University of Sheffield | School of Medicine & Population Health

DENIM
Delivering Effective Non-Invasive ventilation in Motor neuron disease

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Delivering Effective Non-Invasive ventilation in Motor neuron Disease

Better outcomes in MND

Evaluating the effectiveness of an intervention to develop intensive optimisation of non-invasive ventilation in motor neuron disease: a type 3 hybrid implementation-effectiveness, stepped-wedge cluster randomised controlled trial.

RESEARCH PROTOCOL
(Version v3.1) 07August2026
Protocol at NRES Submission

Sheffield CTRU Reference:	**186399**
IRAS Number:	**334849**
REC Reference:	**25/YH/0019**
Sponsor Reference:	**STH22466**
Funding Reference:	**NIHR158715**
ISRCTN	**10105285**
Authorised by Esther Hobson:	**07/01/2025**

DENIM

Delivering **E**ffective **N**on-**I**nvasive ventilation in **M**otor neuron disease using intensive remote support

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

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Abbreviations

Definition of terms

AE	Adverse Event
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MDT	Multidisciplinary Team
NIV	Non-Invasive Ventilation
NHS R&D	National Health Service Research & Development
ODI	Oxygen Desaturation Index
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCHARR	Sheffield Centre for Health And Related Research
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
SWAT	Study Within A Trial

TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1. General information

1.1 Investigator details

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1.3 Sponsor Details

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

Disclaimer: The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care

1.5 Version Control Table

Version stage	Version number	Version date	Protocol updates and finalised by;	Reasons for update
Draft 15 of final	Draft 15 of v1.0	07Jan25	Updates to date and version throughout. Section 1.4 Addition of disclaimer. Section 1.5 Replacement of table to track version control. Section 9.1 Addition of skin tone data collection to validate oximeter data.	Funder request prior to approval
Amendment SA1	2.0	02Sept25	Additional trial statistician added. Section 8.2 Clarification that referenced month 27 is week 116. Section 5.6 Clarifications of day 0 being the day the patient takes the ventilator home. Section 5.7 removal of co-enrolment requiring permission from TSC (this has led to unnecessary missed patient recruitment due to delays in replies from TSC) Section 9, clarification of oximeter process, software and data extraction. Table 2, section 9: Change to structure of table 2, section 9.1, to clarify the data collection for adherence data between weeks 1-4	Clarifications required

			and 9-12. Clarification that S3NIV collected at baseline is not validated due to irrelevant questions. Section 11.2.1 and 11.2.2 Updates to planned analysis populations. Section 12.1 Clarification around NOMAD survey process and how it is delivered via Qualtrics. Section 18 Updated ethics committee details.	
Amendment SA2	3.0	05Dec25	Change to the eligibility criteria to specify when recruitment of inpatients, who stay more than 72 hours, can be permitted as part of the trial	After discussion with TMG, TSC and agreement from funder
Amendment NSA6	3.1	07Aug26	Clarification to the eligibility criteria wording to specify that participants must meet either inclusion criteria 5 **or** inclusion criteria 6. This removed the criteria as separate bullet points and into one prose. Section 4, removal of 1:1. Section 12.1.2 Addition of NOMAD collected at the end of the study (in addition to six months). This was noted at baseline and x2 timepoints on the flow diagram, but not clarified in the text.	After discussion with the data management team clarification to the eligibility criteria to make it easier to complete / understand was required. Other changes identified by statistician to meet SAP, and process eval lead.

Trial Summary

Study title	Delivering Effective Non-Invasive ventilation in Motor neuron disease using intensive remote support (DENIM)
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	National Institute for Health and Care Research: Health and Social Care Delivery Research (HSDR) (NIHR158715)
ISRCTN	10105285
Project start date	01/09/2024
Project end date	31/01/2028
Hypothesis, aims and objectives	**Hypothesis**: The addition of a highly intensive, theory-informed, goal-based NIV optimisation package during the first 12 weeks of NIV initiation will lead to increased NIV adherence (defined as the number of days in which patients use NIV for >4hr/day during week 9-12) ≥ 6 days compared to usual care NIV initiation practices in patients with motor neuron disease. **Aim**: To investigate the effectiveness and cost effectiveness of implementing an intensive, theory-informed goal-based approach to NIV initiation which aims to increase NIV effectiveness in people with motor neuron disease. To determine its impact on NIV use and effectiveness and to explore contextual barriers to normalising such a service within routine clinical practice. **Objectives**: 1. A stepped wedge cluster randomised controlled trial powered to detect if the addition of highly intensive, theory-

	informed goal-based approach during the first 12 weeks of NIV initiation increases NIV use and effectiveness; 2. A process evaluation showing how healthcare professionals' self-reported normalisation of this new approach to NIV optimisation within clinical teams is associated with wear time and other measures of success, with pathways to outcome further elaborated through observations, interviews and surveys; 3. An Cost-Effectiveness Evaluation Alongside a Clinical Trial and long-term cost effectiveness modelling, from an NHS perspective.
Trial design	Open label, stepped wedge cluster randomised controlled superiority trial with process evaluation and cost effectiveness evaluation
Internal pilot/feasibility criteria	Pilot green criteria: 1. Site set up Number of centres recruited first patient: 12 (100%) at study month 14, month six of recruitment period) 2.Participant Recruitment: number of centres achieving their individual target recruitment rate (100%) at study month 20, which is month 12 of recruitment period equating to halfway through recruitment 3.Data collection: NIV adherence (primary outcome) obtained from patients who have completed the study 100% at study month 20, which is month 12 of recruitment period equating to halfway through recruitment 4. Intervention delivery: Patients received a clinical review within the specified time windows

	(week 4, intervention fidelity). 100% at study month 20, which is month 12 of recruitment period equating to halfway through recruitment
Setting	Outpatient or inpatient NIV initiation
Participants	Adults with a diagnosis of MND confirmed by a consultant neurologist and a clinical diagnosis of respiratory insufficiency according to local protocols, published guidelines and/or specialist opinion. And have respiratory insufficiency judged by the treating clinician to be severe enough to warrant long-term domiciliary NIV and requiring NIV optimisation within the duration of the study (12 weeks).
Intervention & control groups	Intervention: A theory-based package of staff education, highly intensive support, monitoring and optimisation using telemonitoring during the first 12 weeks of NIV use Control: standard care
Primary outcome(s)	NIV usage at 12 weeks (the number of days in which patients use NIV for >4hr/day during week 9-12)
Secondary/exploratory outcome(s)	NIV effectiveness: NIV usage (w4), ventilation effectiveness (w4&12) (e.g. tidal volumes, ventilator asynchronies, apnoea hypopnoea index, leak) Patient reported outcome measures (w12): Quality of life (McGill quality of life questionnaire, developed for patients with a life limiting illness), Dyspnoea-12 (measuring respiratory symptoms, sensitive to change), S3NIV (measures respiratory symptoms, sleep quality and NIV-related side effects) Health and social care costs EQ5D

	Survival follow-up minimum 12 weeks, maximum of 27 months
Duration of recruitment period and first enrolment date	1st May 2025, 96 weeks
Duration of follow-up	12 weeks follow up. All participants survival followed up at week 116
Target sample size	252 (12 clusters)
Definition of end of trial	All participants completed 12 weeks of NIV optimisation and all participants survival collected at week 116.

2. Introduction

2.1 Background

Motor neuron disease (MND) is a terminal disease affecting 1 in 300 people. Respiratory failure is the major cause of morbidity and death. People typically die within two to four years. Non-invasive ventilation (NIV) is the only intervention that significantly improves both life expectancy and quality of life in MND[1]. It improves breathlessness, sleep disturbance and fatigue and improves survival by an average of 8 months in early trials[2] and 13 months in real-world observations[3]. Developments in respiratory care now means people with MND may live for years if successfully established on NIV [3–5]. Despite clear evidence of benefit, at least half of patients with MND are unable to gain effective NIV and do not gain the survival and quality of life benefits [5–9]. This is because effective NIV requires:

- *Good adherence*: NIV wear time at least four hours per day
- *Effective ventilation*: delivering adequate tidal volumes to reverse hypercapnoea and hypoxia, in synchrony with the patients' own breathing.

Currently guidelines for initiation of NIV in MND lack sufficient detail to achieve optimal NIV in all patients [10, 11]. NIV initiation occurs in hospitals, outpatient clinics, or homes, depending on service capabilities and patient needs. Waiting for intensive hospital initiation can delay NIV set up and reduce survival, necessitating less intensive outpatient setups. Post-initiation optimization requires periodic face-to-face visits to download NIV data and adjust ventilator settings, typically at two to four weeks and quarterly. This travel burden eventually becomes unfeasible for patients. Specialist staff are typically located in large units with limited capacity for home visits. Although guidelines recommend that staff are adequately trained and patients are effectively monitored, most home care is delivered by staff who are not MND specialists and find it difficult to support highly specialist interventions such as NIV.

The barriers to effective NIV

Previous research has identified the barriers and factors associated with successful NIV adherence and ventilation (Figure 1).

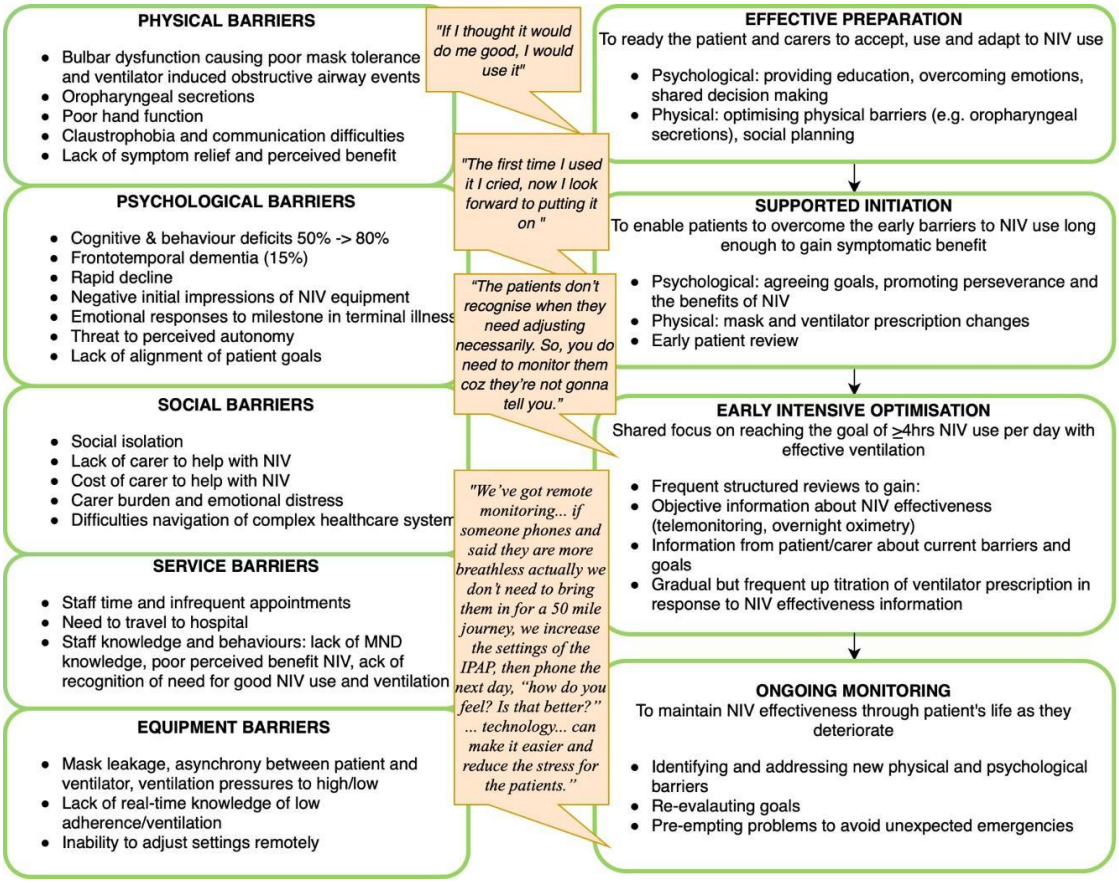


Figure 1 Barriers to effective NIV use and four key steps in the NIV pathway required to address these barriers.

Four key steps in the NIV pathway that are required to address these barriers (Figure 1):

1. **Effective preparation**

   Staff need to work together as a multidisciplinary team (MDT) to address all the barriers experienced by the patient and their carers to ensure they are best prepared to start NIV.

2. **Supported initiation**

   Patients can be quickly demoralised and abandon NIV if they experience problems do not perceive the benefit [12]. Starting and sustaining NIV is hard and provision of psychological and social support and training by healthcare professionals to patients and carers is vital. If patients persevere and begin to recognise symptom improvement, they can overcome these barriers[12].

3. **Early and intensive optimisation**

   Adherence within the first few weeks predicts outcomes[13] and failure to achieve effective ventilation in those with established respiratory failure leads to rapid death[2] or emergency hospital admission. As patients acclimatise to NIV healthcare professionals need to rapidly identify and address problems[14].

4. **Ongoing monitoring**

   Once acclimatised patients will continue to deteriorate, and new barriers will arise which may reduce NIV effectiveness and could cause unexpected physical decline[15]. Improved

monitoring was associated with a 95% one-year adherence[15] but over three quarters of patients required longitudinal adjustments to machine settings for NIV to be optimised, impossible without monitoring.

Telemonitoring in MND provides information about NIV to healthcare professionals without needing any patient involvement. These are securely hosted cloud-based telemonitoring systems provided by the NIV companies. They provide real-time information about NIV adherence (hours used, pattern of usage), and measures of ventilation effectiveness (e.g. tidal volumes achieved, evidence of problems such as mask leakage, measures suggesting airway obstruction, ventilator asynchronies) and allow settings to be changed remotely. This can enable rapid identification and correction of the many identified barriers to NIV success. Telemonitoring improves adherence in sleep apnoea[16] and can support outpatient initiation which is a more cost-effective and faster service than inpatient initiation[17–19]. The technology is increasingly becoming available as standard on modern NIV machines but only a small number of UK MND centres are using telemonitoring in a limited way due to the time, resources and expertise required.

In addition, NIV has a substantial NHS cost (initiation alone costs est. £3575[20]) and using NIV places a high burden on patients, families and carers. Successful NIV involves a multidisciplinary approach with early preparation, supported initiation, early intensive optimisation and ongoing monitoring. This support is not yet ‘normalised’ into routine clinical care for MND.

2.2 Rationale for current study

Patients require universal good standard of NIV care that can be delivered now, to all patients, regardless of geography or NIV centre, harnessing existing and emerging technologies in a sustainable and cost-effective manner.

In order to embed and sustain the support required for effective NIV use, there must be both individual and a service level change within healthcare teams[21]. Normalization Process Theory (NPT [22]) and reference near equivalents from the Consolidated Framework for Implementation Research (CFIR[23]) and Expert Recommendations for Change (ERIC[24]) have guided the theory and structure of a 12 week intense support intervention for MND healthcare teams.

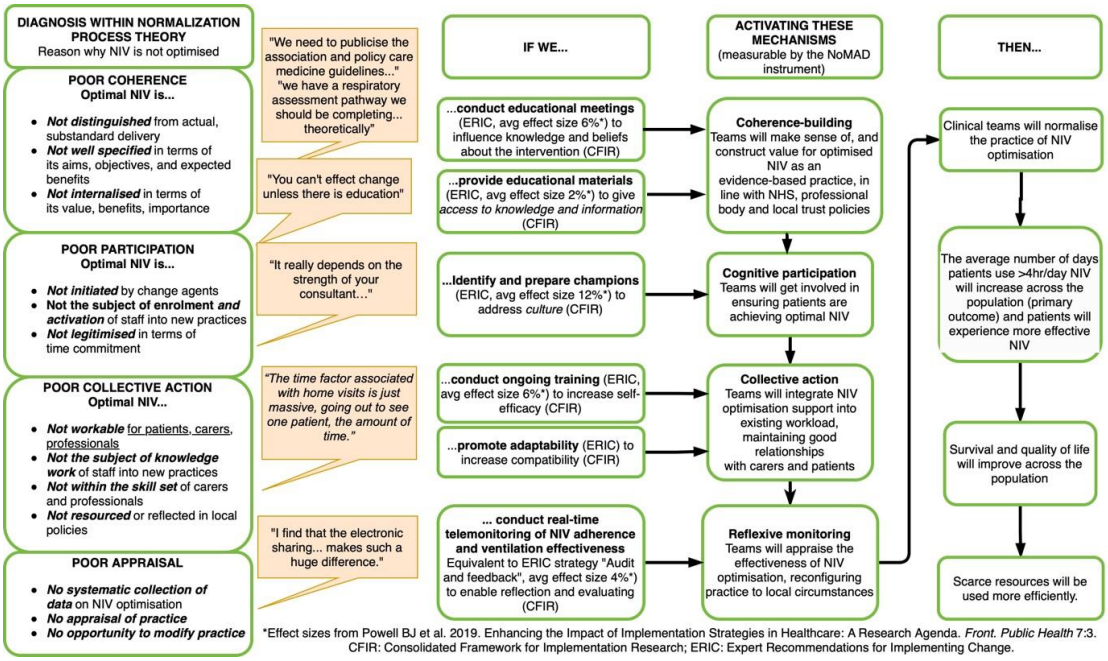


Figure 2 A programme theory articulated using Normalization Process Theory, ERIC, CIFR and empirical data from pilot work and the literature

Optimal use of NIV is not currently 'normalised' in services (implemented, embedded, spread and sustained), because there is poor *coherence*, *participation*, *action* and monitoring.

***Coherence*:** professionals do not see value in optimising adherence and ventilation or differentiate our approach from the way NIV is routinely used. We address this deficit in *knowledge and beliefs* (CFIR) about NIV through *educational meetings* (ERIC, average effect size 6%[25]) and *educational materials* (ERIC, average effect size 2%[25]). Through *building coherence* (NPT mechanism) we aim to increase NIV optimisation.

***Participation*:** We found a universal desire for improvement at both an individual and service level amongst professionals who deliver NIV[15]. However, these individuals (physiotherapists, nurses) do not feel confident enough or lack the resources to enact changes in their clinical practice. To address this deficit in *culture* (CFIR), we will *identify and prepare champions (*local at site and also those within the research network*)* (ERIC, average effect size 12%[25]) in order to increase NIV optimisation.

***Action*:** Healthcare professionals told us they lack the expertise and confidence to review patients, communicate efficiently with the patient/carer and act upon the results. There is a lack of skills needed to coach patients and carers to address the whole range of biopsychosocial barriers and difficulties aligning their approach and long term need to achieve effective NIV to deliver surgical and quality of life benefit with the goals and needs of the individual and the immediate burdens of NIV[21]. Funding constraints (time, equipment) presents a major constraint to the integration of optimised NIV into clinical practice[21]. To address this deficit in self-efficacy (CFIR) we will *conduct ongoing training* (ERIC, average effect size 6%[25]) and *promote adaptability* (ERIC), through empirically observed,

context-specific strategies, such as adjusting monitoring frequency[26]. Through increasing effective collective action, we aim to increase NIV optimisation.

Monitoring: Staff are currently unable to tell if patients are experiencing a problem with NIV. We will address these deficits in *goals and feedback* / *reflecting and evaluating* using real-time telemonitoring of NIV adherence and ventilation effectiveness. Such *audit and feedback* (ERIC) confers an average effect size 4% in implementation science meta-analyses[25].

In line with the new MRC Framework[27], **we have refined a programme theory stating:**

If we:

- activate local clinical leaders/champions, provide educational materials, meetings, outreach/ongoing training and local adaptation

We can help healthcare professionals caring for MND patients to:

- make sense of, and construct value for the timely optimisation of NIV use and ventilation, as an evidence-based practice, in line with NHS, professional local policies;
- get involved in ensuring patients are achieving optimal NIV
- take action, integrating NIV optimisation support into existing workload, maintaining good relationships with patients
- appraise the effectiveness of the NIV optimisation, reconfiguring it to local circumstances.

Then clinical teams will:

- normalise the practice of NIV optimisation

So that NIV is optimised:

- the average number of days patients use >4hr/day NIV will increase across the population (trial primary outcome) and patients will experience more effective NIV

So that outcomes are improved:

- Survival and quality of life will improve across the population
- Scarce resources will be used more efficiently.

Given this theory, can we successfully change clinicians' attitudes and behaviours in order that they can change practice, so they act to intensively optimise NIV? Does this change bring out improvement in NIV effectiveness and clinical outcomes in a cost-effective manner? How can the change in practice be embedded and sustained in clinical practice in MND care centres in the UK?

The study will be conducted in accordance with the protocol and ICH GCP.

3. Aims and objectives

3.1 Hypothesis

The addition of a highly intensive, theory-informed, goal-based NIV optimisation package during the first 12 weeks of NIV initiation will lead to increased NIV adherence (defined as the number of days in which patients use NIV for >4hr/day during week 9-12) compared to usual care NIV initiation practices in patients with motor neuron disease.

3.2 Aims

The primary aim of this study is to evaluate the effectiveness of the DENIM implementation strategy, which is intended to deliver a new intensive NIV initiation service, for patients with motor neuron disease. The secondary aim is to assess the impact of the DENIM strategy on clinical outcomes for these patients, including use and effectiveness. DENIM also aims to understand the cost effectiveness of the new service and explore contextual barriers to normalising such a service within routine clinical practice.

3.3 Objectives

1. To conduct a stepped wedge cluster randomised controlled trial to detect if the addition of highly intensive, theory-informed goal-based approach during the first 12 weeks of NIV initiation increases NIV use and effectiveness;
2. To conduct a process evaluation showing how healthcare professionals' self-reported normalisation of this new approach to NIV optimisation within clinical teams is associated with wear time and other measures of success, with pathways to outcome further elaborated through observations, interviews and surveys;
3. To conduct a Cost-Effectiveness evaluation alongside a clinical trial and long-term cost effectiveness modelling, from an NHS perspective.

4. Trial Design

DENIM is a multicentre, type 3 hybrid implementation-effectiveness, open-label, stepped wedged, cluster-randomised controlled superiority trial of intensive monitoring and optimisation of non-invasive ventilation verses usual care. DENIM will recruit n=252 participants.

12 UK NHS sites will open recruitment for a roll-in period of six months. As sites are opening all patients will be recruited to receive the usual care delivered at that site. Following this, every three months thereafter, two sites each will receive training and all participants at that site will receive the

intervention until all sites have begun using the intervention (recruitment 24 months + final 3 months to allow follow-up, see flow diagram, figure 3). The maximum follow-period will be 27 months (116 weeks). The total duration of the trial is 41 months.

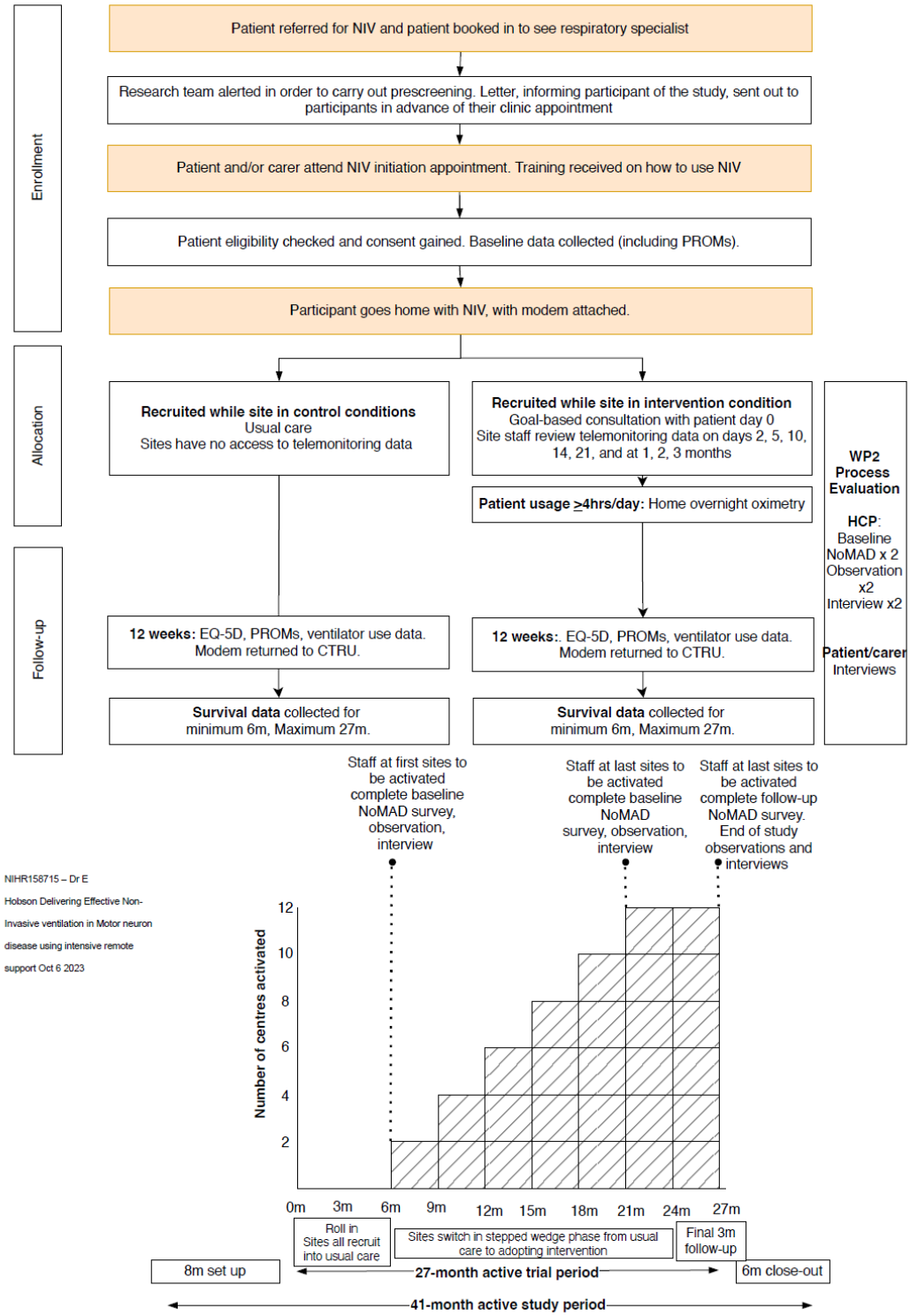


Figure 3. DENIM Trial flow diagram

5. Selection of participants

5.1 Inclusion criteria

1. Aged 18 years or over.
2. Have a diagnosis of MND confirmed by a consultant neurologist
3. A clinical diagnosis of respiratory insufficiency according to local protocols, published guidelines and/or specialist opinion.
4. Respiratory insufficiency judged by the treating clinician to be severe enough to warrant long-term domiciliary NIV and requiring NIV optimisation within the duration of the study (12 weeks).
5. Initiated on NIV at home or in an outpatient setting, or admitted in hospital and is expected to reside in hospital less than 72 hours in an environment with access to inpatient scheduled intensive NIV initiation.
6. Able to provide informed consent. Adults agreeing to try NIV and able to provide assent (evidence of agreement to take part in the study) but unable to provide informed consent will be able to participate if a consultee (close relative or informal carer) provides a consultee declaration.

5.2 Exclusion criteria

1. Already initiated on NIV/CPAP for MND or another reason
2. Using tracheostomy ventilation
3. No way to connect the ventilation software to the internet whilst in the community
4. Not requiring optimisation within 12 weeks (e.g. those given the machine but are unable to commence NIV due to lack of social care).
5. Initiated on NIV in hospital and are expected to reside in hospital more than 72 hours in an environment or with a care plan which includes access to scheduled inpatient intensive NIV initiation*

**Environments/care plans with access to inpatient intensive NIV initiation would include high dependency, intensive care units, respiratory or neuromuscular complex care unit, AND where the patient's care plan includes access to a scheduled specialist review of their NIV initiation at least three times per week. Patients who are expected to stay longer than 72 hours but are not expected to reside in this environment e.g. they are transferred to another ward, hospital or receive a less intensive care plan whilst awaiting social care planning would be eligible for DENIM.*

5.3 Target Healthcare Professionals

DENIM will include healthcare professionals already working within the home ventilation service responsible for delivering NIV, typically physiotherapists or nurses. The wider MND team will be invited to shorter training to familiarise themselves with the intervention and trial procedures.

5.4 Participant identification

A member of the patient's care team will identify and consent eligible participants that have been referred to collaborating centres for NIV. We aim to recruit 252 participants during NIV initiation visits. The local research team will be alerted to carry out pre-screening after referral and notify the central team of any written or spoken translation services required.

5.5 Informed consent process

The trial will be coordinated from the Clinical Trials Research Unit (CTRU) in Sheffield Centre for Health and Related Research (SCHARR). A member of the patient's care team at individual sites will identify and consent potential participants. A letter and information sheet about the study (including summary in the appropriate language) will be sent out in advance of their NIV initiation clinic appointment. Where inpatient recruitment is occurring, a letter and information sheet will be given in person and the potential participant given sufficient time to read, ask questions and consider the study. During their clinic appointment they will be rescreened to check eligibility and given the opportunity to ask questions from both the clinical and research team. No study related procedures will occur before the approved consent form is completed, other than initial case note review for eligibility. We will use NHS language interpretation services where required.

Participants can provide written consent. Witnessed consent can be provided for patients unable to speak, read and/or write and can include the use of a communication aid. Participants may choose to nominate a consultee for the duration of their involvement in the trial. For participants unable to consent due to cognitive decline, a consultee declaration may be sought.

For each participant, the original copies of the signed consent forms will be retained by the investigator in the site file but must be made available for inspection by the study monitor. Patients will also receive a copy of the PIS and their consent form to keep, and a copy will be filed in their medical notes and a copy posted or securely emailed sth.denimtrial@nhs.net to Sheffield CTRU. Consent (or consultee declaration) will be verbally reconfirmed at each study visit, as recommended by Good Clinical Practice Guidelines. A screening log will be maintained for each site, to document all potential

participants screened, whether they were recruited, and any reasons for non-recruitment where this information is available.

Patients who decline to participate will be invited to give consent for the study team to contact them to take part in the ACCESS study, at the point of consent to contact, basic demographic information will be collected.

5.6 Timing of recruitment

Patients initiated in emergency or inpatient settings can be approached and consented within 72 hours of NIV initiation and before discharge. Whilst it is recommended that patients are consented on the day of the NIV initiation, if this is not possible, they can be provided with the telemonitoring equipment and consent, and any baseline data collected remotely. Patients in respiratory failure who have been provided with NIV equipment but are unable to start using it (e.g. due to lack of social care) could be eligible for recruitment at the time NIV is started at the discretion of the study team. Day 0 will be the day in which the participant returns home with the ventilator, with the first day of adherence data collection following this (day 1).

5.7 Co-enrolment guidelines

NIV is part of standard care and there is good evidence that NIV is an effective treatment for people with MND. The trial intervention in DENIM is focused on improving initiation and optimisation of this already proven standard treatment. DENIM will allow co-enrolment in other trials/studies.

6. Trial treatment

6.1 Standard care

All sites commence the trial initiating patients in the usual manner. Local variation in site practice is allowed including some sites who have limited telemonitoring services but sites who have an established telemonitoring optimisation service (e.g. more than one preplanned/scheduled telemonitoring review per month) will be excluded. Sites who provide routinely more than two scheduled reviews with access to telemonitoring data within the first two weeks will also be excluded. Sites initiating in hospital but then do not provide more than two scheduled reviews within two weeks will be included.

Initiation location: initiation can occur at home, outpatients or in hospital.

Standard optimisation which is typically, for all patients, a scheduled follow-up telephone review without telemonitoring data at 2 weeks, face to face review at 12 weeks with/without blood gas measurements +/- NIV data downloads + ad hoc consultations triggered by the patient or staff (based on UK wide survey of practice and site consultations [21]).

Overnight oximetry: a limited number of sites use overnight oximetry as a measurement of NIV effectiveness, usually done once the patients used NIV for >4 hours but typically not routinely scheduled for all patients.

As an incentive, participants who are recruited to receive standard care will be signposted to a selection of patient resources (MND Association leaflets, www.mybreathing.mymnd.co.uk, www.denim-mnd.co.uk).

6-1-1 **Site selections**

Site inclusion criteria:

- Sites providing initiation AND long-term monitoring AND optimization of NIV for patients with MND according to local and national guidelines.

Site exclusion criteria:

- Sites with an established telemonitoring initiation AND optimisation service defined as routinely offering to all patients:
    - More than one preplanned/scheduled telemonitoring review per month
    - More than two scheduled reviews with access to telemonitoring data within the first two weeks.
    - Sites initiating in hospital then providing more than two scheduled reviews.

6.2 Intervention

The trial compares the DENIM implementation strategy, which intends to facilitate a new intensive NIV initiation service to improve NIV delivery, to usual care for NIV initiation and management in MND.

Usual care + a goals-based intensive NIV optimisation package supported by staff training and home telemonitoring.

The DENIM implementation blueprint will outline the aims and justification for the intervention, the scope of the changes proposed and the expected milestones, local/individual adaptations and ways to measure progress/success. The ‘Intervention Workbook’ will guide staff through each individual stage in the initiation pathway including pre-initiation assessment, initiation visit including consultations to align patient and staff goals (NIV Goals), telemonitoring and patient reviews and ventilation optimisation. Training material will be shaped by consultation with sites and PPI.

6.2.1 Staff education and training

We will train staff to have the knowledge, skills and attitudes required to deliver the intervention using the DENIM implementation blueprint. Staff directly involved with initiating NIV will receive four hours of training plus ongoing peer support and an additional one to two hours of additional training during the process. Other members of the MDT will be offered a one-hour webinar to align their practice with the aims of the project. Staff training aims to be minimally disruptive: it will be all remote, and a mixture of four webinars (which will be recorded to allow replay and flexible learning) supported by self-directed learning + access to online resources adapted from www.niv4mnd.co.uk. Training topics will include evidence-based NIV optimisation strategies and solutions, telemonitoring and oximetry data interpretation and NIV adjustment, the unique challenges of MND (e.g. cognitive impairment, bulbar dysfunction), goal setting and coaching skills, psychological principles [28](e.g. Acceptance and Commitment principles[29]), advanced care planning, staff wellbeing, cultural competencies and health literacy awareness. This will be delivered by our research team with support from other staff using telemonitoring and telemonitoring companies. It will be sustained through the trial as a network/ community of practice and we will offer additional workshops, drop in, peer support and leadership.

6.2.2 Initiation, monitoring and optimisation schedule

The implementation blueprint describes each timepoint where staff will provide additional support. This additional time (one hour at initiation, 30 minutes per timepoint after this) has been accounted for in excess treatment costs.

Staff will meet with the patient as usual at initiation of NIV. They will use the Intervention Workbook which prompts them to complete a structured assessment using simple tools to identify potential barriers to NIV (e.g. bulbar function scale (CNS-BFS[30]), saliva scale[47], cognitive impairment screening tool[31]). The workbook also promotes conversations to promote facilitators to NIV use (e.g. symptoms they wish to treat, advanced care planning) and helps adapt the treatment schedule to the patient's goals.

Once the patient returns home staff will review telemonitoring data and communicate with the patient/carer at 2,5,10 days, 2,3,4, 8, 12 weeks post initiation + adhoc (e.g. following patient contact). Staff can remotely adjust NIV settings (either using the device or by telephone), change masks and communicate + provide support to patients/carers as needed. Patients undergo home overnight oximetry when usage >4hrs/day providing additional objective measures of NIV effectiveness [46].

6.2.3 Leadership and change agents

NHS clinician co-applicants and experts in telemonitoring will act as early leaders but the site consultation and training will enable identification of early adopters and change agents who, through the network of ongoing peer support will sustain momentum at sites and with the wider MDT.

6.2.4 Local adaptation and refinement

Our intervention guide will outline the local and individual adaptations allowed during the study. Location adaptation will include limited variation in the patient review schedule and agreed use of telemonitoring and overnight oximetry in usual care. Permitted variation will be based on the current evidence and refined with consultations with sites, experts and local champions and PPI. Ongoing consultations will allow further intervention refinement and support site normalisation of NIV (for example, dissemination of new techniques through local champions).

6.2.5 Intervention fidelity and acceptability

We will observe the clinical activity delivered to a patient receiving the intervention. This is planned as part of the pilot following the recruitment of two patients at each site. This will be combined with the research observations (WP2) and results fed back to the research time and (if appropriate) site team(s) to encourage engagement with the intervention and address any issues. Completeness of the workbooks will be used to understand fidelity to the intervention.

6.2.6 Minimising patient and carer burden

The focus of this intervention is on the training and practice change of clinical staff. The main additional activity for patients and carers during this intervention is increased contact with staff to receive the additional support to use NIV. Most/all of this will be by telephone or in a way that meets their needs. If they wish to use it, patients & carers will receive low burden, accessible resources adapted from existing resources already recommended to support NIV initiation (MyBreathing website + paper resources + “MyNIV” initiation paper/digital care plan). Translations and easy read versions will be available (paper + subtitled videos where possible).

6.2.7 Minimising healthcare professional burden

Whilst staff will be expected to review telemonitoring results frequently and adhere to the goal-based approach, patients/carer contact will be driven by clinical need and options for digital communication will be encouraged (e.g TiM/other patient apps where available, phone, video, text or email) to allow staff to successfully incorporate this into their schedule.

7. Randomisation and enrolment

Randomisation will occur at the site (NHS Trust) level, with sites randomised to either implement the DENIM strategy or continue with usual care for NIV delivery.

This is a cluster-stepped wedge trial. UK NHS sites will open recruitment for a roll-in period of six months. As sites are opening patients will be recruited to receive the usual care delivered at that site.

Following this, every three months thereafter, two sites each will receive training and all new patients at that site will receive the intervention until all sites have begun using the intervention.

Sites will be allocated to start the intervention in a random order using constrained random allocation, an analogue of minimisation for trials randomised at the cluster level[32]. Stratification factors will be centre size, telemonitoring use (% of patients currently used) and location of initiation (% of patients initiated as inpatient).

8. Outcomes

Secondary patient outcomes can be completed at home using a postal or online questionnaire, or if preferred telephone questionnaire. Baseline data is mostly that collected as part of usual care and will assess the severity, risk of death and risk of NIV ineffectiveness. Additional measures collected at baseline aim to describe the potential factors influencing NIV effectiveness e.g. bulbar dysfunction and home situation. The digital healthcare literacy scale[52] is a three-item scale that can be used to identify those likely to need additional support to use technology.

8.1 Primary outcome/endpoint

NIV usage at 12 weeks (the number of days in which patients use NIV for >4hr/day during week 9-12).

8.2 Secondary outcomes/endpoints

- *NIV usage*: NIV usage (first 14 days, first 28 days)
    - the number of days in which patients use NIV for >4hr/day
- NIV usage: NIV usage (first 14 days, first 28 days, weeks 9-12)
    - the average (mean) daily usage
    - the number of patients achieving >4hr/day for > 70% of nights
- Nocturnal respiratory insufficiency using overnight oximetry for a single night at week 12
- Time spent with oxygen saturations <90%
- Oxygen desaturation index (ODI) of 4%
- *Patient reported outcome measures*: week 12: Quality of life (McGill quality of life questionnaire, developed for patients with a life limiting illness[33]), Dyspnoea-12 (measuring respiratory symptoms, sensitive to change[34], S3NIV (measures respiratory symptoms, sleep quality and NIV-related side effects)[35].
- *Health and social care resource use*: including EQ5D
- *Survival* follow-up minimum 12 weeks, maximum of 27 months (week 116)

8.3 Exploratory outcomes/ endpoints

These will help explain the mechanisms by which the intervention may deliver positive outcomes and the mechanisms that might predict good/poor outcome which could potentially refine the intervention:

- Ventilator effectiveness (same timepoints as for usage)
    - Tidal volumes
    - Ventilator asynchronies
    - Apnoea hypopnoea index
    - Leak
- Nocturnal evidence of REM related desaturation
    - evidence of REM related desaturation trace).
- Explanatory implementation outcomes
    - Assessment of changes in barriers and facilitators to implementation at sites, pre and post intervention
    - Fidelity: Percentage completeness of the first consultant workbook
    - Fidelity: Number of times remote monitoring was reviewed at the pre-specific times
    - Fidelity: Number of times workbook was reviewed per participant
    - Fidelity: Number of actions taken

8.4 Internal pilot feasibility study

The initial 12 months of recruitment (study month 20) will run as an internal pilot. Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on feasibility outcomes (Table 1). Two checkpoints will be used: the first for site initiation (at study month 14, month six of recruitment period) and the second for recruitment, intervention delivery and data collection when the first four sites have been switched onto delivering the intervention (at study month 20, which is month 12 of recruitment period equating to halfway through recruitment).

Table 1. Pilot feasibility study criteria

Table 1. Pilot Criteria	Red (% met)	Amber (% met)	Green (% met)
Phase 1. Site Initiation			
1. Site set up (number of centres recruited first patient)	<7 centres (<60%)	7-11 (60-99%)	12 (100%)
Phase 2: Recruitment and follow up			
2. Participant Recruitment (number of centres achieving their individual target recruitment rate)	<7 centres (<60%)	7-11 (60-99%)	12 (100%)
3. NIV adherence (primary outcome) obtained from patients who have completed the study	<70%	70-99%	100%
4. Patients received a clinical review within the specified time windows (week 4, intervention fidelity).	<75%	75-99%	100%

9. Assessments and procedures

Outcome data will be collected by research nurses, consultant and specialist physiotherapist, either in person during ventilation initiation appointment (baseline) or by postal, online or telephone questionnaire (baseline, 12 week visit). Data on survival will be collected up to a maximum of 116 weeks, through medical records. Data on adherence and ventilator effectiveness will be communicated through telemonitoring software to the Sheffield CTRU (control and intervention) and the clinical team (intervention arm only). Patient interaction with staff will be collected by the site on the intervention worksheets, which will form part of the process evaluation analysis.

In the instance of disparity between ventilator data and reported use from participants, the study ventilator data troubleshooting guide will be actioned.

Oximeter data will be collected using the Nonin WristOx 2 3150BLE Wearable Pulse Oximeter. The oximeter will be couriered to and from participants homes to reduce burden to the participants. The oximeter is worn overnight with a one touch activation. Participants will be asked to wear it overnight. Data will be extracted and stored on a secure drive at the University of Sheffield, following CTRU SOPs. More detail about the process can be found in the study specific Oximeter study SOP.

The following windows are permitted for collection of follow up data. However, where these windows missed due to patient availability rather than an error at site, a protocol non-compliance will not be recorded.

- Baseline (day of initiation +/-3 days for questionnaires, and clinical tests within the last month, but not after initiation)
- Week 12 questionnaires +/- 7 days (between week 11,12,13)
- Week 12 oximetry +/- 7 days
- Survival
- NIV usage outcome windows specified in 8.2

Participant study data will be recorded on study-specific case report forms (CRFs) and patient questionnaires and then entered onto a remote web-based data capture system, transferring data to Sheffield CTRU for analysis. All aspects of data management will be provided by the Sheffield CTRU in accordance with their own standard operating procedures.

CTRU's in-house data management system (Prospect) used for the capture and storage of participant data, uses industry standard techniques to provide security, including password authentication and encryption. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. Project-specific procedures for data management will be detailed in a data management protocol.

9.1 Study assessments schedule

Table 2 Assessment schedule

	Baseline	**Week 1, 2, 3, 4**	**Week 8**	**Week 9, 10,11**	**Week 12**	**Max 27 months (approx week 117)**
Age (DOB), gender, weight, height, ethnicity, NHS number, ventilator serial number	X					
Patient completed ALS functional rating scale revised self-completed (ALSFRS-R[REF])	X					
Date of symptom onset, date of diagnosis	X					
Diagnosis of dementia Motor neuron disease Behavioural instrument-(MIND-B)	X					
Presence of gastrostomy	X					
Slow/forced vital capacity, daytime capillary blood gas	X (Optional)					
NIV initial settings	X					
Indication for NIV Urgency of need for NIV	X					
Digital healthcare literacy 3 item scale[52]	X					
Ability to use the mask independently	X					

Number of adults living in household	X					
Clinical Secretion Scale-MND (CSS-MND)[47]	X					
NIV adherence*		●		●	●	
Ventilator effectiveness*		●	●	●	✉/☎/💻●	
Overnight oximetry (including recording skin tone)					✉	
Survival (follow-up min 3m, max 27m)					X	X
EQ-5D	X				✉/☎/💻	
Dyspnoea-12[50]	X				✉/☎/💻	
McGil-R Quality of Life questionnaire[49]	X				✉/☎/💻	
S3NIV [51]					✉/☎/💻	
S3NIV modified (not validated)	X					
Health resource use diary	X				✉/☎/💻	
Patient interactions with clinical team (staff diary)	X	X	X	X	X	
Telemonitoring data – clinical team interaction with system	●	●	●	●	●	
Process evaluation interviews patients and carers			X		X	
Process evaluation observations staff/patient interactions	X	X	X		X	
Process evaluation workbook fidelity assessments		X	X		X	

Additional implementation outcomes

	Control arm	Intervention week at training	Intervention end of study
NOMAD clinical team survey	✉ / 💻	✉ / 💻	✉ / 💻

Key:

✉ Questionnaire/CRF completed on paper and returned via post
☎ Questionnaire/CRF completed over the telephone with local study team
💻 Questionnaire/CRF completed online
X assessment in clinic
● data collected from ventilator telemonitoring system
*NIV adherence is collected as per the ventilator standard operating procedures. The exact procedure may differ between ventilator manufactures, please refer to study specific 'ventilator SOPs' for more guidance.

9.2 Unscheduled visits

For participants in the intervention arm, pages in the workbook for unscheduled visits will be provided to capture ad hoc visits outside of the intervention schedule.

9.3 Participant withdrawals

Participants may wish to withdraw from the study or study treatment, or there may be a clinical need to withdraw the participant.

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

Participants who undergo a switch to tracheostomy ventilation will be withdrawn from the intervention but will be encouraged to continue to provide data at 12 weeks and survival outcomes.

Participants whose capacity to give informed consent to continue in the study is impaired or uncertain during the trial (typically due to impaired communication or the development of dementia) will continue in the trial, as long as they indicate assent through a personal consultee and have expressed no desire to withdraw. If the trial team become aware that a participant has lost capacity to consent, a personal consultee (i.e. family member or friend) will be identified from their care records, if not already known to the team. The patient's clinical care team will confirm consent to contact, and the family member/friend will be sent a personal consultee pack to confirm that they believe the patient would wish to continue participation.

Excessive participant withdrawal from follow-up has a negative impact on a study. Sites will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Centres will explain the options for withdrawal:

- Withdrawal from the DENIM intervention only, i.e. no further intervention delivery visits but the participant remains in the trial. Participants who decide to no longer use NIV and/or receive enhanced support will be encouraged to continue with the trial for data collection purposes

and will be switched to receive usual care which allows them to retry NIV at a later date (without re-entry into the study).

- Withdrawal from the DENIM intervention and all but essential data collection, i.e. survival status / cause of death, and routine data from hospital notes +/- ventilation data
- Withdrawal from the DENIM trial entirely. Unless specified by the participant, all data collected up to this point will be used in the analysis and no further intervention or research visits will be conducted.

Participants who wish to withdraw from the interview component of the study will have their interview data withdrawn, as long as they inform the team of this within four weeks of their interview. After this time has passed, data analysis will have begun, and it will not be possible to remove their data. This will be made clear to participants in the Information Sheet.

9.4 Loss to follow-up

Participants will be defined as lost to follow up only if no data can be collected at the study close. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Table 3. Adverse event definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant. *(refer to SOP PM004 Adverse Events and Serious Adverse Events for more details)*
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.

Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: ● Results in death ● Is life-threatening* ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation** ● Results in persistent or significant disability or incapacity ● Is a congenital anomaly/birth defect ● Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**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, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and within the 12 week follow up period. Only AEs related to the trial or trial processes will be recorded.

AEs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

SAEs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. The CTRU will notify the Sponsor of these events through monthly reports.

10.3 Study specific exemptions

Adverse events related to the normal disease progression of MND will NOT be recorded. These include:

- Respiratory system: dyspnoea, respiratory failure, pneumonia
- Thrombotic events
- Gastro-intestinal: dysphagia, constipation
- General condition: accidental injury (fall related trauma) aggravated condition
- Muscular weakness
- Gastrostomy or complications of gastrostomy insertion
- Tracheostomy (this would be an indication for withdrawal)

Adverse events collected on the case report forms will not be recorded on the AE log. These include:

- death
- botulinium toxin injections
- admission to hospital for problems unrelated to respiratory insufficiency or unrelated to MND (except ICU/HDU admissions which should be recorded)

Adverse events judged by site to be unrelated to MND or the study procedures will not be recorded on the AE log.

10.4 SAE notification procedure

Site staff will be responsible for reporting all SAEs. Once an SAE has been identified, a member of the site research team will complete an SAE form, notifying the site's PI and send this to the CTRU.

All SAE forms must be sent by fax to 0114 222 0870 or email to ctru-saes-group@shef-field.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

SAEs which are related and unexpected will be reported to the sponsor and we will expedite these to the Research Ethics Committee (REC) within 15 days of becoming aware.

10.5 CTRU responsibilities

The Sponsor usually delegates CTRU responsibility for the reporting of SAEs to the regulatory authorities and the research ethics committee, as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

11.1 Sample size

The primary outcome is the number of days in which patients use NIV for >4hr, assuming standard deviation of ten0 days with a high skew. A modest change in survival and quality of life requires a large change in adherence; we assume a mean difference of six days to reflect this. Assuming a conservative estimate where each site recruits, on average one patient per month in months 7-24 and three patients in the six months roll in period this will recruit a total of 252 patients. Allowing for 15% drop-out, 214 participants provide 90% power to detect an increase of six days in adherence assuming an inter-cluster coefficient of 0.05 and a two-sided 5% significance level. The sample size was calculated using a modified version of the Stata stepped wedge macro which allowed non-integer number recruited per step.

11.2 WP1 (main trial) Analysis

Data will be reported and presented according to the CONSORT extension for stepped wedge cluster randomised trials[36] and analysed in accordance with a detailed statistical analysis plan.

11.2.1 Analysis populations

Modified Intention-to-treat population (mITT): composed of all consented participants with outcome data, regardless of protocol deviations or withdrawals. Participants will be analysed based on the intervention they were supposed to receive.

Intention-to-treat population (ITT): composed of all consented participants, regardless of protocol deviations, withdrawals, or the availability of outcome data. Participants will be analysed based on the intervention they were supposed to receive. Outcome data will be imputed under different assumptions for this analysis population.

11.2.2 Statistical analysis

The number of days using NIV >4hrs at week 9-12 following NIV initiation will be analysed using a poison mixed effect model with intervention, step (time) and cluster level randomisation factors (centre size, telemonitoring use and location of initiation) as fixed effects and site as a random effect. Effect sizes will be summarised as the absolute difference in mean days along with its 95% confidence interval and p-value. The primary analysis will be on the mITT analysis population.

Continuous secondary outcomes will be analysed in the same way as the primary outcome. A logistic regression will be undertaken to analyse binary secondary outcomes using a model similar to that for the continuous outcomes. Differences between treatment groups will be reported as odds ratios with associated 95% confidence intervals and p-values. Time to event data will be analysed using a shared frailty Cox model. Secondary outcomes will be analysed for the mITT population.
Methods for handling missing outcome data across the analyses will be described in the statistical analysis plan.

Additional exploratory analyses will investigate whether participant and disease characteristics (e.g. age, sex, time since symptom onset, presence of upper airway secretions) are potential predictors of NIV use or moderators of treatment efficacy.

WP2 (process evaluation) analysis please see section 12.2.

11.3 WP3 Health Economic analysis

The initiation of NIV is estimated to cost the NHS £3,211 per year. However, the actual cost is expected to be significantly higher when factoring in the additional social care needed to support NIV use. A substantial portion of this cost comes from inpatient and emergency care, which are particularly high for MND. This includes £1,603 annually for hospital stays and £918 for emergency home visits[37]. The CE will take an NHS and personal social services cost perspective to determine the cost of non-invasive ventilation (and potential cost savings) and its cost-effectiveness.

It will be reported as incremental cost per QALY gained and net monetary benefit at 12 weeks of follow-up (within-trial analysis) and over a lifetime (decision model). Uncertainty will be shown on a CE acceptability curve and CE plane. QALYs will be derived from the EQ-5D-5L completed by the patient at w0 and w12. The mapping function developed by the NICE Decision Support Unit using the 'EEPRU dataset'[38] will be used to estimate EQ-5D-3L responses, the presently favoured iteration of EQ-5D by NICE[39]. A PPI approved service use questionnaire (low burden) will collect minimal data on the costs at baseline and subsequent follow up weeks. Hence, the analysis of resources will

be of the main costs incurred in people with motor neuron disease, with the resources considered in the survey identified prior to data collection in discussions with the PPI group (likely resources to feature on the survey are high-cost episodes e.g. inpatient/emergency department visits and community appointments and those requiring travel/ambulance and a limited (no more three) high cost MND medications possibly including dosage). We collect cost data at baseline to allow for an analysis that controls for significant differences or high variability across groups.

Unit costs applied to these services will be derived from hospitals or national sources. Caregivers may be required during both day and night, as some patients may need support overnight, and where possible unit costs will reflect the excess staffing costs incurred during night care. To capture the intervention costs, we will collect the number of interactions[40], the type of professional involved in the care from trial records and if available the time of day of the interaction (day or night). We will collect the time per patient via a staff questionnaire completed by all health service staff involved on delivering the intervention. The final administered staff survey at 12 months will collect data on the total time spent on training, preparation, troubleshooting, and other associated activities of delivering the intervention in addition to time per patient contact. This information could be collected from the dedicated staff resource survey at 12 weeks but we will explore the option of collecting this information from the NOMAD clinical team survey at week 12. In addition, we will consider using NOMAD to collect additional information on composition of the staff team, patient contacts and whether they were day/night to validate the information collected from trial records. Bootstrapped results will account for uncertainty in the trial data. The model-based lifetime extrapolation will be of resource use, survival and health utility, supplemented with longer-term survival data collected after 12 weeks. Information on the longer-term resource use and health related quality of life changes from ventilation use will be sourced from the research literature and uncertainty in these values will be explored in sensitivity testing. Where required, the analysis will adjust for baseline costs to address the expected high variability in trial costs between groups, driven by likely substantial individual differences in service use and MND-related treatments (such as emergency visits) that could potentially exceed the intervention costs by a high degree.

12. Ancillary sub-studies

12.1 Embedded process evaluation

In order to understand participant experience and the implementation process (including barriers and facilitators to implementing the new intensive NIV initiation service), a mixed-methods embedded process evaluation will be conducted in accordance to the MRC framework[41]. The primary focus is on implementation outcomes. Quantitative data on NIV usage from participants ventilators will provide clinical context to interpret the implementation findings.

12.1.1 Aims

The process evaluation will aim to understand the following:

1. What is implemented at sites and how the intervention was delivered?

2. How does context affect implementation and outcomes, including staff and patient participants experiences?

3. How did the effects of each intervention occur (mechanisms of impact) and whether these were in line with the expected programme theory set out earlier in the protocol?

12.1.2 Objectives

1. Use the NOMAD survey to understand barriers and facilitator pre and post implementation delivery, in both champions and the wider clinical team.
2. Conduct semi-structured interviews with site staff based on CFIR, to understand barriers and facilitators of the implementation intervention within the healthcare setting.
3. Conduct semi-structured interviews with participants and family members/friends to understand their experiences of the intervention.
4. Assess fidelity of the intervention against the programme theory:
    a. Use quantitative telemonitoring data to identify engagement from site staff
    b. Assess the intervention fidelity by examining 10% of staff worksheets for completeness.
    c. Assess intervention fidelity by observing n=24 participants / staff interactions within clinical consultations
    d. Conduct observations of multidisciplinary team meetings to examine the delivery of the intervention and its impact on the wider team's behaviour.

12.1.2 Methods

A multiple-case design will be used to capture the variation in intervention delivery across sites, explore participant responses to the trial, and barriers and facilitators to implementing the intervention. This will be conducted in all 12 sites. This will document the conditions that are necessary for goal-based approach to NIV to be normalised and obtain the perspective of professionals directly involved in intervention implementation, supporting trial recruitment and supporting participants and their families.

During the control arm phase, all sites will complete the NOMAD questionnaire[42] on Qualtrics. The NOMAD includes questions on role within the team and experience of the intervention. Site assessment forms may also be used to provide local context prior to the intervention. Recruitment to the process evaluation interviews and observations will begin once a site switches on to the

intervention. Data collection will not occur in the first 4 weeks of a site using the intervention. The NOMAD questionnaire will be completed again six months after switching to the intervention arm and at the end of the study. We will supplement data collection with study management logs such as site assessment forms. To inform the fidelity assessment we will audit 10% of worksheets for completeness.

Sampling

Patient participants: Patients will be recruited to participate in both observations and interviews where possible. Purposive sampling will be conducted based on predefined participant diversity criteria, including ethnicity, gender, age, disease severity, NIV use at 4 weeks and digital health literacy levels, completed at baseline. We will examine participant characteristic lists to identify potential participants for contact. We will collect sociodemographic characteristics of participants to enable us to monitor inclusivity and respond if necessary.

We will formally monitor recruitment monthly to ensure that participants with a range of characteristics are being recruited. This will be conducted by EH, AG, CG and the post-doctoral researcher. Additionally, a three-monthly report will be presented to the TMG for reflection and advice on future recruitment. Per site, 1-2 patients will be recruited (up to 24 in total) alongside their family members (approximately 24 in total). Patients can participate without a family member agreeing to consent. Where more than one family member is identified, the patient can identify who they wish to be involved in each interview/observation, ideally someone who is supporting the patient to use NIV. We will obtain consent from family members as they become involved in the process evaluation.

Site participants: Alongside these participants, staff members (n=2 per site) will be recruited to participate in interviews. We will strive to recruit staff members with a range of roles, years of experience working with people with MND, and demographic characteristics. Participants will complete consent forms to participate in interviews, and will be asked to opt-out of observations, rather than providing consent.

Site staff NOMAD survey: We will sample staff who are both actively delivering NIV care and staff with supporting roles. Staff will be sent the survey via Qualtrics link. A unique identified will be generated to link questionnaires across timepoints. The first page of the questionnaire will specify who the investigators are, the purpose of the study, how questionnaire responses will be used, and approximate time for questionnaire completion. Readers will be asked to give their consent on the questionnaire cover page, after reading the information, and before completing the questionnaire. Demographic information will be collected from the questionnaires, such as study site, job title, age,

ethnicity and experience of working with patients with MND. Data will be stored on the University secured drive (see section 14 for details).

Patient participant eligibility criteria

1. Have consented to participate in DENIM
2. Are in the intervention arm
3. Are able and willing to participate in interviews (various options for facilitation available) and/or ethnographic observations
4. If relevant, are willing to share their preferred language for participation with the research team, to allow an appropriate researcher to be identified.

Relative/friend eligibility criteria

5. Relative/friend has consented to participate in DENIM
6. Are able and willing to participate in interviews and/or ethnographic observations
7. If relevant, are willing to share their preferred language for participation with the research team, to allow an appropriate researcher to be identified.

Staff interview eligibility criteria

8. Direct contact with at least one patient who is participating in DENIM
9. Are able and willing to participate in interviews and/or ethnographic observations

Qualitative Interviews

An experienced qualitative researcher will conduct semi-structured interviews framed around CFIR and NPT[22] with staff (n=1-2 per site at two timepoints, schedule as per observations) and patients/carers (n=24, 1-3 per site).

Written informed consent will be obtained from all participants where possible. Where a participant is unable to sign their name, a witness will be identified to witness their consent process. Verbal consent will be obtained before all interviews begin.

Informed consent procedures will be completed before any data is collected and will cover agreement to participate in a) semi-structured interviews, b) ethnographic observations, or c) both. Prior to each interview or observation, consent will be reobtained verbally. Consent will be confirmed on the interview recording, or in observation field notes.

Patient and family member/friend interviews

Patients and family members/friends can choose to participate in interviews separately or together. A topic guide will be developed and examples from observations will be used to stimulate discussion. Interviews will be conversational in nature, following the lead of the participant and their communication preferences. Adjustments include use of email, telephone, video or face-to-face interviews, use of proxies, interpreters and communication devices, use of NIV during the interview, frequent breaks. Participants can decline to answer any questions, to end the interview at any time, and can withdraw their data without providing reasons. Interviews will be approximately 30-60 minutes, dependent on what participants wish to say and their preferred interview pace. Interviews will be audio-recorded and transcribed verbatim.

Informal conversations will be offered to participants who may struggle to participate in semi-structured interviews, so they are able to share experiences. Rather than being arranged separately, these will be conducted shortly following the conclusion of observations, where possible, while the participant is still in the clinic setting. We will supplement this data with data from medical records regarding NIV related care (e.g. letters, reports on appointments), where participants consent to this have been involved in observations (1-2 per site).

Where paid social care professionals (e.g. personal assistants) are included in interviews if they are present to support the patient participant, they should provide consent. Individuals present purely to support patient participants who do not consent will have their data removed following transcription.

12.1.3 Ethnographic observations

We will conduct focused ethnography[43] with two patients-staff interactions per site (n=24 total), observing their experiences and interactions with staff around initiation and use of NIV. Prior to patient recruitment, researchers will conduct familiarisation observations of MDT meetings and broader clinic discussions and observe staff training sessions at up to four sites. This will enable familiarisation with usual care practices within the site. Staff will be informed about the observations through posters in their clinic settings, and given the opportunity to opt out having their patient interactions observed.

Appointment observations will be conducted with patients in their NIV initiation appointment (we anticipate this will be approximately four to six weeks following the start of site intervention adoption) and may include other NIV-related conversations that are planned by clinicians. We will ask both the patient and clinician to confirm the date and time of the appointment, which the researcher will attend. We anticipate spending around two to three hours with each patient, spending time with them whilst they’re in the waiting room, during the appointment, and any time after the appointment in the waiting

room. Posters will be placed around areas that observations will take place in, and staff will be recruited on an opt-out basis.

We will also observe an appointment within the last eight weeks of the study during which time the staff will review the telemonitoring data and (as required) communicate with the patient/carer/MND MDT to act upon any decisions being made. We will ask both the patient and clinician to confirm the date and time of the appointment with the research team.

Observation field notes will include conversations and non-verbal behaviours i.e. body language, and communication between participants, focusing on decision-making, barriers and facilitators to NIV initiation and use, and any identified care needs. The researcher will be a non-participant observer who will attend in person and sit in the corner of the appointment room without contributing to the discussion. Following appointments, researchers will engage in informal conversations with people with MND and their carers to further explore observed experiences. These conversations will take place in confidential spaces, such as the appointment room or another room within the NHS Trust building. We will adapt the format of observations and informal conversations to the abilities and preferences of participants, i.e. their favoured communication method.

12.2 Analysis

Ethnographically informed thematic analysis will be used to conduct line-by-line coding to develop an initial coding framework, drawing together data from observation field notes, informal conversations, medical records, and interviews together. We will analyse multiple sources of data from each individual together where possible (see Data Triangulation below).

Data interpretation will be iterative, building on data collected in WP1. Each interview/focus group transcript and set of field notes will be independently coded and analysed by two researchers, before being applied to the framework. Codes and themes will be compared across participants and sites, to develop a contextualised understanding, incorporating any changes over time. We will explore verbal and non-verbal interactions between participants. PPI representatives will work alongside us to develop and refine themes in smaller group discussion sessions. Staff data will initially be analysed separately to those with people with MND and carers, before the developed themes will be compared and contrasted to produce definitive themes. These themes will be finalised through review and discussion. Analysis will be conducted concurrently with data collection, to monitor data quality and inform subsequent data collection.

Data triangulation

Each case will have four embedded units of analysis; the three aspects of the process evaluation (interviews, ethnographic observations, staff survey), alongside NIV-use data from participants ventilators. We will deductively code ethnographic field notes and interview transcripts to NPT constructs, with a small group of the research team (EH, AG, CM), before sharing this with the wider team. We will then conduct a cross-case framework analysis[44], integrating the results with NoMAD / NIV-use statistics in joint display tables[45]. Differences/changes in adherence will be compared across sites and in relation to measures of normalisation (NoMAD) and site characteristics (caseload, current standard of care) to understand how the programme's efficacy depends on aspects of context. This will identify specific strategies that could improve adherence to the intervention protocols and procedures. We will then share these strategies with those monitoring data quality and across sites, to help improve adherence.

12.3 Accessing Care and Clinical Engagement in Support Services for NIV (ACCESS sub study)

Equality, diversity and inclusion research embedded within the process evaluation

Research question

What are the barriers and enablers to effective recruitment, retention and engagement of participants from underserved MND populations and how might these be addressed?

Aim

To investigate the participants' experiences of barriers and enablers, and intersectional factors (e.g., culture, ethnicity, socioeconomic status) that influence participation in DENIM. We will also speak to participants least likely to participate in MND clinical trials and/or who face the most difficulties receiving the proposed intensive NIV initiation. We will also explore to what extent our EDI component helped facilitate or hinder participation, to make recommendations for this trial and for future trials of complex interventions in long-term neurological conditions.

Inclusion criteria

The study will purposefully sample participants known to be less likely to participate in MND research or gain value from NIV:

- From an ethnic minority and/or where the patient's main language is not English
- Or with low levels of digital health literacy (either those identified by the site teams or those scoring <7 on the 3-Item Measure of Digital Health Care Literacy) [52]
- Women over 80 with bulbar onset disease

Patient interviews

We will also aim to recruit 10-15 patients (+/- carer) who declined to participate in DENIM. For participants who decline to participate in the main trial, the site team will obtain either written or verbal (witnessed) consent from the research team to contact them about participating in this interview. All potential participants will be provided with an information leaflet about the interview by post or in person, with time to consider their participation. If they decide to participate, informed consent will be obtained in writing or via telephone or video call. Telephone and video consent will be audio recorded separately to interview, and stored it for auditing purposes.

We will interview them within four to six weeks of recruitment/decline. Methods for interviews will be the same as the process evaluation (use of translation for materials and interpreters for interviews, telephone/video/face-to-face/email interviews). To minimise burden, we will include additional questions to the topic guide when interviewing participants recruited into the study to explore the research question and seek to overrecruit from the backgrounds described above.

Staff data collection

Existing planned interviews and observations topic guides, as part of the process evaluation, will include a specific focus on diversity and aim to over recruit for observations from these patient populations.

We will make field notes during discussions with consenting site staff during training.

We will add a short questionnaire at the time of the two planned staff surveys (two months prior to sites starting intervention and six months after starting) exploring staff perceived barriers towards recruitment in underserved groups and seek to address these if feasible.

Topic guides will be developed under the guidance of our EDI lead, diverse PPI members and the wider literature on understanding of and attitudes towards clinical trials (in particular complex interventions), barriers and enablers to participation and retention, attitudes towards being in the control/intervention. Documents will be submitted and approved by REC.

13. Trial supervision

13.1 Trial Steering Committee

The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider

recommendations from the DMEC. The TSC will meet every six months from the start of the trial and consist of an independent chair and other professionals with relevant clinical and academic experience and two patient representatives. The TSC has the capability to prematurely close the trial.

13.2 Data Monitoring and Ethics Committee

The Data Monitoring Ethics Committee (DMEC) will consist of an independent statistician, and a independent physicians. There will be no interim analyses other than to confirm the internal pilot / stopping guidelines, but the DMEC will be able to request data and recommend study termination to the TSC/funder on grounds of safety or futility. The DMEC will meet every six months from the start of the trial to review reports provided by the CTRU and assess the progress of the trial.

13.3 Trial Management Group

The Trial Management Group (TMG) is comprised of the CI, trial manager, statistician, data manager, health economist and grant co-applicants. PIs will also be invited to represent sites. The CI will chair monthly meetings with the TMG to discuss the day-to-day implementation of the study. The Trial Manager who will be jointly supervised by the CI and the Assistant Director of the Sheffield CTRU and will liaise with the whole study team. The Trial manager will contact the CI and meet with the Assistant Director of the CTRU regularly.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant.

All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres. All CRFs will only identify the participant by their study ID number.

Study records, including source data, will be stored for 10 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 10 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 10 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 10 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files. Archived documents will be transferred to the Sponsor before destruction.

14.1 Archiving

Data held by the CTRU will be stored in accordance with the CTRU archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on a register, which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

15. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The research staff at each site will enter data from source documents into the study specific Prospect database when available. After data has been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician. Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central and/or on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment and will be documented in the Site Monitoring Plan (SMP). This will include (at a minimum):

1. Source Data Verification (SDV)
2. SAEs/SUSARs – reported to the Sponsor and followed up to resolution

3. Resolution of data queries
4. Investigator site file maintenance
5. Training records for site staff (trial specific and GCP) and appropriate delegation of duties
6. Patient consent procedures
7. Reporting of protocol non-compliances

15.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and, for CTIMPs, the MHRA in writing within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

15.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed or carried out remotely for each participating site before each site recruits their first participant. During this visit/remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to share consent forms with CTRU via [insert study nhs.net account]. This will be made clear to the participant prior to their consent to the trial.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress. The results will be published on a freely accessible database within one year of completion of the trial. Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

We will write an academic paper and lay summary blog and simple video/infographic co-produced with our PPI group. We will also host an online webinar to share our findings.

We will report to the wider MND Research Institute community to provide recommendations for the conduct of other trials ongoing and planned. Findings will also be disseminated to the wider trials community such as the NIHR Trials Methodology Research Partnership, UK Trial Managers Network and Health Research Board (HRB) Trials Methodology Research Network.

17. Finance

The DENIM trial is funded by The National Institute for Health Research (NIHR) Health and Social Care Delivery Research (HSDR) reference NIHR158715. Participants will not be reimbursed for their time in the trial. Further funding details are included in the site agreement.

18. Ethics approval & regulatory compliance

Before initiation of the study at participating site, the protocol, informed consent forms and information materials to be given to the participants will be submitted to Leeds East NHS Research Ethics Committee (ref 25/YH/0019)Any further amendments will be submitted and approved by the HRA and ethics committee.

The study will be submitted to local participating Trusts to confirm Capacity and
Capability before any research activity takes place. The study does not require further regulatory approvals as patients are offered NIV routinely as standard care.

19. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval. A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. Recruitment of study participants will not commence at a site until a letter of of Confirmation of Capacity and Capability (CCC) has been issued.

20. Trial Organisation and Responsibilities

20.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

20.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Study Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient & Public Involvement (PPI)

The study has been designed in conjunction with members of the Sheffield MND Research Advisory Group and Better Outcomes in MND Advisory Group (BOND) and consulted members of the Cicely Saunders Public Involvement Forum. These groups include people living with MND, family members, carers and ex-carers and members of the Motor Neuron Disease Association who are peer supporters and have extensive experience visiting people with MND in their home.

An PPI advisory group of 6-8 people with lived experience of MND, co-chaired by DN (co-applicant) and the project PPI lead, has been established and will meet quarterly. Between meetings group members will receive bi-monthly newsletters and progress emails. The PPI group will contribute to the development of trial processes and documents, including the DENIM PPI Plan.

The PPI Plan will be used as a means of monitoring PPI activity throughout the trial, keeping track of the cost of PPI, and evaluating and reporting on PPI activity at regular intervals. Group members will be invited to attending training sessions to enable them to engage in data analysis alongside the research team.

22. Indemnity / Compensation / Insurance

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

Standard NHS indemnity operates in respect of the clinical treatment that is provided.

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