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PROTOCOL

The FraiLTI (Frailty in chronic Limb-Threatening Ischaemia) Protocol

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Plain English Summary

Why we are undertaking this work: Frailty is a medical term that describes physical weakness, vulnerability or fragility and is often associated with old age. We are undertaking this study to gain an understanding of the occurrence rates and effects of frailty, progressive loss of muscle mass and strength (sarcopenia) and having multiple health issues (multimorbidity) in patients suffering from a severe form of poor leg circulation called chronic limb-threatening ischaemia (CLTI). This is a serious condition affecting blood flow in the limbs and is usually associated with high rates of losing a limb or even death.

What we will do: In this study (FraiLTI), we recruit patients with CLTI who are undergoing an intervention to improve their poor leg circulation. We assess how common frailty, sarcopenia and multimorbidity are among CLTI patients and explore their influence on clinical outcomes. We are aiming to obtain a comprehensive understanding of the situation at a national scale by gathering data from hospitals throughout the UK.

What this means: The results from the FraiLTI study could provide crucial information on the prevalence of health issues such as frailty, muscle loss and weakness, and multiple health conditions among individuals in the UK with severe leg circulation problems, as well as their impact on overall health. This could enable healthcare professionals to identify high-risk patients who need extra care and attention to improve their outcomes. The study will also offer valuable insights for future research and contribute to the overall improvement of care and management for patients with CLTI.

Key words: chronic limb-threatening ischaemia (CLTI), frailty, sarcopenia, multimorbidity, quality of life.

Abstract

Background: Frailty, sarcopenia and multimorbidity are conditions commonly associated with the ageing process, and they are frequently observed in patients with chronic limb-threatening ischaemia (CLTI). Nevertheless, the extent to which these conditions are prevalent within the CLTI patient population has not been adequately examined in the UK. This proposed multicentre observational study aims to investigate the prevalence of these conditions in patients with CLTI and to assess their potential impact on important clinical outcomes including mortality, amputation and quality of life.

Methods: FraiLTI (Frailty in chronic Limb-Threatening Ischaemia) is a multicentre prospective observational study in the UK that that aims to investigate the prevalence of frailty, sarcopenia and multimorbidity associated with CLTI. The secondary objective is to investigate potential correlations between frailty, sarcopenia and multimorbidity, with clinical outcomes such as amputation, mortality, major adverse cardiovascular events and readmission rates within a 90-day period. FraiLTI is led by Newcastle University, supported by the Vascular and Endovascular Research Network (VERN) and funded by the National Institute for Health Research (NIHR) and the Newcastle Hospital Charities. REDCap will be used to collect anonymised patient data. All hospitals with a dedicated vascular centre are eligible to participate. Full ethical approval (21/PR/0750) was granted on 13 July 2021. The study is registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry.

Anticipated impact of the study: This study has the potential to address critical questions identified by the James–Lind Alliance (JLA) Priority Setting Partnership (PSP) in peripheral arterial disease. It is expected to make a substantial contribution to the creation of a prospective CLTI database, integrating essential data on frailty, sarcopenia and multimorbidity that are not currently captured by other registries, despite their profound impact on patient outcomes. This research could provide pivotal insights into the prevalence of frailty, sarcopenia and multimorbidity among the UK's CLTI population and their corresponding effects on clinical outcomes. Findings from the study will be shared at global scientific conferences and submitted to be published in peer-reviewed journals.

Introduction

Frailty, a concept gaining significant attention in recent years, is defined as a clinically recognisable state of increased vulnerability resulting from ageing-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with everyday or acute stressors is compromised.[1] Frailty leaves patients vulnerable to stressors such as illness, trauma or surgery. The high prevalence of frailty, affecting 43.7% of adults aged 65 and older,[2] and its potential impact on health outcomes underscores the importance of this issue.[3]

The elderly population is particularly affected as they are more susceptible to both frailty[4] and cardiovascular pathologies.[5] Frailty has been linked as a predictor for inferior postoperative outcomes[6] as well as numerous adverse health outcomes including falls, disability, hospitalisation and mortality.[7,8] Additionally, frailty is associated with an increased risk of disability, which manifests as limitations in performing activities of daily living (ADL) and impacts a patient's quality of life (QoL).[9,10]

Sarcopenia, a key component of frailty, is characterised by skeletal muscle dysfunction that develops gradually and predominantly affects older patients,[11] leading to reduced strength and muscle mass.[12] Sarcopenia is an independent predictor of mortality following both open and endovascular procedures.[13,14]

Multimorbidity is another significant factor influencing outcomes in patients with chronic limb-threatening ischaemia (CLTI). Previous research in vascular surgery focused primarily on cardiometabolic comorbidities, highlighting the need to investigate the impact of other conditions beyond the central cardiovascular system. Our preliminary retrospective work has shown that sarcopenia[14] and anaemia[15] are negatively associated with survival and limb loss following revascularisation surgery for CLTI.

There are some retrospective data in the literature which suggest that frailty affects survival in those undergoing intervention for CLTI in Japan[16] and the UK.[17] A prospective cohort study from Canada found that frailty was associated with mortality and worsening disability post-intervention. There are also systematic reviews that suggest worse outcomes in a wide range of lower limb vascular operations.[18–20] However, thus far, data on this topic in the UK remain single-centre and retrospective.

FraiLTI (Frailty in chronic Limb-Threatening Ischaemia) is a multicentre prospective observational study in the UK which aims to investigate the prevalence of frailty, sarcopenia and multimorbidity and their effect on outcomes following a diagnosis of CLTI. This patient-led study addresses several questions raised by the James–Lind Alliance (JLA) Priority Setting Partnership (PSP) in Peripheral Arterial Disease (PAD), with a focus on exploring potential causes for poor outcomes.[21]

Methods

Study design

This is a multicentre prospective observational study conducted in UK Vascular Centres led by Newcastle University and supported by the Vascular and Endovascular Research Network (VERN). It is funded by the National Institute of Health Research (NIHR) and the Newcastle Hospitals Charity. Figure 1 is the flow diagram of the study protocol.

Study population

Inclusion

- All adults aged over 18, able to consent and participate with ongoing assessments.
- All patients with CLTI as per the consensus definition (the presence of PAD in combination with rest pain, gangrene or a lower limb ulceration >2 weeks duration),[22] irrespective of pathology, mode of presentation, plan to revascularise, or previous presentations with lower limb arterial disease.

Exclusion

- Admissions for non-CLTI.
- Unable to consent to assessments or participate in study assessments.
- Pregnant women.
- Age <18 years.

Study outcomes

Primary

Prevalence of the following conditions among CLTI patients:

1. Frailty
   - Fried's Frailty Phenotype (FP)
   - Rockwood's Clinical Frailty Scale (CFS)
2. Sarcopenia
   - Grip strength
   - Skeletal muscle area (SMA) at L3
   - Skeletal muscle index (SMI) at L3

   (Cut-offs highlighted below)
3. Multimorbidity (≥2 long-term health conditions)

Secondary

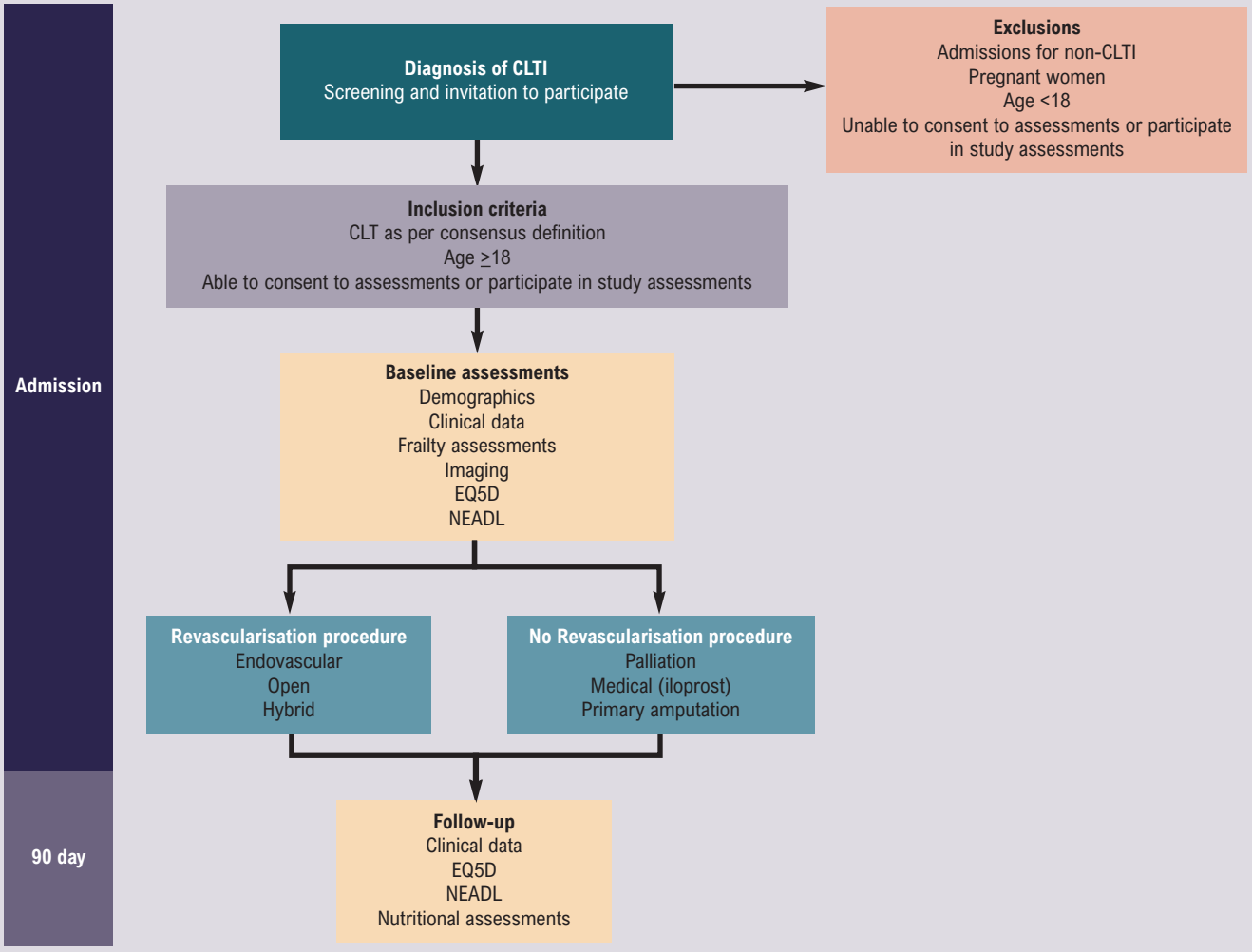
1. Associations between frailty, sarcopenia and multimorbidity with clinical outcomes, including:
   - Mortality
   - Major adverse limb events (MALE)
   - Major adverse cardiovascular events (MACE)
   - Readmission
   - Reinterventions
   - Discharge destination.
2. Impact of CLTI on patients' quality of life as measured by validated QoL assessment tools.

These outcomes will facilitate risk prediction, modelling and the identification of potential targets for intervention in future prospective research.

Recruitment

The FraiLTI study is open to all dedicated vascular centres with one team member acting as site lead clinician, who is the point of contact between the FraiLTI study team and the local team. The study is eligible for the NIHR Associate PI Scheme. All patients

Figure 1 Study flow diagram.



admitted with CLTI have a diagnosis confirmed by the admitting vascular surgeon. Potentially eligible participants are sign-posted to the relevant research team member only after the patient has suggested they would be agreeable for their details to be shared with a member of the research team on the delegation log at each site. Patients are formally screened according to the inclusion and exclusion criteria. All presentation modes are eligible including outpatient clinic, vascular "hot" clinic, and emergency departments.

The FraiLTI study team provides written and verbal versions of the participant information and informed consent. The local study lead is responsible for ensuring that this process is carried out in accordance with Good Clinical Practice (GCP).

Data collection

Anonymised data collected consists of patient demographics (including postcode for social-economic data), presenting symptoms, previous interventions, and admissions in the past six months.

The research team are collecting patient data in a prospective manner through hospital records, both electronic and paper-based. They then enter the collected data onto a custom-made electronic database hosted on the Newcastle Joint Research Office's Research Electronic Data Capture (REDCap) platform.

Definitions

Comorbidities are defined as per the American College of Cardiology guidelines[23] where possible. Diabetes is defined by documented medical history, and hypertension is defined by documented medical history and use of antihypertensive drugs for this purpose, or systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg at admission determined by the average of the first two measurements. Other comorbidities recorded include ischaemic heart disease, stroke, chronic heart failure, atrial fibrillation, hypothyroidism, dementia, anxiety, depression, asthma, chronic obstructive pulmonary disease, osteoarthritis and inflammatory arthropathies.

The following diseases are recorded based on the patient's documented medical history: ischaemic heart disease or prior myocardial infarction, atrial fibrillation, hypertension, cerebrovascular disease (ischaemic stroke, haemorrhagic stroke or transient ischaemic attack), end-stage renal failure requiring dialysis and chronic obstructive pulmonary disease. Preoperative drugs are also recorded from the pre-assessment clinic documentation. Severity of presentation is measured using both the Rutherford classification and the WIfI score.

Laboratory results

Routine clinical care laboratory test results (including haemoglobin, white cell count, albumin, creatinine and estimated glomerular filtration rate, C-reactive protein and HbA_{1c}) are collected, as well as height and weight.

Sarcopenia assessments

CT angiogram

Axial imaging by means of a CT angiogram (where performed) will enable measurement of the skeletal muscle area (SMA) at the 3rd lumbar vertebra (L3) level (for comparison with previous studies), the mid-thigh and mid-calf levels (to enable detection of regional differences in muscle mass) (see Appendix 1 online at www.jvsgbi.com for details of measurement methodology).

We also calculate a value for the L3 skeletal muscle index (SMI) with the following formula:

$$\text{L3 SMI } (^{cm^2}/_{m^2}) = \frac{\text{L3 SMA } (cm^2)}{\text{height}^2\ (m^2)}$$

Cut-offs diagnostic of sarcopenia are 134.0 cm^2 for men and 89.2 cm^2 for women for L3 SMA and 41.6 cm^2/m^2 for men and 32.0 cm^2/m^2 for L3 SMI for women.[24]

Grip strength

Hand grip strength is measured using handgrip dynamometry (see Appendix 2 online at www.jvsgbi.com for detailed methodology).

Frailty assessments

Fried Frailty Index Phenotype

The Fried Frailty Score[1] is measured by combining five domains:

1. Weight loss (>4.5 kg in last year).
2. Low grip (<27 kg for men, <16 kg for women).
3. Low walk speed (we anticipate that most participants will have restricted mobility and so will score a point automatically; a cut-off of <0.8 m/s will be used for those who can undertake a 4 m walk test).
4. Exhaustion (measured using two questions from the Centre of Epidemiologic Studies Depression scale (CES-D scale)[25] used in the original Fried Score).
5. Low physical activity measured using four activity questions used in the English Longitudinal Study of Ageing.[26]

A score of ≥3 or more denotes frailty, 1 or 2 denotes pre-frailty, and zero denotes non-frail.

Rockwood frailty scoring

The Rockwood deficit accumulation model considers frailty as the accumulation of deficits in various domains of functioning including physical, cognitive and social domains.[27,28] This study uses the Clinical Frailty Scale, which categorises patients based on their function, morbidity and central nervous system impairment using a clinician's judgement.[28] Studies have verified that the Clinical Frailty Scale is a reliable predictor of negative outcomes.[29]

Nutrition assessment

We also collect information on activities of daily living, nutritional intake, place of living and mobility aids to provide a comparison for robustness in this disease group.

Quality of life assessment

Participants are invited to complete the Euro-QoL EQ-5D-5L health status assessment[30] and Nottingham Extended Activity of Daily Living scale (NEADL)[31] (see Appendix 3 (EQ-5D-5L) and Appendix 4 (NEADL) online at www.jvsgbi.com - for examples of the questionnaires).

Follow-up (90 days)

Following the baseline data capture, all patients are followed up irrespective of whether they undergo any revascularisation, and their 90-day outcome data are collected (including mortality, MALE, MACE, respiratory and wound-related complications, readmissions, reinterventions and discharge destination).

Participants are invited to receive a telephone call or postal EQ-5D-5L assessment as well as the NEADL. Food diaries are collected over 2 days (ideally one weekday and one weekend day) (see Appendix 5 online at www.jvsgbi.com).

Data management

Data are collected and uploaded onto a secure REDCAP database platform.

In line with General Data Protection Regulations,[32] no identifiable data are uploaded and each patient is assigned a specific audit identification number. The local hospital ID and corresponding audit ID is maintained by the lead clinician at each centre to ensure accurate follow-up data and is securely stored on an appropriate hospital computer.

Data will be kept for two years and then destroyed but will be available to others. A minimum dataset including fully anonymised patient data will be included in the FraiLTI results paper as a supporting information file.

Data analysis

Statistical analysis will be performed using R (R Foundation for Statistical Computing, Vienna, Austria). Normally distributed data will be presented as mean (SD) and hypothesis testing will be performed with unpaired t-tests/Mann–Whitney U tests as appropriate. Categorical data will be analysed by a χ^2 test.

A p value <0.05 will be considered statistically significant for single comparisons.

Kaplan–Meier survival curves will be used with a log-rank test to compare the overall mortality. Cox proportional hazards regression will be performed; hazards ratios (HR) with 95% confidence intervals (CIs) will be reported along with p values.

Binary logistic regression analysis will be used to identify associations with complications and multiple variates will be tested. The resultant significant variables will be presented as odds ratios (OR) with 95% CIs. An OR of >1 indicates an increased likelihood of the event occurring.

The NEADL scores will be analysed as continuous variables using the statistical tests outlined above. EQ-5D data will be analysed using the "eq5d" R package to provide both descriptive data and longitudinal data to assess how quality of life changes over the course of the study. Techniques to be used include the Paretian Classification of Health Change (PCHC)[33] and the Probability of Superiority.[34]

Nutritional data will be entered into Nutritics Professional Plus v5.81, 2022 software and analysed. The average for each participant will be grouped and then analysed. Total energy intake will be reported as kilocalories (kcal) per day and as a percentage of estimated resting energy expenditure using the Mifflin–St Jeor equation.[35] Average total daily intake of macronutrients and micronutrients will be reported. Macronutrients will also be reported relative to body mass. A threshold of 1.2 g/kg body mass/day will be used to identify people with low protein intake.

Regulatory approval and research governance

Full ethical approval (21/PR/0750) was granted on 13 July 2021 for this multicentre prospective observational study. The study is registered on the ISRCTN.

Authorship

This is a national trainee supported research collaborative. It is anticipated that VERN will support the FraiLTI project through one of the streams of collaboration once the regional study is underway. Contributions will be recognised in co-authorship of publications as part of a collaborative research authorship model. This will allow participating clinicians in training to meet the objectives of their training needs whilst providing vital research data, as well as recognising the research activity for the recruiting centre and lead.

Current status

The FraiLTI study recruitment of new centres was between September 2021 and September 2022. The expected date of the last patient to be included is July 2022 and data collection will end in September 2022. The results of this study are expected to be released in early 2024.

Discussion

An internationally agreed definition of frailty remains elusive due to its multifaceted aetiology[36,37] and the challenge of distinguishing it from other geriatric conditions.[38,39] While frailty is considered a geriatric condition and is closely related to ageing, disability and comorbidity, it is unmistakably different.[40,41] For example, despite its higher prevalence among older individuals, frailty cannot be solely attributed to chronological age.[36]

Research has revealed that frailty is not a static condition but rather a dynamic process that results from the compounded effects of multiple factors.[40,42,43] This improved understanding of frailty offers an opportunity to optimise management of underlying factors such as nutritional deficiencies, physical inactivity or chronic diseases, leading to better health outcomes and an improved quality of life.[27,42] Ultimately, this is achieved through correct identification and understanding of the scale of the problem through studies such as this one.[44]

The FraiLTI study represents a pivotal first step in establishing the current prevalence of frailty, sarcopenia and multimorbidity among patients with CLTI in the UK. This initial step is vital to evaluate the scale of the issue and any clinical consequences or associations related to CLTI on a national level. The findings of the study will ultimately inform the development of future intervention studies to improve health outcomes for patients with CLTI, thereby reducing the overall burden of these conditions on the healthcare system.

It is postulated that CLTI patients who also have frailty and/or multimorbidity could be associated with worse clinical outcomes, potentially independent of age. By identifying adverse health outcomes such as quality of life, activities of daily living and mortality, the study aims to enhance the detection of the most vulnerable individuals, thereby improving targeted treatment strategies.

The FraiLTI study is part of a national collaborative research effort led by VERN trainees. By leveraging this platform, the study employs a multicentre design that enables patient recruitment from various locations. This approach boosts the study's statistical power and increases the potential for a larger sample size. The utilisation of data from diverse sites improves the representation of the UK as a whole, which is crucial when analysing prevalence nationwide. These efforts contribute to more robust and impactful findings that advance the knowledge of CLTI and its correlation with frailty. VERN has a proven track record of producing multinational studies that have a large impact, increasing the credibility of this study.[45,46] One limitation of this study will be the inability to determine direct causality between practice and outcome; however, it benefits from being prospective, multicentre and unique in its use of the Fried Frailty phenotype model in this context. Outputs from the FraiLTI study will inform future quality improvement and research projects to improve the care of patients with CLTI.

Pathway to impact

This study is a collaborative effort between patients and clinicians and is supported by the Vascular Society Peripheral Arterial

KEY MESSAGES

- Patients with chronic limb-threatening ischaemia (CLTI) often have many concurrent medical conditions (multimorbidity) and suffer from frailty and sarcopenia.
- The aim of the FraiLTI study is to identify the prevalence of these conditions in those with CLTI.
- This protocol describes the methodology of the FraiLTI study.
- We hope that this study will contribute to the understanding of these conditions in this population and how it affects their outcomes.

Disease Special Interest Group (PAD SIG). The results will be presented to improve patient care at a national and international level. A writing team, including individuals involved in the design, implementation and dissemination of the FraiLTI study, will be responsible for submitting manuscript(s) for publication(s).

The study will prioritise patient and public involvement, working with the JLA PSP to produce a patient-facing lay summary of the results The JLA and Circulation Foundation will also be notified to promote the summary. Additionally, results of the FraiLTI study will be disseminated through VERN's social media accounts, newsletters and dedicated webinars.

Conclusion

The FraiLTI study will provide a comprehensive overview of the prevalence of frailty, multimorbidity and sarcopenia in CLTI patients. As a UK first multicentre prospective study, we set out to provide an understanding of the scale and clinical consequences of CLTI, leading on to the development of large-scale prospective research projects on developing more focused interventions for patients with frailty and sarcopenia with the aim of improving their clinical outcomes.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Appendix 1 Standard operating procedure (SOP) for CT SMA measurements.

The Newcastle upon Tyne Hospitals NHS
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NIHR | Newcastle Biomedical Research Centre

FraiLTI
Frailty in Chronic Limb Threatening Ischaemia

Operation's Manual: Measurement of skeletal muscle area (L3 and lower limb)

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Measuring skeletal muscle area (SMA) at L3

The following instructions may vary between each centre's radiology software. These instructions have been written for Vue PACS software (Version 12.1.5.7014, Carestream Health, Ontario, Canada).

1) Open the relevant cross-sectional imaging (usually a CT angiogram).
2) Select multiplanar reconstruction (MPR)
3) This should give you 4 windows, including the transverse, sagittal and coronal planes.
4) Using the sagittal plane to guide you, navigate the transverse view to the base of L3 (Figure 1)
   Another option here would be to use the transverse view only and count the vertebrae until you are at the level of L3 (only recommended if there is no access to MPR as this can be time consuming and less accurate).
5) Maximise the transverse view at this level.
   The next steps may vary between programs.
6) Using the freeform Region of Interest (ROI) tool draw 2 areas (X and Y) around the following layers (Figure 2, note that the most superficial measurement can be ignored for the purposes of this study).
   X. At the deepest level of the subcutaneous fat/ superficial level of the skeletal muscle
   Y. At the deepest level of the skeletal muscle

   The ROI tool should be measuring area within the shape and NOT the length of the line drawn.
7) Skeletal muscle area = X-Y (cm^2)
8) Ensure your measurements are accurately recorded and exit the scan.

Figure 1 - Sagittal view to confirm level of L3 (represented by horizontal red line)

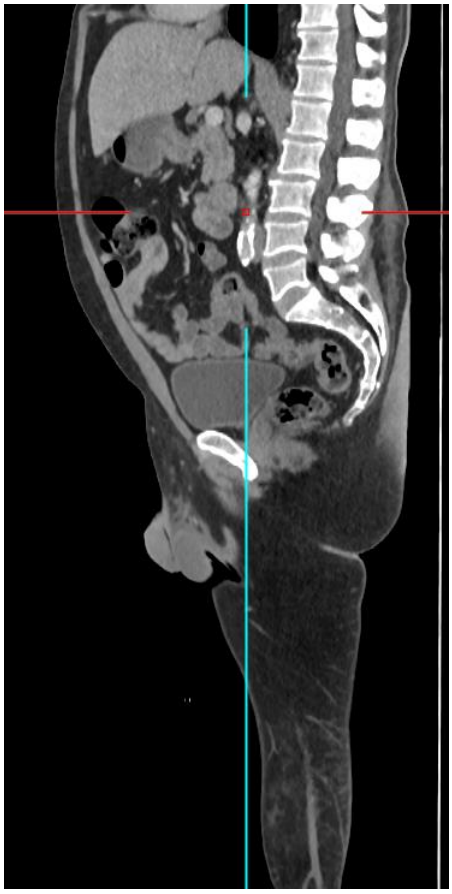
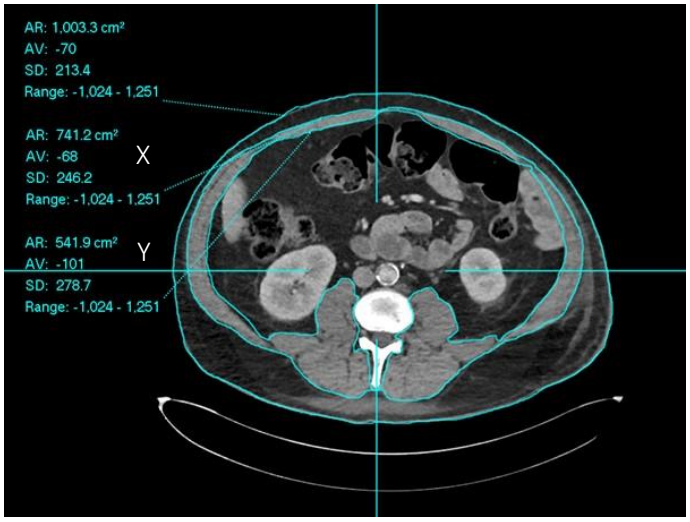


Figure 2 – Transverse view showing measurement methodology



Measuring SMA in the lower limb

Using the sagittal plane on the above MPR identify the ipsilateral (affected leg) femur. Measing 10cm above the Patella, or mid-femur complete a SMA measurement here by enveloping the entire smooth muscle at this level.

Return to the sagittal plane and navigate to the tibial tuberosity. Here a SMA cm^2 measurement is recorded 10cm below the tibial tuberosity.

Appendix 2 Standard operating procedure (SOP) for physical assessments.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

NIHR | Newcastle Biomedical Research Centre

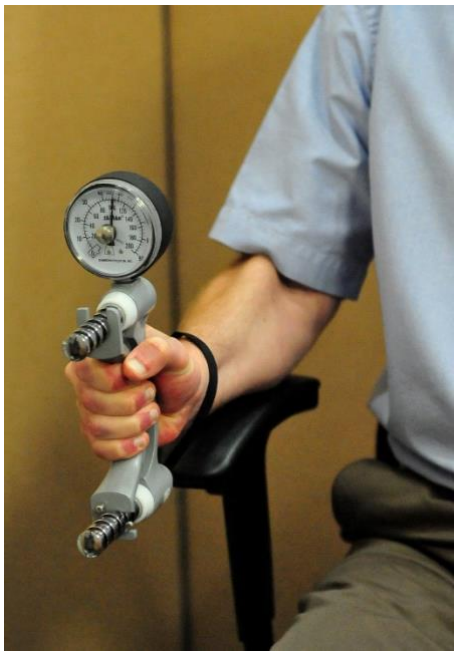
FraiLTI
Frailty in Chronic Limb Threatening Ischaemia

Operation's Manual: Physical Performance Battery

Table of Contents

Measuring Grip strength

Equipment: JAMAR Hydraulic Hand Dynamometer



- Sit the participant comfortably in a standard chair with legs, back support and fixed arms. Use the same chair for every measurement.
- Ask them to rest their forearms on the arms of the chair with their wrist just over the end of the arm of the chair – wrist in a neutral position, thumb facing upwards.
- Demonstrate how to use the Jamar handgrip dynamometer to show that gripping very tightly registers the best score.
- Start with the right hand.
- Position the hand so that the thumb is round one side of the handle and the four fingers are around the other side. The instrument should feel comfortable in the hand. Alter the position of the handle if necessary. One can usually observe if the subject is uncomfortable.
- The observer should rest the base of the dynamometer on the palm of their hand as the subject holds the dynamometer. The aim of this is to support the weight of the dynamometer, but care should be taken not to restrict its movement.
- Encourage the participant to squeeze as long and as tightly as possible or until the needle stops rising. Once the needle stops rising the participant can be instructed to stop squeezing.
- Read grip strength in kilograms from the outside dial and record the result to the nearest 1kg in the CRF.
- Repeat measurement in the left hand.
- Do two further measurements for each hand alternating sides to give three readings in total for each side.
- The best of the six grip strength measurements is used in statistical analyses so encourage the participant to get as high a score as possible.

Chair (sit) to Stand test

Repeated Chair Stands

- ***"Let's do the last movement test. Do ou think it would be safe for you to try to stand up from a chair without using your arms?"***
- ***"The next test measures the strength in your legs."***
- (Demonstrate and explain the procedure.) "***First, fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest."***
- ***"Please stand up keeping your arms folded across your chest."***
- If participant cannot rise without using arms this is the end of their test. Record result in CRF as "Participant unable to complete 5 chair stands".

- (Demonstrate and explain the procedure): "***Please stand up straight as QUICKLY as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch."***
- When the participant is properly seated, say: ***"Ready? Stand"*** and begin timing.
- Count out loud as the participant arises each time, up to five times.
- Stop if participant becomes tired or short of breath during repeated chair stands.
- Stop the stopwatch when he/she has straightened up completely for the fifth time.
- Also stop:
    - If participant uses his/her arms
    - After 1 minute, if participant has not completed rises
    - At your discretion, if concerned for participant's safety
- If the participant stops and appears to be fatigued before completing the five stands, confirm this by asking ***"Can you continue?"***
- If participant says "Yes," continue timing, if participant says "No," stop the Chair Stand Test.
- Record in the CRF how long it took the participant to complete the Chair Stand Test or if they were unable to complete 5 chair stands.

Gait speed test (4-metre walk)

"Now I am going to observe how you normally walk. If you use a cane or other walking aid and you feel you need it to walk a short distance, then you may use it."

A. First Gait Speed Test

- ***"This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street to go to the shop."***
- Demonstrate the walk for the participant.
- ***"Walk all the way past the other end of the tape before you stop. I will walk with you. Do you feel this would be safe?"***
- Have the participant stand with both feet touching the starting line.
- ***"When I want you to start, I will say: "Ready, begin.""*** When the participant acknowledges this instruction say: ***"Ready, begin."***
- Press the start/stop button to start the stopwatch as the participant begins walking.
- Walk behind and to the side of the participant.
- Stop timing when one of the participant's feet is completely across the end line.

B. Second Gait Speed Test

- ***"Now I want you to repeat the walk. Remember to walk at your usual pace, and go all the way past the other end of the course."***
- Have the participant stand with both feet touching the starting line.
- ***"When I want you to start, I will say: "Ready, begin.""*** When the participant acknowledges this instruction say: ***"Ready, begin."***
- Press the start/stop button to start the stopwatch as the participant begins walking.
- Walk behind and to the side of the participant.
- Stop timing when one of the participant's feet is completely across the end line.

  Record the **fastest time** of the two walks in the CRF.

Appendix 3 Clinical research form for EQ-5D-5L..

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

NIHR | Newcastle Biomedical Research Centre

Quality of Life (QoL) assessment tools

FraiLTI
Frailty in Chronic Limb Threatening Ischaemia

Pt Initials: __ __ __

Study No: __ __ __ __ __ __

Date: __ __ / __ __ / __ __
dd mm yy

EQ5D

QoL assessment tools

Baseline ☐ 90 Day ☐

EQ5D

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

☐ I have no problems in walking about
☐ I have some problems in walking about
☐ I am confined to bed

SELF-CARE

☐ I have no problems with self-care
☐ I have some problems washing or dressing myself
☐ I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

☐ I have no problems with performing my usual activities
☐ I have some problems with performing my usual activities
☐ I am unable to perform my usual activities

PAIN / DISCOMFORT

☐ I have no pain or discomfort
☐ I have moderate pain or discomfort
☐ I have extreme pain or discomfort

ANXIETY/DEPRESSION

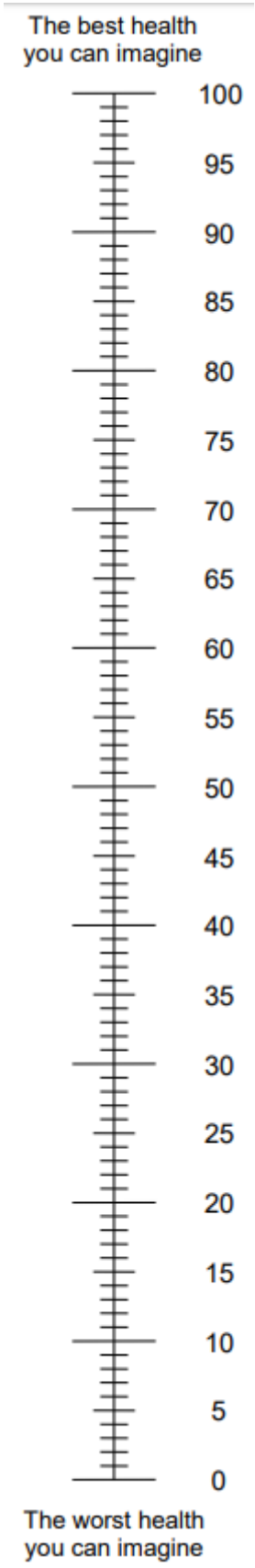
☐ I am not anxious or depressed
☐ I am moderately anxious or depressed
☐ I am extremely anxious or depressed

Please turn over for the final page…

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100
100 means the best health you can imagine.
0 means the worst health you can imagine.

Please mark an X on the scale to indicate how your health is TODAY.



Now, write the number you marked on the scale in the box below

Your health today = ☐

Appendix 4 Clinical research form for NEADL.

The Newcastle upon Tyne Hospitals NHS Foundation Trust

NIHR | Newcastle Biomedical Research Centre

Patient Study ID:_____

FraiLTI Frailty in Chronic Limb Threatening Ischaemia

Pt Initials: __ __ __

Study No: __ __ __ __ __ __

Date: __ __ / __ __ / __ __
dd mm yy

Baseline ☐ 90-day ☐

Nottingham Extended ADL Scale

The following questions are about everyday activities. Please answer by ticking ONE box for each question. Please record what you have ACTUALLY done in the last few weeks.

DID YOU…….	Not at all	with help	on your own	on your own with difficulty
1. Walk around outside?	☐	☐	☐	☐
2. Climb stairs?	☐	☐	☐	☐
3. Get in and out of a car?	☐	☐	☐	☐
4. Walk over uneven ground?	☐	☐	☐	☐
5. Cross roads?	☐	☐	☐	☐
6. Travel on public transport?	☐	☐	☐	☐
7. Manage to feed yourself?	☐	☐	☐	☐
8. Manage to make yourself a hot drink?	☐	☐	☐	☐
9. Take hot drinks from one room to another?	☐	☐	☐	☐
10. Do the washing up?	☐	☐	☐	☐
11. Make yourself a hot snack?	☐	☐	☐	☐

Newcastle Hospitals Charity

	No	With help	On your own with difficulty	On your own
12. Manage your own money when out?	☐	☐	☐	☐
13. Wash small items of clothing?	☐	☐	☐	☐
14. Do your own housework?	☐	☐	☐	☐
15. Do your own shopping?	☐	☐	☐	☐
16. Do a full clothes wash?	☐	☐	☐	☐
17. Read newspapers or books?	☐	☐	☐	☐
18. Use the telephone?	☐	☐	☐	☐
19. Write letters?	☐	☐	☐	☐
20. Go out socially?	☐	☐	☐	☐
21. Manage your own garden?	☐	☐	☐	☐
22. Drive a car?	☐	☐	☐	☐

Appendix 5 Clinical research form for food diary.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Study ID:

FraiLTI
Frailty in Chronic Limb Threatening Ischaemia

Food Diary (Appendix C)

Food Diary

Thank you for taking part in the FraiLTI study.

Please fill in this food diary as best you can re-call for the last two full days. Please be as detailed as possible. We would like you to write down the type of food and drink (including brand names where available), how much you ate and how often. To understand portion size, we would like to know how much of the food you ate. This could be the weight of food or the amount of liquid you drank (volume). You could also include an approximate portion size using everyday household measures (e.g., cups, tablespoons).

Tips:

- If food is packaged please provide the brand name and serving size e.g., Quaker Oat So Simple Original 57g
- Indicate the colour (e.g., white vs wholewheat bread), fat content (e.g., skimmed or whole milk, light or low-fat yogurt) and other characteristics such as “diet” or “reduced sodium/salt” products
- For combination dishes include a description of the main ingredients e.g., lasagne portion: ground beef (1/4 cup), mozzarella cheese (28g), 1/2 cup tomato sauce, 2 pasta sheets
- Please include the cooking method where possible e.g., oven-baked, pan-fried, deep-fried, grilled
- Remember sauces, snacks, oils, spreads, and drinks (including alcohol) all count

An example food diary is shown on the next page.

Please pass this back to the FraiLTI study team.

Please get in touch if you have any questions or concerns. Thank you!

Study ID:

Food Diary (Example)

	Time:	What You Ate:	Portion size (serving or weight)
Breakfast	*7am*	*Porridge oats (plain) cooked with semi skimmed milk* *Banana*	*300g oats* *300ml milk* *1 medium size*
Lunch	*12.30pm*	*Soup – Heinz cream of tomato* *Bread – Hovis wholemeal medium sliced* *Butter- Anchor Spreadable*	*Half can (200g)* *2 x 40g slices* *2 x teaspoons*
Dinner	*7pm*	*Baked potato (medium size) with flesh and skin* *Portion of tuna mayo (full fat mayo)* *Green beans (boiled)*	*300g* *75g tuna with 2 tablespoons mayo* *80g*
Snacks	*11am* *4pm*	*Handful of mixed nuts (peanuts, almonds, walnuts)* *Kitkat*	*Small handful, 30g* *45g bar*
Drinks	*7am* *12.30pm* *8pm*	*Instant black coffee with sugar* *Orange juice (ASDA smooth orange juice from concentrate)* *Red wine*	*One cup (250ml) with one teaspoon sugar* *150ml* *2 x 175ml glass*
Other			

Study ID:

Food Diary day 1 **Date completed:**

	Time:	What You Ate:	Portion size (serving or weight)
Breakfast			
Lunch			
Dinner			
Snacks			
Drinks			
Other			

Study ID:

Food Diary day 2 **Date:**

	Time:	What You Ate:	Portion size (serving or weight)
Breakfast			
Lunch			
Dinner			
Snacks			
Drinks			
Other			