COMBINED PROTOCOL FOLLOWING RESEARCH ETHICS COMMITTEE (REC) FAVOURABLE OPINION AND HEALTH RESEARCH AUTHORITY (HRA) APPROVAL

PROTOCOL INFORMATION

FULL/LONG TITLE OF THE STUDY: The use of neuromuscular electrical **STIM**ulation as a treatment for sarcopenia in people on **H**aemo**D**ialysis

Work package 1: External pilot

Work package 2: Efficacy study (Randomised Controlled Trial)

Work package 3: Health economic evaluation

Work package 4: Optional mechanistic study

SHORT STUDY TITLE / ACRONYM: STIM-HD

FUNDER(S): This study is funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR158852). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FULL/LONG TITLE OF THE STUDY

The use of neuromuscular electrical STIMulation as a treatment for sarcopenia in people on HaemoDialysis – Work Package 1

SHORT STUDY TITLE / ACRONYM

STIM-HD – WP1

PROTOCOL VERSION NUMBER AND DATE: V1.2, 29 January 2025

IRAS number:	347115
Sponsor:	University of Leicester
Sponsor number:	0968
Funder(s) number:	NIHR EME (ref: NIHR158852) This study is funded by the NIHR Efficacy and Mechanism Evaluation (EME) programme (NIHR158852). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
Study registration number	n/a

This protocol has regard for the HRA guidance and the University of Leicester Sponsor Standard Operating Procedures (SOPs).

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the study without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given. Any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

Chief Investigator:	
Name: (please print):	Prof James Burton
Signature:	
Date:	
Principal Investigator:	
Site:	Loughborough University
Name: (please print):	Dr Jakob Skarabot
Signature:	
Date:	

KEY STUDY CONTACTS AND INFORMATION

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Sponsor	Research Governance Office Research & Enterprise Division University of Leicester University Road Leicester LE1 7RH RGOsponsor@le.ac.uk 0116 3736508
Clinical Trials Unit	Not applicable.
Funder(s)	NIHR EME Programme NIHR Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS netsmonitoring@nihr.ac.uk **Funder reference:** NIHR158852
Funding start and end date(s)	01/09/2024 – 29/02/2028
Key Protocol Contributors	Prof Jonathan Folland Dr Emma Watson Prof James Burton Dr Gordon McGregor Ms Niamh Quann
Collaborators	Prof Jonathan Folland Dr Emma Watson Prof James Burton Dr Gordon McGregor

	Prof Indranil Dasgupta Mr Fez Awan
Statistician	Prof Laura Gray Dr Shaun Barber
NIHR Portfolio adopted	Yes

ROLE OF THE STUDY SPONSOR

The Sponsor for this research project is the University of Leicester.

The University of Leicester is responsible for the design, management and outputs of the research. Participating NHS sites and Loughborough University are responsible for the conduct of the study within their organisation.

The Research Governance Office review and approve all iterations of the protocol as part of their Sponsor review and amendment review processes. Further information is available from our Sponsor Standard Operating Procedures webpage.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The study will have a Trial Management Group consisting of key protocol contributors (Dr Jakob Skarabot, Prof Jonathan Folland, Dr Emma Watson, Prof James Burton) that will meet on a monthly basis during the recruitment phase. If the recruitment rate is lower than desired, strategies will be put in place to ensure the recruitment is adequate for completing the study in the planned timeline.

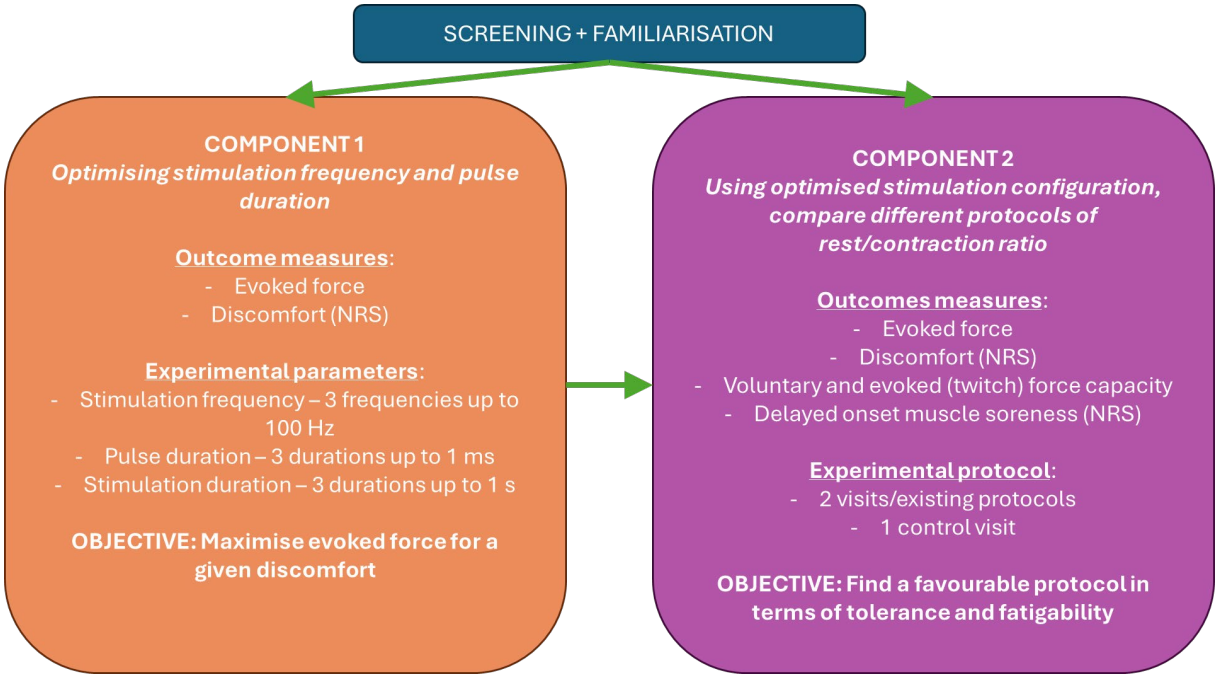
Loughborough University will act as a site where research will be performed, whereas University Hospitals Leicester will act as a Participant Identification Centre.
Prof James Burton will delegate the site principal investigator responsibility to Dr Jakob Skarabot.

CONTENTS

STUDY SUMMARY

Full study Title	The use of neuromuscular electrical STIMulation as a treatment for sarcopenia in people on HaemoDialysis	
Short Study Title	STIM-HD – WP1	
Study Design	**Work package 1:** Cohort observation - basic science study involving procedures with human participants	
Study Participants	Adult haemodialysis patients (age >18 years) undertaking HD for >3 months (home or unit based)	
Sample Size	24	
Planned Study Period	02/12/2024 – 25/07/2025	
	Objectives	**End Points / Outcome Measures**
Primary	To determine the neuromuscular electrical stimulation (NMES) stimulation parameters (frequency, pulse duration, and stimulation duration/number of pulses) that maximise evoked force production of the thigh muscles for a given level of discomfort.	Evoked force Discomfort (numerical rating scale)
Secondary	To compare the perceived discomfort and fatigue responses between two different NMES protocols with different rest/contraction ratios and a control (no stimulation) protocol.	The change in evoked force The change in voluntary force The change in discomfort (numerical rating scale) The change in rate of perceived exertion (CR10 scale) Delayed onset muscle soreness (numerical rating scale)

STUDY FLOW CHART



NRS = Numerical Rating Scale

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CKD	Chronic kidney disease
CRF	Case Report Form
CTU	Clinical Trials Unit
DOMS	Delayed onset muscle soreness
EME	Efficacy and Mechanism Evaluation (Programme)
GCP	Good Clinical Practice
HD	Haemodialysis
Hz	Hertz
ICF	Informed Consent Form
ISF	Investigator Site File
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health and Care Research
NMES	Neuromuscular Electrical Stimulation
NRS	Numerical rating scale
PI	Principal Investigator
PIS	Participant Information Sheet
RPE	Rate of Perceived Exertion
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group

KEY WORDS

Chronic kidney disease, sarcopenia, muscle function

PROTOCOL AMENDMENT HISTORY

Amendment Reference	Protocol version no.	Protocol Date	Author(s) of changes	Summary of changes made
NSA01	1.2	29/01/2025	Niamh Quann	1. Page 8, Study summary table, secondary outcomes: 'The change in rate of perceived exertion (CR10 scale)' added to align with the wording in the Objectives and Outcome Measures/Endpoints table, page 12. 2. Page 19, Section 5.5, Study intervention(s) and comparator(s), Description of study intervention: 'A NMES protocol of 5 sets of 10 contractions with either a 5 or 15 second rest' changed to 'A NMES protocol of 5 sets of 10 contractions. The contractions within each set will be delivered for 3-10 seconds with a between-contraction rest period of 5-30 seconds'. Change made to align with the wording on page 18, section 5.4, Study visits and assessments - COMPONENT 2 Experimental visits.

1 Background and Rationale

Sarcopenia, a loss of muscle mass and strength (1), is a common and costly condition (£2.5 billion to NHS annually) associated with worse clinical outcomes, including poor quality of life, higher hospitalisation rates, and increased mortality. Chronic kidney disease (CKD) is a public health emergency, affecting around 14% of adults in England (2). In advanced CKD, haemodialysis (HD) is often required. Sarcopenia is a frequent complication of CKD, affecting around 28% of people with more advanced disease (3). The consequences of a loss of muscle mass and strength in CKD have additionally been linked to worse quality of life, depression, fracture risk, cardiovascular complications, transplant failure, increased hospitalisation, and death (4).

To counteract the negative effects of sarcopenia, exercise is usually recommended as it can improve muscle strength and mass in people with sarcopenia on HD (5). However, as many as 74% of HD patients are unable or unwilling to participate in such programmes (6), and we have previously reported very poor adherence to exercise in trials (18-47%, (7)). We propose neuromuscular electrical stimulation (NMES) as an alternative treatment for sarcopenia in CKD. Used widely in physiotherapy (8) and clinical settings (9), NMES is a well-tolerated technique that evokes muscle contraction, mimicking exercise.

NMES delivers a series of electrical impulses to the muscular tissue underlying the electrodes that generate action potentials within the motor nerve axons and fibres resulting in a muscle contraction. Though NMES has been found to be safe and tolerable (NICE, IP1741), there are several parameters of an NMES intervention that can be altered which will affect the amount of force generated by the muscle contraction, metabolic stress/fatigue, and how the contractions feel (i.e. perceived tolerability due to discomfort or fatigue). Among others, these include stimulation frequency, stimulation intensity and pulse duration, electrode size and positioning, and the pattern of contraction and rest intervals (duration and repetitions). There is currently no standardised prescription protocol for NMES in CKD. In this study, we intend to maximise NMES tolerability by manipulating the electrical stimulation parameters to maximise muscular force production for a minimum level of discomfort (tolerability and fatigue).

2 Objectives and Outcome Measures/Endpoints

Objectives	Outcome Measures/Endpoints
Primary Objective, Outcome, Timepoint(s)	
To determine the NMES stimulation parameters (frequency, pulse duration, and stimulation duration/number of pulses) that maximise evoked force production of the thigh muscles for a given level of discomfort.	Evoked force Discomfort (numerical rating scale)
Secondary Objective(s), Outcome(s), Timepoint(s)	
To compare the perceived discomfort and fatigue responses between two	The change in evoked force

Objectives	Outcome Measures/Endpoints
different NMES protocols with different rest/contraction ratios and a control (no stimulation) protocol.	The change in voluntary force The change in discomfort (numerical rating scale) The change in rate of perceived exertion (CR10 scale) Delayed onset muscle soreness (numerical rating scale)

3 Study Design

Work package 1 has two components:

COMPONENT 1 – Optimising stimulation configuration for maximal evoked force with minimal discomfort

Participants will visit the laboratory at Loughborough University on two occasions; for a screening and familiarisation session, and an experimental session. These will be performed at least 2 days, and no longer than 14 days apart.

COMPONENT 2 – Comparison of different NMES protocols using the optimised stimulation configuration

Participants will visit the laboratory at Loughborough University on four occasions; for a screening and familiarisation session, two experimental sessions (randomised, counterbalanced order), and a control visit. All visits will occur within a 3-week window.

Participants may take part in both components. In such a case, participants will not be required to attend a second familiarisation session for Component 2. If taking part in both components, the total number of visits will be five, to be completed within a 2-month period.

4 Participant Eligibility Criteria

4.1 Inclusion criteria

1) Undertaking HD for >3 months (home or unit based)
2) Age > 18 years
3) Able to consent

4.2 Exclusion criteria

1) Contraindications to neuromuscular electrical stimulation
   - Lower limb amputation
   - Active skin ulceration or infection
   - Symptomatic lower limb claudication/ischaemia
   - Lower limb deep vein thrombosis <3 months
   - Cardiac pacemaker or implantable cardiac defibrillator

- The presence of metallic material in/around the hips or knees.

2) Conditions known to cause muscle wasting
   - Known neuromuscular disease
   - Active malignancy
3) Scheduled for living donor kidney transplant or plan to change dialysis modality and/or centre in the next 3 months
4) Pregnancy or planning to become pregnant during the course of the study
5) Life expectancy <6 months
6) Current participation in a study with conflicting therapies/outcomes
7) Unable to consent

5 Study Schedule

5.1 Schedule of procedures

Procedures	Visits												
	COMPONENT 1				COMPONENT 2								
	Pre-screening	Screening	Familiarisation	Experimental visit	Recruitment	Screening	Familiarisation	Experimental visit	DOMS	Experimental visit	DOMS	Control	DOMS
Visit Number	**-**	**0**	**1**	**2**	**0*** **	**0****	**1****	**2**	**-**	**3**	**-**	**4**	**-**
Visit window	Day 0	Day 1	Day 2	Day 4-16	Day 0	Day 1	Day 2	Day 4-30	24, 48, 72 hrs post protocol	Day 4-30	72 hrs post protocol	Day 2-28	24, 48, 72 hrs post protocol
Invitation and expression of interest	x				x								
Telephone screening		x				x							
Informed consent			x				x						
Eligibility assessment		x	x			x	x						
Randomisation													
Demographics				x									
Medical history		x		x		x							
Demographic & health questionnaire			x	x			x						
Neuromuscular function			x	x			x	x		x		x	
RPE								x		x		x	
Telephone call to estimate perceived									x		x		x

DOMS using NRS^													
Adverse Event Assessments		x		x				x		x		x	

** Participants may take part in both components. In such a case, participants will not be required to attend a second familiarisation session for Component 2. If taking part in both components, the total number of visits will be five, to be completed within a 2-month period. *** A replacement will be recruited if a participant chooses not to continue with Component 2. ^Participants will estimate the perceived delayed onset muscle soreness (DOMS) using the NRS scale via phone calls for 72 hours (3 days) following each protocol visit.

5.2 Recruitment and identification

Participants will be identified by a member of the clinical team based on the inclusion/exclusion criteria. They will be recruited via the following routes:

1) During or before a routine outpatient clinical appointment. For individuals that may be eligible to take part, participant invitation letters will be sent along with appointment letters. The clinician will formally approach the person about the study during their clinic visit and will provide the individual with an invitation letter and a brief explanation of the study. If they are interested to find out more, they will have the opportunity to speak to a member of the research team (either at University of Leicester or Loughborough University) who will give them a Participant Information Sheet and answer any questions they have. If an individual has not been identified prior to their planned clinic appointment, but the clinician deems them to be eligible they will be given the participant invitation letter together with the Participant Information Sheet and a brief explanation of the study. If they are interested, they will then be given the opportunity to speak to a member of the research team.

2) During a dialysis session or ward round on the unit. The clinician will speak to the individual either as part of a normal ward round, or as a separate initial approach about the study. They will provide the individual with an invitation letter and the participant information sheet, and provide a brief explanation of the study. If they are interested to find out more, they will have the opportunity to speak to a member of the research team (either at University of Leicester or Loughborough University) who will answer any questions they have.

5.2.1 Screening and eligibility assessment

A member of the clinical team will screen potential participants for eligibility using the patient's most recent laboratory test and medical history.

5.2.2 Informed consent

Participants deemed eligible in the recruitment process will initially be given an invitation letter by a member of their usual healthcare team to gauge interest in the study (for details, see section 'Recruitment and Identification'). If they express an interest in the study, participants will be given a Participant Information Sheet. They will then be given at least 24 hours to decide to take part.

All participants who respond to the invitation letters and Participant Information Sheets shall be fully informed of the study protocol and initially considered for eligibility through a phone call. If deemed eligible, they will be invited to attend a screening and a familiarisation session in person. After explaining the procedures and having the opportunity to ask questions participants will be asked to provide written consent. After that, their eligibility will be assessed once more ensuring they meet all inclusion eligibility criteria. No study procedures and tests will be undertaken before written informed consent has been obtained.

Should there be any subsequent amendment to the final protocol, which might affect participation in the study, continuing consent will be obtained using an amended consent form, which will be signed by the participant before any further tests are carried out.

Where possible, translation of the Participant Information Sheet will be provided for non-English speakers to facilitate informed consent. A University of Leicester approved provider (Language Line Solutions) will be utilised.

5.3 Randomisation
For component 2, the order of the visits (protocol 1, protocol 2, or control) will be randomised using a random number generator.

5.3.1 Blinding and code breaking
Not applicable.

5.4 Study visits and assessments
Eligible participants will visit the laboratory at Loughborough University, initially for a screening and familiarisation visit followed by an experimental visit(s). Participants will be advised to avoid strenuous activity the day prior to laboratory visits.

Screening and Familiarisation
Participants will consent to the study, followed by completion of the questionnaire (demographics and health information). After that, they will be familiarised with the procedures of muscle force measurements. For this part, participants will be seated on a custom-made isometric strength testing chair adjusted to the individual's stature (this position on the chair will be replicated in subsequent visits). Participants will then practise the performance of submaximal and maximal voluntary contractions. They will also be familiarised with NMES and the numerical rating scale (NRS; 0 = no discomfort, 10 = unbearable discomfort) to estimate discomfort levels.

COMPONENT 1
Experimental visit
During the experimental visit, participants will be seated on a custom-made isometric strength testing chair. A warm-up of a series of voluntary submaximal contractions will be performed, followed by an assessment of the maximal strength of the thigh muscles. NMES electrodes will then be placed on the thigh muscles. Following that, we will assess the force response to high-frequency NMES using a combination of stimulation frequencies, pulse durations, and number of impulses (i.e. duration of stimulation). In response to each stimulation, participants will assess their discomfort via NRS. For each permutation, the stimulation current will be increased till participants exceed 4/10 on NRS.
The following permutations will be tested:
- Three stimulation frequencies up to 100 Hz
- Three pulse durations up to 1 ms
- Three durations of pulse trains up to 3 s

In total, 27 permutations will be tested. Evoked forces will be recorded in response to each stimulation.

COMPONENT 2
Experimental visits
Two experimental visits will be performed to assess responses to two stimulation protocols with different contraction-to-rest ratios. On each day, responses to one of the two protocols will be tested. The order of protocols will be randomised.
Participants will again be seated on a custom-made isometric strength testing chair. NMES electrodes will then be placed on the thigh muscles. A warm-up of a series of voluntary submaximal contractions will be performed, followed by an assessment of the maximal strength of the thigh muscles. Additionally, a supramaximal single pulse

of NMES will be delivered to the muscle to assess the contractile twitch properties of the thigh muscles.

Participants will then complete a warm-up of low-frequency NMES for 5 mins using an established protocol (up to 4 Hz, low current; (10)). After that, participants will undergo a high-frequency NMES protocol of up to 5 sets of 10 contractions. The contractions within each set will be delivered for 3-10 seconds with a between-contraction rest period of 5-30 seconds, depending on the protocol of the day (randomised order). The high-frequency NMES protocol will use the stimulation configuration that maximised force production at a given discomfort (4/10 on NRS) from Component 1. After each set of NMES-evoked contractions, participants will select a rating of discomfort on the NRS, a rating of perceived exertion on CR10 scale, and then perform an assessment of maximal strength and evoked twitch force. Should NRS exceed 7/10 the protocol will be stopped even if 5 sets had not been completed.

For the 72 hours (3 days) following a protocol, participants will estimate the perceived delayed onset muscle soreness (DOMS) using the NRS (via phone).

Control visit
The control visit will be similar to the experimental visits. The only exception is that instead of the NMES protocol, participants will rest quietly on the chair and then perform measures of voluntary and evoked twitch forces at similar intervals than during the experimental visits (i.e. in the beginning, and then five more times to correspond to the measurements performed after every set of NMES-evoked contractions in experimental visits).

5.5 Study intervention(s) and comparator(s)

5.5.1 Description of study intervention

A NMES protocol of 5 sets of 10 contractions. The contractions within each set will be delivered for 3-10 seconds with a between-contraction rest period of 5-30 seconds".

5.5.2 Description of comparator

Rest of similar duration to the intervention.

5.6 Expenses and benefits

Participants will not be remunerated for their participation. However, due to the visits not forming part of the patients' normal care their travel expenses will be reimbursed at the usual NHS rate of 45p/mile up to the value of £60 per visit. If a patient requires a taxi this can be arranged.

5.7 Early discontinuation/withdrawal of participants

Participants can withdraw from the study at any point, without giving a reason and without any prejudice. If a participant withdraws from the study, or loses the capacity to consent for themselves, data collected up until the point of withdrawal/loss of capacity will be retained and used in the study. Participants will be informed of this via the Participant Information Sheet.

5.8 Definition of end of study

The end of the study will be defined as the time at which all data is collected and analysed.

6 Sample Handling

Not applicable.

7 Safety Reporting

7.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening^ • requires inpatient* hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect • Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: ^The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the study intervention. study
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the study in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

7.2 Reporting procedures for Adverse Events

Participants will be monitored throughout the study for any adverse events during the testing sessions. The occurrence of an adverse event following participation is unlikely.

Common non-life-threatening symptoms such as constipation, diarrhoea, colds, headache, etc. do not need to be reported for this study. Only adverse events **causally related** to the study procedures will be recorded and captured on the Adverse Events log within the participants' CRF. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary. The relationship of AEs to the study will be assessed and signed off by a medically qualified individual who has been delegated the duty on the study Delegation of Authority and Signature Log.

AEs considered related to the study will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, will be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

7.3 Reporting procedures for Serious Adverse Events

It is expected that participants will experience a significant number of underlying health conditions and consequently an increased number of expected hospital admissions. In addition, expected events may occur related to the NMES intervention. NMES induces a muscle contraction via the delivery of a small electrical current. This may cause the muscles to feel sore the next day. There have been several previous studies of NMES in chronic disease patients, including haemodialysis patients that have reported very low rates of SAEs. A recent systematic review and meta-analysis performed by NICE has concluded NMES is safe to use in chronic disease population.

Therefore, only SAEs that are **clearly related** to the study and of a **serious nature** will be subject to **expedited reporting to the Sponsor**. These SAEs include:

- Musculoskeletal injury as a direct result of the outcome assessments or the intervention (NMES)
- Anything else in the investigator's opinion that is related, serious, and unexpected.

These SAEs, occurring from the time of randomisation until end of assessment period, will be reported to the Sponsor immediately and within 24 hours of becoming aware of the event. The following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- relationship to the study procedure or intervention

All other SAEs will be recorded using the SAE Log, which will be kept in the Trial Master File.

Deaths will be recorded as part of the study outcomes and therefore **will not** be subject to expedited reporting.

SAEs will be reported using appropriate forms and according to the Sponsor SOP for reporting serious adverse events. Additional information will be provided if requested to the Sponsor and main Research Ethics Committee (REC). The Principal Investigator or another delegated physician (as agreed by the Sponsor) is responsible for the review and sign off of the SAE and the assessment of causality (i.e. whether an event is related to a study procedure or intervention).
The Sponsor will perform an initial check of the information and ensure that the SAE line listing is reviewed by the Director of Research & Innovation. All SAE information must be recorded on an SAE form and sent to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor.

Copies of all documentation and correspondence relating to SAEs will be stored in the TMF and/or ISF.

Any change of condition or other follow-up information should be emailed to the Sponsor immediately and within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs will be tabulated and summarised, according to system organ class and preferred term, as classified in the Medical Dictionary for Regulatory Activities (MedDRA). No formal statistical testing will be performed. All events will be summarised by seriousness, expectedness and relatedness.
Some SAEs are expected as part of the study, these include: muscle soreness, fatigue, and discomfort. Whilst these SAEs will be recorded as per the described procedures, they will not be reported to the Sponsor.
The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

7.4 Reporting Urgent Safety Measures

The Sponsor, the CI or the local PI at a research site may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. If any urgent safety measures are taken, the CI/Sponsor shall be notified immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the Sponsor and the relevant REC of: the measures taken; reason these measures were taken; the circumstances giving rise to those measures and the plan for further actions.

8 Statistics and Analysis

8.1 Sample size calculation

A sample size of 24 participants will be utilised, as for pilot studies, a sample size of between 24-50 has been recommended (11,12). Purposeful sampling will be undertaken to ensure a representative sample. To ensure the study is appropriately powered, each component will be treated separately; that is, if a given participant does not complete all visits within a given component, a replacement will be recruited.

8.2 Statistical analysis plan

A statistical analysis plan (SAP) will be prepared by the Trial Statisticians and will contain full details of all statistical analyses. The SAP will be agreed with appropriate oversight prior to database lock. Any changes to the original SAP will be detailed along with the reason(s) for changes in subsequent SAPs.

8.2.1 Outcome analysis

To assess the optimal stimulation configuration for maximal evoked force with minimal discomfort a linear regression with evoked muscle force at NRS 4/10 will be compared among different combinations of stimulation parameters. To assess the change in muscle function and discomfort in response to different NMES protocols using the optimised stimulation configuration a linear regression with a change in an outcome variable (voluntary and evoked force, NRS) will be compared between the two NMES protocols and a control.

All data analyses will be performed in R (R studio, R foundation for Statistical Computing, Vienna, Austria) on an encrypted university computer.

8.3 Interim analysis and criteria for the premature termination of the study

No formal stopping rules or interim analyses have been pre-defined or planned. No criteria for early termination of the study have been set.

8.4 Participant population
We will recruit haemodialysis patients (either home or unit based) who have been receiving dialysis for more than 3 months.

8.5 Procedure(s) to account for missing or spurious data
For primary outcome, if <5% of data is missing, a complete case analysis will be performed. If more than 5% of data for the primary outcome is missing, multiple imputation will be performed.

9 Data Management
9.1 Data flow diagram
This is a separate PDF document.

9.2 Source data
Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, consent forms, laboratory results and records. A master copy of the original data will be stored on which no analysis will be performed.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name. All source data will be stored at Loughborough University, in safe conditions (locked filling cabinets in PI's office).

9.3 Data collection tools, handling and record keeping
Each participant will be assigned a unique identification number upon consent and this will be added to all study documents/data collection tools in place of the participant's name.

Force data will be recorded in a digital form and stored on Loughborough University's cloud-based service (OneDrive). The remaining study data will be entered onto a paper Data Log before being entered into the study database stored on Loughborough University computer. Access to the database will be restricted to study staff using a username and password. A copy of the completed participant informed consent form and participant information sheet will be placed in the Trial Master File/Investigator Site File.

A contacts database (which contains participant contact details) will be held separately from the study database for the purposes of contact for future ethically approved research and providing a copy of the study results. Participant's contact details will be held securely at the Loughborough University in accordance with data protection regulations. This will be password protected and managed at site by the research team. Contact details will be deleted once they have been used for their agreed purpose; therefore they might be kept beyond the standard retention period of 6 years.
All data handling and record keeping will be kept in adherence to University of Leicester's, Loughborough University's, and relevant NHS Organisation(s) policies. All

study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, The UK Policy for Health and Social Care Research and the Data Protection Act.

9.4 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections in line with participant consent.
The Chief Investigator and relevant study staff will have access to the data collected as part of this research. Access to the study database will be restricted by role-based permission to authorised study personnel. will be suitably trained on the system prior to being granted access. Individual user accounts will be password-protected and will not be shared between members of the study team.

9.5 Archiving

Archiving of research data, source data, the ISF, consent forms and research-site related files will be arranged by Loughborough University according to local procedures. The TMF will be archived by the University of Leicester and stored for a minimum of 6 years after the study has ended. Storage will comply with the University of Leicester archiving Standard Operating Procedure. Details can be found at: https://le.ac.uk/research/regi/standard-operating-procedures. Destruction of essential documents will require authorisation from the Sponsor.

10 Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH GCP, the principals of the Declaration of Helsinki, relevant regulations and standard operating procedures (SOPs). The Principal Investigator (or their delegate) will be responsible for maintaining the Investigator Site File (as appropriate) and ensuring it is kept 'inspection ready' at all times. The Trial Master File (TMF) will be maintained by the University of Leicester and kept in a folder in a locked cabinet/drawer in a secured room in a secure office environment office at the University of Leicester by the Chief Investigator (or delegate).

10.1 Monitoring, audit and inspection

The University of Leicester as Sponsor operates a risk-based monitoring programme which this study will be subject to.

11 Protocol Compliance

11.1 Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Planned deviations or waivers are not allowed however it is acknowledged that accidental protocol deviations may occur. Any deviations from the protocol will be documented in a protocol deviation form and filed in the Trial Master File/Investigator Site File as applicable.

If a protocol deviation occurs, then the CI (or delegate) will document this in accordance with the University's Standard Operational Procedure (SOP) Identifying and Reporting Deviations and Serious Breaches of GCP and/or the Protocol.
Deviations from the protocol which are found to frequently recur will be explored and where necessary an amendment to the protocol will be made.

11.2 Serious breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or
(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor will be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

12 Ethical and Regulatory Considerations

12.1 Research ethics committee (REC) and regulatory review, approvals/permission/support, compliance and reports

Once the Sponsor Review process is complete authorisation from the University of Leicester's Research Governance Office will be issued to book further regulatory review of the proposed research. NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will occur via the Integrated Research Application System (IRAS). The Chief Investigator will ensure that all regulatory approvals, the local approval at Loughborough University and sponsor green light are in place before participants are approached.

For any required amendment(s) to the study, amendment will be submitted to the sponsor in the first instance for review and approval to submit the amendment for external regulatory approval. Amendments must be implemented following all required ethical, competent authority, site and Sponsor approvals and in line with Sponsor Standard Operating Procedures.

The Research Governance Office's Standard Operating Procedures will be followed for the duration of the study.

The Chief Investigator will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying REC.

A study master file will be maintained for the duration of the study and will be stored for a minimum of 6 years after the study has ended.

12.2 Peer review

Prior to review by the sponsor, the protocol has been through the external peer review as part of the grant submission process. It was externally reviewed by seven experts.

12.3 Patient and public involvement

This pilot study is a direct consequence of the Public and Patient Involvement and Engagement group's involvement in the design of a funded study on the effectiveness of neuromuscular electrical stimulation as a treatment of sarcopenia in haemodialysis patients. Specifically, the group had concerns about the discomfort associated with NMES, which this pilot is attempting to address. The PPIE group meets bimonthly and will be updated on the progress of the study. Patients will also be involved in the study as participants.

12.4 Assessment and management of risk

No aspect of usual care will be altered during the involvement of HD patients in this study. The risk of adverse events requiring emergency care is estimated to be very low following a rigorous screening process employed in the present study. All instrumentation used in the study will be CE-marked. Participants will be explained that partaking in any tests is voluntary and that they can refuse specific tests without explaining why.

Research will take place at Loughborough University. To assess muscle function, participants will perform muscle contractions in a specifically designed isometric knee extension dynamometer (testing chair) instrumented with a strain gauge to measure muscle forces during knee extension contractions. Participants will be habituated to the performance of muscle contractions in the study, and a thorough warm-up involving a series of submaximal contractions will be performed initially. Discomfort and any risk of muscle strain will be minimised by performing static (rather than dynamic) contractions with the participants' legs restrained by a strap connected to a strain gauge. Participants will be informed that some delayed onset muscle soreness may occur due to repeated muscle contractions (as it is common with novel exercise), but this is expected to dissipate in the few days following testing.

Neuromuscular electrical stimulation (NMES) will be delivered using a commercially available device from a high-street provider. As per the systematic review of the National Institute for Health and Care Excellence (NICE) the technique has been deemed safe to use in chronic disease populations (NICE, IP1741). The warm-up associated with muscle function testing (see above) will be performed before NMES to minimise the very low risk of injury and/or delayed onset muscle soreness. There is a very rare, but potential effect of NMES interfering with implantable devices, and therefore participants with a pacemaker or a similar device will be excluded from the study.

Overall, this study is categorised as having no higher risk than that of standard medical care.

12.5 Data protection and patient confidentiality

The Chief Investigator will be the data custodian.

All information collected in the study will be kept strictly confidential.

The Chief Investigator and research team staff will comply with the requirements of the Data Protection Act and General Data Protection Regulation (and other applicable

regulations) concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All digital data will be stored on a cloud-based drive (Loughborough University's OneDrive) on a University of Loughborough computer with the folder being password-protected. Data will only be shared with investigators involved with the study using Microsoft 365 groups, which provides secure, access-controlled, sharing options. Personal data will only be kept until the study closure upon which it will be destroyed. All paper records (informed consent and demographic & health questionnaire) will be stored in a locked filing cabinet in the responsible investigator's office (also locked). Data from the questionnaire will be pseudonymised and converted to a digital format before study closure. The hard copies of study documents will be destroyed upon study closure.

Analysis of the data generated will be undertaken by the Loughborough University Principal Investigator (or Loughborough University researchers) on Loughborough University premises.

Research data will be pseudonymised at Loughborough University before being transferred to the University of Leicester. Pseudonymised research data will be stored for 6 years after the study has ended.

Consent forms, enrolment logs and details of record linkage* (i.e., participant ID numbers/pseudonyms) will be kept for a minimum of 6 years after the study has ended as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data. At the end of this period, approval from the Sponsor will be requested for the destruction of the data.

Participant personal data, collected for the purposes of arranging the study visits, will only be accessed by the research team listed on this protocol. Participants will have signed a consent form to state they have read the participant information sheet and understood it involves data sharing among the research team only. Personal data will be deleted once they have been used for their agreed purpose. Where individuals have consented to receive a copy of the research findings, contact details will be retained until this time. Contact details will be stored securely and separately from participant's research data and clinical information.

The Trial Master File (TMF) will be kept in a folder in a locked cabinet/drawer in a secured room in a secure office environment office at the University of Leicester by the Chief Investigator (or delegate). An Investigator Site File (ISF) will be maintained by Loughborough University by the Principal Investigator (or delegate) in a folder in a locked cabinet/drawer in a secured room in a secure office environment.
Long-term storing will comply with the University of Leicester archiving Standard Operating Procedures.

12.6 Access to the final study dataset

The CI and their appointed deputies will have access to the analysed study dataset following execution of the SAP and completion of the End of Trial Report.

13 Finance and Insurance

13.1 Funding

This study is funded by a grant from the NIHR EME programme (funder ref NIHR158852). The funder will be responsible for funding the study but will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

13.2 Indemnity

Sponsorship and insurance for study design and management will be provided by the University of Leicester.

If a participant is harmed due to negligence and/or the conduct of the study, any claim will be covered by the Loughborough University indemnity arrangements against the risk of claims relating to research studies their staff design and undertake. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, they may contact Loughborough University Research Governance Officer (details provided in Participant Information Sheet). They may also refer to Loughborough University's policies relating to Research Misconduct and Whistle Blowing which are available at: https://www.lboro.ac.uk/internal/research-ethics-integrity/research-integrity/.

14 Dissemination

14.1 Dissemination Policy

The research team owns the data arising from the study. On completion of the study, data will be analysed and tabulated. Upon completion, the data will be analysed and disseminated at relevant national and international conferences, and in journal articles.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Authors will acknowledge that the study was funded by NIHR EME.

15 References

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PROTOCOL INFORMATION

FULL/LONG TITLE OF THE STUDY: The use of neuromuscular electrical **STIM**ulation as a treatment for sarcopenia in people on **H**aemo**D**ialysis: Work packages 2-4

Work package 2: Efficacy study (Randomised Controlled Trial)

Work package 3: Health economic evaluation

Work package 4: Optional mechanistic study

SHORT STUDY TITLE / ACRONYM: STIM-HD

PROTOCOL VERSION NUMBER AND DATE: Version 1.0, 17 October 2024

IRAS NUMBER: 327885

SPONSOR: University of Leicester

SPONSOR REFERENCE NUMBER: 0968

STUDY REGISTRATION: TBC

FUNDER(S): This study is funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR158852). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This protocol has regard for the HRA guidance and the University of Leicester Sponsor Standard Operating Procedures (SOPs).

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research (2017), GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given. Any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

Chief Investigator:	
Name: (please print):	Prof James Burton
Signature:	
Date:	
Principal Investigator:	
Site:	
Name: (please print):	
Signature:	
Date:	

KEY STUDY CONTACTS

Chief Investigator	Professor James Burton Department of Cardiovascular Sciences Clinical Sciences Wing Glenfield Hospital Groby Road Leicester LE3 9QP Jb343@leicester.ac.uk
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Sponsor	Research Governance Office Research & Enterprise Division University of Leicester University Road Leicester LE1 7RH 0116 373 6508 RGOsponsor@leicester.ac.uk
Clinical Trials Unit	Leicester Clinical Trials Unit University of Leicester University Road Leicester LE1 7RH 0116 229 7246 CTU@leicester.ac.uk
Funder(s)	NIHR EME Programme NIHR Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS netsmonitoring@nihr.ac.uk **Funder reference:** NIHR158852
Funder start and end date(s)	01/09/2024 – 29/02/2028
Protocol Contributors	Professor James Burton Dr Emma Watson Professor Jonathan Folland Dr Jakob Skarabot Ms Niamh Quann
Collaborators	Dr Gordon McGregor Professor Indranil Dasgupta Professor Jonathan Folland Dr Jakob Skarabot Professor Nicola Cooper Mr Fez Awan
Statisticians	Professor Laura Gray Dr Shaun Barber
NIHR Portfolio adopted	Yes

CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BIA	Bioelectrical Impedance Analysis
CI	Chief Investigator
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
eGFR	estimated Glomerular Filtration Rate
EME	Efficacy and Mechanism Evaluation
EMG	Electromyography
EQ-5D-5L	EuroQol EQ-5D-5L – Quality of Life questionnaire
EWGSOP2	European Working Group on Sarcopenia in Older People
FEV1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GP PAQ	General Practice Physical Activity Questionnaire
HbA1c	Haemoglobin A1C
HD	Haemodialysis
ICF	Informed Consent Form
ISF	Investigator Site File
ITT	Intention-to-treat analysis
ISWT	Incremental Shuttle Walk Test
KDQoL	Kidney disease quality of life
LCTU	Leicester Clinical Trials Unit
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
NIHR	National Institute for Health and Care Research
NMES	Neuromuscular electrical stimulation
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Patient Participation, Involvement and Experience
PBMC	Peripheral blood mononuclear cells
QoL	Quality of Life
RCT	Randomised Control Trial
RDN	Research Delivery Network
REC	Research Ethics Committee
RNA	Ribonucleic acid
RPE	Rating of perceived exertion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARC-F	Strength, Ambulation, Rising from a chair, Stair climbing and history of Falling
SarQoL	Sarcopenia related quality of life
SONG-HD	Standardised Outcomes in Nephrology - Haemodialysis
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
STS5	Sit to Stand 5
STS60	Sit to Stand 60
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
UKRR	UK Renal Registry
VO_{2Peak}	Maximal Exercise Capacity
WBC	White blood cells

KEY WORDS
Skeletal muscle wasting, physical function, chronic disease, quality of life.

STUDY SUMMARY

Study Title	The use of neuromuscular electrical STIMulation as a treatment for sarcopenia in people on HaemoDialysis – STIM-HD	
Study Design	Prospective, open-label, assessor blind, two-arm, multi-centre, Randomised Controlled Trial	
Study Participants	Adult (>18 years) haemodialysis patients, undertaking HD for >3-months (home or unit-based), with sarcopenia diagnosed by low muscle strength on patient screening.	
Planned Sample Size	228 (114 to the intervention arm and 114 to the control arm) Sub-group for optional mechanistic outcomes: • 50 participants (25 in each arm) will take part in neuromuscular assessments (high-density surface and intramuscular electromyography); • 24 participants (12 per arm) will take part in skeletal muscle biopsies.	
Follow-up Duration	6 months	
Planned Study Period	3.5 years	
	Objectives	**End Points/Outcome Measures**
Primary	To measure the **effect** of a 3-month NMES programme on muscle strength, the core manifestation of sarcopenia, compared with standard care for HD patients	- Isometric strength
Secondary	To measure the effect of a NMES programme on QoL.	- Kidney Disease Quality of Life (KDQoL) questionnaire
	To evaluate the cost-effectiveness of a NMES programme compared with standard care for patients with end-stage kidney disease within an NHS costing perspective	- EuroQol EQ-5D-5L - Resource use questionnaire
	To investigate if NMES results in neuromuscular adaptations and changes in muscle phenotype	- Skeletal muscle biopsy analysis - High density and Intramuscular Electromyography - Evoked responses to femoral nerve stimulation
	To investigate the effect upon muscle mass, physical function and physical activity levels	- Ultrasound - 6-minute walk test or ISWT as space allows - Short Physical Performance Battery - Sit to stand 60 - Bioelectrical impedance - SARC-F questionnaire - SarQoL questionnaire - GP PAQ questionnaire - Accelerometry - Sleep diary - Handgrip Strength
	To measure the safety of the intervention	- Adverse Events relating to the intervention

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
NIHR EME Programme Funder reference: NIHR158852	Financial support

ROLE OF STUDY SPONSOR

The Sponsor of this research is the University of Leicester. The University of Leicester is responsible for the design, management and outputs of the research. Participating NHS sites are responsible for the conduct of the study within their organisation.

The Research Governance Office review and approve all iterations of the protocol as part of their initial Sponsor review and amendment review process. Further information is available from our Sponsor Standard Operating Procedures webpage.

ROLE OF COLLBORATOR(S)

Dr Gordon McGregor and Professor Indranil Dasgupta will support recruitment at University Hospital Coventry and Warwickshire and University Hospitals Birmingham respectively.

Professor Jonathan Folland and Dr Jakob Skarabot will lead the mechanistic neuromuscular adaptation investigation assessments.

Professor Nicola Cooper will oversee the heath economic analysis.

Mr Fez Awan will lead the PPIE work throughout the study.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The Leicester Clinical Trials Unit (LCTU) is providing support for this study. It is a UKCRC registered Clinical Trials Unit with extensive experience of handling data from large multi-centre trials. The LCTU has been involved in the development and design of the protocol since conception of this study and will facilitate study data collection, statistical analysis and reporting and associated quality assurance. The study is sponsored by the University of Leicester.

A Trial Management Group (TMG) including the CI, Trial Co-ordinator, co-applicants and members of the LCTU will direct and oversee the day-to-day running of the study and will meet according to its demands. The TMG will highlight any key day-to-day study-related issues and monitor progress of all research activities to ensure that the study is being delivered on time and to target.

An independent Trial Steering Committee (TSC), with an independent Chair, Expert Statistician, Health Economist, Clinician with relevant expertise, and Lay Representative will be convened to oversee, advise on and monitor the study. A Sponsor representative and a Research Network representative will also be invited to attend as non-voting observers. The TSC will meet at least annually or as required throughout the study. Meeting minutes will be sent to all members, the Sponsor, and the funder, and retained in the Trial Master File (TMF).

An independent Data Safety Monitoring Committee (DSMC), with an independent Chair, Expert Statistician, Clinician with relevant expertise, and Lay Representative will be convened to monitor the study data and make recommendations to the TSC on whether there are any ethical or safety concerns. The DSMC will meet at least annually or as required throughout the study. Meeting minutes will be sent to all members, the Sponsor, the funder, and the TSC, and retained in the TMF.

STUDY FLOW CHART

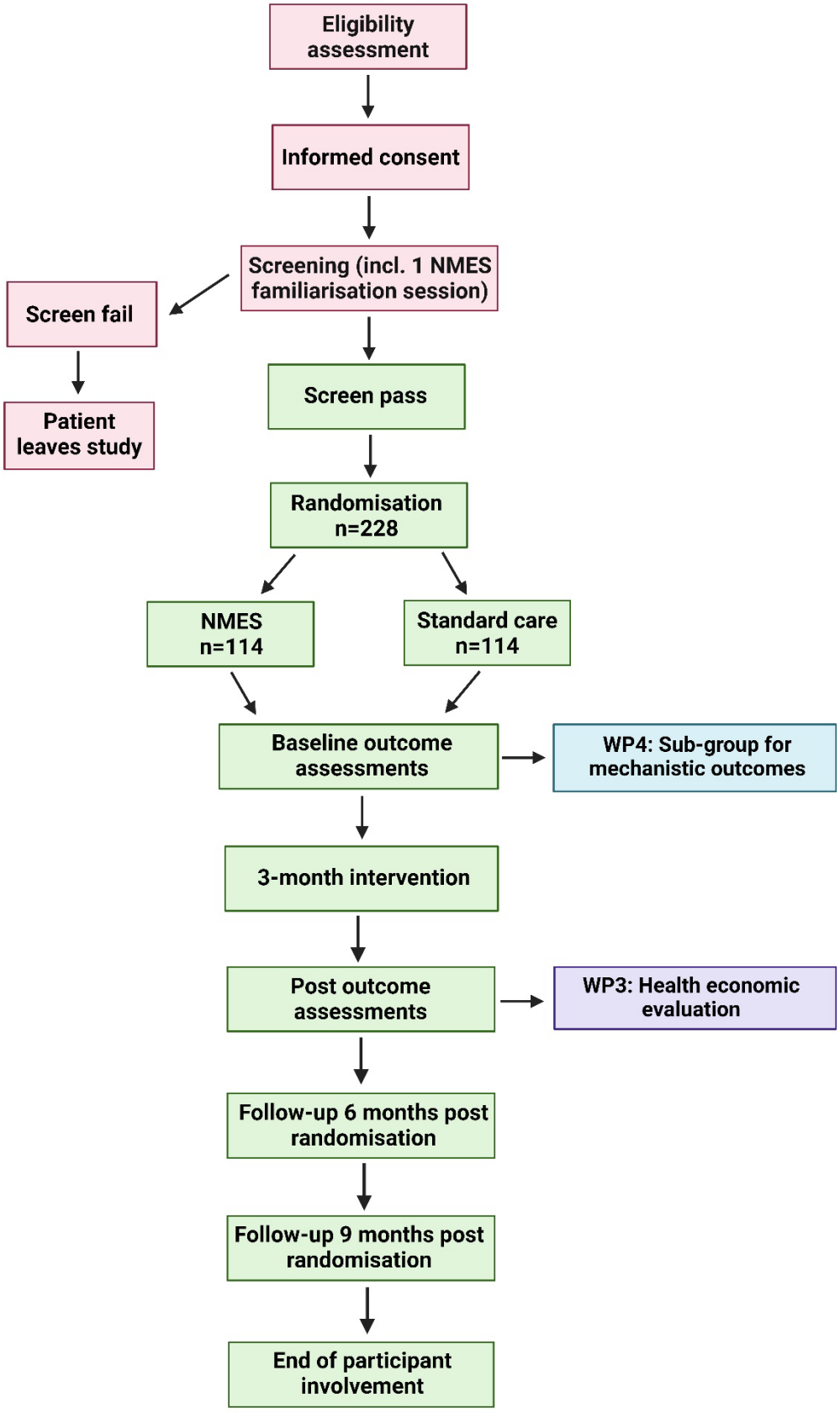

Figure 1: *Flow of participants through the study*

1. BACKGROUND

Sarcopenia is characterised by a loss of muscle strength (the most important characteristic), and mass, as well as low physical performance, and is now classified as a disease in its own right (1). Although often associated with ageing, it is also recognised as a complication of other long term health conditions and is associated with worse clinical outcomes, including poor quality of life (QoL), higher hospitalisation rates and increased mortality. The annual cost of sarcopenia to the NHS is around £2.5 billion (2).

Chronic kidney disease (CKD) is a public health emergency that threatens to overwhelm the NHS, affecting around 14% of adults in England (3). When kidney function drops to the point it can no longer sustain life, a form of renal replacement therapy is required, for example dialysis. There are currently 30,000 adults and children receiving dialysis in the UK, with this number projected to increase to 143,000 by 2033 (4). Sarcopenia is a frequent complication of CKD, affecting around 28% of people with more advanced disease (5-7). Data from our cohort of patients with kidney failure on haemodialysis (HD) shows it is common; 39% of patients have confirmed sarcopenia, a further 10% have probable sarcopenia, and 16% have severe sarcopenia (unpublished observations). Systematic reviews specifically in CKD patients have shown sarcopenia is associated with falls, fractures, cardiovascular events and mortality (7, 8), demonstrating its clinical importance. In the UK, sarcopenia is diagnosed according to the algorithm described and recently updated by the European Working Group on Sarcopenia in Older People (9) (EWGSOP2). Depending upon performance in a range of tests, people can be diagnosed with either probable sarcopenia (the point at which guidelines suggest an intervention should be targeted), confirmed sarcopenia, or severe sarcopenia.

2. RATIONALE

The mainstay of treatment for sarcopenia is lifestyle modification, principally exercise interventions. Exercise has been shown to improve muscle mass and strength in people with sarcopenia on haemodialysis (10, 11). Recent national guidelines from the UK Kidney Association, endorsed by the National Institute for Health and Care Excellence (NICE) and led by authors from this group, routinely recommend dialysis unit-based exercise programmes. Unfortunately, although exercise programmes are likely to be more beneficial from both a cardiovascular and a musculoskeletal point of view, as many as 74% of HD patients are unable or unwilling to participate in such programmes (12, 13). In the recently published CYCLE-HD and PEDAL trials (both undertaken by this group), which investigated dialysis unit-based exercise interventions, of the 2835 patients screened, over 2100 were deemed ineligible (12, 13). Many of the patients were severely deconditioned and adherence to the exercise interventions was extremely low (47% of exercise training sessions prescribed were completed and only 18% adhered exactly to the prescription) (14). Therefore, an accessible alternative is clearly needed.

Neuromuscular electrical stimulation (NMES) is a treatment whereby the application of intermittent electrical stimuli generates involuntary muscle contractions, and might serve as an ‘exercise mimetic’. This therapy is used widely in physiotherapy rehabilitation programmes (15, 16) and is now being used in clinical settings, including in intensive care units (17). NMES could represent an ideal alternative for people on HD who are unable to exercise and therefore prevent the inevitable decline in muscle mass and strength that leads to sarcopenia.

3. RESEARCH QUESTION /OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Research Question: Can NMES be used as a therapy for sarcopenia in people on HD?

Aim: To test the clinical efficacy of NMES as a therapy for sarcopenia in people on HD.

Objectives:

- To measure the effect of a 3-month NMES programme on muscle strength, the core manifestation of sarcopenia, compared with standard care for HD patients
- To measure the effect of a NMES programme on QoL
- To measure the effect of a NMES programme on muscle size and measures of physical function
- To evaluate the cost-effectiveness of a NMES programme compared with standard care for patients with end-stage kidney disease within an NHS costing perspective
- To investigate if NMES results in neuromuscular adaptations and changes in muscle phenotype

3.1 Primary objective

Primary Objective: To measure the effect of a 3-month NMES programme on muscle strength, the core manifestation of sarcopenia, compared with standard care for HD patients.

Null hypothesis: There will be no difference in the change in muscle strength from baseline to 3 months between NMES and standard care groups.

Experimental hypothesis: Three months of NMES will create a significant increase in muscle strength compared to the standard care group.

3.2 Secondary objectives

The secondary objectives are:

- To measure the effect of a NMES programme on QoL
- To evaluate the cost-effectiveness of a NMES programme compared with standard care for patients with end-stage kidney disease within an NHS costing perspective
- To investigate if NMES results in neuromuscular adaptations and changes in muscle phenotype
- To measure the effect of a NMES programme on muscle size and measures of physical function
- To measure the safety of the intervention

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

Primary Endpoint: The primary outcome is change in muscle strength measured using isometric dynamometry from baseline to 3-months.

3.3.2 Secondary endpoints/outcomes

Secondary endpoints:

To compare between randomised groups;

1. Additional efficacy measures
    a. Muscle size and architecture (measured cross-sectional area of rectus femoris using ultrasound, muscle thickness and angle of fibre pennation)
    b. Lower-extremity strength, functional capacity, and balance: The short physical performance battery (SPPB)
    c. Cardiovascular functional capacity and endurance: the 6-minute walk test (or incremental shuttle walk test in the event of space constraints)
    d. Body composition (including lean muscle mass) using bioelectrical impedance
    e. Sit-to-stand-60 test (muscle endurance)
    f. GP Physical Activity questionnaire
    g. Hand Grip strength
    h. Accelerometry and sleep diary
    i. Isometric rate of force development

2. Measures of QoL and social functioning
    a. The Kidney Disease Quality of Life tool (KDQoL)
    b. EQ-5D-5L, a generic multi-attribute health related QOL questionnaire for use in cost utility analysis (health economic analysis).
    c. Levels of fatigue (using SONG-HD score)
    d. SARC-F (validated questionnaire recommended as the screening instrument for sarcopenia in clinical practice by the European Working Group)
    e. Sarcopenia and quality of life (SarQoL questionnaire)
3. NHS Resource use (collected via participant self-completion questionnaire), to be combined with NHS unit costs for use in cost utility analysis
4. Measures of process and tolerability
    a. Number of patients eligible, approached and recruited
    b. Dropout rates and movement between allocated study groups
    c. Tolerability of the intervention to include number of neuromuscular stimulation sessions undertaken and the total time per session (up to 30-minutes).
5. Measures of safety
    a. Adverse events relating to the intervention
6. Measures of neuromuscular adaptations and muscle phenotype
    a. High-density surfacer electromyography, for assessment of quadriceps motor unit recruitment and discharge rate, and conduction velocity during sub-maximum and maximum knee extension contractions.

b. Intramuscular electromyography, for assessment of motor unit potential jiggle and segment jitter, electrophysiological markers of neuromuscular junction transmission stability.
c. Femoral nerve stimulation, for assessment of quadriceps contractile properties.
d. Skeletal muscle biopsy analysis

3.4 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective: To measure the **effect** of a 3-month NMES programme on muscle strength, the core manifestation of sarcopenia, compared with standard care for HD patients	Isometric strength	Screening visit (as a familiarisation session), baseline, 3, 6, 9 months post randomisation
Secondary Objectives To measure the effect of a NMES programme on QoL	The Kidney Disease Quality of Life tool (KDQoL)	Baseline, 3, 6, 9 months post randomisation
To evaluate the cost-effectiveness of a NMES programme compared with standard care for patients with end-stage kidney disease within an NHS costing perspective – health economic evaluation	EQ-5D-5L questionnaire Resource use questionnaire	Baseline, 3, 6, 9 months post randomisation
To measure the effect of a NMES programme on muscle size and measures of physical function	Muscle mass (thickness and cross-sectional area by ultrasound) Muscle quality and architecture (e.g. echo intensity and angle of pennation by ultrasound) Handgrip strength by dynamometry Lower-extremity strength, functional capacity, and balance (using the short physical performance battery (SPPB)) and Sit to stand 60. Cardiovascular functional capacity and endurance (by the 6-minute walk test or the ISWT if space constraints) Body composition (using bioelectrical impedance) Muscle endurance (using the Sit-to-stand-60 test muscle endurance) Isometric rate of force development Physical activity levels (using GP Physical Activity questionnaire and accelerometry)	Baseline, 3, 6, 9 months post randomisation

	Levels of fatigue (using SONG-HD score) Perception of muscle function (using the SarQoL questionnaire) Indices of sarcopenia (using the SARC-F questionnaire).	
To investigate if NMES results in neuromuscular adaptations and changes in muscle phenotype	Motor unit recruitment, and discharge rate, and conduction velocity (using high density electromyography) Motor unit potential jiggle and segment jitter (using intramuscular electromyography) Evoked quadriceps contractile properties Skeletal muscle biopsy analysis	Baseline, 3-months post randomisation.
To measure the safety of the intervention	Adverse Events relating to the intervention	3-months post randomisation

4. STUDY DESIGN

STIM-HD is a prospective, open-label, assessor blind, two-arm, multi-centre, randomised controlled trial. Assessments will be made at baseline and at 3-months post randomisation (i.e. at the end of the intervention period) and at -6 and -9 months post randomisation.

In total, 228 participants (114 per arm, adults with end-stage kidney disease and sarcopenia, who are receiving long-term haemodialysis either in hospital, or at home) will be recruited and randomised to receive either 3-months of NMES or standard care. In addition, 50 participants (25 in each arm) will also take part in the neuromuscular assessments (high-density surface and intramuscular electromyography and 24 participants (12 per arm) for a skeletal muscle biopsy.

Participants will be recruited from 5 hospital and satellite haemodialysis centres from 3 NHS Trusts across the east and west midlands.

5. STUDY SETTING

STIM-HD will be run as a multi-centre study in secondary care across University Hospitals of Leicester NHS Trust (UHL), University Hospitals Coventry and Warwickshire (UHCW) and University Hospitals Birmingham NHS Foundation Trust (UHB).

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Undertaking HD for >3-months (home or unit based)
2. Age >18 years
3. Has sarcopenia diagnosed by low muscle strength on patient screening (<27kg for men and <16kg for women for handgrip strength)
4. Able to give written informed consent

6.2 Exclusion criteria

1. Contra-indications to neuromuscular electrical stimulation therapy including:
   i. Lower limb amputation
   ii. Active skin ulceration or infection
   iii. Symptomatic lower limb claudication/ ischaemia
   iv. Lower limb deep vein thrombosis <3-months
   v. Cardiac pacemaker or implantable cardiac defibrillator
   vi. Metallic hip or knee joint

2. Conditions known to cause muscle wasting
   i. Known neuromuscular disease
   ii. Active malignancy

3. Scheduled for living donor kidney transplant or plan to change dialysis modality or centre in the next 6-months
4. Life expectancy of <6-months
5. Current participation in an interventional trial with conflicting therapies or outcomes
6. Unable to give written informed consent.

Muscle biopsy and intramuscular electromyography specific exclusion criteria

1. On anti-coagulation (e.g. warfarin / Direct Oral Anticoagulant)
2. Bleeding disorder (e.g. haemophilia)
3. On high dose statins (i.e. atorvastatin 80mg), growth hormone or steroids.
4. Deep vein thrombosis

Bioelectrical Impedance specific exclusion criteria

1. Has a pacemaker

7. STUDY SCHEDULE

Visits will be broken up as the participant wishes. The 3-month follow up assessments should be carried out within 2 weeks of completing the intervention, or standard care period where possible.

It is expected that each participant will partake in the study for 10-months in total. 3-months is the end of the intervention period, 6- and 9-months are follow-up.

7.1 Schedule of procedures - NMES group

	Screening	Baseline	Each dialysis session during 3-month intervention period	Monthly	3-months	6-months	9-months
Invitation	1						
Eligibility assessment	1						
Informed consent		1					
Medical history		1					
Muscle strength (hand grip strength) for screening purposes and outcome assessments	1	1			1	1	1
Isometric muscle strength	1 (familiarisation session)	1			1	1	1
Isometric rate of force development	1 (familiarisation session)	1			1	1	1
Muscle size and architecture (ultrasound)		1			1	1	1
Short Physical Performance Battery		1			1	1	1
Sit to Stand 60		1			1	1	1
6-minute walk test/ISWT		1			1	1	1
Bioelectrical Impedance Analysis		1			1	1	1
EQ-5D-5L		1			1	1	1
KDQoL		1			1	1	1
SARC-F		1			1	1	1
SarQoL		1			1	1	1
GPPAQ		1			1	1	1
SONG HD - Fatigue		1			1	1	1
Resource use questionnaire and optional diary		1			1	1	1
Accelerometry		1			1	1	1
Sleep diary		1			1	1	1
Blood sample		1*		1 (routine clinical care)	1*	1*	1*
Neuromuscular electrical stimulation	1		1				

RPE			1				
Blood lactate measurement				1			
Heart Rate Measurement				1			
Skeletal muscle biopsy – NMES group n=12 (Optional)†		2			1		
High Density and Intramuscular electromyography n=25 (Optional)		1			1		
Sub-maximum contractions (for EMG recordings)	1 (familiarisation session)	1			1		
Evoked contractions (femoral nerve stimulation)	1 (familiarisation session)	1			1		
Capture of routine clinical data^		1		1	1	1	1
Adverse event assessments		1	1		1	1	1
Inform GP of study participation		1					

**Represents research blood samples drawn during routine clinical testing. ^Represents routinely collected serum blood results and dialysis data on all dialysis units. †In the NMES group, there is an additional biopsy after the first training session at both baseline and 3-months.*

7.2 Schedule of procedures – Control group

	Screening	**Baseline**	**Each dialysis session during 3-month intervention period**	**Monthly**	**3-months**	**6-months**	**9-months**
Invitation	1						
Eligibility assessment	1						
Informed consent		1					
Medical history		1					
Muscle strength (hand grip strength) for screening purposes and outcome assessments	1	1			1	1	1
Isometric muscle strength	1 (familiarisation session)	1			1	1	1
Isometric rate of force development	1 (familiarisation session)	1			1	1	1
Muscle size and architecture (ultrasound)		1			1	1	1
Short Physical Performance Battery		1			1	1	1
Sit to Stand 60		1			1	1	1

6-minute walk test/ISWT		1			1	1	1
Bioelectrical Impedance Analysis		1			1	1	1
EQ-5D-5L		1			1	1	1
KDQoL		1			1	1	1
SARC-F		1			1	1	1
SarQoL		1			1	1	1
GPPAQ		1			1	1	1
SONG HD - Fatigue		1			1	1	1
Resource use questionnaire and optional diary		1			1	1	1
Accelerometry		1			1	1	1
Sleep diary		1			1	1	1
Blood sample		1*		1 (routine clinical care)	1*	1*	1*
Neuromuscular electrical stimulation	1						
Skeletal muscle biopsy – Control group (n=12) (Optional)		1			1		
High-density surface and Intramuscular electromyography N=25 (Optional)		1			1		
Sub-maximum contractions (for EMG recordings)	1 (familiarisation session)	1			1		
Evoked contractions (femoral nerve stimulation)	1 (familiarisation session)	1			1		
Capture of routine clinical data^		1		1	1	1	1
Adverse event assessments		1	1		1	1	1
Inform GP of study participation		1					

**Represents research blood samples drawn during routine clinical testing. ^Represents routinely collected serum blood results and dialysis data on all dialysis units.*

8. RECRUITMENT

8.1 Participant identification

Potential participants will be identified by a member of the clinical team based upon the exclusion and inclusion criteria. They will be recruited via the following routes:

1) During or before a routine outpatient clinical appointment. For individuals that may be eligible to take part, participant invitation letters will be sent along with appointment letters. The clinician will formally approach the person about the study during their clinic visit and will provide the individual with an invitation letter and a brief explanation of the study. If they are interested to find out more, they will have the opportunity to speak to a member of the research team who will give them a participant information sheet and answer any questions they have. If an individual has not been identified prior to their planned clinic appointment, but the clinician deems them to be eligible they will be given the participant invitation letter together with the participant information sheet and a brief explanation of the study. If they are interested, they will then be given the opportunity to speak to a member of the research team;

2) During a dialysis session or ward round on the unit. The clinician will speak to the individual either as part of a normal ward round, or as a separate initial approach about STIM-HD. They will provide the individual with an invitation letter and the participant information sheet, and provide a brief explanation of the study. If they are interested to find out more, they will have the opportunity to speak to a member of the research team who will answer any questions they have.

8.2 Screening and eligibility assessment

Potential participants will be screened for eligibility by a member of the clinical team using their most recent laboratory tests and medical history.

8.3 Consent

Potentially eligible participants will be initially approached by a member of their usual healthcare team to see if they would like to take part in the study. Patients will be provided with a PIS to take home, or this can be emailed to them. A member of the research team will speak to them a few days later to discuss the exact nature of the study, the implications and constraints of the protocol, and any risks involved in taking part, at a time convenient for the patient, most likely whilst they are receiving dialysis to answer any further questions and to confirm their decision regarding participation. They will be given as much time as they wish to consider their participation and the opportunity to question their GP or other independent parties. If the individual would like to take part, the research team will then organise a suitable time for them to sign the consent form and to complete the assessments. The PIS will clearly state that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Written Informed Consent will be obtained by means of a signed and dated up to date version of the consent by both the individual taking part, and the person who presented and obtained the informed consent. The person who takes consent will be suitably qualified and experienced, and will have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study.

The original signed consent forms will be retained at each study site within the Investigator Site File (ISF) together with a copy of the relevant information sheet. A copy of the signed Informed consent will be given to participants a copy retained in the participant medical notes, and a copy retained for sample transfer.

8.4 Screening post consent

An inclusion criterion is the presence of sarcopenia which is determined by the presence of low muscle strength measured using a hand grip dynamometer (<27kg men and <16kg women). This will be determined after the participant has given consent. If their hand grip strength is found to be below these cut off thresholds, they will be eligible to take part in the study and will be randomised. If their hand grip strength is above these cut off thresholds, they are ineligible and will not be randomised.

As part of the Patient and Public Involvement work that we carried out prior to grant submission, patients suggested to include an opportunity to try the NMES procedure before they are randomised to see how well they are able to tolerate it. For those patients that are eligible, they will be offered the opportunity to try NMES on one occasion. The researcher will talk them through the procedure and explain which parameters will be changed and give the opportunity to control the different parameters to see how they find it. If patients do not think they will be able to tolerate the NMES they can withdraw from the study before they are randomised. As part of the screening visit, we will also familiarise people with the isometric strength measurement, our primary outcome measurement. This is to ensure they are able to complete this assessment with no problem and to eliminate any learning effects in the assessment visit.

8.5 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Not applicable for this study.

8.6 Randomisation

After consent and baseline measurements have been collected, participants will be randomised by a delegated individual at each participating centre to either the intervention (3-months of NMES) or the control group (standard care) in a 1:1 manner. Participants will be allocated using minimisation factors of age and time on dialysis, this will ensure the external validity of the results.

Each participant will be given a unique participant ID number at randomisation. This participant ID number will be used to identify the individual participant throughout the study and will not be re-assigned to any other participant. Due to the nature of the intervention, blinding of the participants and the study team to the randomisation arm is not possible.

Randomisation will be performed using a validated web-based system to maintain allocation concealment. This will be managed by the Leicester Clinical Trials Unit.

8.7 Baseline data

These assessments can be split over multiple visits if the participant wishes.

1) Demographic and clinical information:

Date of birth/age, gender at birth, ethnicity, medical history and medications will be collected from hospital records.

2) Hand Grip Strength

Participants will perform this assessment seated with their feet flat on the floor, or standing if participant cannot be seated using the non-fistula arm. Participants will be asked to squeeze the handheld dynamometer as hard as they can on three occasions with a short rest in between. The highest measurement will be taken.

3) Isometric strength and rate of force development

Participants will be seated in a custom-built dynamometer, with their lower leg secured to a brace in series with a strain gauge force transducer. Following a series of warm-up contractions of gradually increasing force, participants will perform a series of 3-4 brief maximum voluntary contractions lasting ~5 s and separated by ~1 minute of rest, attempting to exert as much force as possible during each contraction. After that, participants will perform 10 efforts of contracting “as fast and as hard as possible” for ~1 s to at least 80% of maximal force (separated by 30-45 seconds of rest) to allow assessments of the rate of force development.

4) Quadriceps Cross-sectional area and architecture

Measures will be taken at mid-point of the thigh, and three measures (within 10%) of rectus femoris cross sectional area will be taken and the mean recorded. Three measures of muscle thickness will be taken and the mean recorded. Images of the quadriceps will be taken (pseudonymised) for later analysis of grayscale (muscle quality). Muscle thickness and angle of pennation will also be measured by ultrasound at points along the quadricep.

5) Short Physical Performance Battery

This involves 3 successive balance tests, side by side stand, semi tandem stand, and full tandem stand, a gait speed test and sit to stand 5 test.

Balance tests

The participant is asked to stand unsupported for 10 seconds with their feet in a certain position (feet together, semi tandem, full tandem). The length of time they are able to remain balanced for in seconds is recorded.

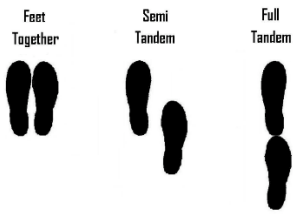

Figure 2: *Image of three foot positions during the balance tests*

Gait Speed

The participant walks between two timing gates or cones at their usual walking pace placed 4m apart. Speed in m/s is recorded.

Sit to Stand 5 test

The participant starts from a seated position on a hard, upright chair (such as a dining chair), with the feet flat on the floor and the knees bent at 90°. For the test, the participant simply stands up fully and then sits down again to the starting position, without using the hands (one cycle). The length of time in seconds that it takes for the individual to complete 5 repetitions is recorded.

6) Sit to Stand 60 test

The participant starts from a seated position on a hard, upright chair (such as a dining chair), with the feet flat on the floor and the knees bent at 90°. For the test, the participant simply stands up fully and then sits down again to the starting position, without using the hands (one cycle). The number of cycles achieved in 60 seconds will be recorded to provide a surrogate measure of muscular endurance.

7) Six-minute walk test

Cones are placed up to 10-30m apart (depending upon space available) and the individual is asked to walk as far as they can in 6 minutes. Distance walked in meters is recorded.

8) Incremental shuttle walk test (ISWT)

The participant walks a level 10m shuttle course at a speed controlled by an external audible bleep signal. The bleep speed progressively increases at 1 minute intervals for a total of 12 stages, and the test is terminated when the participant fails to complete the shuttle course in the allowed time, or reaches volitional exhaustion. We may also ask participants to wear the accelerometer during this test (see section below on accelerometry).

9) Bioelectric Impedance Analysis (BIA)

BIA analysis will be carried out using a free-standing BIA monitor. This is a painless, non-invasive method for measuring fat and fat free mass. Participants will stand on the monitor platform in bare feet and grip the handles firmly while the monitor takes the measurement. The procedure takes around two minutes.

10) Accelerometry

Participants will be asked to wear an accelerometer on their non-dominant wrist for 24 hours/day for 8 days. The participant does not have to do anything with the device apart from wearing it, and once it is fitted on the day of the appointment, it will not need to be removed until the wear period is over. Participants will be asked to return the watch at their next study appointment or hospital visit. Data captured by these devices will allow assessment of physical activity levels and patterns, sedentary time and sleep. Participants will also complete sleep diary over the course of 8 days to complement the data from the accelerometer. Using the diary, participants will record the time they went to sleep, and the time they woke up. Naps will not be recorded. Participants will be given two instructions documents; one containing accelerometer wear instructions and another containing instructions for completing the sleep diary.

11) Questionnaires

Participants will be asked to complete the Kidney Disease Quality of life Tool (KDQoL), EQ-5D-5L questionnaire, SONG-HD questionnaire, the SARC-F questionnaire, GP Physical Activity questionnaire, the SarQoL questionnaire and a resource use questionnaire, which will be combined into one survey pack. The EQ-5D-5L and resource use questionnaire will capture the data needed to perform the health economic evaluation. To minimise recall bias, participants will be offered a resource use diary in which to record their healthcare visits and other related resource use and expenditure to aid completion of the aforementioned self-completed questionnaire. This will be optional.

12) Blood sample*:*

Up to 40ml (approximately 3 tablespoons) venous blood sample will be taken from the arterial dialysis line within the first hour of dialysis. Plasma/serum will be separated and stored at -80ºC before the analyses described below.

Samples will be analysed/used for some or all of the following:

- Markers of metabolism and homeostasis
- Inflammatory markers and immune cell function/activation
- Biomarkers of cardiovascular risk
- Endothelial damage

- Oxidative stress
- Anabolic/catabolic hormones
- microRNA and full RNA expression
- Small extracellular vesicles isolation (exosome/microparticle)
- Genetic analysis (with relevant clause in the consent form)
- Pre-conditioning of cells *in vitro*
- Isolation of peripheral blood mononuclear cells (PBMCs)

8.8 Work Package 4: Optional mechanistic study

Optional mechanistic outcomes will be performed in a sub-group (both study arms) to assess the mechanistic effects of neuromuscular electrical stimulation on skeletal muscle morphology and function in haemodialysis patients. Participants will indicate via the consent form whether or not they wish to participate in the following optional assessments. Participants can still take part in the main study without completing these assessments. These assessments will be performed in centres with appropriate capability and capacity, at baseline and at 3-month follow-up only. These are optional procedures and will only be done in some centres.

1. Skeletal muscle biopsy using the needle biopsy procedure

The number of biopsies that we will take will depend upon which group participants are randomised to. We will collect three samples from the NMES group, and two samples from the Control group:

- NMES group sample 1: Taken at baseline in the days prior to the first NMES session
- NMES group sample 2: Taken 24 hours after the first NMES session. This will provide crucial information on how the muscle has responded to the intervention
- NMES group sample 3: Taken 24 hours after the last NMES session. This will provide crucial information on how the training period has affected the muscles response to the intervention.

- Control group sample 1: Taken at baseline in the days before the start of the 3-month period
- Control group sample 2: Taken in the days at the end of the 3-month period.

Participants will be asked to refrain from eating or drinking anything other than water on the morning of the biopsy. A biopsy sample will be collected using the needle biopsy technique.

A muscle biopsy of the vastus lateralis (quadriceps), or another appropriate muscle will be taken using the needle biopsy procedure. With the participant lying supine, the skin of the thigh is sterilised using either chlorhexidine or iodine solution and anaesthetised using 1% lidocaine injected subcutaneously as local anaesthetic. A small incision (<0.5cm) is then made through the skin, subcutaneous fat and muscle fascia at a mid-thigh and lateral position. Through this incision a 12-guage single use microbiopsy needle is inserted and a small sample of muscle (approx. 100mg) taken. Depending upon the amount of tissue collected additional passes may be required at the same site using the same incision. A steristrip and a bandage are then applied. The whole procedure takes about 15 minutes, and has been used successfully in our previous studies, which was well-tolerated (ExTra CKD ref 13/EM/0344, Explore CKD Ref 15/EM/0467). The administration of local anaesthetic may cause mild discomfort, and there is a small risk of haemorrhage or infection at the site of the biopsy. Following the local anaesthetic, the procedure is not painful, though the site of the biopsy may ache for a day. Analgesia will be offered following the procedure. All biopsies will be performed by trained healthcare professional and had experience of the procedure.

The muscle samples will be analysed for some or all of the following:

- Markers of metabolism and homeostasis
- Muscle morphology/anatomical structure/fibre type
- Protein turnover (protein synthesis and degradation) and events leading to this
- The process of myogenesis (muscle repair and regeneration)
- Neuromuscular function
- Intramuscular inflammation and processes relating to this
- Mitochondria number/function and processes relating to this
- Amino acid content and transport
- RNA and microRNA expression

2. Surface Electromyography (EMG)

Following preparation of the skin, high density grid electrodes will be placed over the surface of the thigh muscles,

prior to the following voluntary muscle contractions below. The EMG grid facilitates recording of muscle electrical activity and subsequent decomposition enables the behavior (recruitment and discharge rate) of individual motor units to be discerned. This technique has been used several times before in clinical populations with no adverse effects (IRAS ID's: 22569, 306712, 321959). Using the same dynamometer as for the isometric strength exercise, participants will complete a series of gradual sub-maximum contractions, by following a target line on the screen to achieve specific sub-maximum contraction levels.

3. Intramuscular Electromyography

The needle insertion location over the vastus lateralis muscle will be identified and cleansed, before insertion of a 26-gauge needle into the leg, ~20-40mm below the surface and into the vastus lateralis muscle. Then whilst the participant is sat on the same isometric dynamometer, participants will complete a further series of low-level gradual sub-maximum contractions.

4. Femoral nerve stimulation

Electrodes will be placed in the femoral triangle just medial of the inguinal ligament and at the top of the femur in order to evoke contractions in response to percutaneous stimulation of the femoral nerve. With participants seated on the same isometric dynamometer, the intensity of stimulation of the femoral nerve will be individualised by gradually increasing the current until a plateau in the evoked twitch response is detected (or the individual's tolerance level is reached, whichever occurs sooner). Then three identical measurement stimulations will be delivered at rest, separated by ~15-20 seconds.

8.9 Neuromuscular electrical stimulation (NMES)

Participants randomised to the NMES group will receive NMES at each dialysis session they attend for 3-months. It will be administered using a commercially available 4-channel portable stimulator with participants either sitting or laid down (however they are usually positioned for dialysis). The skin will be cleaned and then electrodes will be placed upon the thigh muscles. The participants will have control of the NMES device on which they will be able to change the current that is administered. During the first two to three sessions participants will be encouraged to find their initial comfortable level of stimulation intensity (the current) and to get used to how it feels. After the first week the training will be progressed by two methods:

1. Increasing session duration up to a maximum of 30 minutes, if this is not initially achievable (excluding warm up and cool down)
2. Increasing stimulation intensity (current) which determines the strength of the muscle contraction that is induced and therefore how uncomfortable it can feel.

Participants will be encouraged to increase the stimulation intensity beyond their initial comfortable level for a portion of each session. As participants become increasingly familiar with NMES and as they adapt they will be encouraged to progressively increase the stimulation intensity further. This progression will also be guided by their individual rating of perceived exertion (RPE). RPE is a scale that guides exercise intensity. Participants will be familiarised with this in the first few NMES sessions. Participants will be encouraged to achieve a of about '4' or 'somewhat' hard. In addition, a discomfort scale will be shown to the participants to help ensure the stimulation intensity is at the correct level. Exercise intensity will also be monitored through a session using a heart rate monitor to measure heart rate and blood lactate concentrations will be measured at the end of the session. Both of these will be performed once a month to more closely monitor progress.

Heart rate monitor: A heart rate strap will be placed around the middle of the chest and a watch placed on the participants wrist to measure heart rate over the course of the NMES session.

Blood lactate testing: This will be performed at the end of the NMES session using the needle prick technique. Briefly, the skin on the finger (any finger can be used, but preferably the index finger) is cleaned and a single use finger prick needle (like the ones used by diabetics for blood glucose monitoring) is used to punch a small hole in the skin. Blood is absorbed onto a lactate strip and entered into the hand-held analysis device.

Every NMES session will be preceded with and followed by a cool down each of 5-minutes duration that will involve a progressive ramp-up/ ramp-down in stimulation intensity, with the warm-up starting at 20% and finishing at 70% of the maximum intensity used by the individual in the previous session, and the cool down vice versa.

8.10 Follow-up assessments

All outcome assessments made at baseline will be repeated at -3, -6 and -9-months post randomisation with the exception of the optional outcome measures which will be performed at baseline and -3 months only.

8.11 Patient Reported Outcome Measures

Questionnaires

Participants will be asked to complete the KDQoL, EQ-5D-5L questionnaire, SONG-HD questionnaire, SARC-F questionnaire, GP Physical Activity questionnaire, SarQoL questionnaire, and a resource use questionnaire, which will be combined into one survey pack.

8.12 Expenses and benefits

Participants will not be paid for their involvement in the study. However, if visits are required that are not part of their normal care their travel expenses will be reimbursed at the usual NHS rate of 45p/mile up to the value of £60 per visit. If a participant requires a taxi then this can be arranged.

8.13 Work Package 3: Health Economic Evaluation

Renal replacement therapy (dialysis and transplantation) is needed by 64,000 people in the UK alone and has a high cost, consuming 1-2% of the NHS budget (56). These high costs necessitate complex economic modelling of renal interventions which alter quality of life, clinical outcomes, dialysis setting and cost, both within and beyond the study. There are no existing health economic evaluations of neuromuscular electrical stimulation programmes in this or any other cohort of patients with long-term health conditions and as the implementation of any such intervention requires institutional support from dialysis providers; providing evidence that such schemes are cost-effective is therefore crucial (57).

8.13.1 Data sources

Resource use, and expenditure data will be collected from a participant self-completed questionnaire at baseline, 3-months, 6-months and 9-months as well as routine clinical databases (UK Renal Registry (UKRR)). To minimise recall bias, participants will be issued with diaries in which to record their healthcare visits and other related resource use and expenditure to aid completion of the aforementioned self-completed questionnaire. This diary will complement the self-completed questionnaire that participants will complete at baseline, 3-months, 6-months and 9-months. Data collected will focus primarily on healthcare-related, NHS costs (i.e. hospital admissions and length of stay, visits to and from healthcare professionals, medication) with a secondary focus on the perspective of patients and carers (i.e. changes in employment, leisure activities and unpaid care of others due to dialysis, associated travel and intercurrent illness). Resource use data will be combined with unit costs using standard validated tools (18-20) to obtain a cost per patient. To validate the healthcare resource use and expenditure data collected from participants, responses for a sample of participants will be compared to routine clinical data from healthcare secondary care records. We will obtain data on set-up and ongoing staff and resource expenditure from participating sites related to the delivery of the intervention (e.g. NMES consumables, any additional staff time, lengthening of dialysis visit etc.).

Calculation of Quality Adjusted Life Year (QALY): The EQ-5D-5L will be used to determine health state descriptions for the five components (mobility, self-care, usual activities, pain / discomfort and anxiety/discomfort) at baseline, 3-, 6- and 9-months and utility values calculated. Utility scores will be derived from participant responses to the EQ-5D-5L at baseline and 1-, 3- and 6- months. UK utility values will be derived using the approach recommended by NICE, which is currently using the validated mapping function from the existing EQ-5D-3L. These will be used to form Quality Adjusted Life Year (QALY) profiles over the 6-month period, adjusting for any imbalances in baseline EQ-5D-5L scores(21).

8.13.2 Cost effectiveness analysis

The difference in resource use, costs and quality adjusted life years (QALY) between the intervention and control arms will be calculated. An intention to treat and per-protocol analysis will be performed (the latter informing the beyond trial model below). This will reflect set-up and per session costs, ultimately reporting the cost per QALY gained; that is, the ratio of the change in costs to the change in QALYs between the 2 groups. Study results will be extrapolated to explore the potential costs and effect over the longer-term.

8.14 Withdrawal criteria

It will be clearly stated in both the PIS and the consent form that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

If a participant withdraws from the study, or loses capacity to consent, data and samples that have been collected up until the point of withdrawal/loss of capacity will be retained and used in the study.

8.15 End of study

The end of the study will be defined as the point at which all data has been collected and analysed.

9. STORAGE AND ANALYSIS OF CLINICAL SAMPLES

9.1 Arrangements for sample collection

Plasma collection

Venous blood collected from the dialysis line from will be collected into a tube containing EDTA or sodium heparin, centrifuged at 1500g for 10 minutes at 4ºC The resulting plasma will be stored at -80 ºC in 1ml aliquots. Samples will be analysed at the University of Leicester or Loughborough University.

Serum collection

Venous blood collected from the dialysis line from will be collected into plain tubes and left at room temperature for 10 minutes to clot. The sample will then be centrifuged at 2500g for 15 minutes at room temperature. The resulting serum will be stored at -80 ºC in 1ml aliquots. Samples will be analysed at the University of Leicester or Loughborough University.

Peripheral mononuclear blood cell (PBMC) collection

PBMCs will be isolated from whole blood using the Ficoll-Paque Density Centrifugation method. Isolated PBMCs will be stored at -80 ºC until needed. Samples will be analysed at the University of Leicester or Loughborough University.

Skeletal muscle biopsies

Muscle biopsy samples (approx. 100mg) will be treated depending upon the downstream analysis. A portion of the tissue will be immediately be stored in liquid nitrogen, in RNAse later at -80ºC, in electron microscopy fixative, glutaraldehyde, or placed in frozen in chilled isopentane and subsequently stored in liquid nitrogen or embedded in resin. Samples will be analysed at the University of Leicester or Loughborough University.

9.2 Arrangements for sample analysis

Plasma and serum samples will be analysed locally at the University of Leicester, or Loughborough University. We may require samples to be sent to a commercial company for more detailed analysis of proteins (e.g. cytokines) that we are unable to perform in house.

Skeletal muscle samples will be analysed locally at the University of Leicester, or at Loughborough University. If samples are to be sequenced for RNA or microRNAs, this will be performed by a commercial company.

If any sample remains after analysis has been completed and the individual has consented to their samples being retained, we will continue to store the sample for use in future studies that gain ethical approval or enter the sample into a tissue bank. A clause will be added into the consent form to this effect. If participants do not consent to this, any remaining sample will be destroyed after analysis. Samples may be analysed straight away, or stored appropriately until analysis at a later date.

9.3 Storage arrangements for samples

Samples will be stored in laboratories at the University of Leicester and Loughborough University. Samples will be placed under storage conditions as soon as possible after collection. Samples will be stored at each site and transferred to the relevant laboratory in batches every 3-4 months.

With participants' consent, samples remaining following analysis will be retained for future research and following closure of the study, will be transferred to a registered research tissue bank.

9.4 The destruction arrangements for samples

With participants' consent, any tissue remaining at the end of this study will be transferred to a tissue bank. If participants do not consent to this, any remaining samples will be destroyed under witness at a local incineration facility. Any sample destruction will be carefully documented.

It is the responsibility of the study site to ensure that samples are appropriately labelled in accordance with the study procedures to comply with the Data Protection Act. Biological samples collected from participants as part of

this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

10. SAFETY REPORTING

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question

10.2 Reporting procedures for Adverse Events

Common non-life-threatening symptoms such as constipation, diarrhoea, colds, headache, etc. do not need to be reported for this study. Only adverse events **causally related** to the study procedures will be recorded and captured on the Adverse Events log within the participants’ CRF. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary. The relationship of AEs to the study will be assessed and signed off by a medically qualified individual who has been delegated the duty on the study Delegation of Authority and Signature Log.

AEs considered related to the study will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, will be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

10.3 Reporting Procedures for Serious Adverse Events

It is expected that participants will experience a significant number of underlying health conditions and consequently an increased number of expected hospital admissions. In addition, as this is an interventional study, expected events may occur related to the NMES intervention. NMES induces a muscle contraction via the delivery of a small electrical current. This may cause the muscles to feel sore the next day. There have been several previous studies of NMES in chronic disease patients, including haemodialysis patients that have reported very low rates of SAEs. A recent systematic review and meta-analysis performed by NICE has concluded NMES is safe to use in chronic disease population. Events may also be associated with the more invasive outcome measures such as the skeletal muscle biopsy and intramuscular electromyography. The muscle biopsy technique has been used successfully in many of our previous studies (REC ref: 13/EM/0344) and was well tolerated. The administration of local anaesthetic may cause mild discomfort, and there is a small risk of haemorrhage or infection at the biopsy site. Following the local anaesthetic, the procedure is not painful, though the biopsy site may ache for a day. Analgesia will be offered following the procedure. All biopsies will be performed by a doctor who is trained and has experience of the muscle biopsy procedure.

Therefore, only SAEs that are **clearly related** to the study procedures/intervention and of a **serious nature** will be subject to **expedited reporting to the Sponsor**. These SAEs include:

- Musculoskeletal injury as a direct result of the outcome assessments, skeletal muscle biopsy procedure, EMG, or the intervention (NMES)
- Anything else in the investigator's opinion that is related, serious, and unexpected.

These SAEs, occurring from the time of randomisation until end of assessment period, will be reported to the Sponsor immediately and within 24 hours of becoming aware of the event. The following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- relationship to the study procedure or intervention

All other SAEs will be recorded using the SAE Log CRF. SAE data will be recorded on the REDCap database at regular intervals so that the LCTU can generate up-to-date reports for DSMC meetings. The DSMC will review the listings for clinical relevance and advise the TSC and Sponsor on the suitability of the continuance of the study following their review of the ongoing safety data and whether any further data should be collected or additional analyses undertaken.

Deaths will be recorded as part of the study outcomes and therefore **will not** be subject to expedited reporting.

SAEs will be reported using appropriate forms and according to the Sponsor SOP for reporting serious adverse events. Additional information will be provided if requested to the Sponsor and main Research Ethics Committee (REC). The Principal Investigator or another delegated physician (as agreed by the Sponsor) is responsible for the review and sign off of the SAE and the assessment of causality (i.e. whether an event is related to a study procedure or intervention).

The Sponsor will perform an initial check of the information and ensure that the SAE line listing is reviewed by the Director of Research & Innovation. All SAE information must be recorded on an SAE form and sent

to the Sponsor. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and sent to the Sponsor.

Copies of all documentation and correspondence relating to SAEs will be stored in the TMF and/or ISF.
Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs will be tabulated and summarised by treatment group, according to system organ class and preferred term, as classified in the Medical Dictionary for Regulatory Activities (MedDRA). No formal statistical testing will be performed. All events will be summarised by seriousness, expectedness and relatedness.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

10.4 Reporting Urgent Safety Measures

If any urgent safety measures (USM) are taken, the CI/delegate shall immediately, give written notice to the Sponsor and the relevant REC of the measures taken and the circumstances giving rise to those measures. The CI/delegate must inform all Principal Investigators at participating sites of the USM immediately, or within 3 days from the date the measures were taken. The CI/delegate will document this in accordance with the University of Leicester's SOP for Urgent Safety Measures.

11. STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

No minimal clinically important difference (MCID) has been reported for muscle strength as determined by isometric dynamometry in the CKD population. However, our data have shown that a 10Nm increase in muscle strength was associated with a reduction in 3-year mortality of 5% (54). The data we have used in our sample size calculation come from the improvement in strength that has been previously reported by three previous studies of NMES in haemodialysis patients (27, 30, 33) i.e. a mean strength improvements of 21.7Nm and a mean standard deviation of 47.5Nm. A total sample size of 228 participants (114 per arm) is needed to detect a 21.7Nm (SD 47.5Nm) difference (standardised effect size of 0.5 (moderate)) in change in muscle strength between groups at 3-months with 90% power at the 5% significance level. This will also account for an expected 10% total attrition rate, based on our previous data (15).

11.2 Planned recruitment rate

Professors Burton and Dasgupta are both established investigators within their NHS Trusts; all proposed dialysis units fall in the governance of NHS Trusts where they are clinical leads. As the Chief Investigator of the CYCLE-HD study, Professor Burton oversaw recruitment of 130 participants to a 6-month dialysis-based exercise study (using cardiac MRI) at a recruitment rate of 1-2 participants per week across 3 units. Given that the intervention was more complex and of longer duration, with outcome measures more onerous to collect, we believe a recruitment rate of 2-4 participants per week over 21-months is achievable and will comfortably exceed our required sample size of 228.

11.3 Statistical analysis plan

A statistical analysis plan (SAP) will be prepared by the Trial Statisticians and will contain full details of all statistical analyses. The SAP will be agreed with appropriate oversight prior to database lock and published in a study protocol paper. Any changes to the original SAP will be detailed along with the reason(s) for changes in subsequent SAPs. No formal stopping rules or interim analyses have been pre-defined or planned.

11.3.1 Summary of baseline data and flow of participants

Some, or all of the following baseline data will be collected from all participants:

- Demographic information (e.g. height, weight, date of birth, ethnicity, gender)
- Clinical information (e.g. prescriptions, comorbidities, haemoglobin, glucose, hba1c, eGFR, creatinine, WBC, Fev1)
- Isometric strength (N)
- Rectus femoris cross-sectional area (cm^2)
- Fat mass (kg)

- Fat free mass (kg)
- Lean body mass (kg)
- Body fat (%)
- Skeletal muscle mass (kg)
- Appendicular lean mass (kg)
- Muscle thickness (mm)
- Angle of pennation (degrees)
- Distance covered during the 6-minute walk test (m)
- Hand grip strength (kg)
- Sit to stand 5 (secs)
- Sit to stand 60 (repetitions)
- Balance (seconds)
- Gait speed (m/s)
- KDQoL (points)
- GP-PAQ (points)
- ED-5D-5L (points)
- SARC-F (points)
- SONG-HD-fatigue (points)
- SarQoL (points)
- Motor unit recruitment and decruitment threshold (Nm)
- Motor unit discharge frequency (Hz)
- Motor unit conduction velocity (m/s)
- Motor unit potential jiggle and segment jitter (AU)
- Quadriceps twitch contractile properties (Nm)
- Quadriceps maximal M-wave (mV)

Plasma/serum samples will be analysed/used for all or some of:

- Markers of muscle metabolism/homeostasis
- Inflammatory markers and immune function/activation
- Biomarkers of cardiovascular risk
- Endothelial damage
- Oxidative stress
- Anabolic/catabolic hormones
- microRNA expression
- Exosome/micropartical isolation
- Genetic analysis

Skeletal muscle biopsy samples will be analysed for all or some of:

- Markers of muscle metabolism/homeostasis
- Muscle morphology/architecture/fibre type
- Protein turnover (protein synthesis and degradation) and events leading to this
- The process of myogenesis (muscle repair and regeneration)
- Intramuscular inflammation and processes relating to this
- Mitochondria number/function and processes relating to this
- Amino acid content and transport
- RNA and microRNA expression

11.3.2 Descriptive analysis

Data will be checked for outliers and missing values and validated using the defined score ranges for all outcome measures. Baseline data will be summarised by group to assess comparability between treatment arms, and to highlight any characteristic differences. Statistical tests for imbalance will not be carried out.

It is likely that some data may not be available due to death, kidney transplantation, and voluntary withdrawal of participants or lack of completion of individual data items. Where possible the reasons for missing data will be ascertained and reported. Although every effort will be made to minimise crossovers from both intervention arms, the numbers, direction and reasons for participants moving between arms will be recorded and reported in line with CONSORT (Consolidated Standards of Reporting Trials) guidance.

11.3.3 Analysis of primary outcome

The primary analysis will compare the change in muscle strength from baseline to 3-months (i.e. at the end of the intervention period) between randomised groups. The primary analysis will be conducted by intention to treat (ITT) comparing all those randomised to the NMES programme to those who were randomised to standard care. Linear regression with change in muscular strength as the dependent variable, adjusted for baseline value and the minimisation factors (age, time on dialysis), will be used to compare treatment groups, the adjusted mean difference between the treatment arms will be presented with a 95% confidence interval.

11.3.4 Analyses of secondary outcomes

The secondary outcomes will be analysed in a similar manner to the primary outcome. All represent continuous data and therefore linear regression will be used. All analyses will be adjusted for baseline value and the stratification factors. The number of deaths and cardiovascular events expected is relatively low, therefore formal time to event analyses will not be conducted. Kaplan–Meier will be presented to describe the relationship between these events and treatment.

11.4. Subgroup analyses

A priori sub group analysis will include, gender, age, time on dialysis, physical activity levels (i.e. sedentary versus active) and the severity of sarcopenia at baseline (i.e. probable vs severe).

11.5 Adjusted analyses

The primary analysis will be adjusted for the minimisation factors.

11.6 Interim analysis and criteria for the premature termination of the study

No criteria for early termination of the study have been set.

11.7 Participant population

We will recruit haemodialysis patients (either home or unit based) who have been receiving dialysis for more than 3 months.

11.8 Procedure(s) to account for missing or spurious data

By design there will be no missing data for the minimisation factors, if the primary outcome is missing for less than 5% of the study population at baseline and 3-months, a complete case analysis will be conducted. If there is more than 5% missing outcome data, multiple imputation will be used. The imputation will be carried out using the command MI in Stata. MI replaces missing values with multiple sets of simulated values to complete the data, performs standard analysis on each completed dataset, and adjusts the obtained parameter estimates for missing-data uncertainty using Rubin's rules to combine estimates.

12. DATA MANAGEMENT

12.1 Data Flow Diagram

This is a separate PDF document.

12.2 Data collection tools and source document identification

All physical function data will be entered into an electronic case report form (REDCap) and collated on an excel spreadsheet. All pseudonymised lab data will be collated and stored using the lab archives online database as well as in individuals' lab books. These lab books contain pseudonymised results of the experiments performed with the biological samples, the methods used and any variation of these methods and will be used throughout the study.

12.3 Source Data

Source documents collected during this study include, clinical records, completed questionnaires, and ultrasound scans. In addition, all physiological data will be entered into an electronic case report form and will also be considered as source data.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.4 Data handling and record keeping

Each participant will be assigned a unique identification number upon consent and this will be added to all study documents/data collection tools in place of the participant's name. All study data will be entered on to paper CRFs before being entered into the REDCap database. The database will be located on a University of Leicester server.

A copy of the completed participant informed consent form and participant information sheet will be placed in the medical notes of all participants and in the Investigator Site File. A sticker will be placed on the cover of the notes (or inside cover) detailing the study title, contact details of the PI and the fact that the notes should not be destroyed for 6 years from the end of the study. All study visits summaries and relevant SAEs will be recorded in the hospital notes.

A contacts database (containing participant contact details) will be held separately from the study database. Participants' contact details will be held securely in accordance with data protection regulations. This will be password protected and managed by the research team at each site.

All data handling and record keeping will be kept in adherence to University of Leicester's and relevant NHS Organisations' policies. All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, The UK Policy for Health and Social Care Research and the Data Protection Act.

12.5 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections in line with participant consent.
The Chief Investigator and relevant study staff will have access to the data collected as part of this research. Access to the study database will be restricted by role-based permission to authorised study personnel will be suitably trained on the system prior to being granted access. Individual user accounts will be password-protected and will not be shared between members of the study team.

12.6 Archiving

Research data and archived files will be stored for a minimum of 6 years after the study has ended. Storage will comply with the University of Leicester archiving Standard Operating Procedure. Details can be found at: *https://le.ac.uk/research/regi/standard-operating-procedures*. Destruction of essential documents will require authorisation from the Sponsor. Archiving of source data or the Investigator Site File (ISF) for participating sites will be arranged by the relevant participating site.

13. MONITORING, AUDIT & INSPECTION

The University of Leicester as Sponsor operates a risk-based monitoring programme with this study will be subject to.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) review and reports

Once the initial sponsor review process is complete and a sponsor reference number has been allocated, and all requested documentation has been received and checked, authorisation from the University of Leicester's Research Governance Office will be issued to book further review of the proposed research. The University of Leicester's Ethics Committee or NHS Research Ethics Committee and the Health Research Authority will then review the proposal. Agreement in principle is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will be submitted via Integrated Research Application System (IRAS). The Chief Investigator will ensure that all regulatory approvals, confirmation of capacity and capability from NHS sites and sponsor greenlight are in place before participants are approached.

For any required amendments to the study, these will be submitted to the sponsor in the first instance for review and approval to submit the amendment for external regulatory approval. Amendments must be implemented following all required ethical, site and Sponsor approvals and in line with Sponsor Standard Operating Procedures. The Research Governance Office's Standard operational procedures will be followed for the duration of the study.

The Chief Investigator will notify the REC when the study has ended by completing the end of study notification form and will submit a final report of the results within one year after notifying REC.

A Trial Master File will be maintained for the duration of the study and will be stored for 6 years after the study has ended. The only time this could be exceeded, is if samples are being retained beyond the scope of the original study i.e. there is consent for future research. In this circumstance ICFs would have to be retained for as long as the samples are in existence, as we have a legal requirement to prove the samples were obtained with consent.

14.2 Peer review

Prior to review by the sponsor, the protocol has been through the external peer review as part of the grant submission process. It was externally reviewed by seven experts.

14.3 Public and Patient Involvement

Population (P): As part of other NIHR funded research within the dialysis population, we have established a national Patient Participation, Involvement and Experience (PPIE) group comprising people on dialysis and their family / carers. This group, led by our patient co-applicant (Fez Awan) have helped co-develop the research question and study design both for the stage 1 application and subsequently for this stage 2 research plan.

Research question and intervention (I): The PPIE group understood the benefits of regular exercise, but despite motivation and intention, many are unable to exercise consistently. They felt NMES might be a more realistic therapy they would be able to take part in on a regular basis. Reviewing the intervention, a number of improvements were made to the protocol:

- Inclusion (and design) of the external pilot study to assess the tolerability (Work package 1)
- To include issues of comfort (including the pad size and their placement)
- Inclusion of an adapted screening phase to allow potential participants to trial the NMES intervention before consent (and minimise attrition / drop out).
- Input into the randomisation technique (individual vs cluster) for work package 2 and then insight into mitigation strategies to prevent contamination between groups (use of curtains, additional time discussing in clinic rooms) and their acceptability to participants.
- To broaden the eligibility criteria to include home haemodialysis patients and ways to ensure participation is least intrusive to encourage enrolment.

Control (C): All patients were keen to be able to try NMES if they were in the study. However, the PPIE group provided reassurance that patients randomised to standard care would understand the importance of the randomised design (and the 50% chance of being allocated to the control group), minimising the impact of resentful demoralisation. Nevertheless, there was a clear message to ensure that the NMES device was affordable and easy to use as participants may wish to purchase their own after the study (irrespective of group allocation). This has been updated to ensure a commercially available device is used throughout.

Outcome (O): Patients highlighted muscle weakness (which makes up the principal component of the diagnosis of sarcopenia) as one of the most intrusive symptoms they experience. Following feedback from the Funding Committee, the PPIE group were pleased to include additional measures of quality of life (KDQoL) as well as symptom burden (fatigue) that are known to be some of the most important outcomes to people on dialysis. The 6-month extension to the protocol to allow for this additional data collection was seen as a positive step and as with previous studies. There was no anxiety around questionnaire fatigue because the participants are attending for their treatment at that time, in any case. To ensure that the intervention is as easy to undertake by home haemodialysis patients in the community and that the outcome measures are as straightforward to collect, a number of action points were highlighted by the PPIE members:

- To ensure a systematic approach is adopted for screening that ensures people on home haemodialysis are identified
- To allow as much flexibility as possible for scheduling visits at the pre-screening and consent stage (e.g. being able to travel to the nearest dialysis unit rather than hospital centre)
- To offer easy access to remote support and regular scheduled ‘check-ins’ to help ensure adherence to the intervention.

14.4 Assessment and management of risk

The main risks involved in this study are:

1. Tests of physical function: As with all exercise there is a small risk of injury. All tests will be carried out by a trained member of the team and explained and demonstrated to all participants. Before the test is carried out, participants will undergo a familiarisation test where they can practice and get used to how the test

feels. All the tests that we have included here are routinely used in long-term conditions, and they will all be carried out in a hospital setting.

2. NMES procedure: This evokes a muscle contraction, so it is likely that following the first few sessions especially, participants will feel sore afterwards, much like when you have lifted weights after having not done this exercise for a while. This soreness will likely last a day or two at the start of the programme, but is not due to damage to the muscle, but is the normal response to having performed unaccustomed exercise.
3. Intramuscular electromyography: Intramuscular EMG involves inserting a thin needle (similar size to acupuncture) into the muscle during low level contractions. Intramuscular EMG is a routine clinical procedure with reports of complications being very rare. The possibility of bleeding is very low, and occasionally bruising around the insertion site is possible though rare. We have used this technique several times before in clinical populations with no adverse events (IRAS IDs: 22569, 306712, 321959)
4. Femoral nerve stimulation: stimulation of the femoral nerve can result in some brief discomfort in the area under the stimulating (cathode) electrode due to local skin receptor activation and this effect is usually perceived as a tingling sensation that accompanies involuntary muscle twitch contractions. This discomfort disappears as soon as the stimulation ceases (1 ms pulse). Familiarisation will be performed to minimise discomfort and participants will be monitored throughout this procedure to ensure that discomfort is not excessive. There are rare reports of the stimulation interfering with implantable devices and rare reports of skin burns; therefore, participants with a pacemaker or a similar device, and participants with metal objects around the area of stimulation (i.e., in/around the hip joint) will be excluded.
5. Blood sampling: samples will be collected from the participants specifically for research purposes only. A 40ml / 2 tablespoon blood sample will be collected from the arterial dialysis line within the first hour of dialysis to prevent the need for additional needling over participants' direct clinical care. The procedure to collect blood for blood lactate analysis may cause some bruising of the finger tips.
6. Skeletal muscle biopsy: Participants will undergo a biopsy of the thigh muscle. The biopsies will be performed under local anaesthetic by a clinician experienced in the technique. With the participant lying supine, the skin of the thigh is cleaned thoroughly using iodine solution, and 4-5ml 1% lignocaine injected subcutaneously as a local anaesthetic. A small incision (<0.5cm) is made through the skin, subcutaneous fat and muscle fascia at a mid-thigh and lateral position. Through this incision a 12-guage microbiopsy need is inserted and a small sample (approx. 100mg, the size of a pea) is taken. This technique has been used in our previous studies and was well tolerated (13/EM/0344; 10/H0406/50; 15/EM/0467). The administration of local anaesthetic causes mild discomfort and there is a small risk of haemorrhage or infection at the site of the biopsy. The procedure is not painful following the local anaesthetic, though the site of the biopsy may ache for a day. Analgesia will be offered following a biopsy.
7. Fasting: The muscle biopsy needs to be taken in the fasted condition. The participants will therefore be asked to refrain from eating or drinking anything except water on the day of the procedure until after the biopsy has been collected. For samples that are collected by the needle biopsy technique, we will schedule the appointments for the morning to reduce the time until the participant can eat, but this fasting may cause some inconvenience and discomfort (hunger).
8. Questionnaire burden: We are asking participants to complete seven questionnaires which will take about 75 minutes to complete. However, they are all quite short and simple to complete and participants will have the option of taking them home to either bring back on your next visit to the dialysis unit, or post them back to the research team.

14.5 Regulatory Compliance

The study will not commence until it has received a favourable opinion from REC, HRA and has been given the green light by the Sponsor.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

14.6 Protocol Compliance

14.6.1 Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the TMF/ISF as applicable. If a protocol deviation occurs, then the CI (or delegate) will document this in accordance with the University of Leicester's SOP for Identifying and Reporting Deviations and Serious Breaches of GCP and/or

the Protocol. Deviations from the protocol which are found to frequently recur will be explored and where necessary an amendment to the protocol will be made.

14.6.2 Serious breaches

A “serious breach” is a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or
(b) the scientific value of the research.

In the event that a serious breach is suspected, the Sponsor will be contacted within one working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor, and, if appropriate, the Sponsor will report it to the approving REC and relevant NHS host organisation within seven calendar days.

14.7 Data Protection and Participant Confidentiality

All information collected in the study will be kept strictly confidential.

The Chief Investigator will be the data custodian.

The Chief Investigator and research team will comply with the requirements of the General Data Protection Regulation (and other applicable regulations) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

Analysis of the data generated will be undertaken by the Leicester Clinical Trials Unit on University of Leicester premises. All collected data and electronic confidential information will be held on a secure password-protected database accessible to only essential personnel at each participating site. Research data will be pseudonymised at participating sites before being transferred to the University of Leicester.

Pseudonymised research data will be stored for a minimum of six years after the study has ended, unless there is explicit consent for the data to be retained beyond the scope of the original research project, in which case it would be kept indefinitely

Consent forms, enrolment logs and details of record linkage (i.e., participant ID numbers/pseudonyms) will be kept for a minimum of 6 years after the study has ended as part of the research data so that in the event of the data being challenged, this will allow for verification of the quality of the data. At the end of this period approval from the Sponsor will be requested for the destruction of the data.

While participants are taking part in the study their contact details will be available to the researchers so that they can contact the participant to arrange the details of their research involvement. These will be deleted once they have been used for their agreed purpose. Where individuals have consented to receive a copy of the research findings, contact details will be retained until this time. Contact details will be stored securely and separately from participants’ research data and clinical information.

The TMF will be kept a folder in a locked cabinet/drawer in a secured room in a secure office environment office at the University of Leicester by the Chief Investigator (or delegate). ISFs will be kept at the relevant NHS organisations and will be stored in a secure environment. Storage will adhere to each organisational policy on storage.

14.8 Financial arrangements

This study is funded by a grant from the NIHR EME programme (funder ref NIHR158852). Additional support and resources for the study will be provided by the participating Trusts and their corresponding NIHR Research Delivery Networks (RDN). The funder will be responsible for funding the study but will not be part of the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

14.9 Indemnity

Sponsorship and insurance for study design and management will be provided by the University of Leicester. If a participant is harmed due to negligence and/or the conduct of the study, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical studies. If a study participant wishes to make a

complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them. Details of this are made available to participants in the PIS.

14.10 Post study care

Not applicable.

14.11 Access to the final study dataset

The Chief Investigator and their appointed deputies will have access to the analysed study dataset following execution of the SAP and completion of the End of Trial Report.

15. DISSEMINATION POLICY

Upon completion, the data will be analysed and disseminated at relevant national and international scientific/medical conferences, as well as patient led conferences and workshops. The data will be published in a high impact journal as well as disseminated on social media and via blogs. A video of the results will be made to increase accessibility for patients. In addition, if participants have indicated on the consent form they wish to receive a copy of the results, this will be sent to them upon study completion which will be written in collaboration with our PPIE group.

Authorship on the manuscript will be determined by the CI according to contribution to the study after discussion with the TSC, and according to the guidelines of leading medical journals. The TSC will be responsible for approval of all manuscripts arising from the study prior to submission for publication. All publications will quote the clinical study's registration number and will acknowledge the participating investigators, TSC and DSMC, LCTU, the Sponsor and the Funder. The study will be reported in line with the CONSORT statement, which is an evidence-based, minimum set of recommendations for reporting randomised trials.

Upon completion of the study, all data sets will be deposited with the University of Leicester's research database repository (https://leicester.figshare.com). Any sequencing work that has been carried out will be deposited with the NCBI Gene Expression Omnibus and the R and python code will be made available in github.

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17. Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made