Non-CTIMP Protocol Template

FULL/LONG TITLE OF THE TRIAL Effect of immuno-nutrition on markers of sarcopenia and systemic inflammation in a haemodialysis population: a feasibility randomised controlled trial.	
SHORT TITLE/ACRONYM Immuno-nutrition and sarcopenia in haemodialysis/IMMUNOSH	
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Chief Investigator:	Dr Daniela Viramontes Hörner
Local Trial Reference:	UHDB/2024/062
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Modification History

Modification No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	30 June 2026	Daniela Viramontes Hörner	Changes were made in page 26 confirming that the end of the trial will be when all plasma samples have been analysed

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's Standard Operating Procedures (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 investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through the same public registry as the trial was registered within 12 months of declaring the end of trial, as well as offering a summary of results written in lay language to trial participants or (where appropriate) their representatives, and that an honest accurate and transparent account of the trial will be given, and that any discrepancies from the trial as planned in this protocol will be explained.

Protocol v2.0 authorisation signatures:

Chief Investigator:

Signature:	……..	Date:
Name (please print):		

For and on behalf of the Trial Sponsor (if required):

Signature:		Date:
	……..	
		……/……/……
Name (please print):	……..	
Position:		
	……..	

KEY TRIAL CONTACTS

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TRIAL SUMMARY

Trial Title:	Effect of immuno-nutrition on markers of sarcopenia and systemic inflammation in a haemodialysis population: a feasibility randomised controlled trial.
Local Trial Reference:	UHDB/2024/062
Study Design:	Feasibility randomised controlled trial
Trial Population:	*Inclusion criteria:* • Age: ≥18 years (no upper age limit). • Dialysis regime of ≥3 haemodialysis sessions/week for ≥3 hours using biocompatible dialysers. • Able to give informed consent. *Exclusion criteria:* • Treatment with immunosuppressant drugs. • Body mass index ≥35 kg/m^2 • Pregnancy, breast feeding or intending pregnancy. • Expected survival <6 months. • Hospitalisation at time of screening. • Known intolerance/allergy to either supplement (or isolated ingredients). • Pre-dialysis serum potassium >5.3 mmol/L
Planned Number of Trial locations:	1
Planned Sample Size:	70
Treatment Duration:	24 weeks
Follow Up Duration:	No follow-up
Planned Start Date:	01 August 2026
Planned Recruitment End Date:	31 January 2027
Planned Trial End Date:	29 February 2028
Research Question/Aims:	**Research question** What is the feasibility of conducting a randomised trial of immuno-nutrition compared to standard oral nutritional supplementation in people receiving haemodialysis, to assess the impact on markers of sarcopenia, systemic inflammation and health-related quality of life (HRQoL)? **Primary objectives:** • To assess the feasibility of recruitment and randomisation to the trial. • To assess adherence, safety and acceptability of the intervention. • To evaluate feasibility of conducting the trial at the participating location. • To assess the effect of different durations of intervention to identify the optimum period for a future trial. • To determine the optimal primary endpoint for a future trial. **Secondary objectives** To investigate the effect of immuno-nutrition on muscle strength, body composition, physical performance, prevalence of sarcopenia, dietary intake, biochemical blood variables, inflammatory markers and HRQoL.

FUNDING AND SUPPORT IN KIND

Funder	**Financial and Non-Financial Support Given**
National Institute for Health and Care Research NIHR Grange House 15 Church Street Twickenham TW1 3NL	£293,526.00

ROLES & RESPONSIBILITIES

Sponsor

The Sponsor, University Hospitals of Derby & Burton NHS Foundation Trust (UHDB), takes on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this trial, but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The trial is funded by the National Institute for Health and Care Research (NIHR)

Trial Management Committees

Trial Management Group

The Trial Management Group (TMG) will be responsible for the day-to-day management of research activities during study set up, recruitment and follow-up, and close-down and analysis. TMG will meet at least 6 times throughout the duration of the project. TMG members will include the Chief Investigator (CI), Co-Investigators, Patient and Public Involvement/Engagement (PPIE) representative, renal research champion, as well as trial manager and trial statistician from Derby Clinical Trials Support Unit (DCTSU). Any problems with trial conduct and participating trial locations will be raised and addressed during TMG meetings.

Trial Steering Committee

The Trial Steering Committee (TSC) will be responsible for monitoring the progress of the trial, adherence to the protocol and applicable regulations, as well as safety data. TSC will meet approximately 3 times throughout the duration of the project. TSC members will include an independent Chair, an independent clinician, an independent statistician/methodologist and a member of the public. Minutes of the meetings should be sent to the NIHR project manager, and if there is anything that will be discussed at an upcoming meeting that particularly requires the funder's attention, the NIHR project manager will attend those as needed.

Protocol Contributors

A number of protocol contributors have been involved in the development of this protocol, these include the CI Dr Daniela Viramontes Hörner, Co-Investigators Prof Maarten Taal, Prof Beth Phillips and Prof Nicholas Selby, PPIE representative Chris Stait, Trial statistician Komel Khabra, Data Manager Victoria Chester and Trial Manager Kirsty Brown. Protocol contributors are responsible for inputting into the design of the trial, ensuring that it is designed transparently and efficiently.

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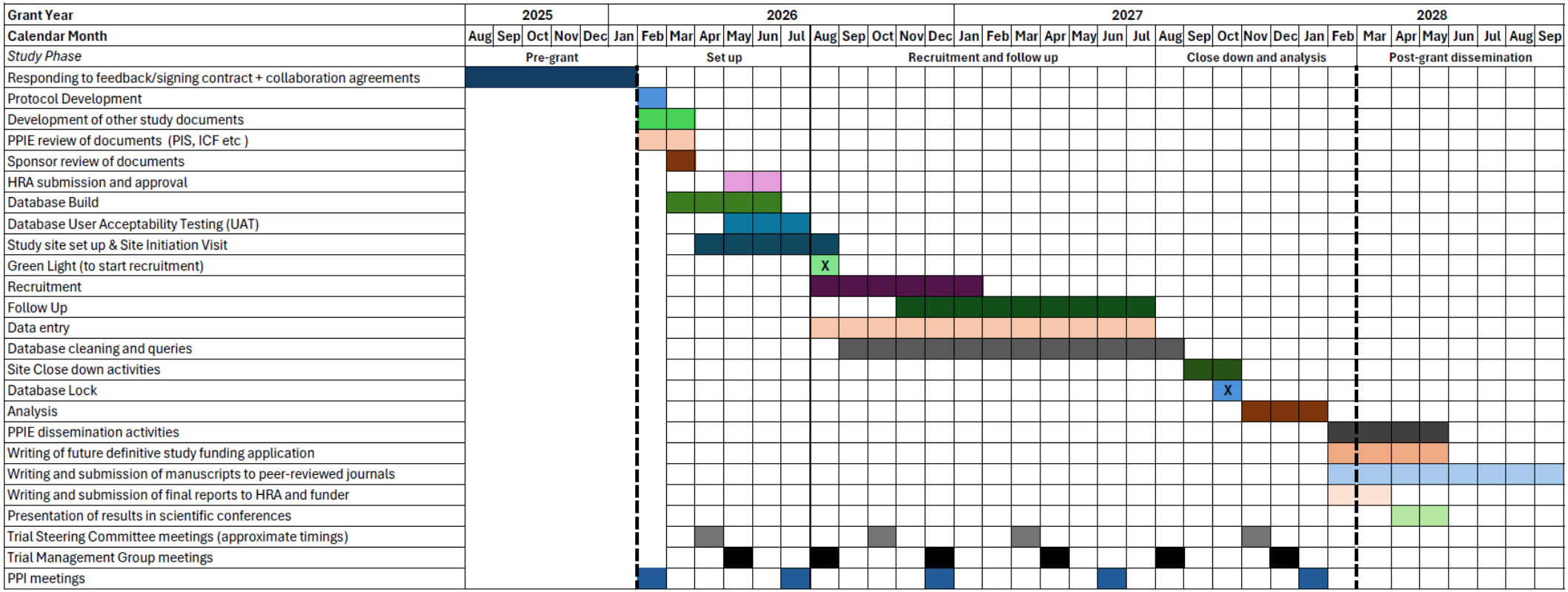
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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CI	Chief Investigator
CKD	Chronic Kidney Disease
CKRI	Centre for Kidney Research and Innovation
COMAP	Centre of Metabolism, Ageing & Physiology
DCTSU	Derby Clinical Trials Support Unit
eCRF	Electronic Case Report Form
EIA	Equality Impact Assessment
GLL	Green zone Lower Limit
HGS	Handgrip Strength
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
IL	Interleukin
IQR	Interquartile Range
ISRCTN	International Standard Randomised Controlled Trials
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health and Care Research
ONS	Oral Nutritional Supplement
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RET	Resistance Exercise Training
RUL	Red zone Upper Limit
SAE	Serious Adverse Event
SD	Standard Deviation
SMM	Skeletal Muscle Mass
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UHDB	University Hospitals of Derby and Burton NHS Foundation Trust

PROJECT GANTT CHART



A schedule of assessments in Table format is included in Appendix 1

TRIAL PROTOCOL

1. BACKGROUND

People receiving haemodialysis represent a uniquely vulnerable population with a high prevalence of frailty and multimorbidity, poor health-related quality of life (HRQoL) and greatly increased risk of death[1]. In this context, sarcopenia is a musculoskeletal disorder that encompasses:

- reduced muscle strength as the key characteristic,
- decreased skeletal muscle mass (SMM), and
- low physical performance[2].

The global prevalence of sarcopenia across the wide spectrum of chronic kidney disease (CKD) is estimated to be 24.5%. However, compared to people with CKD not requiring dialysis:

- sarcopenia is more common among people receiving haemodialysis (28.8% vs. 16.7%),
- prevalence of low muscle strength is higher in the haemodialysis population (51.1% vs. 19.6%),
- low SMM is more prevalent in people receiving dialysis (32.2% vs. 19.7%), and perhaps most importantly,
- severe sarcopenia (i.e., low muscle strength, SMM *and* physical performance) is remarkably more common in people on dialysis (26.2% vs. 3.0%)[3].

In the haemodialysis population, markers of sarcopenia, particularly low muscle strength and decreased SMM, are strong predictors of frailty, disability and increased mortality; they severely affect HRQoL, and increase both number and length of hospitalisations, which result in higher healthcare costs[4, 5].

Multiple factors contribute to the development of sarcopenia in those receiving haemodialysis, including:

- reduced appetite and therefore food intake[4], resulting in lack of dietary amino acids which are an essential anabolic stimulus[6],
- muscle protein breakdown during haemodialysis[7], reflected by amino acid efflux from muscle[8],
- physical inactivity[4] (i.e., the absence of the second most potent anabolic stimulus, contractile activity), and
- presence of diabetes and heart disease which are associated with muscle wasting[9].

Additionally, increased systemic inflammation, a frequent complication in the haemodialysis population, has been postulated to be a primary driver of SMM and strength loss[4, 9]. To illustrate the magnitude of this problem, it has been reported that people on haemodialysis lose an average of 9.5% of their SMM in 1 year[10], with associated significant reductions in muscle strength. Moreover, and key to the research proposed herein, systemic inflammation has been shown to markedly accelerate SMM and strength losses[11].

Dietetic advice and standard oral nutritional supplements (ONS) have not proven successful in stimulating muscle protein synthesis, or increasing SMM in people receiving haemodialysis[12]. This lack of improvement in SMM appears to relate to the persistent systemic inflammation seen in this patient population, which plays a major role in the development of "anabolic resistance", a physiological state that inhibits optimal rates of muscle protein synthesis being achieved despite adequate calorie and protein intake/availability[4, 13].

Immuno-nutrition supplements are high in calories and protein (similar to standard ONS), but also contain a unique combination of nutrients (i.e., omega-3 fatty acids, L-arginine and nucleotides)[14] that have been shown to:

- improve markers of nutritional status (e.g., serum albumin and prealbumin, body weight, nutritional intake) and decrease systemic inflammation in pre-surgical settings[15].
- reduce systemic inflammation, post-operative infections and length of hospitalisation in people with cancer after major surgery[16];
- maintain physical function and mid-arm muscle circumference (a surrogate marker of SMM[17, 18]), and improve phase angle (a measure of cellular health and muscle mass[19]) in people with colorectal, oesophageal, and head and neck cancers[20-22]; and
- decrease systemic inflammation in trauma and orthopaedic settings, as well as in COVID-19 and critically ill burns patients[23-26].

The proposed project will repurpose (from peri-operative settings[27]) an immuno-nutrition supplement (Oral Impact®, Nestle) to simultaneously address systemic inflammation and sarcopenia for the first time in people receiving haemodialysis.

2. RATIONALE

Sarcopenia is more highly prevalent and severe in people receiving haemodialysis than in the general population, and has a major impact on HRQoL, the need for hospitalisation and survival[3, 4]. Additionally, sarcopenia is associated with considerable healthcare expenditure. For instance, the annual excess cost in the US and UK for treating and/or caring for individuals with sarcopenia is estimated at $18.5 billion and £2.5 billion, respectively[28, 29]. Although the problem of sarcopenia in haemodialysis is widely acknowledged, dietetic support and standard ONS are not effective at improving markers of sarcopenia, predominantly because systemic inflammation attenuates the anabolic effects of dietary protein[30-32].

In addition to the benefits of immuno-nutrition described above, we have previously conducted a 6-week single-centre, observational cohort study[33] to assess the acceptability of immuno-nutrition to people receiving haemodialysis and explore the impact on markers of systemic inflammation and sarcopenia in 14 participants. We observed that immuno-nutrition was acceptable to patients, free of adverse effects, and associated with an increase in muscle strength, maintenance of SMM, and decrease in at least one marker of inflammation. These positive results support a further assessment of the impact of immuno-nutrition on markers of sarcopenia and systemic inflammation in a randomised controlled trial (RCT). Therefore, we will conduct a feasibility RCT to investigate key areas

of uncertainty (e.g., participant recruitment and retention, testing the trial protocol, and exploring potential outcome measures) before conducting a future definitive RCT.

If we confirm feasibility, we will use the data collected to design a definitive trial. If this shows clinical efficacy, we will have identified a simple intervention to address the challenging problems of inflammation, malnutrition and sarcopenia in a vulnerable population. The fact that the nutritional supplement that we propose to use has already been identified by patients as "acceptable/nice" and is commercially available, means that this intervention could be rapidly implemented as part of the clinical care for people receiving haemodialysis in the UK and globally.

It must be recognised that there is evidence to suggest that combining resistance exercise training (RET) with ONS promotes muscle protein synthesis, and therefore counteracts the progressive SMM loss seen in the haemodialysis population[34]. A combined intervention is beyond the scope of the current research proposal. However, if provision of immuno-nutrition alone proves to be beneficial, then future research would assess whether immuno-nutrition in combination with RET (or other contractile strategy) has additional benefit.

Any intervention that decreases the prevalence of sarcopenia in people receiving haemodialysis can be expected to improve HRQoL, reduce the need for hospitalisation, increase independence and consequently lower both health and social care use/costs, as well as prolong survival[3, 4, 29].

Improvement and/or maintenance of SMM and strength is important for haemodialysis patients awaiting a kidney transplant because it is likely that this will facilitate more rapid recovery after transplant surgery[35]. Indeed, the proposal to use an “immuno-nutrition” approach in this study is based on evidence that a similar approach improved outcomes in people with cancer after major surgery[36].

An intervention to improve markers of sarcopenia is also critical for those haemodialysis patients (unfortunately the majority) who are not suitable for a kidney transplant because their age or the presence of comorbidities places them at unacceptable risk of peri-operative complications or immunosuppression-related adverse outcomes[37]. These people face the rest of their lives on haemodialysis and any intervention that improves their health and quality of life is extremely valuable.

In fact, we have previously discussed studies concerning muscle-related problems in people receiving haemodialysis with our local patient and public involvement and engagement (PPIE) group and received feedback that this was an extremely important area to patients because of the high levels of fatigue and reduced physical function that this patient population experience. Also, the idea of studying a new supplement with immuno-modulating properties was well-accepted and considered innovative by our PPIE group.

2.1. Assessment and Management of Risk

The proposed project will involve taking an immuno-nutrition supplement or a standard ONS (usual care), as well as following usual dietetic advice provided by NHS renal dietitians, all of which are not expected to be associated with any risks. Additionally, we have previously conducted an observational

feasibility study and observed that the immuno-nutrition supplement was free of adverse effects, including hyperkalaemia and fluid overload[33].

The results and the feasibility data collected from this feasibility RCT will help inform the design of a definitive, multi-centre RCT. An improvement in markers of sarcopenia in people receiving haemodialysis with an immuno-nutrition supplement could lead to improved HRQoL, reduce hospitalisations, increase independence, lower health/social care use/costs, and prolong survival. On completion of this project, a subsequent definitive RCT could inform and improve treatment of sarcopenia which could have life-changing physical and mental health benefits to people receiving haemodialysis, while also lowering healthcare costs.

3. RESEARCH QUESTIONS / OBJECTIVES

3.1. Primary Research Question / Objectives

Research question

What is the feasibility of conducting a randomised trial of immuno-nutrition compared to standard ONS in people receiving haemodialysis, to assess the impact on markers of sarcopenia, systemic inflammation and HRQoL?

Primary objectives:

- To assess the feasibility of recruitment and randomisation to the trial.
- To assess adherence, safety and acceptability of the intervention.
- To evaluate feasibility of conducting the trial at the participating location.
- To assess the effect of different durations of intervention to identify the optimum period for a future trial.
- To determine the optimal primary endpoint for a future trial.

3.2. Secondary Objectives

To investigate the effect of immuno-nutrition on muscle strength, body composition, physical performance, prevalence of sarcopenia, dietary intake, biochemical blood variables, inflammatory markers and HRQoL.

4. OUTCOMES

4.1. Primary Outcome

The primary outcome will be the feasibility of conducting an RCT of immuno-nutrition vs standard ONS. Feasibility outcomes will include the following:

- Screening, eligibility, consent, approach, refusal and randomisation rates.
- Completion of trial and secondary outcomes at each study visit.
- Adherence, acceptability and safety of treatments (i.e., immuno-nutrition and standard ONS).

4.2. Secondary Outcomes

Secondary outcomes will include:

- Muscle strength assessed with handgrip strength (HGS).
- Body composition assessed with bioelectrical impedance analysis.
- Physical performance assessed with the Short Physical Performance Battery (SPPB).
- Prevalence of sarcopenia and severe sarcopenia, according to the definition from the European Working Group on Sarcopenia in Older People.
- Dietary intake assessed with 3-day food diaries.
- Biochemical blood variables including haemoglobin, urea, creatinine, potassium, phosphate, calcium, albumin, total protein and parathyroid hormone.
- Plasma levels of pro-inflammatory cytokines (interleukin [IL]-6 and IL-8).
- HRQoL assessed using the Kidney Disease Quality of Life 36-item short-form survey.

5. STUDY DESIGN

This will be a single-centre, feasibility, parallel RCT. Participants will be randomly allocated in a 1:1 ratio to the control group (standard ONS) or the intervention group (immuno-nutrition supplement). Both groups will take one supplement daily for 24 weeks.

5.1. Progression Criteria

Progression to a future definitive trial will be guided by the following predefined feasibility criteria:

Progression Criteria	Stop	Proceed with changes	Proceed without changes
Patients randomised (both groups)	≤43 participants (corresponding to 20% recruitment rate)	44 - 69 participants	70 participants
Adhered to treatment (taking ≥75% of doses; intervention group)	≤50%	51%-74%	≥75%

6. TRIAL SETTING

This feasibility RCT will be conducted in the Royal Derby Hospital renal dialysis unit (main unit) and Lichfield dialysis unit (satellite unit). This is to ensure that feasibility is tested in both main dialysis and satellite dialysis unit environments, which will allow for a much wider number of dialysis units to be included in the definitive trial.

7. ELIGIBILITY CRITERIA

7.1. Inclusion Criteria

- Age: ≥18 years (no upper age limit).
- Dialysis regime of ≥3 haemodialysis sessions/week for ≥3 hours using biocompatible dialysers.
- Able to give informed consent.

7.2. Exclusion Criteria

- Treatment with immunosuppressant drugs.
- Body mass index (BMI) >35 kg/m^2
- Pregnancy, breast feeding or intending pregnancy.
- Expected survival <6 months (prognosis assessed and determined by an experienced consultant nephrologist).
- Hospitalisation at time of screening.
- Known intolerance/allergy to either supplement (or isolated ingredients).
- Pre-dialysis serum potassium >5.3 mmol/L

7.3. Co-Enrolment

We do not intend to explicitly exclude those who may be participants in other studies, but the research team may review on a case-by-case basis taking into consideration any impact concurrent participation may have on successful completion of the trial assessment visits, on the trial outcomes and participant safety. This will not include participation in CTIMPs or interventional device trials.

8. TRIAL PROCEDURES

8.1. Screening

Potential participants will be identified by members of the usual healthcare team (which may include members of the research team). Patient details will be assessed against the inclusion and exclusion criteria, and only those who meet the inclusion criteria and without exclusion criteria will be invited to participate.

Pre-dialysis serum potassium levels are reported monthly in electronic medical records as part of routine clinical blood tests. However, if these were missing, research haemodialysis nurses will request a blood test to determine serum potassium.

If a patient is not eligible due to a serum potassium >5.3 mmol/L and/or hospitalisation at the time of screening (i.e., screen failure), then a member of the research team will reassess eligibility within 1 month. These patients may be screened multiple times.

Electronic screening and recruitment logs will capture important diversity data, including age, sex, ethnicity, civil status, religion or belief, and socioeconomic status. These logs will also include information regarding whether patients met eligibility criteria or not, the reasons for not being eligible for trial participation, or if they were eligible but declined participation (with reasons if provided). These activities are part of the Action Plan designed during the Equality Impact Assessment (EIA – Appendix 2), which was conducted to examine if any aspects of the study design could adversely affect those with protected characteristics. We will revisit and update the EIA throughout the research cycle as needed, which will allow for adjustments based on emerging data or changing circumstances.

8.2. Patient Identification

We will advertise this feasibility RCT both within the hospital setting (e.g., with posters on the dialysis units) and also via a Centre for Kidney Research and Innovation (CKRI) newsletter to help widen participation. We will ask our PPIE representatives to advise on the format and content of these adverts. We will include photos/images in participant-facing materials to facilitate understanding and have appointed a "renal research champion" (i.e., a member of the public or patient who is passionate about research and has experience in taking part in research) who can help support with recruitment and retention.

We will also engage with other healthcare staff. We will inform consultant nephrologists that their patient has been enrolled. We will also provide information about the trial to clinicians, haemodialysis nursing staff and renal dietitians, which will potentially help them to recognise and refer potential participants.

Following review of the eligibility criteria against electronic medical records, a member of the research team will meet with potential participants in person (during their haemodialysis session) to provide the initial details of the trial and participant information sheet (PIS).

Participants will then be given at least 48 hours to consider whether they wish to participate before being re-contacted by a member of the research team (i.e., during the participant's next haemodialysis session). If participants wish to take part in the trial, a member of the research team will discuss the PIS further if needed and give participants the opportunity to ask questions.

8.3. Consent

The process for obtaining participant informed consent will be in accordance with the Research Ethics Committee (REC) guidance, Good Clinical Practice and any other regulatory requirements that might be introduced.

The CI retains overall responsibility for the informed consent of participants and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the REC approved protocol and applicable guidelines and regulations.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial (including the collection of identifiable participant data, unless the trial has prior approval from the Confidentiality Advisory Group and the REC).

Detailed information will be provided on the trial to ensure that participants understand the purpose and potential risks involved. If needed, the hospital interpreter and translator services will be available to assist with discussion of the trial, the PIS, Informed Consent Form (ICF), and be available for the duration of the trial if required (e.g., during follow-up assessments). The ICF and PIS will be available printed in other languages.

All participants will provide written informed consent. The ICF will be signed and dated by the participant before they enter the trial. The CI will explain the details of the trial ensuring that the participant has sufficient time to consider participating or not, and will answer any questions that the participant has concerning trial participation.

The decision regarding participation in the trial is entirely voluntary. The CI or their nominee shall emphasize to them that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care. Participants will be asked for their reason for withdrawal; however, they do not have to provide one. Participants will be made aware (via the PIS and ICF) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

The CI will inform participants of any relevant information that becomes available during the course of the trial and will discuss with them whether they wish to continue with the trial. If applicable, they will be asked to sign revised consent forms.

If the consent form is amended during the trial, the CI shall follow all applicable regulatory requirements pertaining to approval of the amended consent form by the REC and use of the amended form (including for ongoing participants).

8.4. The Randomisation Scheme

Participants will be randomised in a 1:1 ratio stratified using mixed block sizes to: a) the control group (standard ONS) or b) the intervention group (immuno-nutrition supplement).

The control group will take daily one bottle (125ml) of Fortisip Compact Protein®, Nutricia Advanced Medical Nutrition (one of the most common ONS used as usual care for the haemodialysis population in the NHS) for 24 weeks.

The intervention group will take daily one sachet (74g) dissolved in 125ml of water of an immuno-nutrition supplement (Oral Impact®, Nestle) for 24 weeks.

Participants in both groups will continue to receive individualised dietetic advice delivered by the NHS renal dietitians who are members of the participants' usual clinical care team.

Consumption of both nutritional supplements will be supervised during haemodialysis sessions (thrice weekly) and self-reported (written and counting returned sachets/bottles) on non-dialysis days. Participants will receive precise instructions on how and when to take the supplements with close monitoring by the research team to encourage adherence.

8.4.1. Method of Implementing the Allocation Sequence

Randomisation will be completed after informed consent has been obtained and will be conducted in real-time via the Dacima study database/electronic case report form (eCRF) by authorised trial location staff.

A manual backup randomisation process will not be implemented, as this is a non-urgent feasibility study and any short delay in randomisation will not impact participant safety or trial integrity. Dacima system downtime is expected to be minimal. In the unlikely event that the Dacima system is unavailable, randomisation will be deferred until access is restored.

In the event of system downtime or any other technical difficulties with randomisation, the DCTSU team should be contacted via **uhdb.immunoshstudy@nhs.net** during office hours (Monday to Friday, 9 am – 5 pm).

8.5. Blinding

Due to the nature of the intervention and differences in supplementation administration, blinding of participants and investigators will not be possible and so this will be an open-label trial.

8.6. Unblinding

This is an open-label trial.

8.7. Trial Assessments

Screening and Recruitment

Screening, eligibility, consent, approach, refusal and randomisation rates will be recorded in screening and enrolment logs as part of the screening and recruitment process. The screening and enrolment logs will also collect reasons for non-eligibility, not being approached, not consenting and not being randomised.

Randomisation will occur during the recruitment visit after informed consent has been obtained and before any baseline trial assessments are conducted.

Baseline Assessments

Electronic medical records will be used to collect baseline participant characteristics, including age, sex, ethnicity, civil status, religion or belief, socioeconomic status, smoking status, time since dialysis initiation, dialysis adequacy, current medication and medical history (i.e., current and previous/historical comorbidities).

A pre-dialysis blood sample will be taken fortnightly for the first month after commencing treatment in both groups to monitor serum potassium levels (safety outcome measure), and then once a month until the end of the intervention period at week 24.

The Rockwood Clinical Frailty Scale[38] will be conducted at baseline in order to provide an assessment of frailty in our study population.

Assessment of trial outcomes, including HGS, body composition, physical performance, sarcopenia status, dietary intake, routine blood results, pre-dialysis cytokine samples and HRQoL will also be collected at the baseline visit prior to commencing treatment as detailed in the section below.

Assessments at Weeks 12, 18 and 24

The following assessments/tests will be conducted at 12, 18 and 24 weeks (+/-2 days) of treatment in both groups:

- HGS will be measured using the Takei 5401 handgrip digital dynamometer (Takei Scientific Instruments) within the first hour of haemodialysis treatment. The highest value of 3 attempts in the non-fistula arm will be recorded as HGS.

- Body composition will be assessed via bioelectrical impedance analysis (InBody 770, already available in the department). Body composition parameters will include BMI, total body water, extracellular and intracellular water, fat-free/lean body mass, SMM, SMM index, body fat mass and percentage, body cell mass, and phase angle. This assessment will not be conducted in participants who have a pacemaker, implanted defibrillator, or other electronic life-sustaining device, as the low-level electrical currents may interfere with their function.

- Physical performance will be assessed with the Short Physical Performance Battery (SPPB) which consists of repeated chair stand, gait speed, and balance tests. Each item is scored 0-4 points and the total SPPB score ranges 0-12 points. A score of ≤8 points indicates low physical performance[2]. This assessment will not be conducted in participants who are unable to stand (e.g., wheelchair users).

- Prevalence of sarcopenia and severe sarcopenia will be reported according to the well-established consensus definition from the European Working Group on Sarcopenia in Older People[2].

- Three-day food diaries (one dialysis day, one non-dialysis day and one weekend day) will be completed by participants following written instructions and will be analysed using Nutritics Food Data and Management Software to assess dietary energy (kcal) and macronutrient (protein, fat and carbohydrate) intake.

- Results from routine clinical blood tests will be collected from electronic medical records and will include haemoglobin, urea, creatinine, potassium, phosphate, calcium, albumin, total protein, and parathyroid hormone concentration.

- Pre-dialysis blood samples (10mL) will be centrifuged to obtain at least 2mL of plasma which will be stored at -80°C for subsequent analysis of pro-inflammatory cytokines (IL-6 and IL-8) via enzyme-linked immunosorbent assays.

- HRQoL will be assessed using the Kidney Disease Quality of Life 36-item short-form survey[39].

Adherence to both immuno-nutrition and standard nutritional supplements will be assessed once a month until the end of the intervention period at week 24 as the proportion of participants who comply with taking the supplements as instructed through the treatment period.

Acceptability will be assessed after the end of the intervention period at week 24 through participant questionnaire (refer to section 8.7.1. Qualitative Assessments for details).

Reporting of adverse events (AEs) during the trial and participant reported tolerability of the immuno-nutrition supplement and the standard ONS (which are also safety outcome measures) will be monitored throughout the intervention period (i.e., after baseline assessment to 24 weeks). Tolerability will be assessed by presence/absence of gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea, bloating).

8.7.1. Qualitative Assessments

Acceptability of both nutritional supplements will take place on completion of the treatment period at week 24, and be assessed using a semi-structured written questionnaire (previously used in studies assessing acceptability of nutritional supplements[40, 41]) which will include perceptions of taste, smell and consistency of both the immuno-nutrition and standard supplements.

Participants will respond to questions about these acceptability parameters as Yes or No, and if their response is No, they will be further asked to explain the reason for the same. The nutritional supplements will be considered "acceptable" if the participant does not perceive problems of undesirable taste, smell and consistency. The questionnaire will also include questions to assess participants opinions on long-term intake of the supplements.

8.8. Change to Participation

Participants will be withdrawn from the trial if they:

- Withdraw their consent at any time.
- Become pregnant.
- Receive a kidney transplant.

Participants do not have to provide a reason for withdrawal of consent. Participants will also be withdrawn if it is deemed unsafe or is found to be impossible to proceed in the opinion of the members of the research team. If this is the case, the CI will communicate and explain this decision to participants, who will have the opportunity to ask questions to understand why their participation had to stop.

Participants may be withdrawn from the trial either at their own request or at the discretion of the members of the research team. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the PIS and ICF) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Data that is collected prior to withdrawal will be kept and analysed as part of the data set. The date, time and reason (if provided) for participant withdrawal will be documented on the eCRF. The eCRF will also contain a section with the "types of change to participation" possible for the trial, including:

1. Stopped participation in all aspects of the trial.

2. Stopped immuno-nutrition or standard ONS only, but continue with all trial assessments.

3. Stopped immuno-nutrition or standard ONS and any of the following trial assessments:

STUDY ASSESSMENT	STOPPED
HGS measurement	Yes ☐ No ☐
Body composition assessment	Yes ☐ No ☐
Physical performance assessment	Yes ☐ No ☐
Completion of food diaries	Yes ☐ No ☐
Recording of routine blood tests	Yes ☐ No ☐
Pre-dialysis blood sample collection	Yes ☐ No ☐
HRQoL questionnaire	Yes ☐ No ☐

4. Continued with immuno-nutrition or standard ONS, but stopped all or any of the following study assessments:

STUDY ASSESSMENT	STOPPED
HGS measurement	Yes ☐ No ☐
Body composition assessment	Yes ☐ No ☐
Physical performance assessment	Yes ☐ No ☐
Completion of food diaries	Yes ☐ No ☐
Recording of routine blood tests	Yes ☐ No ☐
Pre-dialysis blood sample collection	Yes ☐ No ☐
HRQoL questionnaire	Yes ☐ No ☐

If a participant fails to attend for their scheduled dialysis session and a trial assessment was due to be completed during that missed dialysis session, a member of the research team will try to contact them by telephone within 24 hours of their next dialysis session. Multiple attempts at contact will be made by the research team over a period of 2 weeks before stating that a participant has been lost to follow-up.

Participants will not be replaced if they withdraw from the trial.

8.9. Storage and Analysis of Samples

Pre-dialysis blood samples (10 mL) will be collected using sample collection tubes (provided by the Centre of Metabolism, Ageing & Physiology [COMAP]) containing EDTA as an anticoagulant. Samples will be centrifuged for 15 minutes at 2000 x g at room temperature within 30 minutes of collection. At least 2 mL of plasma will be stored at -80°C for future analysis of IL-6 and IL-8 at the University of Nottingham COMAP lab.

Samples will be stored in a linked pseudonymised format and labelled with a unique trial identity code number.

Where participants do not agree to the future use of the samples, they will be destroyed in accordance with the Human Tissue Act, 2004.

Routine blood samples will be taken at both Renal Dialysis Units (i.e., Derby and Lichfield) and transferred to the local NHS laboratory (which is serviced and managed according to national standards and governance frameworks) at the Royal Derby Hospital for routine biochemistry and haematology testing. These samples will be labelled according to NHS requirements. No DNA or RNA extraction will occur as part of this trial. Following analysis, samples will be destroyed according to local practice.

8.10. End of Trial

The trial will end when all plasma samples have been analysed. The CI will notify the Sponsor and REC within 90 days of the end of the trial. The final report will be written within 12 months of the end of the trial.

9. SAFETY REPORTING

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to trial procedures.
Related AE	An untoward and unintended response in a participant to a trial procedure. This means that a causal relationship between the trial procedure and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.
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.
Related SAE	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial procedures.
Related & Unexpected SAE	A SAE that: • is believed with reasonable probability to be due to one of the trial procedures.

	• the nature and severity of which is not consistent with the information provided in the protocol (i.e., it is not listed as an expected occurrence).

9.2. Operational Definitions for (S)AEs

An AE does include a/an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

The following are recognised complications related to chronic haemodialysis and will be recorded on the CRF, but do not need to be reported separately on an AE/SAE form:

• Related to dialysis: fistula bruising, dizziness, cramps, hypotension, minor bleeding.
• Hospital admission for vascular access, acute coronary syndromes, arrhythmias, stroke, pneumonia and infections.
• Death.

An AE does not include a/an:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition that led to the procedure is an AE.

2. Pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and/or convenience admissions).

4. Disease or disorder being studied, or sign or symptom associated with the disease or disorder, unless more severe than expected for the participant's condition.

5. Overdose of concurrent medication without any signs or symptoms.

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in the SAE definition.

9.3. Recording and Reporting SAEs

Any participant who experiences an AE may be withdrawn from the trial at the discretion of the members of the research team. The overall risk of an AE directly connected to the trial is low.

All AEs and SAEs must be recorded from the time of written informed consent until after the last visit. All SAEs occurring during the duration of the trial must be recorded by the CI within the eCRF. The CI is responsible for checking for AEs and SAEs when participants attend for their haemodialysis sessions.

Participants will be asked to contact a member of the research team immediately in the event of any AE. All AEs will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial treatments are not the cause. The CI shall be informed immediately of any SAEs and shall determine seriousness and causality in conjunction with honorary consultant nephrologist and co-investigator Prof Maarten Taal.

All related and unexpected SAEs must be reported by the CI using the 'non-CTIMP safety report to REC form' from the Health Research Authority (HRA) website. The completed form should be submitted to the Sponsor and REC within 15 days of the CI becoming aware of the event. Safety information will be reviewed during TMG meetings.

UHDB contact information:
Email: uhdb.randdsae@nhs.net

9.3.1. Assessment of AEs and SAEs

All AEs and SAEs will be assessed for severity, expectedness and causality.

9.3.1.1 Severity

Honorary consultant nephrologist and co-investigator Prof Maarten Taal will determine the severity of the AE as follows:

- **Mild:** no interference with daily activities.
- **Moderate:** moderate interference with daily activities.
- **Severe:** considerable interference with daily activities (e.g. inability to work).

NOTE: to avoid confusion or misunderstanding, the term "severe" is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as "serious" which is described in the safety definitions.

9.3.1.2 Causality

Clinical judgement should be used to determine the relationship between the trial procedures and the occurrence of each AE.

- Not-related: There is no evidence of a causal relationship between the event and trial procedures.
- Related: There is evidence of a causal relationship between the event and trial procedures (i.e., a relationship to the trial procedures cannot be completely ruled out).

Assessment of causality will be conducted by honorary consultant nephrologist and co-investigator Prof Maarten Taal.

9.3.1.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to trial procedures.

- Expected: Event previously identified and described in the protocol.
- Unexpected: Event not previously described in the protocol.

The expectedness assessment is delegated to honorary consultant nephrologist and co-investigator Prof Maarten Taal.

9.4. Pregnancy reporting

If a participant becomes pregnant or is suspected to be pregnant from the time of consent up to the final trial visit, they will be withdrawn from the trial. There is no follow-up reporting required.

9.5. Reporting Urgent Safety Measures

An urgent safety measure (USM) is an action taken that the sponsor and investigator may take in order to protect the participants of a trial against any immediate hazard to their health or safety. USMs may be implemented at any time without first notifying the REC.

If any urgent safety measure is taken, the research team should inform the Sponsor within 24 hours using the Sponsor's safety incident reporting form. The Sponsor will inform the REC and participating trial locations of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

10. DATA HANDLING

The CI will be responsible for collecting participant data regarding primary and secondary outcome measures. The CI/Trial location staff will perform the randomisation as described in section 8.4.1. DCTSU will be responsible for the electronic database design, build and data entry and validation of all trial outcome data. The provider of the electronic data capture system (Dacima) will be responsible for hosting and storage of the trial data.

10.1. System and Compliance

Electronic CRFs will be the primary data collection instrument, hosted on Dacima, a cloud-based data capture system compliant with ICH-GCP (21 CRF Part 11) and MHRA guidelines for computerised systems.

Each participant will be assigned a trial identity code number for use on eCRFs, other trial documents and the electronic database. The CI will record in the enrolment log the participant's name, NHS number and participant's trial identity code number to permit identification of all participants enrolled in the trial. This shall be kept securely in the Trial Master File (TMF).

10.2. Source Data

The source documents for each participant will consist of the baseline participant characteristics detailed in section 8.7, as well as the routine blood tests results (including pre-dialysis serum potassium) collected from the participant's electronic medical records. These data will be transferred into the eCRF for each participant.

Source documents will also include the consent forms, (electronic) screening and enrolment logs, semi-structured questionnaire for acceptability assessment, Rockwood Clinical Frailty Scale (assessment of frailty), Kidney Disease Quality of Life 36-item short-form survey (HRQoL assessment), printed results from body composition assessment, dietary intake assessment results from Nutritics Food Data and Management Software (analysis of food diaries), and the eCRF, which will also contain data regarding adherence to nutritional supplements, HGS, SPPB score, prevalence of sarcopenia and severe sarcopenia, and results from pro-inflammatory cytokine analyses.

10.3. Data Workflow

DCTSU will design the electronic database to capture all trial outcome data in accordance with the best principles of data management.

When data are entered into the electronic database, validation checks will be performed on the data to ensure accuracy and consistency according to the study Data Validation Plan. All data queries generated as a result of these checks will be available for resolution by the trial location online. After data entry is complete, all data queries have been resolved, and any required coding is complete, the database will be locked and released for statistical analysis.

10.4. Data Access and Security

Direct access will be granted to authorised representatives from the Sponsor, DCTSU, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

All documents will be stored safely in confidential conditions. With the exception of regulatory authorities, only authorised members of the study team will have access to source documents.

Access to the study database will be role-specific and password protected. DCTSU Data Manager will control access, granting access to trial locations as recorded on the Delegation Log(s). The CI, DCTSU staff and location staff will be given appropriate access & permissions dependent on their role.

Each participant will be assigned a participant ID for use on study forms, other study documents and the electronic database. The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation within the trial. If any patient information needs to be sent to a third party, the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

Data will be stored on NHS computers on drives that are regularly backed up to a centrally hosted server (in the UK).

10.5. Archiving

At the end of the trial, following completion of the end of trial report, UHDB will securely archive all centrally held trial-related documentation for a minimum of 5 years.

At the end of the defined archive period, arrangements for confidential destruction will be made. It is the responsibility of the CI to ensure that data and all essential documents relating to the trial are retained securely for a minimum of 5 years after the end of the trial and in accordance with national legislation.

All archived documents must continue to be available for inspection by appropriate authorities upon request.

11. STATISTICS AND DATA ANALYSIS

11.1. Sample Size Calculation

Sample size calculation follows the method of using red-amber-green cutoffs to define progression criteria[42]. The green zone lower limit (GLL) signals to proceed if the criteria rate meets or exceeds this threshold, while the red zone upper limit (RUL) indicates stopping if the rate falls at or below it. Each criterion tests whether the rate falls in the red zone (null hypothesis) or green zone (alternative hypothesis). A sample size with 90% power ensures a 90% chance of not getting a red signal if the true rate lies in the green zone.

The first progression criterion, assessing randomisation rate, requires a GLL of 33%[33] and an RUL of 20%. A one-sample proportion test with 90% power and 5% significance suggests 51 eligible patients to be approached per group, totalling 102 across both groups. Based solely on only the first criterion and with a 33% randomisation rate, we would require 34 patients in total.

For the second criterion, evaluating adherence in the intervention group, the GLL is ≥75%[43] and the RUL is ≤50% (level categorised as “poor” adherence and associated with increased risk of hospital admissions)[44, 45]. With 90% power, 35 randomised patients per group are needed, totalling 70 across both groups.

Based on both progression criteria, we require 70 randomised patients and with a 33% recruitment rate, 213 eligible patients will need to be approached.

11.2. Planned Recruitment Duration

Recruitment of 70 participants over 24 weeks will require an average recruitment rate of 3 per week overall, which we consider feasible based on previous substantial experience recruiting to studies investigating aspects of nutrition in people receiving dialysis[33].

The trial will recruit from two dialysis units (Derby and Lichfield) with a total of approximately 324 haemodialysis patients. Applying feasibility assumptions from this previous study[33] of 80% eligibility, 95% approached and 33% randomised, we estimate that 71 patients from Derby and 9 from Lichfield

can be randomised from the existing population over the recruitment period. Additionally, Derby receives approximately 4 new patients per month and Lichfield 2 new patients per month which will contribute further to the recruitment pool.

11.3. Statistical Analysis

11.3.1. Summary of Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarize the distribution of baseline variables in the intervention (immuno-nutrition) and control (standard ONS) groups. Continuous baseline variables (e.g., age, BMI, frailty score, time since dialysis initiation, dialysis adequacy) will be reported with means & standard deviations (SD), if shown to be normally distributed, using a combined skewness and kurtosis test, otherwise will be reported with medians & Interquartile Ranges (IQR). Categorical variables (e.g., sex, ethnicity, civil status, religion or belief, socioeconomic status, smoking status, current medication, medical history [including presence of co-morbidities]) will be reported with frequencies & percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/participants:

- Screened
- Assessed for eligibility (add footnote for number of patients who have been screened more than once)
- Frequency of each reason for not being eligible,
- Found eligible,
- Patients approached,
- Excluded before consent (and the frequency of each reason for exclusion),
- Consented,
- Excluded before randomisation (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated intervention,
- That did not receive each allocated intervention,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each analysis group,
- Completed each follow up assessment (12, 18 and 24 weeks) for each analysis group,
- Analysed for each analysis group, and
- Not analysed (and the frequency of each reason for not being analysed) for each analysis group.

11.3.2. Primary Outcome Analysis

Descriptive statistics will be used to describe all feasibility outcomes. Frequencies and percentages with the 95% Confidence Intervals (CIs) using the Exact Binomial method will be presented.

Screening: The number of patients who are screened will be provided as a total.

Eligibility rate: The eligibility rate will be defined as the proportion of eligible patients out of the total number of patients screened.

Approach rate: The approach rate will be defined as the proportion of patients approached out of the total number of eligible patients .

Consent rate: The consent rate will be defined as the proportion of patients who provide informed consent out of the total number of patients approached.

Refusal rate: The refusal rate will be defined as the proportion of patients who refuse to take part in the study out of the total number of patients approached.

Randomisation rate: The randomisation rate will be defined as the proportion of patients who get randomised to take part in the study out of the total number of patients approached.

Completion rates: Completion of each outcome assessment will be calculated at each appropriate study visit. This is defined as the number of participants completing the assessment out of the participants who are still expected to complete the assessment at that visit (i.e. those who remain in the trial and have not withdrawn consent for follow-up assessments). This will be assessed in the ITT population.

Adherence rate: Adherence will be calculated for each participant as the proportion of daily doses taken out each month throughout 24 weeks and overall. Adherence will be summarised by treatment group using the median (IQR) adherence percentage. Adherence rate will be reported as the proportion of participants who meet the pre-specified adherence threshold of 75%. This will be assessed in the ITT population.

Acceptability: Acceptability will be described as proportions for acceptability of taste, smell and consistency. Other questions will be analysed as described in Section 11.12 (Qualitative Analysis).

Safety: Safety data (including AEs, SAEs, participant reported tolerability of nutritional supplements and serum potassium levels) will be summarised using descriptive statistics, including frequencies and proportions for any categorical data and mean (SD) or median (IQR) for any continuous data, as appropriate. This will be summarised in the Safety Population (SP).

11.3.3. Secondary Outcomes Analysis

All secondary outcomes will be assessed in the Intention-to-treat (ITT) population. Secondary outcomes will be summarised at each assessment visit as mean (SD) or median (IQR), as appropriate for continuous variables, and frequencies and percentages for categorical variables.

Secondary outcomes will be analysed using regression models to explore the potential signals of effect and to inform the design of a future definitive trial.

For continuous outcomes, including HGS, body composition measures, SPPB, biochemical blood variables, dietary energy and macronutrient intake, inflammatory biomarkers (IL-6 and IL-8) and HRQoL, linear mixed-effects regression models will be fitted including fixed-effects for group, visit (baseline, 12, 18 and 24 weeks) and an interaction term (visit x group), and random intercept for participant to account for repeated measurements.

For categorical outcomes, including sarcopenia and severe sarcopenia status, mixed-effects logistic or ordinal logistic (as appropriate) regression models will be used, including fixed-effects for group, visit and interaction term (visit x group) with random intercept for participants.

These models will allow examination of both between-group differences over time and within-group changes across the study period.

Analyses of secondary outcomes will be exploratory. P-values will be presented but interpreted cautiously, with emphasis placed on effect estimates and 95% CIs. The primary aim of these analyses is to signify signals of effect and to inform the section of the primary outcome and optimal timepoint for a future definitive trial.

11.4. Subgroup Analyses

Diabetes is an independent contributor to sarcopenia in people receiving haemodialysis[46], and sarcopenia traits such as low muscle mass and strength are more common in men compared to women[47]. Therefore, exploratory subgroup analyses will be undertaken to examine differences between participants with and without diabetes and between men and women (based on sex assigned at birth). These analyses will be exploratory, and any differences will be interpreted cautiously and used only to inform the design and stratification considerations for a future definitive trial.

11.5. Adjusted Analyses

No adjusted analyses will be performed, as this is a feasibility study and the regression models specified in Section 11.3 are exploratory and unadjusted.

11.6. Interim Analysis and Criteria for the Premature Termination of the Trial

As this is a feasibility study with minimal risk of harm, we do not plan to conduct an interim analysis.

The Sponsor may suspend or prematurely terminate either the entire trial, or the trial at an individual location, for significant reasons that must be documented (e.g., an unacceptable risk to participants or serious repeated deviations from the protocol/regulations). If this occurs, the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e., participants, investigators, participating trial locations, REC, regulatory bodies).

11.7. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- Intention-to-treat (ITT): All randomised participants.
- Safety population set (SP): All participants who were administered at least one dose of the immuno-nutrition supplement or the standard ONS.

11.8. Sensitivity Analysis

No sensitivity analyses will be conducted.

11.9. Procedure(s) to Account for Missing or Spurious Data

No formal imputation of missing data will be undertaken, as this is a feasibility study and analyses are exploratory. Descriptive summaries will be based on available data only. For secondary outcomes analysed using mixed-effects regression models, all available data will be used under the missing-at-random assumption, without imputing missing values.

11.10. Other Statistical Considerations

No additional statistical considerations are required.

11.11. Health Economic Evaluation

A health economic component will be included in the future definitive trial to support implementation. In this feasibility RCT, disease-specific quality of life information will be assessed using the Kidney Disease Quality of Life 36-item short-form survey, and the cost of the intervention will be documented. These data will inform the design of a health economic analysis as part of the future definitive trial.

11.12. Qualitative Analysis

Descriptive analysis will be conducted for acceptability parameters, and will be presented as frequencies and percentages.

The Framework Method[48] will be used to analyse the responses to open-ended questions (e.g., opinions on long-term intake of the supplements). The Framework Method is a type of thematic analysis that involves coding and organising data in order to provide a structured interpretation of the data, which is finally presented in themes.

12. MONITORING, AUDIT & INSPECTION

The CI must ensure that source documents and other documentation for this trial are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor may visit the participating trial locations to conduct audits/inspections.

Monitoring and source data verification will be conducted by the Sponsor according to their requirements, based on the risk assessment of the trial. As a low-risk trial, routine monitoring is not expected but may be conducted on an ad-hoc bases. The trial may be audited by the Sponsor at any time, according to the Sponsor's audit programme.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Peer review

This research project has been peer reviewed as part of the NIHR Research for Patient Benefit Programme application process.

13.2. Public and Patient Involvement

The CKRI has an active PPIE group comprised of members with lived experience of various forms of kidney disease, dialysis and transplantation. The group meets approximately 3 times per year and participates in the development of research projects and grant applications.

We have previously discussed studies concerning muscle-related problems in people receiving haemodialysis and received feedback from the CKRI PPIE group that this was an extremely important area to patients because of the high levels of fatigue and reduced physical function that this patient population experience. Also, the idea of studying a new supplement with immuno-modulating properties was well-accepted and considered innovative by our PPIE group. Additionally, in our previous feasibility study[33], feedback from participants was positive with the majority (n=12) reporting that the immuno-nutrition supplement tasted pleasant, consistency was "not too thick" and the volume was acceptable. This specific proposal was presented again at a CKRI PPIE group meeting on 10 March 2025 and received strong support from PPIE representatives.

Both our PPIE representative (Mr Stait) and CKRI PPIE members have further contributed to this research project by assisting in editing and revising the plain English summary.

Activities supervised by the PPIE lead (Prof Nicholas Selby) and led by our PPIE representative and CKRI PPIE group will include:

- Involvement in the oversight of this research during trial set up and delivery. Between scheduled PPIE meetings, ad hoc working via email or Teams meetings will occur as needed.

- Review and comment on all participant-facing materials to ensure that they are easily understood by patients.

- Comment on our progress with the trial, including recruitment, retention and feedback from participants. We will present information to our PPIE representative and CKRI PPIE members about these aspects to allow them to make informed comments. We will seek suggestions to help with solutions to problems that may be identified during the trial.

- We will ask PPIE members (including PPIE representative) to reflect on their role and what they have learned and share learning from this as part of our overall dissemination plan.

- Organisation of an event for trial participants to share the results from the trial, and involvement in preparing patient-facing materials for further dissemination to the wider patient and public body.

Using the INVOLVE calculator, we have budgeted to pay for their time to attend meetings, review and prepare documents, and organise the event for dissemination of the results.

13.3. Research Ethics Committee (REC) & Regulatory Considerations

The study will be conducted in compliance with the approved protocol and the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments (most recently, the Medicines for Human Use (Clinical Trials) (Modification) Regulations 2025).

The protocol and all related documentation (e.g. ICF, PIS, questionnaires) have been reviewed and received favourable approval by a Research Ethics Committee (REC). Members of the research team will not begin any participant activities until approval from the HRA and REC has been obtained and documented. All documentation and correspondence must be retained in the TMF. Substantial modifications that require HRA and REC review (where applicable) will not be implemented until the HRA and REC grant a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

The CI is responsible for notifying the REC of the end of the trial within 90 days. Within one year of the end of the trial, the CI will submit a final report with the results, including any publications/abstracts to the REC.

Before any trial location can enrol a participant into the trial, confirmation of capacity must be sought from the location's research and development (R&D) department. In addition, for any modification that will potentially affect the location's permission, the research team must confirm with the location's R&D department that permission is ongoing.

13.4. Protocol Compliance / Non-compliance Reporting

The CI is responsible for ensuring that the trial is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable; however, accidental protocol deviations (non-compliances) may happen and as such these must be recorded. Non-compliances should be recorded in the CRF and/or a non-compliance log kept in the TMF. All non-compliances should be reviewed and assessed by the CI (or appropriately delegated individual, e.g. project/trial manager) to determine if they meet the criteria of a "serious breach". Non-compliances which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

13.5. Notification of Serious Breaches to Good Clinical Practice and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e., SOPs), or regulatory requirements which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or
(b) The scientific value of the trial.

If the CI (or delegate) is unsure if a non-compliance meets these criteria, they should consult the Sponsor for further guidance.

If a serious breach is identified, the CI should notify the Sponsor immediately (i.e., within 1 working day) using the 'Non-CTIMP Notification of a Serious Breach' form. The report will be reviewed by the Sponsor and CI, and where appropriate, the Sponsor will notify the REC within 7 calendar days of being made aware of the breach.

13.6. Data Protection and Patient Confidentiality

The trial will be conducted in accordance with the Data Protection Act 2018 and UK GDPR. The CI must ensure that participant's anonymity is maintained throughout the trial and following completion of the trial.

Participants will be identified on all trial specific documents (except for the ICF and enrolment log) only by the participants' unique identity code number. This identifier will be recorded on documents, biological samples and the database. The TMF will hold an enrolment log detailing the unique identity code number alongside the names and NHS numbers of all participants enrolled in the trial. All documents will be stored securely with access restricted to members of the research team and authorised personnel.

UHDB will be the Data Controller for the purposes of the UK GDPR as regards personal data processing for research purposes.

The CI, Dr Daniela Viramontes Hörner will act as the custodian of the data generated in the trial.

UHBD as sponsor and Data Controller will meet its transparency obligations under the UK GDPR through the use of the HR recommended transparency wording.

13.7. Financial and Other Competing Interests for the Chief Investigator and Committee Members for the Overall Study Management

The CI, Co-Investigators, and staff members from DCTSU have no financial and/or other competing interests to declare.

13.8. Indemnity

As UHDB is acting as the research Sponsor for this study, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances, an ex-gratia payment may be offered.

13.9. Modifications

If changes to the trial are required, these must be discussed with the Sponsor, who is responsible for deciding if a modification is required and if it should be deemed substantial or a modification of an

important detail. Substantial modifications will be submitted to the relevant regulatory bodies (REC, HRA) for review and approval. The modifications will only be implemented after approval and a favourable opinion have been obtained. Modifications of important details will be submitted to the HRA for their approval/ acknowledgment. Modifications will not be implemented until all relevant approvals are in place.

13.10. Access to Final Trial Dataset

The CI Dr Daniela Viramontes Hörner, Co-Investigators Prof Maarten Taal, Prof Nicholas Selby and Prof Beth Phillips, as well as staff members from DCTSU will have access to the final trial dataset.

14. DISSEMINATION POLICY

14.1. Dissemination Policy

Data arising from the study will be owned by the Sponsor and shared with collaborators in accordance with the Terms and Conditions of the study Collaboration Agreement. Relevant reporting guidelines *e.g.* CONSORT will be followed depending on the type of publication *e.g.* trial, qualitative paper. The sponsor and NIHR will be acknowledged on all forms of dissemination. Publications and conference posters will be submitted to the sponsor prior to submission. A final study report will be submitted to the sponsor with a shortened PPI friendly version published on the study website. Participating investigators do not have permission to publish trial data without the approval of the Sponsor in line with the study Collaboration Agreement. Study participants will be notified of publications *via* the study newsletters and *via* email if they choose to provide contact details. It will not be possible for participants to request specific results, instead, participants will be informed at the time if they have a wound complication or not. Our PPI group will inform the dissemination strategy and will contribute towards dissemination *e.g.* webinars, publications, podcasts.

Results will be presented at both national and international scientific conferences and submitted to peer-reviewed journals for publication as soon as data analysis is completed. NIHR will be acknowledged in all publications. All peer-reviewed articles must be immediately, freely and openly accessible/discoverable to all according to the NIHR Open Access publication policy.

This trial will be registered with “International Standard Randomised Controlled Trials”, a publicly accessible database.

As mentioned in section 13.2, our PPIE representative and CKRI PPIE members will organise an event for trial participants to disseminate the results. They will also be involved in preparing patient-facing materials for further dissemination to the wider patient and public body. If some participants are unable to attend the event, the CI will make sure to provide them with a written lay summary of the results.

We will liaise with kidney charities and patient groups (e.g., Kidney Care UK and National Kidney Federation) so that the trial results are published on their websites. We will ensure that the patient voice is heard in dissemination messages and that diversity of target audiences is considered, as this has been raised in our PPIE group meetings (e.g., non-English speakers).

We will also share our results with professional and patient organisations including the British Dietetic Association Renal Nutrition Group, UK Kidney Association, Kidney Care UK, National Kidney Foundation and the International Society of Renal Nutrition and Metabolism.

On completion of the trial, the data will be analysed and tabulated, and a final trial report prepared and submitted to the NIHR and HRA. The final trial report will be published in the HRA website https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

14.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

Authorship on the final trial report, as well as in publications will be granted to authors who meet the criteria defined by The International Committee of Medical Journal Editors including 1) making substantial contributions to the conception, design, data, or interpretation of the work; 2) critically revising the manuscript for intellectual content; 3) giving final approval of the version to be published; and 4) agreeing to be accountable for the accuracy and integrity of the entire work.

CRediT (Contributor Roles Taxonomy) author statements will also be provided during the peer-reviewed journal submission process and will appear in the published paper.

Professional medical writers will not be hired.

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16. APPENDICES

16.1. Appendix 1 – Schedule of Assessments

Trial Procedures/Assessments	Screening	Recruitment	Baseline	Weeks			Post-treatment
				12	18	24	
				(-/+ 2 days)			
Eligibility assessment	x						
Study discussed and PIS given		x					
Informed consent		x					
Randomisation		x					
Participant characteristics			x				
Clinical Frailty Scale			x				
Handgrip strength			x	x	x	x	
Body composition			x	x	x	x	
Physical performance			x	x	x	x	
Prevalence of sarcopenia			x	x	x	x	
3-day food diaries			x	x	x	x	
Routine blood tests[A]			x	x	x	x	
Pre-dialysis blood samples for analysis of inflammation			x	x	x	x	
Quality of life questionnaire			x	x	x	x	
Treatment adherence[B]				x		x	
Acceptability of treatments							x
Safety outcome assessments		x	x	x	x	x	

NOTES:

A - Serum Potassium required for eligibility check and taken fortnightly for the first month and monthly until week 24.

B – Treatment adherence will be assessed monthly (i.e., at 4, 8, 12, 16, 20 and 24 weeks).

16.2. Appendix 2 - Equality Impact Assessment

This Equality Impact Assessment was completed according to the Equality Impact Assessment form template – NIHR Applied Research Collaboration East Midlands and The Centre for Ethnic Health Research. Version 7: 30th June 2025.

1. Entitle and give a brief description of the research, study, review or proposal

Research title

Effect of immuno-nutrition on markers of sarcopenia and systemic inflammation in a haemodialysis population: a feasibility randomised controlled trial.

Background

Low muscle mass and strength (i.e., sarcopenia) are common problems in people receiving haemodialysis which lead to poor quality of life and a higher risk of death[1]. Inflammation, caused by the body's defence (immune) system being activated in response to infection or injury, is another common factor that causes loss of muscle mass and strength in people on haemodialysis[2].

Standard food supplements are not effective at increasing muscle mass and strength in people on haemodialysis. This is because inflammation limits protein from food being converted into muscle[2, 3].

"Immuno-nutrition" is a new form of food supplement that provides calories and protein like other standard food supplements but also contains extra nutrients that reduce inflammation[4]. In previous studies, immuno-nutrition has been shown to benefit people with cancer, another patient group with high inflammation[5].

Recently, we showed that immuno-nutrition improved muscle strength and decreased inflammation in a small study of 14 people on haemodialysis[6].

Therefore, the purpose of this research is to test the study methods and procedures, and to collect information that will help us design a larger, definitive study.

Study design

This will be a feasibility randomised controlled trial. We have planned a two-centre study to ensure that feasibility is tested in both main dialysis and satellite dialysis unit environments, which will allow for a larger number of dialysis units to be included in the definitive study.

Participants will be randomly assigned (similar to picking names from a hat) to the intervention group (immuno-nutrition supplement) or the usual care group (standard food supplement). Both groups will take one supplement daily for 24 weeks.

Research/study location

The study will be conducted in the Royal Derby Hospital renal dialysis unit (main unit) and Lichfield dialysis centre (satellite unit).

Planned sample size
We plan to recruit 70 participants over 24 weeks.

Planned study period
This is a 25-month research project. Timelines for delivery are as follows:

- Months 0-7: obtaining study approvals and trial location set up.
- Months 7-24: study recruitment, follow-up assessments, data input and analysis.
- Month 25 and post-grant: dissemination activities and writing of reports, manuscripts and future funding application.

Number of participants per group
A total of 70 participants will be randomly assigned to the usual care group (standard food supplement, n=35) or the intervention group (immuno-nutrition supplement, n=35).

Characteristics of study participants
We will invite adult patients (≥18 years; no upper age limit) receiving three haemodialysis sessions per week for at least 3 hours and who are able to give informed consent.

2. What are the key aims and benefits of the research, study, review or proposal?

Aims
The primary objective of this study is to investigate key areas of uncertainty including participant recruitment and retention; adherence, acceptability and safety of the intervention; testing the study methods and procedures; and exploring potential outcome measures. This information will help us design a larger, definitive study.

Secondary objectives include investigating the effect of immuno-nutrition compared to a standard food supplement on:

- Markers of sarcopenia, including muscle strength, muscle mass and physical function,
- Food intake,
- Biochemical blood variables,
- Blood levels of inflammation, and
- Quality of life.

Benefits
If we confirm feasibility, we will use the data collected to design a definitive study. If this shows clinical efficacy, we will have identified a simple intervention to address the challenging problems of inflammation, malnutrition and sarcopenia in a vulnerable population. The fact that the immuno-nutrition supplement that we propose to use has already been identified by patients as "acceptable/nice" and is commercially available, means that this intervention could be rapidly implemented as part of the clinical care for people receiving haemodialysis in the UK and globally.

Any intervention that decreases the prevalence of sarcopenia in people receiving haemodialysis can be expected to improve quality of life, reduce the need for hospitalisation, increase independence and consequently lower both health and social care use/costs, as well as prolong survival[1, 2, 7].

Improvement and/or maintenance of muscle mass and strength is important for people on haemodialysis awaiting a kidney transplant because it is likely that this will help more rapid recovery after transplant surgery. Indeed, the proposal to use an "immuno-nutrition" approach in this study is based on evidence that a similar approach improved outcomes in people with cancer after major surgery[8].

An intervention to improve markers of sarcopenia is also critical for those people on haemodialysis (unfortunately the majority) who are not suitable for a kidney transplant because their age or the presence of multiple health conditions places them at unacceptable risk of complications before, during, and/or after surgery, or immunosuppression-related side effects[9]. These people face the rest of their lives on haemodialysis and any intervention that improves their health and quality of life is extremely valuable.

3. Identify any previous equalities related research or consultation relevant to your research, study, review or proposal

Overview

The current feasibility study is exploring the effect of immuno-nutrition compared to standard nutritional supplementation on markers of sarcopenia and systemic inflammation in a haemodialysis population.

Previous research related to how this musculoskeletal disorder interplays with different characteristics in people receiving haemodialysis and how this may impact equalities within our study is explored below. This includes associations between sarcopenia and age, sex, ethnicity/race, socioeconomic status, marital status, disability, sexual orientation and gender reassignment, and religion or belief.

Prevalence of sarcopenia

Sarcopenia is a musculoskeletal disorder that encompasses:

- reduced muscle strength as the key characteristic,
- decreased muscle mass, which confirms the diagnosis, and
- low physical performance, as a measure of severity[10].

The reported prevalence of sarcopenia in the general population (healthy adults >60 years old) is 10%[11], while the global prevalence of sarcopenia across the wide spectrum of chronic kidney disease (CKD) is estimated to be 24.5%. However, compared to people with CKD not requiring dialysis:

- sarcopenia is more common among people receiving haemodialysis (28.8% vs.16.7%),
- prevalence of low muscle strength is higher in the haemodialysis population (51.1% vs.19.6%),

- low muscle mass is more prevalent in people receiving dialysis (32.2% vs.19.7%), and perhaps most importantly,
- severe sarcopenia (i.e., low muscle strength, muscle mass *and* physical performance) is remarkably more common in people on dialysis (26.2% vs. 3.0%)[1].

Sarcopenia and age

The prevalence of sarcopenia is higher in people receiving haemodialysis who are older compared to their younger counterparts. For example, one study reported that 26.5% of people aged ≥65 years had sarcopenia compared to 8.3% of people aged <65 years[12]. Moreover, older age has been consistently identified as an independent determinant of sarcopenia in dialysis populations[1, 13].

Sarcopenia and sex

Studies investigating sex-related differences in the overall prevalence of sarcopenia suggest that there is no significant difference between men and women (25.8% vs 25.7%)[1]. However, sex seems to have an impact on specific sarcopenia-related traits, for instance, low muscle mass and strength are more common in men compared to women[1, 14], while physical performance is lower in women compared to men[15].

Sarcopenia and ethnicity/race

Previous research studies have shown that ethnic/racial differences exist in the prevalence of sarcopenia among people receiving dialysis; however, those differences depend heavily on which diagnostic criteria and cut-off points for muscle mass and strength are used[16]. For example, Asian dialysis populations often show a higher prevalence of sarcopenia compared to White and Black populations when the European sarcopenia diagnostic criteria are applied: Asian 58.1% vs Black 18.8% vs White 36.6%[17]. Nevertheless, when using the Asian sarcopenia diagnostic criteria, the prevalence of sarcopenia decreases to 36.9%[13].

On the other hand, the cut-off points for low muscle mass used in different sarcopenia diagnostic definitions were developed in White/European or North American populations. Using these thresholds in Black people (who often have higher muscle mass compared to other ethnicities) may therefore underestimate the true prevalence of sarcopenia in this population[16, 17].

Sarcopenia and socioeconomic and marital status

Currently, there are no studies reporting specifically on the prevalence of sarcopenia by socioeconomic and/or marital status in the haemodialysis population. However, there is limited evidence that suggests that lower socioeconomic status, greater social frailty (defined as a state where individuals experience deficiencies in social needs, support, resources, and satisfaction), as well as single marital status are independently associated with higher sarcopenia risk[18-20].

Sarcopenia and disability

Functional dependence (i.e., physical disability) is highly prevalent in the haemodialysis population. For instance, it has been reported that 81% of people receiving haemodialysis in the UK have some degree of functional dependence, while the global prevalence of “fully functional dependency" in the haemodialysis population has been estimated to be between 9-25%[21]. Sarcopenia significantly exacerbates the challenges in carrying out activities of daily living and, consequently, increases

functional dependence[16]. It has been reported that 68% of people receiving haemodialysis who are fully functional dependent have sarcopenia, while severe sarcopenia is present in 53-62%[22].

On the other hand, there is no evidence reporting on the prevalence of sarcopenia in people receiving haemodialysis who also have learning/intellectual disabilities. However, the prevalence of sarcopenia in an older population (≥50 years old) with intellectual disabilities has been reported to be 14.3%[23]. Additionally, individuals with learning disabilities have risk factors that increase their susceptibility to sarcopenia, for example, reduced physical activity, mobility impairments, a higher burden of chronic diseases, particularly cardiometabolic diseases, as well as a greater risk of advanced CKD[23-25].

Sarcopenia, sexual orientation and gender reassignment

There is no published data reporting on the prevalence of sarcopenia in people receiving haemodialysis by sexual orientation and/or gender reassignment. However, there is evidence that suggests that LGBT+ adults ≥50 years old have a higher prevalence of diabetes, CKD and heart disease, and are more likely to report limitations in activities of daily living, financial instability and unemployment/inability to work, all of which are known risk factors for sarcopenia[26].

Sarcopenia and religion or belief

There are no studies reporting on the prevalence of sarcopenia in people receiving haemodialysis by religious affiliation or faith group (e.g., Christian, Muslim, Hindu, Buddhist). However, factors associated with religion such as dietary practices[27] and social or private religious activities[28] might have an impact on sarcopenia risk, but this would be speculative in the absence of data.

4. Describe how the research, study, review or proposal will (or may) affect or impact upon equality.

This project and the subsequent randomised controlled trial will help to address health inequalities in the theme of end-stage kidney disease proposed by Kidney Research UK in their report on kidney health inequalities[29].

People who require haemodialysis represent an extremely vulnerable population who often experience poor quality of life and reduced life expectancy[30], and they are disadvantaged as a group by a lack of research and evidenced-based interventions to improve their nutritional status (particularly markers of sarcopenia) and address the high prevalence of frailty and multiple medical conditions which prevent them being considered eligible for kidney transplantation. Moreover, and as referenced above, the prevalence of sarcopenia is higher in older people and in those with functional dependence/physical disabilities, and the risk of developing sarcopenia may be higher in those with social deprivation and learning disabilities.

The proposed project seeks to explore “immuno-nutrition” as an intervention to improve sarcopenia, which will consequently help to improve the health of people on haemodialysis generally, and in particular, in groups who are disadvantaged. For instance:

- Immuno-nutrition may have greater relevance to minority ethnic communities as they have a higher prevalence of CKD, progress faster to needing dialysis treatment, live in the highest areas of deprivation, and have higher rates of food insecurity and malnutrition[29, 31, 32].

- Based on extensive prior knowledge of muscle protein metabolism in both males and females[33, 34], it is expected that immuno-nutrition will have equal efficacy in both sexes.

- Immuno-nutrition lessens the need for high-level physical or cognitive functioning and as such mitigates potential inequalities for provision of this intervention.

- Given that advancing age is a known contributor to sarcopenia, immuno-nutrition is potentially even more important for older people on haemodialysis.

In this project, we want to ensure that the research is representative of the patients that we serve. As part of this, it is also important to ensure that steps are taken where necessary to ensure the work does not perpetuate or exacerbate inequalities. We acknowledge statistics that suggest people from ethnic minorities, those with no formal qualifications and lower socioeconomic groups feel less confident about being treated with dignity and respect in research[35]. We will therefore make efforts to change these perceptions.

We demonstrate that our project is inclusive and that protected characteristics have been considered and addressed as follows:

- We have designed this project with patient involvement so that we address the previous situation where research funding and priorities are often mismatched with communities' desires or healthcare needs. We are therefore confident that the research questions that we seek to address are priority areas for patients.

- We will offer participation to all people receiving haemodialysis at our centres who meet the eligibility criteria, regardless of any protected characteristics. One of our exclusion criteria, however, includes pregnancy and lactation, a rare situation in dialysis populations. We have thought about this carefully. Unfortunately, successful outcomes of pregnancies in women receiving dialysis are difficult to achieve and require very intensive and specialised support which are not compatible with the scope of this study.

- We will translate study documents including participant information sheets, consent forms, instructions for completing food diaries and quality of life questionnaires and use translation services when needed for patients who do not speak English adequately to discuss the research and understand the written information provided. Interpreters will also be available when conducting study assessments.

- As per advice from our Inclusion and Involvement manager, we will include relatives and carers in discussions about potential participation. This will be particularly important for people with learning difficulties and poor literacy skills. We will also identify the best ways to help with completion of study assessments (e.g., 24-hour dietary recalls can be conducted by a member of the research team instead of food diaries being completed by the participant).

- Additional aspects of study design, in particular ensuring that the same research staff member conducts all study assessments and provision of multiple opportunities to ask questions will also help to build trust.

- Recruitment, provision of food supplements and study assessments will occur during routine haemodialysis sessions to minimise travel and cost barriers.

5. Identify who – from the Protected Characteristic groupings or other relevant underserved or disadvantaged communities – will (or may) be affected, how and any necessary action(s)

Age	**Positive impact**	**Negative impact**	**No impact**	**Impact not known**
	☑			
Please explain your assessment: All participants in this study will be 18 years of age or older. Therefore, the proposed nutritional intervention (immuno-nutrition) is likely to have a positive impact on all adults receiving haemodialysis treatment. The prevalence of sarcopenia is higher in older people; hence, immuno-nutrition has further potential to have greater beneficial impact for this group.				

Disability	**Positive impact**	**Negative impact**	**No impact**	**Impact not known**
	☑	☑		
Please explain your assessment: Given that functional dependence is highly prevalent in the haemodialysis population, and sarcopenia is more common in people receiving haemodialysis who are fully functional dependent, immuno-nutrition is likely to have a positive impact in this group. A positive impact of immuno-nutrition is also expected for those people on haemodialysis who have learning/intellectual disabilities, as it has been reported that these individuals have risk factors that increase their susceptibility to sarcopenia. Nevertheless, without any reasonable mitigation actions, there may be a potential negative impact for individuals with learning/intellectual disabilities as they may have difficulty understanding complex research information, dietary/supplement intake instructions, reporting of symptoms and giving informed consent without additional support. The research team will minimise this impact by 1) providing additional time and support during the consent process and study assessments; 2) ensuring carers/family members are present to facilitate the informed consent process and understanding of information and instructions; 3) designing easy-to-read participant-facing materials with simplified language, symbols, and visuals; and 4) identifying the best ways for completion of study assessments.				

Gender reassignment	Positive impact	Negative impact	No impact	Impact not known
	☑			☑

Please explain your assessment:

The impact of immuno-nutrition to the intersecting communities of people receiving haemodialysis with sarcopenia and trans people/those reassigning is Not Known. However, given that known risk factors for sarcopenia are common in the LGBT+ community, immuno-nutrition could have a beneficial impact for this group.

Marriage and civil partnership	Positive impact	Negative impact	No impact	Impact not known
	☑			☑

Please explain your assessment:

We suggest that the impact of immuno-nutrition on people in this group is Not Known. However, there might be some positive impact in people who are single, as there is evidence to suggest that single marital status is independently associated with higher sarcopenia risk.

Pregnancy and maternity	Positive impact	Negative impact	No impact	Impact not known
				☑

Please explain your assessment:

As mentioned above, one of our exclusion criteria includes pregnancy and lactation. Since very intensive and specialised support is required for this group, and this is not compatible with the scope of this study, the impact of immuno-nutrition is therefore Not Known.

Race	Positive impact	Negative impact	No impact	Impact not known
	☑	☑		

Please explain your assessment:

Given that known risk factors for sarcopenia are more common in minority ethnic communities, there is likely to be a positive impact of immuno-nutrition in this group. However, some minority ethnic groups may be less likely to participate in this study due to language barriers and mistrust of research staff. Therefore, if proactive mitigation measures are not implemented, the potential for negative impact relating to race and ethnicity would be high.

The research team will minimise this impact by 1) translating participant-facing materials and involving interpreters during the informed consent process and completion of study assessments; 2) designing culturally appropriate and accessible recruitment and participant-facing materials; 3) ensuring the same research staff member conducts all study assessments; and 4) providing multiple opportunities to ask questions.

Sex	Positive impact	Negative impact	No impact	Impact not known
	☑			

Please explain your assessment:

Given that the prevalence of sarcopenia is similar between males and females, it is expected that immuno-nutrition will have an equal positive impact in both sexes.

Religion or belief	Positive impact	Negative impact	No impact	Impact not known
		☑		☑

Please explain your assessment:

Given that there is no evidence about the prevalence of sarcopenia in people from different religions/beliefs, the impact of immuno-nutrition in this group is Not Known.

There is the possibility of a negative impact as immuno-nutrition and standard supplements may contain ingredients that conflict with certain cultural or religious dietary practices, and therefore some participants may feel unable to take part. Both supplements have Halal diet certifications; however, only the standard supplement is suitable for Kosher and vegetarian diets. This would represent a **justifiable negative impact** on grounds of religion or belief (as well as race/ethnicity), as the intervention being studied is not available in all acceptable forms. However, this limitation is inherent to the nature of the research question, which seeks to evaluate a specific supplement with defined ingredients.

The research team will minimise this impact by:

- Clearly explaining the supplement composition during the informed consent process.
- Documenting any exclusions on cultural or dietary grounds to maintain transparency.
- Exploring, where possible, the availability of acceptable alternative formulations from the manufacturer for future work.
- Acknowledging this limitation explicitly in dissemination materials and publications, to inform interpretation and promote future inclusive product development.

Sexual orientation	Positive impact	Negative impact	No impact	Impact not known
	☑			☑

Please explain your assessment:

Similar to the above section on gender reassignment, the impact is Not Known. However, given that known risk factors for sarcopenia are common in the LGBT+ community, immuno-nutrition could have a beneficial impact for this group.

Other: Socioeconomic status	Positive impact	Negative impact	No impact	Impact not known
	☑			☑

Please explain your assessment:

Given that there is no evidence about the prevalence of sarcopenia in people from different socioeconomic backgrounds, the impact of immuno-nutrition in this group is Not Known. However, there might be a positive impact for people in lower socioeconomic groups, as this has been identified as an independent risk factor for sarcopenia.

6. Provide a summary of the main equality issues identified through this analysis.

We consider there to be a **positive impact** of immuno-nutrition for a number of groups identified as protected characteristics under the Equality Act 2010. These are summarised as follows:

- **Age,** particularly older age as the prevalence of sarcopenia is higher in this group.
- **Disability,** as the prevalence of sarcopenia is higher in people who are fully functional dependent and the susceptibility for sarcopenia is higher in people with learning/intellectual disabilities.
- **Sex,** equal impact on both males and females.
- **Race,** as known risk factors for sarcopenia are more common in minority ethnic communities, and the prevalence of sarcopenia may also be higher in these groups.

Negative impacts have been identified for the groups of learning/intellectual disability, race and religion or belief mainly due to communication/language barriers, mistrust of research staff and composition of food supplements. We will implement several measures to address these negative impacts, which have been described above.

We suggest that the impact of immuno-nutrition on the protected characteristics of gender reassignment, marriage and civil partnership, pregnancy and maternity, religion or belief, sexual orientation and socioeconomic status is **Not Known**. However, immuno-nutrition could have a **beneficial/positive impact** on single people and those from the LGBT+ community and low socioeconomic backgrounds as known risk factors for sarcopenia are more common in these groups.

7. How will you monitor and evaluate the equality impact of your study?

During study delivery, we will compile screening and enrolment logs, as well as Case Report Forms, that will capture important equality/diversity data. We will review these throughout recruitment so that we can identify any mismatches that develop between groups that are eligible, participants that consent or refuse to participate, and those who withdraw from the study. These data will also allow for comparisons with the demographic make-up of the whole haemodialysis population at both dialysis centres. We will present and discuss these data to our Patient and Public Involvement and Engagement (PPIE) group at the PPIE meetings associated to this study.

We will ensure that all members of the research team complete Equality, Diversity and Inclusion (EDI) training, as well as cultural competency training.

Following their participation, patients will be asked to provide feedback on their experience. We will review these questionnaires for any evidence that participants from underserved groups had a different experience from the majority and to explore if they faced any particular challenges.

In the final project report, we will include an analysis of demographic data of participants versus the demographic data of our whole haemodialysis population to identify whether our study population was adequately representative. We will also report on the experience of participants from underserved groups. We will ensure that any learning gained from this study in relation to improving inclusivity and adequate representation for all patient groups is applied to future research studies within our Centre for Kidney Research and Innovation research group by sharing this at our regular monthly research meetings.

8. Use the Action Plan to record the actions that need to be taken to address the issues identified in this form

Action	By when?	Responsibility of?	Monitored through (by and when)?	Impact
Completion of EDI and cultural competency training	Before start of recruitment	All members of the research team	Certificate/record of attendance should be received before the start of recruitment	Enhance research quality and validity; improve participant engagement and trust; and foster an inclusive research environment
Translate and design accessible participant-facing materials	Pre-recruitment, recruitment and follow-up periods (12 months)	Chief Investigator, patient representatives and research champion	Monthly through the whole recruitment and follow-up periods using enrolment logs and CRFs	Translation of materials and making them accessible will potentially increase recruitment of participants with protected characteristics such as race and learning/intellectual disabilities
Recruitment of study participants by equality/diversity data	Recruitment period (6 months)	Chief Investigator	Monthly through the whole recruitment period using screening and enrolment logs. We will present and discuss these data at our PPIE meetings	Assess diversity through screening of protected characteristics and ensure appropriate representation
Record reasons for ineligibility, refusal and withdrawal	Recruitment and follow-up periods (12 months)	Chief Investigator	Monthly through the whole recruitment and follow-up periods using screening and enrolment logs, as well as CRFs. We will present and discuss these data at our PPIE meetings	Maintain transparency and assess impact of protected characteristics on ineligibility, refusal and withdrawals
Collection of participant feedback	End of study participation	Chief Investigator and research champion	Following their participation, patients will be asked to provide feedback on their experience via a questionnaire	Understanding whether participants from underserved groups had a different experience from the majority and to explore if they faced any particular challenges
Analysis of equality/diversity data	End of study	Chief Investigator and Trial Statisticians	Analysis of equality/diversity data of participants versus equality/diversity data of our whole haemodialysis population to be included in the final project report	Identify whether our study population was adequately representative

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