FraiLTI
Frailty in Chronic Limb Threatening Ischaemia

FraiLTI Study: (Frailty in chronic Limb Threatening Ischaemia) Study

A multicentre prospective observational study to investigate the prevalence and short-term impact of frailty, multi-morbidity and sarcopenia in chronic limb threatening ischaemia (CLTI)

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Protocol Amendments

Amendment Number	Protocol Version	Date of Amendment	Date of Approval

Signatures

For and on behalf of the Study Sponsor:
Signature: Date:

..../...../.....
Name (please print):

Position:

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Chief Investigator:
Signature: Date:

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Position:
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Associate Chief Investigator:
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	Northern Vascular Centre Research Team; Noala Parr, Jenny Fairburn, Martin Catterson and Anthony Robson.

Study summary

Full study title	A Multicentre Prospective observational study to investigate the prevalence and short-term impact of frailty, anaemia, sarcopenia and multimorbidity in chronic limb threatening ischaemia (CLTI)	
Short study title	**FraiLTI** - **F**railty in Chronic **L**imb **T**hreatening **I**schaemia	
Study aim	To assess the prevalence and short-term impact of frailty, anaemia, sarcopenia and multiple long-term conditions on patients admitted with CLTI.	
Study design	Multicentre Observational Study	
Study participants	Patients admitted with all presentation of CLTI at a designated vascular centre	
Sample size	Approximately 30 from each centre over six months (10 centres)	
Planned study period	9 months (from first recruit)	
	Objectives	**Outcome Measures**
Primary	Identify the prevalence of frailty and multi-morbidity among CLTI patients using standardised assessments.	Grip strength assessment and sarcopenia on cross-sectional imaging.
Secondary	To understand if frailty, multi-morbidity and poly pharmacy are associated with adverse clinical outcomes.	1) Major-lower limb amputation rate at 3 months (limb-loss or amputation) 2) Survival at 3 months (who is alive at the three-month timepoint) 3) Re-interventions (repeat surgery or procedures) 4) Length of hospital stay 5) Discharge home 6) Re-admissions and re-intervention (who is re-admitted to hospital or needs further admission and procedures)

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Summary of Research Program

This prospective project forms part of a wider research theme investigating frailty, sarcopenia, multiple long-term conditions and anaemia on outcomes following vascular and endovascular surgery. It is hoped that this research will identify areas for prospective optimization and improvement in clinical and patient-reported outcomes. FrailTI is being conducted with a team of experts and specialists in Older Peoples Medicine, sarcopenia, anaemia, anaesthesia and vascular surgery within a complementary multi-disciplinary team including physiotherapy and occupational therapists, in partnership with patients.

A particular interest within this research theme is those patients with chronic limb threatening ischaemia (CLTI). CLTI has been highlighted as a UK national priority by a recent Delphi consensus[1] supported by the RCS England and the Vascular Society of Great Britain and Ireland (VSGBI). This identified improving the clinical outcomes for CLTI and other associated conditions (diabetic foot disease, major lower limb amputation) as top ten research priorities among vascular specialists, vascular nurses and vascular technologists. This is a pivotal first step in developing the understanding of frailty in CLTI in a UK first study. This study will provide an understanding of the scale of the problem and any clinical consequence or association for CLTI revascularisation. It is anticipated that FraiLTI data will be used in the development of large-scale prospective research aimed at benefiting the care of UK and worldwide vascular patients with CLTI.

Background

FraiLTI (Frailty in chronic Limb Threatening Ischaemia) is a UK first, multi-centre prospective observational study evaluating the impact of frailty, sarcopenia and multi-morbidity on outcomes following vascular intervention for Chronic limb threatening ischaemia (CLTI). CLTI is a patient-led JLA priority for vascular research[1], as outcomes may be worse in those with multi-morbidity and potentially frailty.

Frailty, traditionally defined as an age-related multisystem decline[2] leaves patients vulnerable to stressors such as illness, trauma or surgery. Some surgical specialties have identified that the presence of frailty is associated with inferior clinical outcomes for example, patients with frailty under-going major colorectal surgery had a worse survival and a longer stay in the intensive care unit[3].

A key component of frailty is sarcopenia - skeletal muscle dysfunction that develops over a period of time and typically affects older patients[4] leading to reduced strength and muscle mass. Some evidence exists that sarcopenia alone leads to worse survival following endovascular surgery[5] and following elective joint replacement[6]. The association of frailty and the interaction with sarcopenia is not fully understood nor is the interaction within high risk CLTI patients.

Multiple long-term conditions (multimorbidity) is also an important factor potentially affecting outcomes. Most work to date in vascular surgery has focussed on cardiometabolic comorbidities, and there is a need to examine the impact of multimorbidity including conditions out with the central cardiovascular system. Our preliminary retrospective work has identified that both anaemia[7] and sarcopenia (publication accepted 2021) are adversely associated with survival and limb loss following revascularization surgery for CLTI. Older patients undergoing aneurysm surgery may well be at greater risk of adverse outcome [8], but many patients with CLTI are relatively young and fall under the radar before proceeding to in-hospital intervention or major surgery to attempt to save limb. Multimorbidity has been shown to reduce cardiovascular quality of life (9) and worse survival in related populations such as those with heart failure patients (10))

It is postulated that CLTI patients with frailty and/or multi-morbidity, may be associated with worse outcomes, potentially independent of age. FraiLTI has been developed to assess the nationwide scale of the problem and to develop a platform on which to build future intervention studies to mitigate the impact of frailty, sarcopenia and multimorbidity in this group of patients

Aim

1. The ***primary aim*** of the study is to identify the prevalence of frailty, sarcopenia and multimorbidity among chronic limb threatening ischaemia (CLTI) patients.
2. The ***secondary aim*** is to identify any associations with patient led and prioritised clinical outcomes such as survival, limb-loss, cardiovascular events or re-admission as well as those with non-salvageable CLTI. This will facilitate risk prediction, modelling and identify potential targets for intervention in future prospective research.

Study Design

This is a multi-centre prospective observational study.

Population

All patients presenting to the vascular service with chronic limb threatening ischaemia as defined by the Global CLTI guidelines[11] are eligible for participation, irrespective of mode or eventual plan for revascularisation

Recruitment

All patients admitted with CLTI[11] to a dedicated vascular centre will be invited to participate by a member of the clinical team. Confirmation of CLTI diagnosis will be made by the admitting vascular specialist. Potentially eligible participants will be sign-posted to the relevant research team member only after the patient has suggested they would be happy/agreeable to for their details to be shared with a member of the research team on the delegation log at each site. At this point the FraiLTI researcher will approach the patients with the initial information. After a period of consideration, typically 24hours, patients will then be formally screened according to the inclusion and exclusion criteria. All presentation modes will be eligible including out-patient clinic, emergency clinic, emergency department and general practitioner referrals. This will allow the capture of the breadth of CLTI disease and give information on the mode of referral of CLTI patients in the context of frailty. Recruitment and enrolment will be performed by a vascular or surgical trainee's, research teams and wider networks as long as all research training requirements have been met.

Eligibility

Patients meeting the below inclusion criteria will be invited to participate in the FraiLTI study.

Inclusion

- All adults over 18, able to consent and participate with ongoing assessments
- All chronic limb-threatening ischaemia patients as per consensus definition irrespective of mode or presentation or plan to revascularize.

Exclusion

- Admissions for non-CLTI
- Unable to agree to assessments or participate in study assessments
- Pregnant women

- Under 18.

Consent

Written and verbal versions of the participant information and informed consent will be presented to the participants by a FraiLTI study team member. This will occur after member of the clinical care team has made the patient aware of the study and gain initial notification of interest in some cases there will be shared clinical and research roles at each recruiting site. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and have been authorised to do so by the Chief Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Study Master File (SMF) or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes. Written informed consent for participation in the study will be obtained by a doctor (SpR) or an appropriately qualified research nurse or research fellow (medically trained with appropriate consent training).

Study Methodology

Data collection

Baseline data:

The data collected will consist of patient demographics (including postcode for social-economic data), presenting symptoms, previous interventions and admissions in the past six months. Comorbidities were defined as per the Society of Vascular Surgery (SVS) guidelines where possible[12]; diabetes was defined by documented medical history, the use of oral antidiabetic agents or insulin or fasting plasma glucose levels of at least 1.26 g/L; hypertension was 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. The following diseases were recorded based on

the patient's documented medical history: Ischaemic heart disease or prior myocardial infarction, atrial fibrillation, hypertension, cerebrovascular disease (stroke; including ischemic or haemorrhagic stroke as well as transient ischemic attack), end-stage renal failure requiring dialysis and a documented diagnosis of chronic obstructive pulmonary disease. The number of pre-operative drugs will also be recorded from the pre-assessment clinic documentation.

Routine clinical care laboratory test results (including haemoglobin, white-cell count, albumin, creatinine and eGFR, C-reactive protein and HbA1C) will be collected as well as height and weight.

Axial imaging by means of a CT-Angiogram (where performed) will enable measurement of skeletal muscle area at the L3 level (for comparison with previous studies), the mid-thigh and mid-calf levels (to enable detection of regional differences in muscle mass).

Physical performance will be measured by maximal grip strength will be measured using handgrip dynamometry, and the five times sit to stand test will be used to assess lower limb power[13]. The Fried frailty score[14] will be measured by combining five domains: weight loss (>4.5kg in last year), low grip (<27kg for men, <16kg for women), low walk speed (we anticipate that most participants will have restricted mobility and so will score a point automatically; a cut-off of <0.8m/s will be used for those that can undertake a 4m walk test), exhaustion (measured using two questions from the centre of epidemiologic studies depression scale (CES-D) scale used in the original Fried score) and low physical activity, measured using four activity questions used in the English Longitudinal Study of Ageing[15]. A score of 3 or more will denote frailty, 1 or 2 prefrailty, and zero denotes non-frail. We will also collect information on, activities of daily living, nutritional intake, place of living and mobility aids as well as the Rockwood clinical frailty scale to provide comparison for robustness in this disease group. Participants will be invited to complete the Euro-QoL EQ5D-5L health status assessment.

Procedure and discharge related data:

Following the baseline data capture, details on any surgical or endovascular procedure performed, the total duration of hospital admission, the discharge environment or package of care and mobility will be recorded. All patients who agree to participate will be followed up irrespective of whether they undergo any revascularisation.

Post-operative outcomes:

By review of electronic records 90-days outcome data will be collected. This will include, length of stay (days), death, major adverse limb event (MALE/limb-loss), myocardial and cerebrovascular events (MACE; major adverse cerebrovascular events) and re-admission or re-intervention. Participants will also be invited to receive a telephone call or postal EQ5D assessment for completion. The number of day alive out of hospital will be recorded.

Follow-up

Patients will be followed up using electronic patient records. Data as outlined above will be captured. Those patients who agreed to postal or telephone EQ5D assessment will also be assessed at 90 days as well as the Nottingham extended activity of daily living scale where possible. Any patients re-admitted and undergoing repeat CTA imaging within the time frame will also have their skeletal muscle areas re-captured to provide some longitudinal data where possible.

Sample-size

This study seeks to gather preliminary data to enable future sample size calculations. Although an accurate sample size calculation is not possible without such pilot data, we estimate that a sample size of 200 participants would be sufficient to detect a frailty prevalence of 25% with a precision of +-5% (i.e. 95% CI 20% to 30%). This prevalence is a conservative estimate, based on our local retrospective data for sarcopenia, where the prevalence is approximately 25% of CLTI patients. Frailty rates are estimated to be similar or higher. We aim to recruit a minimum of 40 patients per centre from a minimum of five centres giving a total of 200 patients. So far through national enquiry 10 UK vascular centres have agreed to participation following successful ethical approval. Through our collaborative work we have also been approached by the Fiona Stanley Hospital, Perth, Australia as potential collaborator.

Statistical Analysis

Data were recorded in a dedicated database. Normally distributed data are presented as mean (SD), and hypothesis testing performed with paired and unpaired t-tests. Non-normally distributed data are presented as median (IQR) values with analysis using Mann-Whitney U test for unrelated samples and Wilcoxon signed rank test (WSR) for paired data. Categorical data were analysed by means of chi squared (χ^2) or, if necessary, Fisher's exact test. All data were collected during the dedicated clinic follow-up. Statistical analysis was performed using SPSS version 24 (SPSS, IBM, Chicago, Illinois, USA). A p value of <0.05 was considered statistically significant for single comparisons. Kaplan-Meier survival curves were used with log-rank test to compare the overall mortality. Cox Regression analysis will be performed. Hazards ratios (HR) with 95% confidence intervals (CI's) are reported along with p-values. A HR of greater than 1 indicates a shorter time to death and a HR of less than 1 indicates a longer time-to-death. Binary logistic regression analysis will be used to identify associations with complications and multiple variates will be tested. The resultant significant variables are presented as odds ratios (OR) with 95% CI's. An OR of greater than 1 indicates and increased likelihood of the event occurring.

Study monitoring

- This is a low-risk study and major safety issues are not anticipated.
- The study may be subject to inspection and audit by the study sponsor (NUTH).
- This is to ensure that the study is conducted to a high standard in accordance with the protocol, the principles of GCP, relevant regulations, guidelines and with regard to patient safety.

Serious adverse event monitoring and reporting

- This is a low-risk study and major safety issues are not anticipated.
- The study may be subject to inspection and audit by the study sponsor (NUTH).
- This is to ensure that the study is conducted to a high standard in accordance with the protocol, the principles of GCP, relevant regulations, guidelines and with regard to patient safety.

Ethics and regulation

This study is undergoing local research and development approval prior to submission to ethics for full and appropriate national research ethical committee approval. Each recruiting centre will then be expected to gain local R and D approval to participate with all recruiting individuals having the required good clinical practice certification for research engagement. (INSERT REC Approvals)

VERN – The Vascular and Endovascular Research Network

This is a national trainee led 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, as such national ethical approval for multi-centre recruitment has been applied for. Contributions will be recognised in co-author ship of publications as part of a collaborative research authorship model. This will allow participating surgeons 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.

Confidentiality and Data Handling

- Personal data will be regarded as strictly confidential
- An NHS computer will be used for all inputting of data onto a database. This will be password protected and have IT security measures offered by the Freeman Hospital IT department.
- No data will leave the study site
- The study will comply with the Data Protection Act 1998 and Caldicott Principles
- All study records and investigator Site Files will be kept at site in a locked filing cabinet with restricted access

Insurance and Finance

- The Newcastle upon Tyne Hospitals NHS Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care
- NHS Indemnity covers NHS staff conducting the trial for potential liability in respect of harm arising from the conduct of the study.

Study publication/reports

- Publication will be the responsibility of the PI and collaborators
- Authorship principles will follow the International Medical Editors conventions as follows: Each author should have participated significantly in the work to take responsibility for the content. This participation should include (a) conception or design, or analysis and interpretation of data, or both; (b) drafting the article or revising it for critically important content; and (c) final approval of the version to be published. The collaborative model will be employed leading to PubMed index authorship for all collaboratives.
- The outcomes of this study will be published in peer review journals and presented at local, national and international meetings and conferences
- Individuals will not be identified from any study report

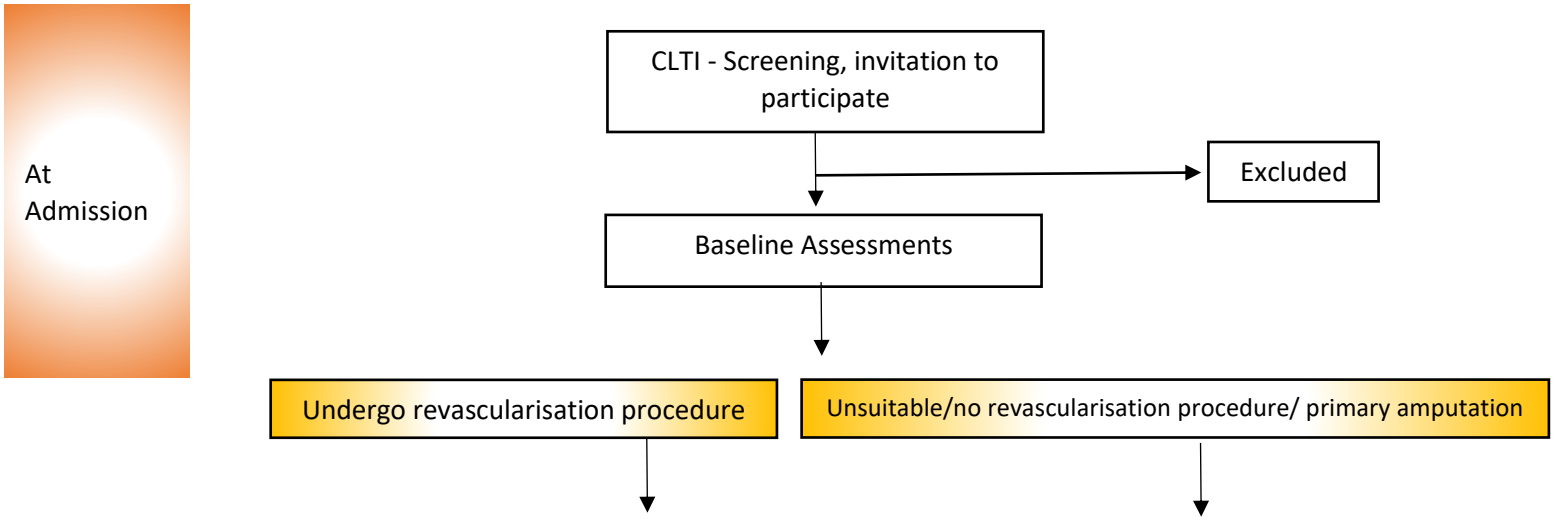
Ongoing research

The results and data collected in the FraiLTI study will be used to develop future research into frailty and the associated conditions. Based on the study data gained, it is likely that there will be identification of key associations. This will allow the development of optimisation strategies and work packages as part of a prospective study. The FraiLTI results are pivotal foundations to further research and application for funding with the aim of improving clinical and patient reported outcomes in an evidence-based fashion.

Intellectual Property

There will be no intellectual property generated by the study.

Study Flow



At 90-days

90-day clinical outcomes MACE/ MALE re-admission and re-intervention data. QOL assessment

References

1. Smith GE, Long J, Wallace T, Carradice D, Chetter IC, Vascular Research C. Identifying the research priorities of healthcare professionals in UK vascular surgery: modified Delphi approach. *BJS Open* 2020.
2. R54 - Age-related physical debility.
3. Crozier-Shaw G, Joyce WP. Too frail for surgery? A frailty index in major colorectal surgery. *ANZ J Surg* 2018; **88**(12): 1302-5.
4. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**(1): 16-31.
5. Newton DH, Kim C, Lee N, Wolfe L, Pfeifer J, Amendola M. Sarcopenia predicts poor long-term survival in patients undergoing endovascular aortic aneurysm repair. *J Vasc Surg* 2018; **67**(2): 453-9.
6. Schmucker AM, Hupert N, Mandl LA. The Impact of Frailty on Short-Term Outcomes After Elective Hip and Knee Arthroplasty in Older Adults: A Systematic Review. *Geriatric Orthopaedic Surgery & Rehabilitation* 2019; **10**: 2151459319835109.
7. Nandhra S, Boylan L, Prentis J, Nesbitt C. The influence of pre-operative anaemia on clinical outcomes following infra-inguinal bypass surgery. *Ann Vasc Surg* 2019.
8. Wang J, Zou Y, Zhao J, et al. The Impact of Frailty on Outcomes of Elderly Patients After Major Vascular Surgery: A Systematic Review and Meta-analysis. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 2018; **56**(4): 591-602.
9. Han B, Li Q, Chen X. Frailty and postoperative complications in older Chinese adults undergoing major thoracic and abdominal surgery. *Clin Interv Aging* 2019; **14**: 947-57.
10. Ghaffarian AA, Foss WT, Donald G, et al. Prognostic implications of diagnosing frailty and sarcopenia in vascular surgery practice. *J Vasc Surg* 2019; **70**(3): 892-900.
11. Conte MS, Bradbury AW, Kolh P, et al. Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. *Eur J Vasc Endovasc Surg* 2019; **58**(1s): S1-S109.e33.
12. Al Falluji N, Lawrence-Nelson J, Kostis JB, et al. Effect of anemia on 1-year mortality in patients with acute myocardial infarction. *Am Heart J* 2002; **144**(4): 636-41.
13. Bohannon RW. Test-retest reliability of the five-repetition sit-to-stand test: a systematic review of the literature involving adults. *J Strength Cond Res* 2011; **25**(11): 3205-7.
14. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**(3): M146-56.
15. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol* 2013; **42**(6): 1640-8.

Appendix