriorated…. It doesn't really significantly affect me at all because, I like to think I'm a reasonably intelligent man and I know things are deteriorating." Patient 184*
Which questions best reflected the experiences of patients and carers?	
Questions about mood/emotions best reflected their experiences	*"I think the best ones are the ones about how it makes you feel and how it affects your mood etc. That's very important …." Patient 122*
The carer burden accurately captured the experience of carers	*"It was a strange one cos [the ZBI] was asking you what I feel about spending the time with him, that I don't have time for meself…. Yeah, it is quite a thing cos you're always thinking… "Has he got enough drinks? … then anything to eat?"… I don't like to be too far away from him, even though I'm in the house … in case summat happened and he needs me." Carer 091*
Carer strain is linked to patient and carer wellbeing	*"…obviously if strains exist, become too much for the carer, then the patient, to a degree, suffers.." Carer 229*
Mood/emotions affected patients health and functional abilities	*"Feelings of anxiousness can affect my legs, and I know that. I try not to control, try not to get anxious about situations but sometimes it's hard when you know, your are going to move from A to B, you're going to get anxious about it." Patient 076*

Table 29 Weaknesses with the questionnaires identified.

SF-36 questionnaires failed to reflect the experience of life with MND	
SF-36 questions were too subjective	*"That's sort of looking at question [SF-36], and putting down, you're limited and then you sort of realise; I can't really do that; and you don't think about it all the time do you? Some of them I wanted to put "sometimes", you know… sometimes I have but I've just gone for on the whole" Patient 408*
Patients found it difficult to assess their global health and were unsure whether to include MND in the assessment	*"Patient : It's slightly confusing when they ask about health because it's hard to take the MND out of the equation, I think. Apart from that I would be very healthy." Patient 116* *"Patient : My health other than the illness? (Pause) Taking the illness into account I would say poor, but if I ignore the, the illness I would say very good." Patient 137 [referring to SF-36]*
Patients felt "healthy" despite having MND	*" To be honest, I feel great. So does that say I'm excellent. But you know that you're not, so you can't be excellent." Patient 175 [referring to SF-36]*
Carers felt they had no health problems and felt the QoL questions were not relevant	*"I mean this: [reads] "I feel as if I'm slowed down"; it's not because of caring for you but because I'm getting older… I can't do a forward roll over a gatepost anymore!" Carer 137 [referring to SF-36]*
Those with severe disability had few "daily activities" on which to assess the impact of MND	*"Patient : It doesn't affect my work because I don't do any! Q: It's housework as well. Patient : No. I don't do any! I do a little bit." Patient 070 [referring to SF-36]*
Other weaknesses	
Participants found it difficult to quantify the time taken by domestic jobs that are usually shared	*" But there are things now… I'll say "its time for a cup of tea". It will always be me that makes it. I'm not saying I resent it, because P can't do it… But I don't class that as care… Carer 175 [referring to informal care question]*
Questions should better reflect patients' functional abilities and coping strategies	*"It's about monitoring really, and with these questionnaires you are not able to say how you manage. If we know we are going out for a full day, then P knows not to plan anything for the next day because he's gonna be tired." Carer 076*
Answering questions may be difficult if they not want to admit they have problems	*"….It's like C was saying, you've just got to be honest and sometimes that's really hard cos you don't want to admit that maybe you're not as good as you were". Patient 408*

Table 30 The calculated total sample sizes for the two approaches to calculating the endpoint at different effect sizes.

These were calculated by the trial statistician and based on the parameters stated above.

	Single time point		Longitudinal[19]	
	Unadjusted	**+30% drop-out**	**Unadjusted**	**+30% drop-out**
Effect size				
0.2 SD	n=1052	n=1503	n=396	n=566
0.3 SD	n= 468	n= 669	n=176	n=251
0.4 SD	n= 264	n= 377	n=100	n=143
0.5 SD	n= 170	n= 243	n=64	n=91

[19] Assuming one baseline and four follow-ups with a common correlation of 0.5.

Telehealth in motor neurone disease to increase access to specialist multidisciplinary care: a pilot, feasibility study.

Hobson EV., Bradburn M., Baird WO, Cooper CL, Mawson S, Quinn A, Shaw PJ, Walsh T, McDermott CJ

Supplementary data files

Telehealth in Motor Neurone Disease

Telehealth in Motor Neurone Disease: A single centre, randomised controlled feasibility and pilot study of the use of the TiM telehealth system to deliver highly specialised care in Motor Neurone Disease at a distance

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

CLAHRC for South Yorkshire

General Information

Sponsor identifier: 17165
National Institute for Health Research Portfolio ID: 17022
Trial Identifier: ISRCTN26675465

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This study is a non-commercial, portfolio study supported by the DeNDRoN (Dementia and Neurodegenerative Diseases Clinical Research Network). It is funded through a National Institute for Health Research Doctoral Research Fellowship grant.

Abbreviations

AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire – long form
ALS-FRS-R	Amyotrophic lateral sclerosis rating scale-revised
BiPAP	Bi-level positive pressure non-invasive ventilation
CBI	Carer burden inventory
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated standards of reporting trials
CRF	Clinical Research Facility, Sheffield Teaching Hospitals
CSS-MND	Clinical Saliva Scale for Motor Neurone disease
CTRU	Clinical trials research unit, University of Sheffield
EQ-5D-3L	EuroQol Group Health Questionnaire,
GCP	Good clinical practice
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
MCSI	Modified Caregiver Strain Index
MDT	Multidisciplinary team
MND	Motor neurone disease
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NIHR	National Institute for Heath Research
NIV	Non-invasive ventilation
PHQ	Patient Health Questionnaire
PI	Principal Investigator
SAE	Serious adverse event
ScHARR	School of Health and Related Research, University of Sheffield
SF-36 RAND	36-Item Short Form Survey from the RAND Medical Outcomes Study
SITraN	Sheffield Institute of Translational Neuroscience
STH	Sheffield Teaching Hospitals
SU	Sheffield University
Telecare	A system of sensors, alarms or communication in the home used to support safe living
Telehealth	Remote monitoring of patients physiology or patient reported measures, forwarded to a central service with the aim to diagnoses or monitor a medical condition
Telemedicine	Videoconferencing consultation
TMG	Trial management Group
TSC	Trial Steering Committee
TiM	Telehealth in Motor neurone disease
TM	Trial manager

Contents

This document describes a clinical study. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to investigators in the study.

1. Telehealth in Motor Neurone Disease: The TiM ™ Study

Telehealth in Motor Neurone Disease: A single centre, randomised controlled pilot study of the use of the TiM ™ telehealth system to deliver highly specialised care in Motor Neurone Disease at a distance.

Abstract

Objectives

People with motor neurone disease benefit from the specialist care provided by multidisciplinary teams. As their disease progresses patients struggle to attend hospital and find it difficult to access the care they need. The aim of the TiM system is to improve access to this specialist care by using technology to monitor, educate and communicate with our patients and their carers.

This is a pilot study of the TiM ™ telehealth system. The pilot study is designed to assess the feasibility, acceptability and safety of the telehealth system in clinical practice and of conducting a full study of the system. It will also allow a process evaluation of the system to determine how the telehealth system could be effectively utilised within an NHS service.

Methods

This is a single-centre, randomized controlled mixed methods pilot study of the TiM ™ telehealth system. It will recruit 40 patients along with their primary informal carer. 20 will be assigned to use the TiM system for a minimum of 6 months (intervention) and 20 will be assigned usual care (control). Quantitative outcome data will be collected at baseline, three and six months, six monthly thereafter and at the end of the trial. Qualitative interviews with participants and staff and analysis of the system in use will enable a process evaluation of the system and the trial methodology. It will also assess the safety of the system in a clinical setting.

Results

Results of this pilot will determine whether a large, multi-centre full trial is appropriate and enable further development of the TiM system. It is proposed that the TiM system could be adopted into the care of patients with MND throughout the UK.

2. Lay summary

Motor neurone disease is a condition affecting approximately 5 000 people in the UK. It results in progressive weakness in muscles causing paralysis, disability, and eventually death after an average of only three to five years. To receive the expert care provided by motor neurone disease multidisciplinary teams most patients have to travel to regional centres, whilst community-based care is usually provided by non-specialist teams. Between clinic appointments and towards the end of their lives when patients are unable to travel to clinic and they may be unable to access the specialist assessment and care provided in these centres.

Telehealth has been shown to increase access to specialist care in patients with chronic disease, regardless of geography or the ability to travel. The overall purpose of this pilot study is to test the feasibility and acceptability of the TiM telehealth system. The TiM system is web-based system that enables weekly monitoring of patients and carers' health and wellbeing. It has been developed by the Sheffield Motor Neurone Disease Care Centre team in partnership with industry (Abbott Healthcare Products Ltd and Carematix) and other experts within the NHS and the University of Sheffield. The study will also determine whether it would be feasible to conduct a larger study of the system to examine the effectiveness of the TiM system.

Patients with motor neurone disease who are cared for by the Sheffield motor neurone disease clinic will be invited to take part in the trial. 40 patients will be recruited. Their primary informal carer (usually their spouse or close relative) will also be invited to participate in carer monitoring. All patients will continue their usual care but half will also be randomised to use the TiM telehealth system for a minimum of six months.

Information about the participants will be collected at the start, three and six months, and then every six months until the end of the trial by postal questionnaires and during routine appointments. Up to 20 participants in the control group will be interviewed at the start at the trial to explore their experiences on completing the postal questionnaires. Up to 20 participants who are using the TiM system will be interviewed at one and six months to understand the effect the trial and the system has on their lives in more depth. The clinical staff will also be interviewed at the end of the trial.

A pilot study is a small-scale study that is carried out to determine whether a larger study is practical. It will also enable the identification and resolution of any problems with either the telehealth system or the trial procedures.

3. Background

There are approximately 5 000 people in the UK suffering from motor neurone disease (MND) at any one time (1). MND is an incurable disease causing progressive weakness of muscles involving the limbs, speech and swallowing leading to progressive disability and eventual respiratory failure. The average life expectancy following diagnosis is two to three years but the course of MND can vary from only a few months to over 10 years. The distress and burden of the disease affects patients, their family and carers and the relenting progression of disability causes social, emotional and financial strain (2, 3).

There are 22 specialist multidisciplinary MND care centres in the UK. Expert clinicians and therapists offer interventions such as riluzole (which can improve survival by approximately two to three months) and gastrostomy feeding to promote good nutrition (4). Treatment of respiratory failure with non-invasive ventilation (NIV) improves both quality of life and life-expectancy by, on average, 11 months (5). Attendance at specialist MND clinics has also been reported to improve survival independent of these other interventions (6, 7).

The traditional model of care is to review patients at the MND centre at fixed regular intervals. This model is not responsive to patient or carer needs (which can change rapidly) and requires the patient and their family to undertake progressively more difficult journeys to clinic at a time predicted by the clinician at their last meeting. Given the burden associated with travelling to clinic, it is important that visits occur when they are most needed. Some patients whose needs have not changed may not benefit from a clinic appointment at the previously predicted interval whereas others may need more timely intervention.

The highly specialist services provided by the MND clinic are contrasted by the services most patients receive in their community (8). These community teams, who have limited experience in caring for patients with MND, are usually the first point of contact for patients between clinic visits. Lack of expertise in MND amongst community teams and limited access to specialist staff and equipment (particularly at the end stages of the disease) causes patients and their carers to experience significant difficulties (2, 3, 9-12). Research conducted in SITraN and by others, highlights the major impact that caring for someone with MND has on the physical and emotional well being of carers, as well as patients (3, 11, 13-16). Where access to specialist services and community support is limited, this impact is even more notable (3, 11, 13-16). This is particularly a problem in the later stages, when it is usually impossible to attend clinic, when arguably the most care is needed. It is therefore essential that the input from the specialist centre is still possible both between visits and when patients become unable to travel.

Telehealth to provide specialist care in MND

In the last few years, technology has developed sufficiently to allow high quality communication between patient and their care team at a potentially reasonable cost.

Trials have shown that telehealth is an acceptable way to improve access to specialist expertise and facilitate self-management patients with long-term health conditions (17-21). In some cases this approach has been associated with a reduction in hospital admissions (17, 18, 20). In 2012, in response to research evidence and the need to provide cost-effective care to an expanding population of patients with chronic disease, the UK government created the "3millionlives" campaign (22). This project in aims foster NHS, academic and industry collaboration in order to provide telehealth services to up to three million people with chronic health and social care needs in the UK.

The problems faced in MND are unlike many common chronic diseases in which telehealth has been previously trialed. Care for MND requires holistic and multi-disciplinary expertise and the use of uncommon interventions such as non-invasive ventilation and gastrostomy feeding. To date, use of telehealth in MND is limited, although small studies do show promise in certain niche areas. Telehealth systems using telephone consultation have been developed with some success in Italy and Portugal, to remotely manage patients who require home ventilation. These systems were associated with a reduction in emergency healthcare usage; more efficient use of staff time and potential cost savings (23-28) In Holland and rural Scotland, MND services have used video-conferencing (29, 30). Both approaches have potential benefits but telehealth used in this way is labour intensive and costly and care is driven by the priorities identified by the clinician rather than those of the patient. No telehealth system has been developed to provide frequent, holistic and highly specialist care to patients with MND at all stages of their illness.

We propose that telehealth could enable people with MND to have better access to the specialist monitoring and care that they require. Patients with MND are able to accurately report their level of disability and appropriate questions can identify new symptoms or early signs of respiratory failure (31-33). These features would suggest that a system of remote, question-based monitoring could provide regular, accurate clinical information to enable the clinician to detect and better manage problems without the patient needing to attend hospital. Telehealth provides the opportunity to provide education and reassurance and support to enable patients to better manage their own care (a core requirement of the National Service Framework for Long-term Conditions (34)).

There are estimated to be 10 million people in the UK living with a neurological condition (1). Both the common diseases such as Parkinson's disease and epilepsy and rarer conditions such as muscular dystrophy and MND require specialist, multidisciplinary support from specialist services. A successful telehealth system may therefore be able to improve the services provided to many patients in the UK and their families.

4. Summary and hypothesis

Summary

We will undertake a pilot study of the use of the TiM telehealth system to improve the care of patients and their carers living with motor neurone disease. Whilst telehealth services have been used successfully in other long-term conditions, no service of this kind exists for patients with motor neurone disease. A pilot randomised controlled trial will employ a mixed methods approach to explore the feasibility and acceptability of using the TiM system to improve access to specialist care in MND. The pilot study will also explore the feasibility of a full-scale trial.

Hypothesis

The TiM telehealth system will:

- Improve the quality of life of patients with MND
- Improved clinical outcomes for patients with MND
- Improve quality of life and other measures of well being for the primary informal carers of patients living with MND.
- Be acceptable to patients, carers and staff
- Lead to more cost effective utilisation of heath care resources

5 Research objectives

5a. Objectives of the pilot study

- Determine the requirements of a full-scale study of the TiM system
  - Determine recruitment, retention and withdrawal rates.
  - Determine the most acceptable and appropriate outcome measure(s) that reflect the impact of the TiM system on patients and carers and health resources.
  - Provide an estimate of the resources required to conduct a full-scale study.
- Study the use of the TiM system in clinical practice
  - Assess the relationship between the benefits of the TiM system perceived by staff and participants with those captured by the outcome measures
  - Assessing participants' use and compliance with the TiM system
  - Health-care staff qualitative interviews and focus group
- Assess the safety of the TiM system using:
  - A shadow monitoring protocol
  - Health-care staff qualitative interviews and focus group
  - Analysis of technical and clinical adverse events

5b. Objectives of the full-scale study

Proposed primary end-point

- Patient quality of life (outcome measure(s) to be determined in the pilot trial)

Proposed secondary end-points

Patient outcomes

- Severity of pain
- Severity of oropharygeal secretions
- Incidence of depression and anxiety
- Time from diagnosis to death

Carer outcomes

- Quality of life
- Carer Burden
- Incidence of depression and anxiety

Health economic outcomes involving a cost utility analysis using costs of the system, costs of associated care requirements, EQ5D and patient survival

Safety of the TiM system

- Frequency of adverse events

5c. Justification of the pilot study

Since this type of telehealth has never been evaluated in those with MND a pilot study is necessary to determine how a full-scale evaluation of its clinical and cost-effectiveness could be conducted and to gain a better understanding of how the TiM system would work. This includes evaluating recruitment and retention, as well and resource requirements. By evaluating compliance and safety monitoring and using qualitative the study will also enable a better understanding of how the telehealth system is used by patients, carers and staff.

A number of the proposed benefits of telehealth such as improving quality of life, providing reassurance and support, prompting self-care and a more efficient use of resources (18, 35-40) may be difficult to quantify. The validated measures of quality of life most commonly used in research (EQ5D and SF-36) were not specifically designed for patients with MND or their carers. The ALSAQ-40 tool better encompasses dimensions of life that are particularly affected by MND such as social and emotional function but it is unclear whether the ALSAQ-40 would fully reflect the impact of telehealth (41).

Data from quantitative elements of a randomised controlled trial will not, in isolation determine which outcome measures best reflect the impact of the intervention. It would also not fully explain how the TiM system would be used in the real world and what factors would influence its adoption and success. Utilising mixed methods will allow the combination of quantitative data with more in-depth results from qualitative interviews that will explore participants' experiences in more depth. It will also allow explanation of outcomes that occurred (particularly those that were unexpected) and understand why (and in what context) aspects of the system were successful or unsuccessful which could lead to improvements in the TiM system.

6. Study Methodology

We will conduct a randomised controlled pilot trial comparing the TiM telehealth service and standard care with standard care alone. The intervention and follow-up period will be a minimum of 6 months. Quantitative data will be collected at 0, 3 and 6 months then every six months until the patient finishes the trial. Qualitative data will be collected at baseline in the control arm and at 1 and 6 months for a selection of patients in the intervention arm.

6a. Participant recruitment and selection

Pre-screening will identify a list of potential patients who cared for by the Sheffield Teaching Hospitals MND care centre clinic as part of usual care using the MND care centre "ARC" clinical database. Each patient will be assigned a number. The Clinical Research Facility at the Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS trust will generate random numbers to identify the patients to invite. These patients will be sent a letter of invitation to participate. This will be accompanied by patient and carer information leaflets and a return slip to indicate their interest. Those who do not return the slip will be followed up by telephone or at clinic, if appropriate a minimum of once and a maximum of twice. A log will be kept in order to complete the CONSORT diagram (Appendix 2) (42).

Patients and their primary carer who express an interest will be invited to discuss the trial in a face-to-face meeting with the PI and also via telephone with their consultant neurologist (Dr. Christopher McDermott or Professor Dame Pamela Shaw, Sheffield Teaching Hospitals MND Care Centre). The Sheffield MND Care Centre sees approximately 120 new patients with MND per year. At any time there are approximately 300 patients attending clinic. We expect to be able to recruit a minimum of four patients per month.

Participants in the intervention arm will be invited to participate in qualitative interviews, conducted at month one and month six. Purposive sampling will be used to reflect the variation and predefined patient prognostic factors thereby capturing a range of experiences. Interviews will continue until data saturation is reached or 20 interviews have been conducted. All participants assigned to the control arm will be invited to be interviewed after completion of the baseline questionnaires to determine the feasibility and acceptability of these measures and their views on participating in the trial. The qualitative component will provide information not easily obtained from questionnaires that will facilitate understanding of the intervention from the perspective of all stakeholder groups.

6b. Consent

Following indication of their interest to participant potential participants will be met at a mutually agreeable location, preferably the patients' home. They will have further opportunity to discuss the trial with the PI and decide whether they wish to participate. Willing participants will be asked to give informed written consent or use an appropriate witnessed alternative (which may include verbal consent or via a communication device) for screening and involvement in the trial. Carer consent will be obtained by full written consent.

In versions prior to V1.5 of the protocol both patient and carer consent were required. V1.5. has amended the inclusion criteria to allow a patient to participate with carer participation.

If one or both consent to the study a member of the study team will initiate the screening process. Participants will be screened and recruited by the PI according to the CONSORT principles and Good Clinical Practice (42, 43).

Those who decline participation will be invited to give their reasons in order to identify common factors; this may help recruitment strategies and identify potential problems for compliance. Basic anonymised details of these patients (age, gender, reason for exclusion) will be collected on all eligible patients in order to fulfill the CONSORT flow chart (Appendix 2) (42, 43).

6c. Randomisation

Once recruited, randomisation will be performed using the independent web-based system http://www.sealedenvelope.com using block randomisation. All patients and carers will be assigned an anonymous individual study code, and a recruitment log held by the research team in SITraN.

6b. Inclusion and exclusion criteria

Inclusion criteria:

- Patients aged 18 years or over who have attended the MND clinic at the Royal Hallamshire Hospital, Sheffield.
- Patients with amyotrophic lateral sclerosis diagnosed by a consultant neurologist with symptom onset within the last three years.
    - Or
- Patients with amyotrophic lateral sclerosis, primary muscular atrophy or progressive lateral sclerosis diagnosed by a consultant neurologist with a deterioration in their condition as evidenced by a deterioration in the ALS functional rating score (ALSFRS-R) by at least two points during the previous 18 months.
- Live within 120 minute drive from Sheffield

Exclusion criteria:
The main circumstances where patients or carers will be excluded are those in which individuals would be unable to use the telehealth system or give informed consent.

- Patients attend another MND care centre in the UK.
- Significant impairment in decision making capacity preventing informed consent by the subject due to a major mental disorder including fronto-temporal dementia.
- Patient unable to use the TiM system due to physical, intellectual or language difficulties and unwilling to permit carer to operate it on their behalf. Patients will be asked to complete two questions used within the TiM system, with, or without the help to their carer to verify their ability to use the system.
- ~~The patient has no eligible informal carer willing to participate in the trial~~ (V1.5)
- Insufficient mobile telephone reception in the patients' home to use the TiM system.
- Any other major impairment that may affect their ability to participate in the study

Carer inclusion criteria

- Age 18 years or older
- Person identified by the patient as the major provider of informal care (emotional and/or practical support) to the patient and provides more than one hour per week of unpaid care
- Carer willing to allow data they provide during the trial to be shared by the research team with their own doctor in the event of serious clinical need.

Carer exclusion criteria

- Significant decision making capacity preventing informed consent due to a major mental disorder.
- Carer unable to use the TiM system due to physical, intellectual or language difficulties. Carers will be asked to complete two questions used within the TiM system to verify their ability to use the system.

- Inability to participate in the study due to other major physical or mental illness or language difficulties.
- Professional carers receiving direct payment for their services.

6e. Withdrawal

Participants will be followed up until the end of the study, death, or withdrawal. Those wishing to withdraw will be given the opportunity to speak to a member of the study team. Participants are free to withdraw from the intervention or study at any time. As a pilot study, importance of understanding reasons for withdrawal is recognised. This will be explained to the participants in the information leaflets. The importance of understanding reasons for withdrawal and the characteristics of these participants is recognised given the nature of the study. This will be explained to the participants in the information leaflets.

Withdrawal criteria

1. Patient request
2. Carer request
3. Patient loses capacity to continue to provide consent

If a Patient withdraws from the study arrangements will be made for the equipment to be collected or returned. Where appropriate participants will be invited to give the reasons for withdrawal.

Patients will also be given the option of:

1. Withdrawal from the intervention but remain within the study. Study data will only be collected at clinic visits at 3 and 6 months and six monthly until the end of the study.
2. Withdrawal from the study. Unless the participant objects, any data collected up to this point would be retained and used in study analysis. Participant agrees to allow contact to give safety and survival data.
3. Withdrawal from the study entirely. Unless the participant objects, any data collected up to this point would be retained and used in study analysis. If the participant does not wish to be contacted with regard to safety or survival data, no further contact with regard to this study will be made.

In the event that the patient dies or loses the capacity to provide consent they will be withdrawn from the trial but any data collected up to that point would be retained and used in study analysis. Carers would also be withdrawn at this point.

If the carer participant withdraws the patient can opt to continue to use the system or withdraw. If appropriate, carers will be invited to give reasons for withdrawal.

6f. Compliance

Steps have been taken to encourage compliance with the weekly schedule. Patients will receive regular messages on the system to invite them to complete a scheduled telehealth session. They will receive feedback on their compliance record and an

encouraging message at the start of each visit. Those who fail to complete the session within one day will be reminded by text and via the telehealth system. If after two weeks they do not enter data they will be contacted by the PI and offered more support and training. Compliance data will be analysed as part of the process evaluation.

Compliance with the patient reported outcome measures would be monitored by the CRF nurse. She will contact the participants to support data collection, identify and chase missing data and feedback to the PI. In the event of missing data the CRF nurse will telephone the patients/carer after two weeks. She will contact them a minimum of twice and a maximum of three times to chase the data. A contact log will be kept.

6g. Sample size

The study aims to recruit a total of 40 patients and their carers. 20 patients and their primary carer will be randomised to the intervention arm (a minimum of 6 months use of the TiM telehealth plus usual care) and 20 patents and their carer in the control arm (usual care).

Since the proposed trial is primarily an assessment of the acceptability of the intervention and the feasibility of a full trial, the proposed sample size is not based on standard statistical parameters such as a clinically relevant difference between groups. Instead, the sample size is justified on the grounds of quantifying patient variance (i.e. the standard deviation) in the proposed outcome measures (in particular quality of life measures) and on feasibility of the full trial, as follows:

- A sample size of 40 patients allows a standard deviation to be estimated to within a precision of ±20% of its true underlying value with 90% confidence. This estimate will be synthesised with standard deviations observed in other published studies (e.g. (41, 44-47) and on-going trials within SITraN (48, 49), to provide a robust estimate for use in the sample size calculation for the full trial.

- Given the rarity of MND, any definitive study will be infeasible if the required sample size is substantial. Assuming the upper limit for feasible UK study is around 200-300 patients in total, it follows that the full study would need powering to detect a standardised effect size of at least 0.4 SDs. This pilot trial will provide a preliminary assessment of whether the intervention might feasibly achieve this, and inform the choice of outcome measures for the proposed full study.

This sample size is also in keeping with the proposal of 12 evaluable patients per arm in a pilot study (after withdrawal or drop-out) (50).

6h. Blinding

The PI will not be blinded to the randomisation as they are responsible for training the participants to use the TiM system and any on-going technical or training requirements. The treating clinicians will not be blinded to the arm of the intervention as they are responsible for the clinical care of the patient and reviewing the data and the Shadow Monitoring System.

The PI will enter screening baseline data. Participant reported outcome measures after this will be collected by an independent research nurse from the Sheffield Teaching Hospitals Clinical Research Facility who will facilitate collection of these surveys by post or, if preferred by the patient, in person. They will enter the details into the study database.

Following the end of the trial and database lockdown the PI will analyse the two groups of data whilst remaining blinded to the allocation of the two groups. The STH CRF will hold the database code to identify the allocated groups.

The PI will conduct the qualitative interviews and collect the system use data and will not be blinded to these measures.

7. Study treatment

Standard clinical care – Intervention arm and Standard care arm

Usual clinical care will continue throughout for participants in both arms of the study. All participants will continue to be invited to the Sheffield MND Care Centre Clinic for routine review. They will be seen by their consultant neurologist and the MND multidisciplinary team, according to their routine two- to three-monthly schedule. All patients will have access to the MND telephone helpline provided by the Sheffield MND care team.

The TiM system - Intervention arm

Those in the intervention arm will use the TiM system, in addition to standard clinical care. All necessary hardware, software, data transfer and support costs for the TiM system will be met by Abbott Healthcare Products Ltd in collaboration with Carematix.

Patients will be provided with a TiM patient hub: a handheld, touch screen Samsung Galaxy tablet computer that communicates with the MND specialist nurse's TiM clinician system at the Sheffield MND Care Centre. Patients will be asked to use the system at least weekly. Each week the telehealth hub asks the patient a series of questions to detect common problems found in MND, such as worsening mobility, or swallow, symptoms of depression, anxiety, pain, saliva and spasms. Some of the questions closely match validated scoring scales (e.g. the ALS Revised Functional Rating Score (51) and the depression and anxiety short screen: PHQ-4) but others have been specifically designed by the clinical team to be used in the telehealth system. The TiM system also enquires about symptoms of respiratory insufficiency and infection, nutrition and social care. Patients using specialist equipment, such as non-invasive ventilation or gastrostomy tubes will additionally be asked to report problems related to the intervention. The TiM system can also weigh patients weekly and monitor patients' overnight oximetry using established telehealth monitors.

Carers will also be asked to complete a weekly telehealth session in order to monitor their well being. The TiM system includes a carer strain screen and the PHQ-4 depression and anxiety screen. There is also the opportunity with the telehealth system for patients or carers to trigger an adhoc session if issues arise during the week about which they wish to inform the centre. Interspersed through the questions are educational messages and users have access to a bank of educational resources within the hub.

The patient and carer responses are transmitted (via an encrypted 3G mobile signal) to the Carematix server. The responses undergo immediate computational analysis, using pre-determined clinical algorithms, which assigns an alert level to each response. This limits the amount of nurse's time required to use the system. An automated acknowledgement is sent back to the user indicating whether to expect contact from the MND centre based on the results and the timescale for the response.

Each day the MND nurse will log into the TiM system and will be presented with the responses from all patients using the TiM system. They will be automatically alerted to any important changes. Urgent alerts include any new and severe symptom or any new problem that poses a major risk to the patient or carer (e.g. choking, falling, respiratory insufficiency). Routine alerts include any other deterioration in the patient's ALSFRS-R or any new symptom. An appropriately timely response will be made to each alert level. Patients will be reminded to seek urgent medical attention in an emergency.

The information on patient status may facilitate rescheduling of appointments according to patient need rather than the fixed intervals used at present (e.g. the appointment could be delayed if the patient is well, and the TiM system has activated no new alerts). As the feasibility and safety of the TiM system has not been previously evaluated, during the TiM trial patients will continue to attend routine clinic appointments and no patient will have their clinic delayed. The feasibility and safety of rescheduling appointments will be examined using a shadow monitoring protocol (detailed later).

Patients and carers will undergo a training session and a follow-up telephone call after two weeks. The TiM system has been designed to be user friendly and to encourage compliance with the weekly sessions. Face-to-face training with the hub system will be offered at the start of the intervention. Support will be available throughout the trial in the hub. Compliance will be monitored and should patients not complete the TiM system for three weeks in a row, contact will be made to offer more training or support.

The TiM system has been designed by the applicant in collaboration with her supervisors, the Sheffield MND team, Abbott Healthcare Products Ltd. and Carematix. Carematix have experience in delivering similar home telemonitoring systems in other diseases. In developing the system, expertise has also been sought from those developing telehealth services in other diseases in the University of Sheffield and NIHR CLARHC for South Yorkshire. These included the School of Health and Related Research (ScHARR) SMART consortium (Self Management supported by Assistive, Rehabilitation and Telecare technologies), NIHR CLAHRC SY Telehealth & Care Technologies (TaCT) for Long Term Conditions theme, and Devices for Dignity (52).

8. Data collection

8a. Quantitative data collection

Data collection will occur at baseline, three months and six months at the end of the study. Participant data will be completed using postal and telephone questionnaires to minimize patient burden and cost. The study will continue for a minimum of six months. Follow-up will continue until the last participant has used the system for six months. The maximum proposed follow-up will be 18 months.

Patient measures

Baseline measures:

- Age
- Gender
- Experience with technology (frequency of use of a computer, tablet or smart phone)
- Major health condition that could impact on the use of telehealth (including mood disorder, other symptomatic chronic disease)
- Medication

Outcome measures will be collected at 0, 3 and 6 months, then every six months until the end of the study and finally at the end of the study:

- Quality of life measures
  - ALSAQ-40 (an MND disease specific quality of life score (41))
  - SF-36-RAND
  - EQ-5D+D (EQ-5Q-3L with a dignity bolt-on)
- Clinical outcomes
  - ALSFRS-R (an MND disease specific functional rating score (51)
  - Pain score (modified Likert scale)
  - CSS-MND Saliva Severity Scale (designed for use with MND patients) plus global change scale
  - Hospital Anxiety and Depression Scale
- Health resource usage questionnaire
- Patient experience questionnaire

Carer measures

Baseline measures:

- Age
- Gender
- Frequency of use of a computer, tablet or smart phone
- Major health that could impact on the use of telehealth
- Relationship to patient
- Number of hours spent per week providing care for patient

Outcome measures will be collected at 0, 3 and 6 months and at the end of the study:

- SF-36 RAND
- 12 item Zarit Burden Inventory (53)
- Hospital Anxiety and Depression Scale (54)
- Carer satisfaction questionnaire

Data will be collected to evaluate the conduct of the trial including:

- Participant compliance with the weekly telehealth session
- Rate of completion of outcome measures
- Rates of recruitment and withdrawal
- Participant actual and perceived time burden associated with the system
- Time spent by the MND nurse using TiM system and responding to alerts or queries generated by the system.

8b. Qualitative sub-study

Intervention patient and carer interviews

Qualitative semi-structured interviews will be conducted with patients and carers in the intervention arm. Participants randomized into the intervention arm will be invited to take part in interviews. Baseline interviews will occur at one month after the intervention is started. A further interview will be conducted at 6 months. Six months is considered an appropriate timeframe for patients to become familiar with the intervention and its impact on quality of life.

Interviews will be conducted until data saturation is reached. The interviews will draw directly upon peoples' own experience and views, within the context of everyday lives to explore topics including

- Participants experience and expectations of technology
- Participants' expectations of telehealth services
- Barriers and aids to recruitment
- Compliance with the TiM system
- How the TiM system is used at home by patients and their carers
- The impact of using the TiM system on their lives and well-being
- The impact of education on their day-to-day lives
- The experiences of carers monitoring
- Whether the outcome measures used capture the changes in participants well being associated with using the TiM system.
- How the system would be used outside a trial

The early phase interview will explore participants' expectations of technology and the TiM system, the views on the system, their experiences of training and using the equipment. The later phase will explore further how the TiM system influenced their care and quality of life, mental well being as their condition changed. It will also identify barriers and facilitators to adoption of the TiM system.

The applicant will agree pre-defined topic schedules (see Appendix B) developed from the literature, expert consensus and discussion with the trial management group with supervision from Dr. Wendy Baird, an experienced qualitative researcher (School of Health and Related Research, Sheffield University). The PI will conduct interviews in the participants' home. The PI will conduct qualitative interviews until data saturation is reached (55). Interviews will be audio- recorded, transcribed verbatim and analysed with coding and retrieval of data supported by NVivo software.

Due to the nature of MND consideration will be given to participants' needs. The research team has experience in conducting qualitative interviews with patients and carers and these interviews will be conducted in a similar fashion. Often patients with MND prefer to be interviewed with their carer. This also aids communication where patients have speech difficulties and allows participants to support each other whilst discussing sensitive issues. Patients can use communication devices and all participants will be provided with a brief topic guide prior to the interview to facilitate participation for those with communication difficulties. Interviews will be limited to approximately one hour to reduce burden and fatigue. If participants prefer to be interviewed together carers will also be offered separate interviews where possible.

Field notes will also be collected by the PI during the face-to-face training using the TiM system to determine participants' early reactions to using the system and their needs for training.

Control group interviews

Following randomization, those patients and carers who are assigned the control arm will complete the baseline questionnaires. They will then have a short (15-20 minute) semi-structured interview with the PI. This will focus on their experiences and opinions of the baseline questionnaires. It will examine whether they were easy or difficult to complete, whether they were acceptable or caused distress to complete and which questions most reflected their condition and current quality of life.

The interviews, topic guides and analysis will be conducted in the same way as described in the previous section. Topic guides will not be provided before the interview but participants invited to submit any further comments to the research team either in writing or telephone following the interview. It is expected that patients and carers will be interviewed together. Interviews will continue until data saturation is reached or a maximum of 10 interviews conducted.

Staff interviews

At least five staff that care for the participants will undergo one-to-one semi structured interview by the PI during and at the end of the intervention. This will include the two responsible consultant clinicians (Dr Chris McDermott and Professor Pamela Shaw), at least one MND specialist nurse who has used the telehealth system and two members of the MND community team who have cared for participants. They will allow them to draw on their experiences of the TiM system in more depth. A staff information leaflet will be provided and written consent will be required prior to any interview.

Topics will include

- The day-to-day use of the TiM system
- The impact of the TiM system on clinical care of patients and carers
- The safety and accuracy of the system
- Barriers and aids to adoption of the TiM system.
- Views on amending the appointment schedule

These will be planned and conducted in the same manner as the participant interviews under the supervision of Dr Wendy Baird. An interview with the MND nurse and clinicians using the system will be scheduled early in the trial to capture any problems with training and set up of the system. At the end of the trial further interviews will be held with the MND team as described above.

Following the interviews a focus group with the clinical team will be held to draw together all the information gathered from the patient and staff interviews. It will be chaired by Dr Wendy Baird, independent qualitative researcher, transcribed and analysed by the PI under her supervision.

The qualitative findings will facilitate the exploration of any issues and challenges, which may arise from using TiM from the perspective of all stakeholder groups. The findings will enhance understanding of the feasibility of using TiM and assist with the interpretation of the clinical data from the perspective of patients and clinicians.

8c. Shadow monitoring protocol

In order to determine the safety of a remote monitoring system that may enable clinicians to make decisions regarding a patient's management the trial will also collect data on clinicians' opinion on the accuracy of the data displayed by the TiM system. This is referred to as the shadow monitoring protocol.

Prior to each patient's face-to-face visit (depending on their appointment schedule) the treating MND doctor will be asked to conduct a remote assessment of the patient by reviewing the TiM system clinical information. They will be asked to indicate, given the information provided by the TiM system, whether they would change their patient's appointment. The patient would attend the appointment as scheduled and after the appointment the clinician would be asked whether the appointment schedule time was correct. They would also be asked to indicate whether they felt that the information displayed on the TiM system was a safe and accurate reflection of the patient's condition and whether it influenced their clinic visit. Clinicians will also indicate whether the TiM system had affected the consultation. They will also report any adverse events identified. Should patients be unable to travel to clinic they will be offered a telephone consultation at the usual scheduled time. The same Shadow Monitoring questions and need to report adverse events will apply.

The results of this shadow monitoring will be triangulated with the qualitative sub-study and will influence the later interview topic guide.

8d Process evaluation

Data regarding the TiM system use by patients, carers and staff will be will be collected in order to understand how the system could be used in the NHS MND care process. It will also collect data regarding the extra time and resources required to manage the problems generated by the TiM system. It will be triangulated with data gained from the qualitative sub-study, adverse event log and shadow monitoring protocol.

9. Analysis

The PI will conduct analysis with regular supervision from the TMG.

9a. Feasibility and quantitative analysis

The feasibility of a full trial will be determined by analysis of

- Recruitment rates
- Retention rates
- Compliance rates
- Sample size calculations as detailed above

The safety, acceptability and feasibility of use of the TiM system

- Incidence of adverse events (clinical and related to the TiM system functionality)
- Information collected using the Shadow Monitoring process
- Qualitative data analysis

The PI and the CRF study nurse will be responsible for chasing missing data. The CRF nurse is responsible for chasing the questionnaire data and will telephone the patients a minimum of once and maximum of twice to chase unreturned questionnaires or clarify missing data within the questionnaire packs. They will report monthly to the PI. For the main outcome measures, (SF-36 and ALSAQ-40) protocols are provided for managing missing data if necessary. Participants who withdraw will be encouraged to continue to be followed up and reasons for withdrawal ascertained where possible. In the proposed larger, efficacy trial intention to treat analysis will be adopted.

Quantitative analysis will be undertaken in a similar manner for all endpoints. The change from baseline at each time point will be analysed using analysis of covariance in which the covariates are treatment group and the baseline value. For instance, the change in ALSFRS-r at six months will be analysed with treatment group and baseline ALSFRS-r as covariates. The mean (standard deviation) change in each group, the difference between groups and its associated 95% confidence interval will be reported. No formal hypothesis testing will be undertaken for this pilot study.

9b. Qualitative analysis

Data from the interviews will be recorded, transcribed and undergo Framework analysis (56). Although Framework analysis was developed for applied policy it has proved useful in applied health research. Analysis will be ongoing and iterative involving concurrent data collection and analysis, with systematics efforts to check and refine developing categories of data. Themes and hypothesis identified in the early phases of data collection will inform the areas of investigation in later interviews. Regular meetings with supervisors will review the data analysis, explore respondents' underlying reasoning, discuss deviant cases and reach agreement on recurrent themes and findings. The PI's field notes and reflexive diary will also be reviewed and used to inform the analysis of qualitative data. Dr Wendy Baird, an independent, experienced qualitative research, will supervise this stage of the work.

Results from the qualitative analysis will be triangulated, for example, to explore the reasons why problems with the trial methodology or TiM system have occurred. Both themes and anonymous verbatim comments will be published to demonstrate the findings.

10. Data entry, security and confidentiality

Clinical quantitative data input will be the responsibility of the PI (baseline) and CRF study nurses (months 3 and 6, and at the end of the study). Data quality will be the responsibility of CRF nurses and PI who will report back to the TMC and TSC. The qualitative data and system usage data will be the responsibility of the PI. Data (including audio-recordings) will be collected and retained in accordance with the Data Protection Act 1998 and Caldicott Principles. Anonymised study data will be entered onto a validated database system designed to an agreed specification between the PI and Sheffield CTRU and securely stored on the SU intranet. The PI and the CRF research nurses will have access to data on the database through the use of usernames and encrypted passwords. Study documents will be retained in a secure location during and after the study has finished.

All source documents will be retained for a period of at least 5 years following the end of the study, as per the CTRU SOP. Where study related information is documented in medical records those records will be retained for at least 5 years after the last patient last visit

The data provided through the TiM system will be collected using a secure web-app accessed by the participants by a unique username and password. It will be stored on a secure server that will be available through a web-portal hosted by Carematix to the clinical team using secure usernames and password.

For the purposes of the trial each participant will be given a unique TiM system code. This will allow all data to be relayed through the web-app without any associated patient identifiable features. This code will be held separately and stored securely on the STH intranet to allow individual identification by the MND care team. The clinician will display only the anonymous code. This will be accessed through a secure portal with usernames and passwords. No identifiable information will be stored on the patient hub or on the TiM server. The technology providers will have no access to patient identifiable information. Any technology problems will be dealt with by the research team and participants will have no contact with the technology providers.

The system has a full electronic audit trail and will be regularly backed up and will be held in a way that conforms to STH information governance procedures.

Access to source data

Monitoring and audit by the relevant health authorities will be permitted by the sponsor. These include the Research Ethics Committee and local R&D departments. The sponsor will be allowed to monitor and audit the study at each site and be allowed access to source data and documents for these purposes.

11. Safety and safety assessments

We do not envisage any serious safety or adverse events associated with the intervention. The system does not give individual advice to a patient or recommend change in management without input from a clinician. The trial protocol requires patients to continue with their usual care including planned outpatient appointments and the Shadow Monitoring Protocol will evaluate whether the data provided by the TiM system is felt to accurately reflect the patients' clinical condition. The responsible clinician who is a consultant neurologist with specialist experience in MND and research will continue to review the patient on a regular basis (unless the patient is unable to attend clinic) and will have overall responsibility for their care throughout the trial. The specialist MND nurses using the TiM system have extensive experience in managing patients via the existing MND helpline.

The database will automatically alert the trial manager to any carer scoring 11 or more of the Hospital Anxiety and Depression score collected as part of the outcome measures. This will allow the trial manger to identify those carers who may require further support.

Adverse Event Reporting
All adverse events will be reported in accordance with the Sheffield CTRU Adverse Event and Serious Adverse Events SOP.

Participants will be monitored for adverse clinical events and efforts will be made to ascertain whether the TiM system influenced the event or could have predicted the event. These include unplanned admissions and deaths. Non-clinical events relating to the use of the telehealth hub will recorded e.g. failure to record or deliver information to and from the clinical interface.

In research other than CTIMPs an adverse event is defined as: is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or, if present at baseline, appears to worsen AND is temporally associated with medical treatment or procedure, **REGARDLESS** of the attribution (i.e., relationship of event to medical treatment or procedure).

Serious Adverse Event (SAE)
In research other than CTIMPs, the National Research Ethics Service defines a Serious Adverse Event (SAE) is defined as an untoward occurrence that:
(a) results in death;
(b) is life-threatening*;
(c) requires hospitalization** or prolongation of existing hospitalization**;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

*"life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. **Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the

hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

Adverse event exclusions

The only adverse event that will be excluded is:

1. Standard or expected disease progression.

Adverse event inclusions

All serious adverse events will be reported. These include deaths of participants and emergency admissions. We will attempt to determine whether the use of the TiM system contributed to the event, in particular whether there was any delay in seeking help due to the use of the system.

Assessment of Adverse Events

The following criteria will be used when assessing adverse events: Intensity (severity):
Mild - does not interfere with routine activities
Moderate - interferes with routine activities
Severe - impossible to perform routine activities

Relationship to the study treatment:
Unrelated - There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely - There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible - There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable - There is insufficient or contradictory information which cannot be supplemented or verified

Reporting procedures

All study participants will be encouraged to contact and inform their site research team if they experience any new medical problem or are admitted to hospital. Those that are not picked up through general contact will be identified at their routine 2-3 monthly outpatient appointments either in person or by telephone as part of the Shadow Monitoring Protocol. The patients' consultant neurologist (Dr. Chris McDermott or Professor Dame Pamela Shaw) will enquire about any adverse events since the previous visit and record these on the adverse event paper CRF and database. For any Serious Adverse Events an SAE paper CRF and database entry will be completed. The PI and consultant neurologist will assess the event and the CRF will be kept in the site file. Serious adverse events will be reported to the TSC, TMG and the sponsor if deemed by

either to be related to the trial. Reports of related and unexpected SAEs will be submitted to the ethics committee within 15 days of the chief investigator becoming aware of the event. This will use the National Research Ethics Service Report of Serious Adverse Event form. Information will also be included in the routine progress reports to the sponsor and ethics committee. Routine safety data and all SAEs that the TMG or TSC deems to be related to the trial will also be reported to the technology provider in the same manner.

Any suspected adverse drug reaction would be assessed and reported to the MHRA as part of clinicians' routine pharmacovigilance responsibilities using the Yellow Card Scheme. The technology provider, Abbott Healthcare Products Ltd. manufactures a number of drugs (listed in Appendix A). Any suspected adverse drug reaction involving an Abbott Healthcare Products Ltd. drug would also be reported to the manufacturer in the same manner, within 24 hours of receipt by the CI or the next working day for reports received out of hours. Such reports should be sent to ukpharmacovigilance@abbott.com. On a monthly basis the PI will send a reconciliation list of all the reports sent to the Abbott Pharmacovigilance Department within that month to ensure that all the appropriate information has been exchanged. Should any discrepancies arise, both parties will immediately seek to resolve them.

12. Ethical considerations

The study will be conducted in accordance to Good Clinical Practice Guidelines and subject to Research Ethics Committee favourable opinion. The study received a favorable approval from an independent panel representing the NIHR, which funds Dr. Esther Hobson's NIHR Doctoral Fellowship Award.

The study has approval from the Sheffield Teaching Hospitals NHS Foundation Trust's Research and Development department. It has also received favourable review from Dr. Mike Bradburn, study statistician at ScHARR, Dr. Cindy Cooper, director of CTRU and ScHARR, and Dr. Wendy Baird of the Yorkshire and Humber Research and Design service, Professor Alicia O'Cathain, Professor of Health Services Research, ScHARR and Professor Dame Pamela Shaw, SITraN. The application will be submitted through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms, CRF's and questionnaires will be present in the site files before initiation of the study and patient recruitment.

It is recognized that patients with MND may be frail and nearing at the end stages of their lives. The research team has extensive experience in conducting clinical trials in this population. The study design has attempted to limit the burden imposed by the study by avoiding unnecessary study visits (by combining them with scheduled visits), collecting data in the participants' homes at their convenience and limiting the study procedures to the minimum necessary. The intervention has been designed in collaboration with patients and carers to maximize ease of use and minimize impact on participants' lives. It is appreciated that there are a number of questionnaires that require completion. Given one aim of the study is to determine the most appropriate outcome measures to evaluate efficacy of the TiM system there are more questions than would be used in a large scale trial. These have been reviewed by the Sheffield MND Research Advisory Group (the local PPI group) and the lay members of the TSC (David Stelmach) and TMG (Anne Quinn) to ensure acceptability. Participants will be supported by the CRF nurse to complete these at their convenience in a manner selected by the participant (either by post, telephone or in person).

There are other clinical studies ongoing in the Sheffield MND care centre. Involvement in other studies would not preclude patients from entering this study. Consideration of the burden involved in the study, potential impact on the outcome of the study and the patients' expressed priorities will be considered before patients are approached to be involved. If involvement in this study excludes patients from entering another clinical trial patients will be given the option to withdraw from this study.

The potential conflict of interest between the role of the clinical team in caring for patients and their role as researchers is recognized. The study design has considered the impact of this conflict on the participants choices and also any potential bias. Whilst PI is a doctor working within the MND team she is a specialty training registrar and overall responsibility for the patients' clinical care will remain with the consultant neurologist rather than the PI. Whilst she may have already cared for potential participants, following an invite to participate in the trial will no longer see these patients in their routine clinical appointments and her role will be as a researcher.

The dual role of the PI as a doctor and researcher has been previously evaluated. The professional background of a doctor may actually aid the building of a research relationship, allow patients to be more open and comfortable with discussing their health with someone who they already trust (56). In order successfully identify any potential bias the purpose of the research and nature of the PI's role will be emphasized throughout the study, the PI will keep a reflexive diary and field notes and identify any potential bias. Where bias is most likely, i.e. in the collection of outcome measures steps have been taken to limit this: the quantitative outcome measures will be collected by an independent study nurse and the qualitative interview structure and topic guides have been planned with supervision from an independent researcher Dr. Wendy Baird. The PI will be supervised, as part of her PhD by independent academics: Dr. Cindy Cooper and Dr. Mike Bradburn (focusing mainly on the trial methodology and conduct, and quantative data analysis), Dr. Wendy Baird and Professor Sue Mawson (qualitative work and service evaluation). If, during the research, participants identify any medical problems, the PI has a duty of care and will make arrangements to deal with these problems. This might involve signposting them to appropriate services or liaising with the clinical team. A log of these activities will be kept and reviewed by the TMG.

When the participants have prior knowledge of the researcher they may feel a sense of duty and feel pressurized to participate (57). Ground rules, informed consent, confidentiality, freedom to stop and what to expect will be discussed with all participants. Participants will be approached by letter and they will be required to contact the study team allowing them to consider the trial in detail first. It will be explained to the patient (both verbally and in the information leaflets and consent forms) that participation is voluntary and will not affect their ongoing care. The information leaflet differentiates the research process and their usual care. It will be made clear, particularly in the interview phase that the PI's role is as a researcher and the aim of the study is to critically analyse service provision and that whilst comments, particular negative comments, will be passed back to the care team they will treated with confidence and respect.

Whilst the carer participant is not a patient of the Sheffield MND team the research team have a duty of care to the carer. There may be circumstances where the carer may disclose information that requires medical care, for example disclosing symptoms of depression or anxiety. At the start of the trial the carer participants' GP will be informed of the trial. In the event of a serious risk being identified the research team will discuss this in confidence with the carer and make arrangements to resolve the problem. This might include referral to his or her own GP or other health professional. Carer participants will be informed of these procedures in the Carer information leaflet and consent form. Confidentiality will be maintained in accordance with the General Medical Council's guidance on Confidentiality (58).

Upon publication of the qualitative interviews it may be possible to identify participants' comments although this will be avoided if possible. This is explained to participants in the Interview Information Leaflets and on the consent form.

13. Finance and indemnity

The trial has been financed through an NIHR doctoral fellowship grant and details have been drawn up in a separate agreement.

This is an NHS sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial.

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical trial.

14. Reporting and dissemination

Results of the study will be disseminated in peer reviewed scientific journals and clinical and academic conferences. Details of the study will also be made available on the SITraN and ScHARR websites, blogs and social media and through local MND groups. Summaries of the research will be updated periodically on the SITraN website to inform readers of the ongoing progress. Following publication contact with other UK MND care centres will be made to disseminate the findings and assess buy-in potential for a full study if this is appropriate.

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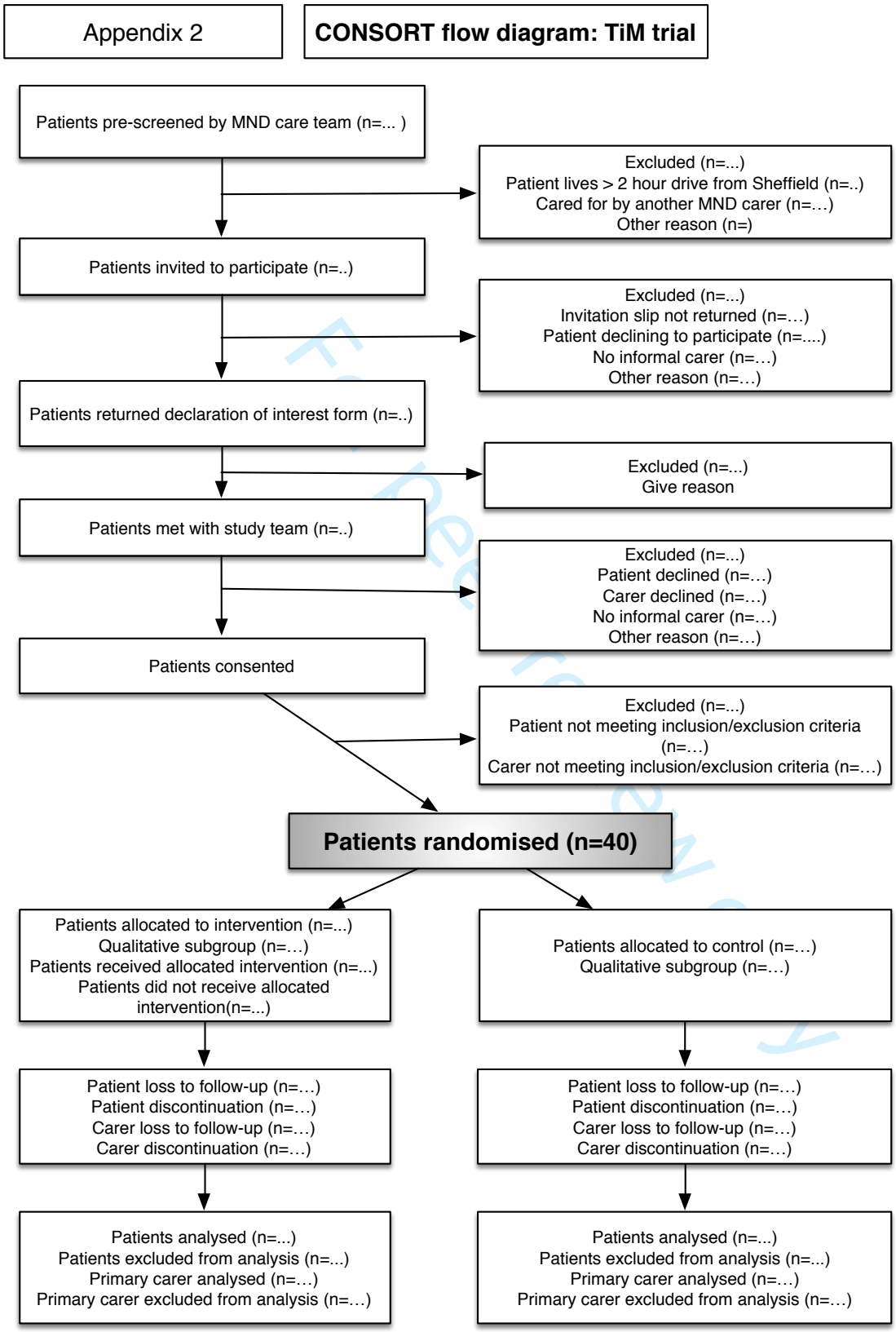
Appendix 1: Drugs produced by Abbott Healthcare Ltd.

Fenofibrate
Pancreatin
Moxonidine
Estradiol/dydrogesterone
Mebeverine
Betahistine
Fluvoxamine maleate
Lactulose
Estradiol, oral applications
Influenza virus vaccine
Eprosartan mesylate
Ibuprofen
Flurbiprofen
Propafenone
Clarithromycin
Verapamil

Appendix 2: CONSORT flow diagram



Appendix 3 Qualitative interview topic guides

Baseline interview (control group)

"I'd just like to reiterate that everything you say in the interview is confidential to me and the research team. If anything you say is used in a publication then it will be anonymous. I'll be recording the interview to make sure I've don't miss anything important. It will take about 15 minutes but we can stop if you wish. If you have any questions I can answer them now or at the end of the interview. There aren't any right or wrong answers - I'm simply interested in your experience and your views. I'd like to know how you found filling in the questionnaire booklet. The questions are designed to understand more about your condition and experiences of MND."

For patients:

- Some are asking quite personal questions. How do you feel about that?
- Do you think the questionnaires asked questions about your life with MND?
- Did you find any of the questionnaires confusing?
- Did you find any of the questionnaires upsetting?
- What would you think about filling in these questionnaires again?
- If so, how would you fill them in?
- If you needed help, how would you fill in your questionnaire?

For carers

- Did you find any of the questionnaires confusing?
- Did you find any of the questionnaires upsetting?
- Some are asking quite personal questions. How do you feel about that?
- What would you think about filling in these questionnaires again?

Intervention group

Interviews will be conducted at 1 and 6 months. Early interview results will guide later interviews. Participants will be provided with the topic guide questions prior to the interview in order for them to communicate their answers easily. The main focus of the interviews is on:

- Participants experience and expectations of technology
- Participants' expectations of telehealth services
- Barriers and aids to recruitment and compliance with the TiM system
- How the TiM system is used at home by patients and their carers
- The impact of using the TiM system on their lives and well-being
- The impact of education on their day-to-day lives
- The experiences of carers monitoring
- Whether the outcome measures used capture the changes in participants well being associated with using the TiM system.
- How the system would be used outside a trial

1-month interview (intervention group)

"I'd just like to reiterate that everything you say in the interview is confidential to me and the research team. If anything you say is used in a publication then it will be anonymous. I'll be recording the interview to make sure I've don't miss anything important. It will take about an hour but we can stop at any time if you wish. If you have any questions I can answer them now or at the end of the interview. There aren't any right or wrong answers. I'd like to here about your experiences of starting using the TiM system and of MND care. You remember you received some questions in the post, we'll be going over those subjects again today"

Previous experiences in MND care

- Can you tell me a little about how you came to get the diagnosis of MND?
- What have your experiences been since then?
- Can you tell me about your last MND hospital clinic visit?
- Have you used the MND helpline?
- How do you manage if you have a question or problem?
- What would you say you are most worried about?
- How do you think your MND team have helped you?
- How do you think your care could be better?
- What problems do you think have been most troublesome?
- How much do you know about MND?

For carers

- How do you get the support you need as a carer?
- How do you find the help the MND team gives?
- How do you think your care could be better?
- What problems do you think have been most troublesome?
- How much do you know about MND?

Expectations of the TiM system

- Before the start of the study what technology did you use?
- What did you expect the TiM system would be like?
- Is there anything you would have hoped it would have?
- Is there anything that worried you about it?

Experiences of training and starting to use the TiM system

- What did you think when you first saw it?
- How did you find the training?
- Do you remember what it was like using it for the first time?

Barriers and facilitators to using the TiM system

- Is there anything things you like about it?
- Is there anything you don't like?
- Has it worked every time as you expected?
- Do you think you will continue to use it regularly? Why?
- What have you told your friends about it?

For the carer

- How have you found using the TiM system?
- What was it like using it for the first time?
- How have you found the questions?

6-month interview (intervention group)

"I'd just like to reiterate that everything you say in the interview is confidential to me and the research team. If anything you say is used in a publication then it will be anonymous. I'll be recording the interview to make sure I've don't miss anything important. It will take about an hour but we can stop at any time if you wish. If you have any questions I can answer them now or at the end of the interview. There aren't any right or wrong answers. I'd like to here about your experiences of using the TiM system and how it has affected your life and your MND care. You remember you received some questions in the post, we'll be going over those subjects again today"

For patients:

- How have you found using the TiM system?
- How often do you use it?
- Is it easy to use?
- Have there been any problems with it?
- Has the MND nurse contacted you about your answers?
- Have you talked about your answers during your clinic visits?
- How has it changed your MND care?
- Have you used the education section or the problem list?
- Would you like to use it as part of your routine care?
- How would you improve it?

For carers

- How have you found answering the questions?
- Has the MND nurse contacted you about your own well being?
- Would you like to use it as part of your routine care?

Telehealth in Motor Neurone Disease

Telehealth in Motor Neurone Disease (TiM): A mixed methods, randomised controlled, pilot study of the use of the TiM telehealth system to deliver highly specialised care in Motor Neurone Disease, at a distance

Statistical Analysis Plan Version 1.3 17/8/16

Authored by

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Contents

List of Abbreviations

AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire – long form
ALS-FRS-R	Amyotrophic lateral sclerosis rating scale-revised
CI	Confidence Interval
CONSORT	Consolidated standards of reporting trials
CRF	Case Report Form
CSS-MND	Clinical Saliva Scale for Motor Neurone disease
CTRU	Clinical trials research unit, University of Sheffield
EQ-5D-3L	EuroQol Group Health Questionnaire
EQ-5D+D	EQ-5D questionnaire with dignity bolt-on
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for human use
ITT	Intention To Treat
QoL	Quality of life
MND	Motor neurone disease
NIV	Non-invasive ventilation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-36 RAND	36-Item Short Form Survey from the RAND Medical Outcomes Study
SITraN	Sheffield Institute of Translational Neuroscience
SOP	Standard operating procedure
Telehealth	Remote monitoring of patients physiology or patient reported measures, forwarded to a central service with the aim to diagnoses or monitor a medical condition
TMG	Trial management Group
TSC	Trial Steering Committee
TiM	Telehealth in Motor neurone disease
TM	Trial manager (EH)
ZBI	Zarit Burden Index

1. Introduction, Study Design & Objectives

This Statistical Analysis Plan (SAP) is written in conjunction with the ICH E9 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for human use; ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9), applicable standard operating procedures (SOPs) from the Sheffield Clinical Trials Research Unit (CTRU) and trial documents (Protocol, case report form (CRF) and Data Validation Specifications). This SAP will guide the trial manager (TM) and Trial Statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study.

1.1 Study Background

This is a single-centre, pilot, mixed methods, randomised controlled trial to explore the feasibility and acceptability of using the TiM (Telehealth in Motor Neurone Disease (MND)) system in clinical practice and explore the feasibility of a larger, multicentre trial. This plans refers to the TiM trial protocol V1.5 April 2015.

All analyses will be performed in a validated statistical software package such as GraphPad prism.

1.2 Primary Objectives

As this is a pilot study, no formal primary clinical outcome will be defined. Instead, the trial will assess the feasibility and requirements of a full-scale study of the TiM as defined by the as successful recruitment of 40 eligible patients and their primary carer; and the feasibility, acceptability, safety and use of the TiM system within a health service. The specific objectives and outcomes of this study are separated into two groups: feasibility and clinical outcomes.

1.2.1 Feasibility Outcomes

Feasibility of a full-scale study

- To make a decision on the primary outcome for the main trial. The mechanism for choosing this outcome will be informed by statistical considerations which are detailed in section 6.7.
- Number of potentially eligible patients among the pool of patients under the care of the Sheffield MND care centre
- Number/characteristics of eligible patients approached for the study:
- List of reasons for declining/refused consent;
- Participant attrition rate
- List of reasons for attrition
- Number of missing values/incomplete cases (see **Error! Reference source not found.**)

- Treatment receipt/adherence;
- Patient, carer and clinician views on intervention/research protocol (using qualitative methods).

Feasibility/safety of TiM system:

- Treatment receipt/participant and staff adherence
- Participant and clinician acceptability of the intervention (using qualitative methods and the TiM system experience questionnaire and Shadow monitoring protocol)
- Patient, carer and clinician views on intervention (using qualitative methods);
- Incidence of TiM system technical problems;
- Incidence of adverse events related to intervention.

Participant and clinician views will be investigated using qualitative interviews (described in the protocol). Participant and clinician acceptability will be reported based on TiM system experience questionnaire and Shadow monitoring questionnaire.

1.2.2 Clinical Outcomes

The following clinical outcomes will be reported using self-completed questionnaires baseline, 3, 6, 12 and 18 months.

Patient outcomes

- Quality of life (QoL) measures
  - ALSAQ-40 (an MND disease specific quality of life score)
  - SF-36-RAND
  - EQ-5D+D (EQ-5Q-3L with a dignity bolt-on)
- Clinical outcomes
  - ALS-FRS-R (an MND disease specific functional rating score
  - Pain score (modified Likert scale)
  - CSS-MND Saliva Severity Scale (designed for use with MND patients) plus global change scale
  - Hospital Anxiety and Depression Scale (HADS)
- Health resource usage questionnaire
- Patient experience questionnaire
- TiM experience questionnaire

Carer outcomes

- SF-36 RAND
- 12 item Zarit Burden Inventory (ZBI) (53)
- Hospital Anxiety and Depression Scale (54)
- Carer satisfaction questionnaire

The following safety outcomes will be assessed at every clinical visit:

- Incidence of adverse events (AEs)
- Clinician satisfaction

2 Sample Size Estimation

The study aims to recruit a total of 40 patients and their carers. 20 patients and their primary carer will be randomised to the intervention arm (a minimum of 6 months use of the TiM telehealth plus usual care) and 20 patents and their carer in the control arm (usual care).

Since the proposed trial is primarily an assessment of the acceptability of the intervention and the feasibility of a full trial, the proposed sample size is not based on standard statistical parameters such as a clinically relevant difference between groups. Instead, the sample size is justified on the grounds of quantifying patient variance (i.e. the standard deviation) in the proposed outcome measures (in particular quality of life measures) and on feasibility of the full trial, as follows:

- A sample size of 40 patients allows a standard deviation to be estimated to within a precision of ±20% of its true underlying value with 90% confidence. This estimate will be synthesised by combining baselines measurements of quality of life measurement standard deviations with those observed in other published studies and on-going trials within SITraN, to provide a robust estimate for use in the sample size calculation for the full trial.

- Given the rarity of MND, any definitive study will be infeasible if the required sample size is substantial. Assuming the upper limit for feasible UK study is around 200-300 patients in total, it follows that the full study would need powering to detect a standardised effect size of at least 0.4 SDs. This pilot trial will provide a preliminary assessment of whether the intervention might feasibly achieve this, and inform the choice of outcome measures for the proposed full study.

This sample size is also in keeping with the proposal of 12 evaluable patients per arm in a pilot study (after withdrawal or drop-out) (1).

3 Randomisation & Blinding

Randomisation is conducted according to the protocol.

The patient, clinicians, TM and trial team are not blinded to the outcomes. Data entry for follow-up clinical outcomes was performed by an independent research nurse, not involved in the study. Blinding of this nurse was impractical given additional measures were collected for those in the intervention group. The TM will undertake the analysis under the supervision of the independent trial statistician. Blinding during analysis was impractical given the small number of participants who had with unique and characteristics which are likely to be identifiable to the TM. This will be reported as a limitation

4 Interim Analysis & Study Monitoring.

This is a pilot study with no planned interim analysis or early stopping. Two committees have been set up to govern the conduct of the study:

- Trial Steering Committee (TSC)
- Trial Management Group (TMG)

Decisions to stop the trial early on grounds of safety will be made by the Trial Steering Committee or funding body. There will not be a Data Monitoring and Ethics Committee for this study as it is considered low risk. No interim analysis is planned.

The TM will receive notifications of all carers whose Hospital Anxiety and Depression subscores exceed 11. These events will be recorded as AEs, reported to the TMG and TSG during the study and reported in the analysis.

5 Data Sources, Evaluability & Study Populations

5.1 Data Sources

Data used in this study will come from data entered onto CRFs and questionnaires and from data entered directly on the CTRU database (PROSPECT). The data will be stored on the database with the exception of the randomisation list which is held on www.sealedenvelope.com and allocation verified by the data management team. Electronic data will be extracted from the system during the trial for the purpose of checking (validating) and trial progress reports. Access to PROSPECT is controlled by usernames and encrypted passwords, and a privilege management feature will be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data.

5.2 Data Collection

Data will be collected from the participants and their carers at:

- Consent and Screening, eligibility and baseline
- Month 3, 6, 12 and 18
- Each clinic visit (Shadow monitoring protocol)
- End of study (participant status alive/dead and date of death).

Due to the pilot nature of the study there are no predefined protocol non compliances other than misrandomisation or randomisation in error. Intervention adherence will be assess as an outcome (see section 6.5).

5.3 Protocol non compliances

Due to the pilot nature of the study there are no predefined protocol non compliances other than misrandomisation or randomisation in error. Intervention adherence will be assess as an outcome (see section 6.5).

5.4 Study Population

Described in the protocol.

5.5 Analysis Populations

The intention to treat population (ITT) includes all patients for whom consent is obtained and who are randomised to treatment. This is the primary analysis set and endpoints will be summarised for the intention to treat population unless stated otherwise.

6 Statistical Analysis

6.1 General considerations

As the trial is a pilot parallel group randomised controlled trial, data will be reported and presented according to the proposed modifications for reporting pilot trials as well as the Consolidated standards of reporting trials (CONSORT) statement (2,3). The analysis will be performed on an ITT basis. The final analysis will be performed after data lock by the TM under the supervision of the study statistician who will also be responsible for quality checking the results.

Each planned follow-up timepoint will use a time window to ensure that responses have been collected within a reasonable time frame. The time windows allow a slippage of four weeks at 3 months and six weeks thereafter, as outlined below:

3 months: **within 61-91 days following randomisation**

6 months: **within 140-224 days following randomisation**

12 months: **within 323-407days following randomisation**

18 months: **within 506-590 days following randomisation**

6.2 Recruitment and attrition rates

Relevant summaries related to recruitment, consent and patient throughput will be reported and presented in a CONSORT flow diagram (see appendix, Figure 1).

The following will be reported:
The number of (potential) participants;

- Potentially eligible as identified by the study team at participating centres,
- Approached for the study,
- Not randomised (with reasons),
- Randomised,
    - allocated to treatment
    - allocated to control
- Withdrawn and lost to follow up (with reasons),
- Discontinuing TiM intervention,
    - reasons for discontinuation
- Included and excluded from analysis,
    - Reasons for exclusion.

6.2.1 Eligibility

Described in the study protocol

6.2.2 Participant Attrition

The rate of attrition will be reported (defined as the proportion of the consented and randomised participants who withdrew or were lost to follow up). The reasons for attrition, where provided, will be reported as number and percentage in each category.

6.3 Status of participants and completion of outcome measures

We will report the status of patients and carers at each time point.

At each time-point we will report the number of patients and carers:

- Returning the postal questionnaire booklet
- Completing each questionnaire

We will report these by treatment group and overall.

For the patient and carer questionnaires the response rate at each time point (measured as the total number of questionnaires completed as a fraction of total number of patients alive) will be reported. An example table is given in section 0 (Table 1).

6.4 Baseline Characteristics

The baseline demographics and clinical characteristics of the participants will be reported. For the continuous variables, (e.g. age) either mean and standard deviation will be presented or median and inter quartile range (IQR) depending on the distribution of the data. The number of observations used in each calculation will be presented alongside the summaries. For the categorical variables, the number and percentage of participants in each of the categories and the total number of observations will be presented.

All baseline summaries will be presented and reported for each treatment group and in total. An example of the table of baseline summaries is given in section 0 (

Table 2). No statistical significance testing will be done to test baseline imbalances between the intervention arms but any noteworthy differences will be descriptively reported.

The following summaries will be presented:

Demographics	Age, gender, technology use
MND Characteristics	Age of onset, disease duration, classification of MND (e.g. ALS, PMA, PLS), clinical stage of MND, use of non-invasive ventilation (NIV)/gastrostomy, riluzole use
Carer demographics	Age, gender, relationship to patient, technology use
Patient reported outcomes	ALS-FRS-R (including upper limb function), ALSAQ40, RAND36 and subscores, CSS-MND, HADS, pain score, EQ-5D+D, patient experience, health resource use (number and type of clinical encounters and hospital admissions in last 3 months, carer requirements)
Carer reported outcomes	RAND36, ZBI, HADS, carer experience

6.5 TiM Treatment adherence

Intervention adherence will be reported as the number of TiM sessions attended within between recruitment and the end of March 2016 and the mean and SD of percent adherence. We will also report adherence at 1, 3, 6, 9, 12, 15 and 18 months.

We will also report

- **The number and percentage of participants that completed 50% and 75% of expected sessions.**
- **A description of the adherence of each patient and carer using the TiM over the course of the trial.**

Any reasons for poor adherence will be reported where available although it was not possible to identify reasons for all missed sessions.

Cumulative session attendance will be displayed for each participant using a spaghetti plot to illustrate intervention adherence.

The number and percentage of participants that withdrew from the TiM intervention will be reported, alongside listings of:

- **Reasons for withdrawing from intervention, where provided**
- **Number of TiM sessions (and %) before withdrawing from intervention**

6.6 Clinical outcomes

Descriptive statistics will be presented for the clinical outcomes; significance testing will not be undertaken. Continuous outcome measures will be presented as mean differences between groups and their associated 95% confidence intervals (CI). For categorical outcomes, the number and percentages falling into different categories and potential differences between groups in terms of the percentages in each category will be presented, together with their confidence intervals. Clinical outcomes will be presented for the ITT set with available 6 month and 12 month outcome data.

6.6.1 Patient outcomes

The following outcomes measured at 3, 6, 12, 18 months will be presented by group and overall.

The following patient –reported quality of life outcomes will be reported.

ALSAQ-40	Individual scores of five sub-scales and a summary aggregate score: ▪ physical mobility ▪ activities of daily living and independence ▪ eating and drinking ▪ communication ▪ emotional reactions
RAND-36	A summary of the eight sub-scales and two aggregated scales: ▪ Physical Functioning ▪ Role Limitations due to Physical Problems ▪ General Health Perceptions ▪ Vitality ▪ Social Functioning ▪ Role Limitations due to Emotional Problems ▪ General Mental Health ▪ Health Transition ▪ Aggregate physical health ▪ Aggregate mental health
EQ-5D+D	Health utility (as derived from the five questions) Thermometer health scale Health utility plus dignity (as derived five questions plus

	dignity bolt-on)

In each case the within-group results will be summarised as mean (SD), and the difference between the two as the mean difference together with its CI. Forest plots of confidence intervals of different widths (e.g. 95%, 90%, 80%) with respect to the treatment difference in the overall ALSAQ40 score and RAND36 (mental and physical domain) will be used to illustrate the strength of preliminary evidence (see Figure 2) (Lee, 2014).

In each case, the summaries will be presented by treatment group and time point (see Table 3 and

ll be presented for the clinical outcomes; significance testing will not be undertaken. significance testing will not be undertaken. Continuous outcome measures will be ignificance testing will not be undertaken. Continuous outcome measures will be presented as mean differences between groups and their associated 95% confidence erences between groups and their associated 95% confidence intervals (CI). For 5% confidence intervals (CI). For categorical outcomes, the number and percentages % confidence intervals (CI). For categorical outcomes, the number and percentages ntages falling into different categories and potential differences between groups in potential differences between groups in terms of the percentages in each category will potential differences between groups in terms of the percentages in each category will ome data.

ll be presented by group and overall.

tcomes will be reported.

ary aggregate score:

obility

g

-36

le 3 and

e number of patients alive and the number of patients completing the outcome score mean and SD

ure will be scored as described below and compared, where possible and relevant to

ompared, where possible and relevant to population values.

be scored as described in Ware et al (4). In the case of partially completed

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C034</uuid><priority>0</priority><publications></publications></citation>(4). In

publications></citation>(4). In the case of partially completed questionnaires, scores

questionnaires, scores will be calculated for domains in which at least 50% of the

ons have been answered. Taking physical functioning as example, if at least five of the

ns have been answered. Taking physical functioning as example, if at least five of the

lity (Q1-10), activities of daily living/independence (Q11-20), eating and drinking,

ity (Q1-10), activities of daily living/independence (Q11-20), eating and drinking, (Q21-

(Q21-23) communication (Q24-30), emotional functioning (Q31-40). Each question is

unctioning (Q31-40). Each question is scored 0 (never) to 4 (always/cannot do at all).

nctioning (Q31-40). Each question is scored 0 (never) to 4 (always/cannot do at all).

5 +Q6 +Q7 +Q8 + Q9 + Q10)/40) x 100.

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The following other clinical outcomes will be presented:

Hospital anxiety and depression score	The Anxiety and Depression subscores
Pain (Likert scale)	Current and average weekly score
ALS-FRS-R	Total score
CSS MND	Total score % patients reporting a clinically significant improvement or worsening (according to Global change CSS-MND self-reported statement)
Clinical encounters	The number of clinical encounters in the 6 months following randomisation, by type and location and reason
Hospital admissions	The number and percentage of patients admitted to hospital, and the number of hospitalisations, by type, location and reason

The HADS anxiety and depression inventories will be scored using the approach of Zigmond and Snaith (7). Each domain will be calculated as the sum of seven questions, each of which is scored 0-3, giving a total score which ranges from 0 and 21. In the case of partially completed questionnaires, the domain will be scored and upweighted provided at least four of the seven questions have been answered.

Self-completed revised ALS functional rating scale (ALS-FRS-R) consists of 12 questions scoring 0-4 (8). Sub-domains include upper limb, lower limb, bulbar and respiratory.

Pain score: the current level of pain (0-10 likely scale) and the average current weekly level of pain (0-10) will be represented as a mean and SD.

Modified CSS MND saliva score is awaiting validation. The total score is the total of all answers scoring 0-3 for each question A to J (9). The percentage of patients reporting a change on the saliva clinical change assessment will be reported.

6.6.2 Carer clinical outcomes

The following carer-reported QoL outcomes will be presented is the same manner as described for the patients.

- RAND 36
- HADS

- Zarit Burden Index

The each of the 12 items in the shortened Zarit burden inventory is scored 0 (Never) to 4 (nearly always) (10). A total score between 0 and 48 will be reported.

6.6.3 Health economic outcomes

A complete health economic analysis is beyond the scope of this plan. However, descriptions of the following clinical outcomes will be reported, by group and overall:

Clinical encounters	The number of clinical encounters recorded at each encounter following randomisation, by type and location.
Hospital admissions	The number and percentage of patients admitted to hospital recorded at each encounter. the number of hospitalisations
Informal care requirements	The number of hours of informal care recorded by patients.
Formal care requirements	The number of hours of formal care recorded by patients.

6.6.4 Patient experiences

The following will be reported by group and overall.

Patient care experience	Percentage of patients agreeing and disagreeing with each satisfaction statement
Carer care experience	Percentage of carer agreeing and disagreeing with each satisfaction statement
Patient TiM experience (intervention only)	Percentage of patients agreeing and disagreeing with each satisfaction statement
Carer TiM experience (intervention only)	Percentage of carer agreeing and disagreeing with each satisfaction statement

All free text responses will be reported.

6.6.5 Safety

Adverse events are recorded at every clinic appointment and patients will report health resource use and hospital admissions. Reported admissions will be followed up by the

TM and records as serious adverse events. HADS carer scores will be calculated and reported to the TM for action on an ongoing basis during the trial if either the depression or the anxiety subscore exceeds 11. These will be reported to the TSC during the trial and reported in the analysis and recorded as adverse events.

Advents Events (AEs) will be reported as number and percentage of patients overall and by treatment group but no formal statistical analysis is planned. The following summaries will be presented;

AEs	The number and percentage* of patients reporting an AE and the number of AEs in total
AEs by category	The number and percentage* of patients reporting an AE and the number of AEs for each pre-defined category (pain, acute infection, fractures)
Serious AEs (SAEs)	The number and percentage* of patients reporting an SAE and the number of SAEs in total
Treatment-related AEs	The number and percentage* of patients reporting a treatment related AE and the number of treatment related AEs
All AEs	A listing of all AEs including - Description / Site / Signs and Symptoms - Severity - Relationship - Action taken - Outcome - Seriousness

*defined as a percentage of all patients randomised.

6.7 Estimation of primary outcome and sample size for a main trial

The variability in clinical outcomes will be reported as standard deviation by treatment group and overall alongside their upper 80% confidence limits to get a robust estimate of SD (as recommended by Kieser, 2007), and observed treatment difference.

Descriptive assessment will be used to inform sample size calculations for the definitive study. These assessments will be calculated for candidate measures for the full trial (RAND-36 and ALSAQ40), and will be based on:

- Observed treatment difference at 6 and 12 months
- Standard Deviation;
- Correlation between baseline and 6 month measurements;
- The extent of missing data in each outcome;
- Participant feedback on the most appropriate assessment (analysed qualitatively).

The standard deviation used in the sample size calculation will be derived from the residual variance of the regression model for which the outcome is the 6-month response and the covariates are treatment group and baseline.
A table of sample size estimates for a definitive study stratified by outcome measure and power (80%, 90%) will be provided. E.g. Table 5

6.8 Economic Evaluation Analysis

No economic analysis will be conducted but patient health resource use will be reported.

6.9 TiM process evaluation

The following will be reported:

Patient and carer feasibility:

- The time taken to complete each TiM session by patient and carer (mean, range). TiM session time is automatically recorded by the application but total time between starting and completing and session is recorded. This includes any time delay because the patient pauses using the session and recommences it later e.g. the next day. Outliers will be identified and excluded with definition of outlier reported (e.g. > 600% of the average time);
- Adherence to weekly TiM sessions (see 6.5);

Clinical feasibility:

- Number, range and % of patient and carer sessions that trigger an overall red, amber and green flag;
- Number, range and % of patient and carer sub-sections that trigger an overall red, amber and green flag;
- Time taken for nurse to use the telehealth system per week, collected by nurse diary (mean, range, SD and time per patient enrolled in the system);
- Number of notes entered per patient.
- Shadow monitoring protocol (intervention)
    - Number of pre-clinic shadow monitoring forms completed
    - Number of clinic shadow monitoring forms completed
    - Clinician satisfaction: % agree/disagree with each statement
    - Free text comments will be reported.

7 Detailed Statistical Methods & Calculations

7.1 Missing Spurious & Unused Data

The extent of missing data will be reported. No sensitivity analyses involving imputation for missing data will be performed. Any spurious data will be queried and checked for consistency with data management before data lock.

Patient and carer questionnaires will be scored only if all relevant items that make up a domain are completed with the exception of RAND 36, HADS and ALSAQ40.

8 Implementation of the Analysis Plan

This SAP will be used as a work description for the statistician involved in the trial. All analyses will be performed by the TM (under the supervision of Trial Statistician MB).

Initially, blinded data will be delivered to the TM and MB by the data manager to define analysis sets and test statistical programs. Any queries will be communicated to the study and data manager prior to database lock. The database will be locked after agreement between the statistician, data manager and study manager. No changes will be made once the data has been locked. Database freeze and lock will be conducted in accordance with SOP DM012.

9 Modifications to the Original Protocol Analysis Statement

None

10 Appendix

Figure 1: CONSORT flow diagram

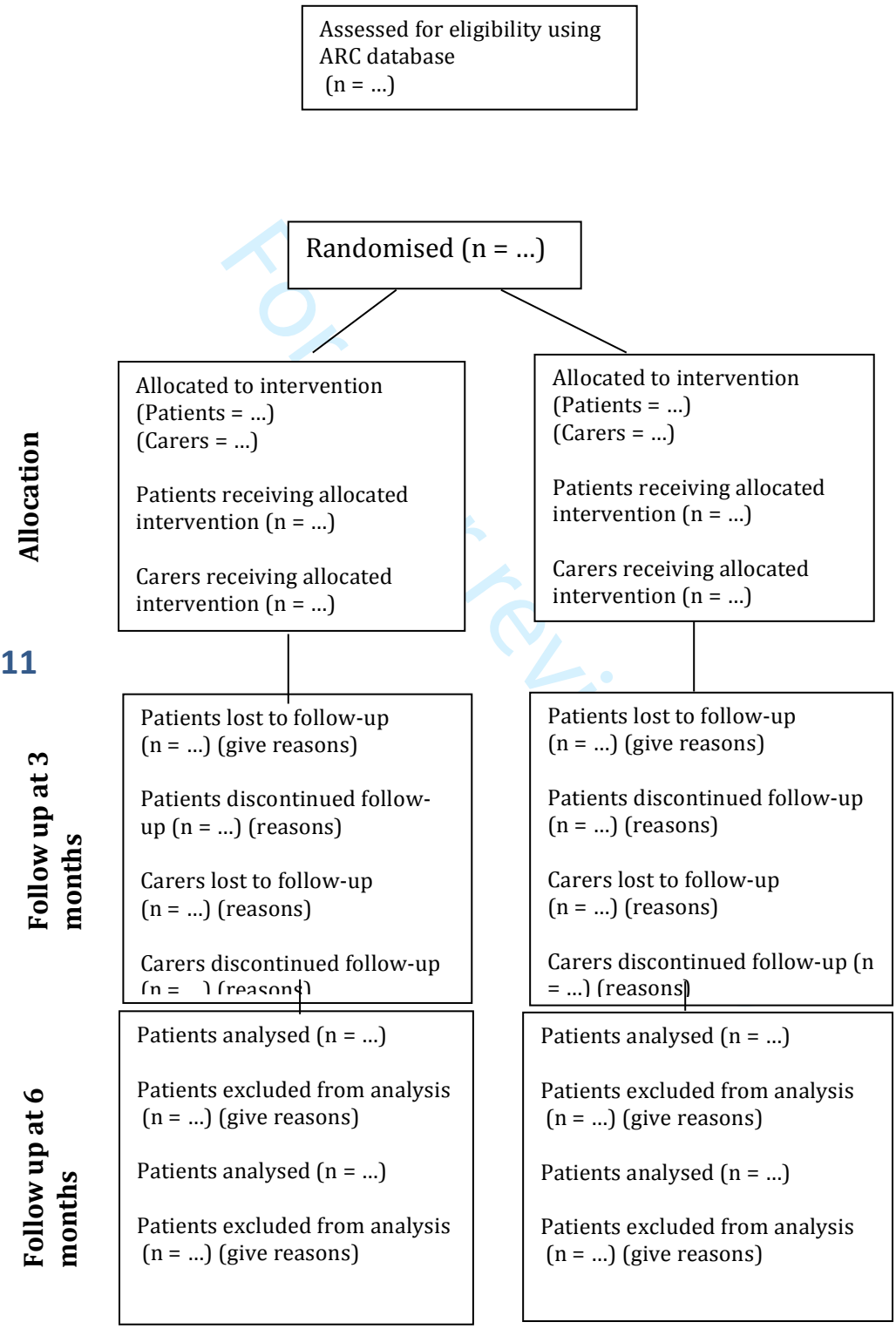
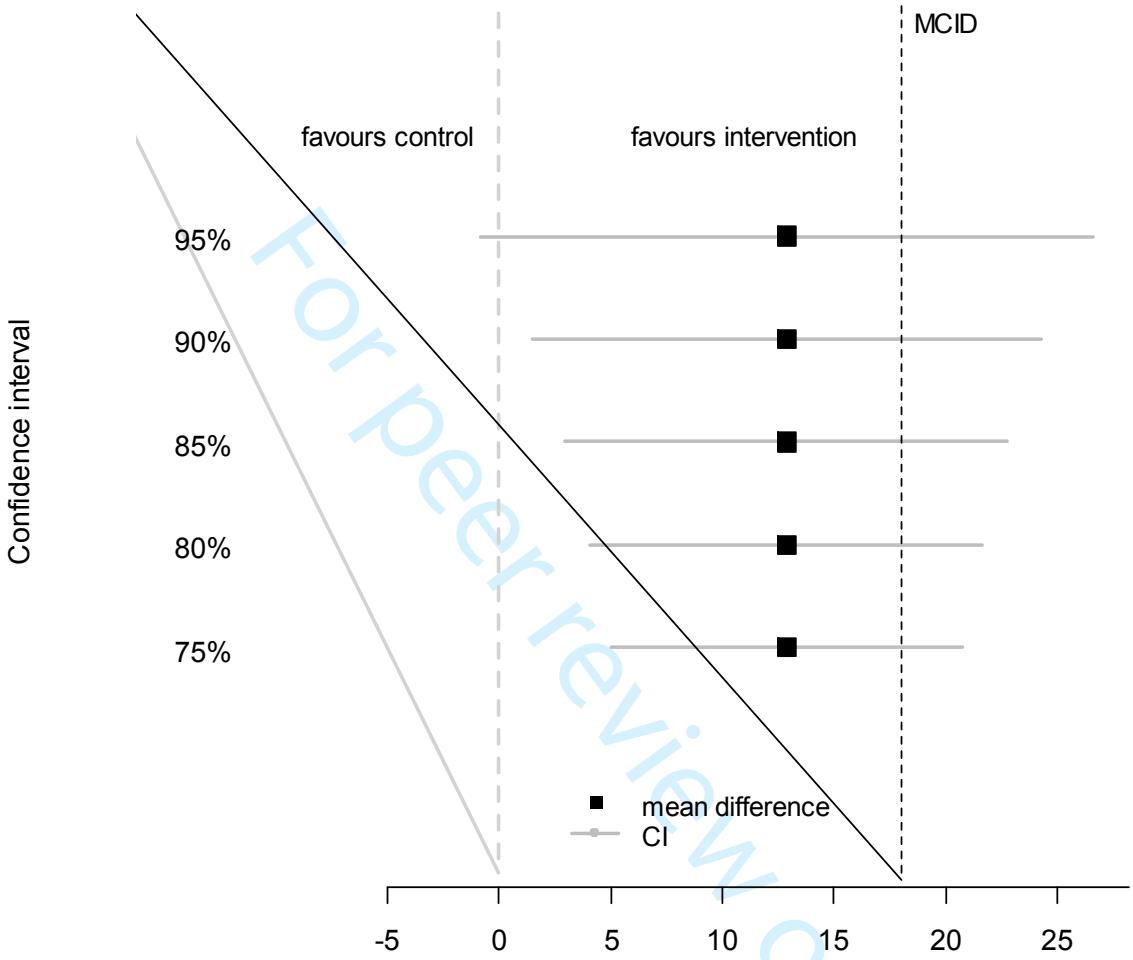


Figure 2: Mean difference in ALSAQ40 with confidence intervals



10.2 Example Tables and Figures

Note: The following tables are examples and do not include all outcome measures that will be included in the analysis.

Table 1: Participant status

	3 months	6 months	12 months	18 months
Telehealth				
Completed	N=	N=		
Not completed				
Died				
Withdrew from study				
Completed questionnaire but not within time window				
Incomplete				
Control				
Completed	N=	N=		
Not completed				
Died				
Withdrew from study				
Completed questionnaire but not within time window				
Incomplete				

*Completed includes questionnaires that were sufficiently complete to be used in the statistical analysis. Uncompleted refers to questionnaire booklets that were not returned. Incomplete refers to questionnaire booklets that were returned but insufficiently complete to be used in statistical analysis.

Table 2: Participant baseline characteristics by treatment group

Characteristic	Scoring	Control (n=xx)	Intervention (n=xx)	All (n=xx)
Age (years)	Mean(SD, range)	x (xx)	x (xx)	x (xx)
	N	n	n	n
Gender	Male	n (%)	n (%)	n (%)
	Female	n (%)	n (%)	n (%)
	N	N	n	n
ALS-FRS-R	Mean(SD, range)	x (xx)	x (xx)	x (xx)
	N	n	n	n
King's clinical stage	Stage 1 Stage 2…etc.	x (xx)	x (xx)	x (xx)
	N	n	n	n

This will be extended to include the other baseline variables measured.

Table 3: Display of outcome data by time, illustrated for pain

	Baseline	3 months			
Outcome		Mean (SD)	Change from baseline	*…repeat for other timepoints*	
Current pain: Mean (SD)	Mean (SD)	N= Mean (SD)	Mean (CI)		
Control	Mean (SD)	N= Mean (SD)	Mean (CI)		
Average pain: Mean (SD)	Mean (SD)	N= Mean (SD)	Mean (CI)		
Control	Mean (SD)	N= Mean (SD)	Mean (CI)		

Table 4: Clinical outcomes at six months: control vs intervention

	Change from baseline						
	Intervention			Control			
Outcome	n	Mean	SD	n	Mean	SD	Mean difference (95% CI)
ALSAQ40	x	xx	xx	x	xx	xx	xx (xx to xx)
RAND 36 (agg. physical)	x	xx	xx	x	xx	xx	xx (xx to xx)
RAND 36 (agg. mental)	x	xx	xx	x	xx	xx	xx (xx to xx)
HADS anxiety	x	xx	xx	x	xx	xx	xx (xx to xx)
HADS depression	x	xx	xx	x	xx	xx	xx (xx to xx)
Pain	x	xx	xx	x	xx	xx	xx (xx to xx)
…							

Table 5: Sample size considerations for candidate primary outcome measures

	Effect size		Standard deviation		Power (%)	Number /group	Number /group + attrition
Outcome	**MCID**	**Observed***					
ALSAQ-40 total	xx	Xx	Observed	xx	80	NN	NN
					90	NN	NN
			Upper 80%CI	xx	80	NN	NN
					90	NN	NN
RAND-36							
Agg physical	5	Xx	Observed	xx	80	NN	NN
					90	NN	NN
			Upper 80%CI	xx	80	NN	NN
					90	NN	NN
Agg mental	5	xx	…				
…repeat for other candidate measures							

**nb Observed effect size is for reference and is not used in sample size calculation*

Shadow monitoring form

[Intervention]

T

Appointment summary

Date of clinic d d m m y y y y

Neurologist completing form ☐ CMD ☐ PJS ☐ Other → specify

Mode of contact ☐ Face-to-face ☐ Telephone

Type of appointment ☐ Routine ☐ Unscheduled

Related to telehealth ☐ Yes ☐ No

Details

Next scheduled visit weeks

Adverse events

Any adverse events (including hospital visits) since last visit? ☐ Yes ☐ No

*Please complete **Adverse event** or **Hospital attendance** form and contact CI immediately*

Any adverse drug reactions since last visit? ☐ Yes ☐ No

*Please complete **Adverse event** form and contact CI immediately*

TiM

	Completely disagree	Disagree	Neutral	Agree	Completely agree
The TiM data gave an accurate picture of the patient's current condition	☐	☐	☐	☐	☐
The TiM data could enable me to make appropriate decisions about the patient without seeing them in clinic	☐	☐	☐	☐	☐
The TiM data gave useful information about the carer's current condition	☐	☐	☐	☐	☐
The TiM was a positive influence on the consultation	☐	☐	☐	☐	☐
Prior to the patient attending you said you would arrange the patient to attend clinic in _____ weeks. Do you think this was an appropriate decision?	☐	☐	☐	☐	☐

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported in section
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Page 1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	Background
	2b	Specific objectives or research questions for pilot trial	Aims of the study
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	Study design
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	Eligibility criteria
Participants	4a	Eligibility criteria for participants	Eligibility criteria
	4b	Settings and locations where the data were collected	Eligibility criteria
	4c	How participants were identified and consented	Recruitment
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Intervention, parallel paper and publication
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	Data collection, Table 1
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	n/a
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	Sample size
Sample size	7a	Rationale for numbers in the pilot trial	Sample size
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Randomisation
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	Randomisation
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Randomisation

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Randomisation
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Blinding, bias and study conduct
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	Data collection
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	CONSORT diagram
	13b	For each group, losses and exclusions after randomisation, together with reasons	CONSORT diagram
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Recruitment
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Supplementary data file
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplementary data file
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Supplementary data file
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Adverse events
	19a	If relevant, other important unintended consequences	Parallel publication
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	Discussion
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	Discussion
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	Discussion
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	Discussion
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	Study design
Protocol	24	Where the pilot trial protocol can be accessed, if available	Supplementary file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Acknowledgements and funding
	26	Ethical approval or approval by research review committee, confirmed with reference number	Study design