JRMO Research Protocol for Interventional Studies

Full Title	Lateral compression type-1 fracture fixation in the elderly, a randomised controlled trial
Short Title:	L1FE
Trial registration:	L1FE will be registered on International Standard Randomised Controlled Trial Number (ISRCTN: 16478561)

Sponsor	Barts Health NHS Trust
IRAS Number	255609, (263397 Scotland only)
REC Reference	19/LO/0555
Chief Investigator	Mr Peter Bates, Barts Health NHS Trust
Funder	The National Institute for Health Research Health Technology Assessment programme (reference number: 16/167/57)

Amendment number	**Revised Protocol Version Number and date**	**Details of changes made** (including justification if required)
Substantial Amendment 1	V2 20.01.2020	1) Protocol prepared for submission to regulatory authorities in Scotland and Northern Ireland (due to inclusion of patients that lack capacity) (sections 9.5.1 and 12). 2) Changes to Key Trial Contacts in Section 2. 3) Clarification added to inclusion criteria (Section 5 and 9.1.2) following feedback from participating sites. 4) Collection of EQ-5D-5L one week prior to injury at Baseline for patients that lack capacity. (section 9.3.1) 5) Adverse Events of Special Interest defined and AE reporting procedure clarified (section 9.3.2 and 11.3). 6) Clarification to data collection at 2 weeks and late discharge (section 9). 7) Clarification added to SWAT protocol (Appendix 1) 8) Clarification to text and correction of typographical errors and formatting has been added throughout the document.
NA (Changes requested during REC review)	V2.1 14.04.2020	Section 12.2 Consent and 15 Access to data were both updated to consistently refer to the consultee declaration process as well as the consent process

1. Contents

2. Key Trial Contacts

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	Trial Management Group ***Chair:*** Mr Peter Bates	

3. Glossary

AE	Adverse event
AESI	Adverse Event of Special Interest
CEAS	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRN	Clinical Research Network
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DICOM	Digital Imaging and Communications in Medicine
DMEC	Data Monitoring and Ethics Committee
DRI	Disability Rating Index
EQ5D-5L	EuroQol 5 Dimension, 5-Level scale
ExFIX	External Fixation
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICER	Incremental Cost Effectiveness Ratio
IP	Intellectual Property
IRAS	Integrated Research Application System
ITT	Intention To Treat
MRC	Medical Research Council
MTCs	Major Trauma Centres
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
NRS	Numerical Rating Scale
ONS	Office of National Statistics

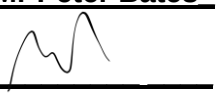
ORIF	Open Reduction and Internal Fixation
PACS	Picture Archive and Communication System
PI	Principal Investigator
PIC	Participant Identification Centre (for a study)
PIL	Participant/ Patient Information Leaflet
PROMIS	Patient Reported Outcome Measures Information System
PSSP	Personal Social Services Perspective
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
TULIP	**T**rial of s**u**rgical versus non-surgical treatment of **l**ateral compression **i**njuries of the **p**elvis with complete sacral fractures (LC-1) in the non-fragility fracture patient - a feasibility study
TUG	Timed Up and Go Test
UTI	Urinary Tract Infection
VTE	Venous Thromboembolism
YTU	York Trials Unit

4. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Mr Peter Bates**

Signature: 

Date:

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: _____

Signature: _____

Date: _____

5. Summary and synopsis

Scientific Title	Lateral compression Type-1 fracture fixation in the elderly, a randomised controlled trial	
Public title	L1FE	
Countries of recruitment	England, Scotland, Wales and Northern Ireland	
Health condition studied	Lateral compression Type-1 fragility fractures of the pelvic ring	
Interventions	**Arm 1:** Anterior internal surgical fixation device (i.e. INFIX)	**Arm 2:** Non-surgical management
Key Inclusion and Exclusion Criteria	INCLUSION CRITERIA: • Patients aged 60 years or older; • An LC-1 pelvic fracture, arising from a fall from standing height or less; • Patient still unable to mobilise to a distance of around 3 meters and back due to pelvic pain (or perceived pelvic pain) 72 hours after injury. Use of a walking aid and/or supervision are permitted. EXCLUSION CRITERIA: • Unable to perform surgery within 10 days of injury; • Surgery is contra-indicated because patient is not fit for anaesthetic (spinal or general) or soft tissue concerns; • Patients who were non-ambulatory or required physical assistance to walk prior to their injury (use of a walking aid is permitted); • Concomitant injury or poly-trauma that impedes mobilization; • Fracture configurations not amenable to internal fixation using INFIX with or without ilio-sacral screws.	
Trial Design	Parallel randomised controlled trial, with an internal pilot	

Trial Participants	Aged 60 years and older	
Planned Sample Size	600	
Follow up duration	2 weeks, discharge, 6 weeks, 12 weeks, 6 months and 12 months (N.B. 12 month point only applies to those who opt-in and reach that timepoint within the trial follow up period)	
Planned Trial Period	1st October 2018 to 30th Sept 2022 (target date of first enrolment 1st April 2019)	
Outcomes	Primary	Secondary
	Health related quality of life: EQ-5D-5L	Physical function: Patient Reported Outcome Measure Information System (PROMIS): Lower Extremity Function; Timed Up and Go Test (TUG). Global Mental Health: PROMIS Scale v1.2 – Global Health Mental 2a Pain : Numeric Rating Scale (NRS); Delirium: 4AT Rapid Test; Abbreviated Mental Test Score (AMTS) Imaging Assessments Resource use: e.g. impact on the NHS Complications and Adverse Events; Mortality

6. Introduction

6.1 Lateral compression Type-1 (LC-1) fractures

Lateral Compression Type-1 (LC-1) fractures are a common fragility fracture in older adults, especially those with osteoporosis. They typically involve a transverse fracture (horizontal to the vertical axis) of the pubic ramus, which is perceived by the patient as groin pain when they mobilise. There is often also a 'buckle' fracture to the sacrum posteriorly, which is felt as low-back/buttock pain when moving the legs. LC-1 fractures result from a low energy fall from a standing height or less and most often affect women, with the likelihood of fracture increasing with age (1-3).

LC-1 fractures are painful, almost always resulting in a period of reduced mobility. While this period may only last for a month or two, it is estimated that 25% of patients experience pain for up to five years afterwards (4). There are two types of LC-1 fracture: stable fractures, in which patients are able to mobilise, albeit with some degree of pain, and unstable fractures, where pain strongly affects a patient's ability to 'get going'. Patients with unstable fractures are at greater risk of immobility-related complications (5). These complications include respiratory tract infections (RTI), urinary tract infections (UTI), pressure sores, and venous thromboembolic events (VTE) such as deep vein thrombosis or pulmonary embolism (5, 6). These individuals are also at risk of systemic sarcopoenia (irreversible muscle wasting), disabling loss of confidence and permanently decreased levels of independence, often leading to increased care requirements. Inability to return to independent living can result in utilisation of intermediate care or residential facilities (7, 8). Such is the loss of confidence and muscle strength/conditioning in certain patients following LC-1 fracture, they do not regain their pre-injury level of ambulation or their prior independence with activities of daily living (1, 3, 9, 10). Additionally, individuals with LC-1 fractures have reported emotional stress, family strain, employment and financial difficulty, sleep disturbance, and anxiety (11). Pelvic fractures are also associated with increased mortality, particularly in the first two months (8); UK in-hospital mortality is 9%, and at three months is 13% (12). All-cause mortality following pelvic fracture is around 50% at three years (2). Progress in the treatment of LC-1 fractures is needed to improve outcomes and quality of life (QOL).

With an ageing population, the incidence of pelvic fractures is rising. The UK age-specific incidence of pelvic fractures (based on a single centre) has increased from

39.6/100,000 (95% CI: 31.8 to 48.1) in 1997 to 71.61/100,000 (58.4 to 81.0) in 2007-2008 amongst people 65 years and older; 84% of these had pubic rami fractures (13). This increase is supported by evidence from other countries e.g. in Finland (based on national data) where the incidence, amongst people 60-years and older, has increased from 20/100,000 in 1970 to 92/100,000 in 1997 (14). The estimated median treatment cost of pelvic ring fractures in Europe (acute hospital, surgery, rehabilitation, physiotherapy, and work-related absence) is €33,710 per patient (interquartile range €23,266 to €51,012), which is more costly than hip fractures (15).

6.2 Cognitive function

A significant number of patients in this elderly group will have impaired cognitive function, either because of chronic/longstanding illness, such as dementia, or because of acute illness coinciding with their fall, such as chest or urinary infection. However, patients with reduced cognitive function still experience pain and outcomes of orthopaedic fracture treatment in the elderly have consistently shown patients to benefit from pain relief, regardless of their mental state at the time (16). We therefore consider that those with impaired capacity have as much to gain from inclusion in the study as those with full capacity.

6.3 Current management of low impact LC-1 Fractures

Fractures involving the upper end of the femur in the elderly (also known as ‘hip fractures’), are invariably treated surgically, with either internal fixation of the bone or joint replacement being mandated within 36-hours of injury (17, 18). This is because the long-term risks to the patient resulting from prolonged immobility due to pain are much more severe and long-lasting than the immediate risks of surgery, when applied to the patient population.. Despite unstable LC-1 fractures being similarly disabling in terms of pain and immobility and occurring in the same patient group as hip fractures, to date, pelvic surgeons have been reluctant to offer surgery to patients with LC-1 fractures. The current standard of care for LC-1 fractures is for patients to take pain killers and mobilise as best they can until the fracture eventually heals. This stark difference in treatment rationale between two similarly disabling injuries has persisted because traditional pelvic implants carry poor fixation (‘bite’) in low-quality osteoporotic bone around the pelvis. In essence, the difference in treatment between hip fractures and LC-1 fractures can be explained by the fact that the latter have not had a good surgical solution to treat them, whereas hip fractures have.

Until recently, there has not been an effective operation to treat osteoporotic LC-1 fractures. External fixators, consisting of pins inside the pelvis connected to bars and clamps outside of the skin, are cumbersome, poorly tolerated and carry a high incidence of pin-site infections and soft tissue problems (19). An alternative is surgical fixation of the back of the pelvis with ilio-sacral screws (3). Although these are effective for certain fracture configurations, in the majority of elderly patients, these screws carry poor 'purchase' in osteoporotic bone (5), leading to ineffective fracture stabilisation and persistence of pain. Thus, the current standard treatment for low impact LC-1 fractures in the UK is non-operative management and to 'mobilise as pain allows' (5, 20, 21). For many patients this is successful; getting up within a few days of injury and mobilising with an assistive device. However, as outlined above, pain due to an unstable fracture can lead to immobility leaving this predominantly elderly population at risk of significant complications.

6.4 Current evidence and justification for study

The INFIX is a type of anterior pelvic fixation device that resembles a traditional external fixator, in that it has screws that are secured into the pelvic bone and these are connected together by a metal bar across the front of the patient. The difference from the traditional external fixation is that devices such as INFIX are fitted internally, sitting entirely underneath the patient's skin, with no external metalwork visible. This has two major benefits over external fixation: it is much less cumbersome and inconvenient to patients, compared with pins, clamps and bars protruding out of the skin. It also does not have pin-sites (where the bone-pins exit through the skin), which make traditional external fixation very susceptible to local infection. The INFIX technique involves percutaneous placement of screws in the pelvic bone and connects them with a bar under the skin (22). The pelvic bone where the screws are placed is generally strong and easy to visualise intra-operatively, even in very osteoporotic bone, making internal fixation (e.g. INFIX) a much more appealing surgical option for these fractures. Although a proportion of implants need to be removed; this is usually done as a day case. INFIX is now widely used in younger patients with high energy fractures. It is now a well described technique with a number of peer-reviewed series confirming the safety of the technique (23). It is

therefore a widely-practiced, rather than 'novel' technique and is technically straightforward to carry out.

In order to assess the evidence for use of surgical fixation in the treatment of low energy LC-1 fractures in older adults, our team has undertaken a systematic review (24). There are currently no robust evaluations, particularly randomised controlled trials (RCTs), of the effectiveness of internal fixation with INFIX in patients with osteoporotic LC-1 fractures. The review identified five case series, four retrospective (25-29). Participants were 64 or over and most had sustained injury from a low energy fall. A variety of fixation types were used. Of the total of 225 patients in the five studies, most had internal devices, with 25 external fixation: most patients had more than one type of fixation.

In the only series evaluating INFIX alone, 19 of the 29 patients had LC-1 fractures(27). Six patients had anterior fixation with INFIX alone and the remaining 23 had INFIX with additional internal fixation. Post operatively 22 of the 29 (76%) returned to their premorbid walking status, and a further six patients had some deterioration but remained ambulatory. Chronic pain (n=3, 10.3%) and painful lateral femoral cutaneous nerve hyperaesthesia (n=8, 27.5%) were prevalent after INFIX fixation. Other complications reported included: failure to return to premorbid walking status, infections, implant loosening, pneumonia, and thrombosis.

Our search of clinicaltrials.gov for ongoing studies identified a trial in the United States of operative vs non-operative management of patients aged between 18 and 80 with lateral compression type 1, 2 and 3 pelvic fractures in 130 participants. The aim of the trial is to determine which patients would benefit from early surgical stabilization(30). We are also aware that NIHR Research for Patient Benefit (RfPB) have funded TULIP, a feasibility trial of surgical versus nonsurgical treatment of LC-1 fractures of the pelvis in non-fragility fracture patients. The current study is complementary to TULIP as it investigates the excluded population.

The pelvic fracture community is at a key point in considering adopting internal fixation devices such as INFIX in the management of LC-1 fractures. In August 2016, we conducted a survey of 32 pelvic surgeons across the UK, of whom 29 responded; 70% felt there was a potential role for treating older patients with low-energy LC-1 fractures with INFIX if they fail to mobilise effectively due to pain.

We now have a device which has the potential ability to effectively stabilise LC-1 fractures in older adults. The intervention is now increasingly used by pelvic surgeons in Major Trauma Centres for people with high energy fractures. However, more evidence of effectiveness is needed to evaluate the use of the INFIX device in this group of elderly patients with fragility fractures. The timing is therefore right for a high quality RCT, specifically in older adults, to investigate the effectiveness, safety and cost-effectiveness of internal fixation with devices such as INFIX compared to nonsurgical treatment.

7. Study objectives

7.1 Aim

To investigate the clinical and cost effectiveness of surgical fixation with INFIX compared to non-surgical management of LC-1 fragility fractures in older adults.

7.2 Objectives

Our objectives are to:

1. Undertake a 12 month internal pilot to obtain robust estimates of recruitment and confirm trial feasibility.

2. Undertake a parallel group multi-centre RCT to assess the effectiveness of surgical fixation with INFIX versus non-surgical management of LC-1 fragility fractures in older adults. The primary outcome is average patient quality of life and function, over the study time period, assessed by the patient-reported outcome measure, EQ-5D-5L (measured at baseline, 2 weeks, 6 weeks, 12 weeks and 6 months).

3. Undertake an economic evaluation to compare the cost-effectiveness of surgical fixation compared to non-surgical management, to determine the most efficient provision of future care and to describe the resource impact on the NHS for the two treatment options.

4. Undertake a long term review of patient wellbeing (EQ-5D-5L and mortality) 12 months after entering the trial.

8. Trial design

The proposed study will be a multi-centre, randomised controlled superiority trial, with an internal pilot phase to assess the assumptions about recruitment and provide guidance on optimising the trial processes. A report will be provided to the funder and subject to approval from the funder (assuming feasibility has been established) we will proceed to the main trial.

9. Methods

9.1 Setting

The study will be undertaken in NHS Major Trauma Centres (MTCs) with orthopaedic surgeons specialising in pelvic injuries or Trauma Units where there are surgeons experienced in doing these operations or have the capacity to be trained.

9.1.1 Eligibility criteria

We will include all adult patients (60 years or older) with LC-1 fractures who meet the eligibility criteria below.

9.1.2 Inclusion criteria

- Patients aged 60 years or older;
- An LC-1 pelvic fracture, arising from a low energy fall from standing height or less;
- Patient still unable to mobilise to a distance of around 3 meters and back due to pelvic pain (or perceived pelvic pain) 72 hours after injury. Use of a walking aid and/or supervision are permitted.

9.1.3 Exclusion criteria

- Unable to perform surgery within 10 days of injury;
- Surgery is contra-indicated because patient is not fit for anaesthetic (spinal or general) or soft tissue concerns;
- Patients who were non-ambulatory or required physical assistance to walk, prior to their injury (use of a walking aid is permitted);
- Concomitant injury or poly-trauma that impedes mobilization;

- Fracture configurations not amenable to internal fixation using INFIX, with or without ilio-sacral screws.

9.2 Interventions

Eligible and consenting patients will be randomly allocated to either surgical fixation with INFIX device, or non-operative management.

9.2.1 Surgical fixation

Anterior pelvic fixators such as the INFIX device are fitted internally, under the patient's skin. The technique involves percutaneous placement of long pedicle screws within the pelvic bone and connects them with a rod under the skin. The primary fixation for every patient is INFIX. If the surgeon feels that the particular fracture configuration in a patient warrants supplementary ilio-sacral screw fixation, this is permissible under the trial, provided adequate intra-operative pelvic imaging can be achieved.

Post operatively, patients will receive physiotherapy as per standard of care along with the L1FE trial physiotherapy leaflet. Post-operative instructions should state, 'immediate weight bearing, as pain allows'. The goals of physiotherapy are to improve function, strength and range of movement in both legs, while aiming to get patients back to independent mobility as soon as possible.

9.2.2 Non-operative management

Standard care for LC-1 fractures in the UK is to mobilise patients as pain allows. Patients are routinely seen by a physiotherapy team. The goals of physiotherapy are (as above) to improve function, strength and range of movement in both legs, while aiming to get patients back to independent mobility as soon as possible.

In either the operative or non-operative group, if any patient's course is complicated by excessive pain when mobilising, a repeat radiograph is clinically indicated, followed by review by a pelvic surgeon, as would be the normal standard of care.

9.2.3 Rehabilitation

All patients randomised into either of the two groups will also receive the standardised L1FE trial-specific, physiotherapy leaflet detailing suggested exercises to perform. This leaflet is intended to supplement and not replace advice given by the site physiotherapy team.

9.3 Outcomes

9.3.1 Primary Outcome

The primary outcome measure is average patient quality of life, over the study time period, assessed by the patient-reported outcome measure, EuroQol 5 Dimensions (5L) utility score (EQ-5D-5L). The EQ-5D-5L is a validated generic patient-reported outcome measure (www.euroqol.org), including validation in patients with hip fractures and orthopaedic patients with cognitive impairment (31). The descriptive system has five health domains (mobility; self-care; usual activities; pain/discomfort and anxiety/depression) with five response options for each domain (no problems, slight problems, moderate problems, severe problems and extreme problems). In addition it has a health status visual analogue scale (VAS) which measures self-rated health with endpoints ranging from 'the best health you can imagine' to 'the worst health you can imagine'. The EQ-5D-5L will be scored according to the User Guide (32). The measure is easily completed and can be completed by proxy (which is important for our clinical population) and it can also be scored for those who have died during follow-up. EQ-5D-5L data will be collected in either patient questionnaires or in proxy questionnaires for those who lack capacity. EQ-5D-5L will be collected at baseline (for today and one week prior to injury), 2 weeks, 6 weeks, 12 weeks, and 6 month time points, as well as an optional 12 month follow up point for those recruited early within the study (and reach this time point within the planned follow-up period). Baseline questionnaires will be completed prior to randomisation.

9.3.2 Secondary outcomes

Physical function:

Patient Reported Outcome Measures Information System (PROMIS) Lower Extremity Function

PROMIS is a set of validated person-centred measures that evaluates physical, mental, and social health in adults and children (33). The full item bank can be used

for computer adaptive testing but is also available in a range of subscales and short forms to measure different aspects of health. Lower extremity function is an extremely important outcome domain for people with a LC-1 fracture, due to the impact of the injury on ability to mobilise. This brief test (Lower Extremity Function), for administration as a paper based questionnaire, is designed to reduce responder burden and has been deemed to have good face validity with our PPI group. PROMIS Lower Extremity Function data will be collected in the patient questionnaires (or proxy questionnaires for those who lack capacity) at baseline, 2 weeks, 6 weeks, 12 weeks and 6 month time points.

Timed Up and Go Test (TUG)

This test assesses walking speed, mobility, balance, and fall risk. It is an established test used routinely in practice and has been validated for reliability (34-37). An LC-1 fracture can impact significantly on ability to mobilise and this clinic-based measure will complement the patient reported outcome measure PROMIS Physical function. TUG will only be performed at 12 week follow up point.

Global Mental Health:

PROMIS Scale v1.2 – Global Health Mental 2a

The PROMIS measurement system also contains a two question subscale on global mental health. Inclusion of this subscale was highly commended by our PPI group. This data will be collected in the patient and proxy questionnaires at baseline, 2 weeks, 6 weeks, 12 weeks and 6 month time points.

Pain:

Numeric Rating Scale (NRS)

This is a unidimensional measure of pain intensity in adults (38). We will use an 11-point numeric scale with 0 representing ‘no pain’ and 10 representing ‘worst imaginable pain’ to measure average pain over the last week (39). This data will be collected from people with capacity only, in the patient questionnaires at baseline, 2 weeks, 6 weeks, 12 weeks and 6 month time points as well as an optional 12 month follow up point for those recruited early within the study.

Delirium:

Abbreviated Mental Test Score (AMTS)

This short, verbal test is widely used in clinical practice to screen for confusion and dementia (40, 41). It is used across many areas of medicine and despite being developed in 1972(41), recent data confirms it's validity in emergency admissions in older adults within UK hospitals (40) This test will be conducted at baseline, two weeks and at 12 weeks. Repeat assessment at 12 weeks will confirm whether delirium is temporary or represents a permanent change.

4AT Rapid Assessment Test for Delirium

This is a short, practical instrument validated for detecting delirium routinely used in clinical practice (42-44). Post-operative delirium is a known complication for the elderly, particularly those with dementia. The incidence in a hip fracture surgery population has been calculated as 24% (45). Therefore, its use as an outcome measure will be to monitor this potential adverse effect of surgery. Post-operative delirium is associated with higher costs, functional decline, increased length of stay, discharge to a nursing home or care home, and higher mortality(46). Therefore, understanding which participants exhibit post-operative delirium will aid in the interpretation of the findings and outcomes post intervention. The strengths of using the 4AT Rapid Assessment Test for Delirium is that it can be used on patients that are drowsy or agitated (which is common after surgery), it does not require specialist training, and takes less than 2 minutes. This test will be conducted at baseline, two weeks and at 12 weeks. Repeat assessment at 12 weeks will confirm whether delirium is temporary or represents a permanent change.

Imaging Assessments:

Medical imaging, including CT scans and X-rays routinely used for the investigation and follow-up of patients with LC-1 pelvic fractures following surgical or conservative management will be undertaken as part of standard NHS practice. The routine imaging performed on admission will be used to confirm eligibility.

A radiologic assessment of the pelvis will be performed at the 12 week visit for all participants. These x-rays would be standard care for patients undergoing surgical

fixation but may be over and above what is routine practice for patients being managed conservatively.

Resource Use:

Information on resource use throughout patients' hospital stays and at discharge will be collected to assess the impact on the NHS as part of the economic evaluation. Data collected in clinic case report forms (CRFs) will include, length of hospital stay, medication, surgery details and details of therapy during rehabilitation. The 2 week and late discharge CRFs will also collect details on any aids or adaptations required and any change of place of residence (e.g. own home to residential care home) relative to baseline, Resource use data will also be collected in the 12 week patient questionnaire, from patients with capacity only. This will include information on any re-admittance to hospital, outpatient care received, any additional medications, aids or adaptions since discharge and return to work.

Complications and Adverse Events:

Information on expected complications, including additional surgery will be collected in the hospital CRFs at 2 weeksat 12 weeks and at discharge (if after 2 weeks). Expected complications that will be recorded will include (but not be limited to) the following: neurological complications, deep wound infection (using Centres for Disease Control (CDC) and Prevention definition)(47), superficial infection (using CDC definition), rehospitalisation, re-operation (including removal of implant) and skin problems.

Lateral Cutaneous Nerve Injury is an Adverse Event of Special Interest (AESI), and information on this will be collected on an Adverse Event (AE) form. Patients will also be asked about this in the 2 week, 6week, 12 week and 6 month questionnaires, as well as in the 12 month questionnaires for those who agree to this additional follow-up.

Information on any unexpected Adverse Events or any expected or unexpected Adverse Events that become Serious Adverse Events (SAEs) will be reported on the appropriate AE or SAE report form. Adverse Events will be reported for the duration

of the patients follow up period, either 6 months or 12 months (for those who agree to this additional follow-up) .

Mortality:

Mortality rates of 10-15% have been reported in this population 6 months after the fracture. Therefore, checks will be made on patients' status before mailing out follow up questionnaires at 6 and 12 months. Mortality will be reported as an outcome at 6 months, (and 12 months for those patients that agree to this additional follow-up).

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In Table 1 we outline the schedule of events for L1FE.

Table 1: L1FE Schedule of events

		Study Period					
		Post Allocation					
Time point	**Enrolment / Baseline (prior to randomisation)**	**Randomisation**	**2 Weeks**	**6 Weeks**	**12 Weeks**	**6 Months**	**12 Months[c]**
Eligibility screen	X						
Informed consent	X						
Demographic data[d]	X						
Randomisation		X					
Surgical Fixation		X					
Non-operative management		X					
EQ-5D-5L	X[a]		X	X	X	X	X
PROMIS (LEF and GMH)	X		X	X	X	X	
TUG					X		
Pain NRS[g]	X[b]		X	X	X	X	X
AMTS	X		X		X		
4AT	X		X		X		
Mortality						X	X
Resource Use Data			X[f]		X	X[e]	X[e]
Imaging					X		
Complications			X		X		
Adverse event reporting	X →	→	→	→	→	X	X
Change in status form	X →	→	→	→	→	→	X

[a] Data collected for a week before the injury as well as on the day of baseline assessment. [b] This question will ask about their pain, since their injury only. [c] Optional follow-up time point for those patients that reach this timepoint within the planned follow-up period. [d] Patient demographic data collected will include DOB, gender, ethnicity, lifestyle, medical history and current medications, details of the fracture and any concomitant injuries and Rockwood frailty score in the week prior to injury. [e] Collected for patients with capacity only. [f] If the patient has not been discharged by the 2 week timepoint, health resource data will be collected via review of medical records following the point of discharge.

9.4 Sample size

The primary outcome is the EQ-5D-5L. To be conservative, we took the lowest published estimate of the Minimal Clinical Important Differences (MCID) (0.074) (48) with an estimated standard deviation of 0.25 (estimated from the 0.30 reported by the Adachi et al. for the 3L version (49) and adjusted down to account for the 5L version's greater sensitivity). Based on these assumptions we would need to analyse 480 participants (240 per group) and, after accounting for loss to follow-up of 20%, we would need to recruit and randomise 600 participants for a study with 90% power (2p = 0.05).

9.5 Participant recruitment

Figure 1 outlines the pelvic fracture treatment flowchart and how it fits into our recruitment plans for the trial. Potentially eligible patients will be recruited from inpatient wards (both surgical and geriatric/medical) in addition to orthopaedic outpatient clinics and the Emergency Department. Individual centres may be able to recruit from their wider trauma network (i.e. from their local Trauma Units), provided a functioning referral stream for these patients is in place. All units will be supported to develop a process for identifying elderly LC-1 fragility fracture patients early in their admission process and this is likely to vary between centres.

9.5.1 Recruitment strategy

Our recruitment strategy will prioritise setting up MTCs during the recruitment phase of the trial. The research team will work closely with the treating clinicians at each centre to optimise the screening and recruitment for their local circumstances. Participating surgeons must be experienced in the procedure or have attended one of the planned training sessions, or received individual training approved by the CI.

The research associate will screen all potentially eligible patients 60 years old and over, admitted with an LC-1 fracture around 72 hours after admission. Where patients are unable to mobilise after three days, a member of the research team will

approach them providing information about the study as well as the Patient Information Sheet and the optional Summary Patient Information Sheet. Patients will have the opportunity to ask questions of the surgeon and the local research team. Patient eligibility must be confirmed by a delegated surgeon or clinician.

The study will include patients who lack capacity, as appropriate consultee declaration will be sought from a personal or nominated consultee (in England, Wales and Northern Ireland) or consent will be sought from a Guardian, Welfare Attorney or nearest relative (in Scotland) (see section 12.2 for full details).

Consent will be sought for follow-up beyond the duration of the trial to allow the possibility of future long-term follow-up including the use of routinely collected Hospital Episode Statistics (HES) and Office of National Statistics (ONS) data.

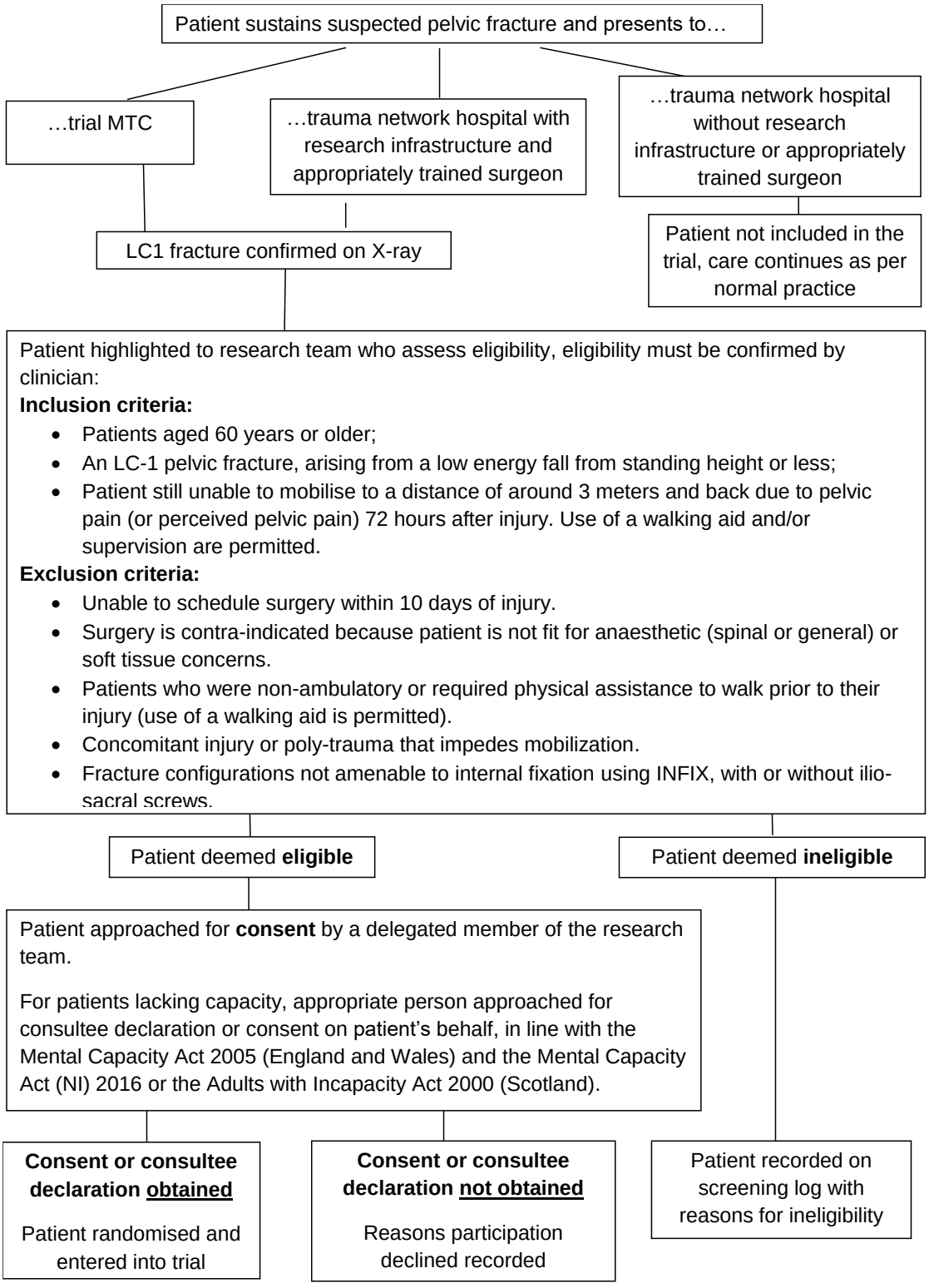

Figure 1: Recruitment Flowchart

9.5.2 Internal pilot

We will undertake a 12 month pilot study to test our assumptions about recruitment and confirm whether the trial is feasible. The internal pilot will be reviewed by the Data Monitoring Committee (DMC) and the funder to determine whether the study progresses to the full trial. The internal pilot will address the question of whether there are a sufficient number of eligible patients identified and recruited in 12 months to make the trial viable within the proposed 36 month recruitment period.

We will set up a minimum of 19 sites during the pilot with the aim of including all interested sites by month 13. We plan to set up a minimum of six sites in each of the first two quarters and the final seven sites in the third quarter. The majority of eligible sites will be included in the pilot providing a representative sample of the sites that will be used in the main study. Based on data from Barts, Nottingham, Bristol and Cambridge, we estimate that each centre will on average see 50-60 potentially eligible patients aged 60 years or over each year. Assuming recruitment of one patient per site per month we aim to randomise 148 patients in the 12 month pilot phase. A minimum of nineteen sites recruiting one participant per month each from their set up date to the end of the recruitment period will ensure the target of randomising 600 participants is reached. Any additional sites that we recruit to the trial will allow the achievement of target ahead of time if we recruit at the expected rate. An average recruitment rate of one patient per centre per month would support a decision to progress to the main trial. An average rate of 0.80 to 0.99 per centre per month would suggest that a decision to progress may be supportable depending on other supplementary information available (e.g. number and characteristics of potential participants not approached, proportion not meeting eligibility criteria and reasons, proportion declining participation and reasons why) and whether any of the factors impeding recruitment could be remedied.

9.6 Randomisation

Randomisation will be undertaken by York Trials Unit. When patients have consented and their baseline forms have been completed, the recruiting research associate/nurse/clinician will contact York Trials Unit (YTU), either by telephone or via the internet, to access a secure randomisation service. The randomisation service will record information and check patient eligibility to avoid inappropriate entry of patients into the trial. YTU will then perform independent and concealed random

allocation (1:1), using computer generated random permuted blocks of random sizes, stratified by centre. The patient will be allocated to either surgical fixation or non-surgical management.

9.6.1 Allocation concealment and blinding

Patients and treating clinicians will be informed of the allocation. As with many surgical trials, where the surgical site is clearly visible, it is not feasible to blind patients, surgeons or outcome assessors. The primary outcome is a patient-reported measure, mitigating surgeon influence. All staff involved in checking, entering, and analysing questionnaire responses will be blind to patients' treatment allocation. All recruiting centres will have surgeons who are familiar with the two approaches and use them as part of routine NHS care.

9.7 Data collection methods

Data will be collected at recruiting sites or by post from participants, then returned to YTU for scanning and processing. All reporting of data collection will be undertaken in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.

Data will be collected at baseline (prior to randomisation), 2 weeks, 6 weeks, 12 weeks and 6 month and optional 12 months post-randomisation. Baseline, 2 week and 12 week data will be collected at recruiting sites by a research associate (a member of the clinical research staff), if the patient has been discharged prior to 2 weeks the patient or proxy questionnaire will need to be completed by telephone interview. If the patient has not been discharged by the 2 week timepoint, health resource data will be collected both at the 2 week timepoint and via review of medical records following the point of discharge. The 6 week, 6 month and 12 month follow up data will be collected via postal questionnaires or telephone interview (unless the patient is still in hospital or attending a hospital clinic). The 12 week follow-up collection will take place in clinic as a follow-up appointment at this time is part of post-surgical routine care in most centres.. The 12 week questionnaire will be completed in clinic where possible. Participants unable to attend clinic at the 12 week timepoint,will be sent the questionnaire via post. A clinical assessment will take place at this follow-up point for both groups including radiologic assessment of pelvic position in the operative group. The non-operative group will follow current standard care except that all participants will undergo radiographic assessment at 12 weeks. The Timed Up and Go test will also be administered as part of this assessment.

9.7.1 Internal pilot data collection

Screening logs will be kept by participating centres throughout the trial. We will collect data on: number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent and reasons why; proportion of patients providing consent who are randomised. We will also collect data on the proportion of patients randomised who do not receive the randomly allocated treatment and reasons why. For each of the above we will collect data on whether consent was sought from a patient, or for patients who lack capacity whether a personal or nominated consultee was asked to give declaration (applicable in England, Wales and Northern Ireland) or whether a Guardian, Welfare Attorney or nearest relative was approached to give consent (applicable in Scotland).

Details of all participating surgeon's experience with the INFIX procedure will be collected as part of the trial. During site set up, the training delivered to sites will cover equipoise. The assumption of surgeon equipoise will be monitored during recruitment by scanning reasons for exclusion during screening and reasons for crossover following randomisation that may reflect surgeon preferences. This data will inform whether the study progresses from internal pilot to full study and will be used throughout the trial to monitor progress and identify potential areas to target to improve recruitment rates.

9.8 Follow up

To minimise attrition, we will use multiple methods to keep in contact with participants. We will ask participants for full contact details (including mobile phone number and email address). Participants will complete the questionnaire by post unless the participant is still in hospital, or when attending a hospital clinic for the 12 week review. A pre-notification letter will be sent one week before the postal follow-up questionnaires are due at 6 weeks, 6 months, and 12 months to help prime participants and find out if they are no longer at their address. A text message reminder will also be sent on the day participants are expected to receive the postal questionnaire at these time points. This has been shown to significantly reduce time to questionnaire response (50). At 6 weeks follow-up there will be a 1 week and 2 week postal reminder (and a 3 week telephone reminder); at 6 and 12 month follow-

up there will be a 2 week and 4 week postal reminder and 6 week telephone reminder.

The participant questionnaire will be completed at the 12 week visit wherever possible. If York Trials Unit do not receive the questionnaire within 3 weeks of the expected visit, and sites confirm that the participant has not attended the visit or the questionnaire was not completed, participants will then be posted the 12 week questionnaire. Postal reminders will then be sent 1 and 2 weeks later with a 3 week telephone call, in line with the other time points.

The telephone reminder will give participants the option to complete an abridged questionnaire (a minimum of the EQ-5D). The study team will also call the participant when there is missing data on the primary outcome (and other missing data as feasible) when the questionnaire is returned. We will also write newsletters during the trial to keep the participants informed and engaged with the trial which can enhance response rates (51).

Mortality checks will be completed at 6 and 12 months, prior to the relevant postal questionnaires being sent by York Trials Unit. The purpose of these checks is to reduce the risk of questionnaires being sent to patients that are deceased. For sites in England, a designated member of the research team within Barts Health NHS Trust will access the NHS Spine in England to determine participant mortality status. NHS numbers will be collected by York Trials Unit who will regularly send a list to the designated member of the research team from Barts Health NHS Trust to check for mortality status. For hospitals in Scotland, Wales and Northern Ireland, sites will use a patient identifier like an NHS number to use services that will allow us to check on participant mortality. Local sites may conduct mortality checks for their patients ahead of the 12 week review (when the participant is seen in clinic) in line with their usual clinical practice.

A management system which will be used to track participant recruitment and study status as well as CRF returns. Data from CRFs will be processed by administrative personnel. Data will be verified through cross checking of the data against the hard copy of the CRF. The trial coordinator and statistician will write a Validation Plan for the CRFs in consultation with the YTU Data Manager. The Plan will include detailed coding for the CRFs and data query resolution rules/procedures. Quality Control will

be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

9.9 Study Within a Trial (SWAT)

Randomised controlled trials are the key stone of evidence-based healthcare. Trial teams often experience difficulties with maintaining follow-up and questionnaire response rates from participants, which can introduce bias, reduce the sample size and statistical power and affect the validity, reliability and generalisability of findings (52-56).

There is a need to develop and test interventions to improve retention of participants. One method is to 'embed' trials of retention interventions in ongoing randomised trials. Testing interventions in ongoing trials ensures causality of intervention effectiveness is assessed [4] and avoids limitations associated with testing in a quasi-randomised controlled trial, or non-randomised setting such as the feasibility of intervention implementation. These embedded trials are often referred to as a Study Within a Trial or SWAT.

The L1FE trial will act as a host trial for an embedded trial which aims to look at an intervention to improve retention. The protocol for this SWAT can be found in Appendix 1

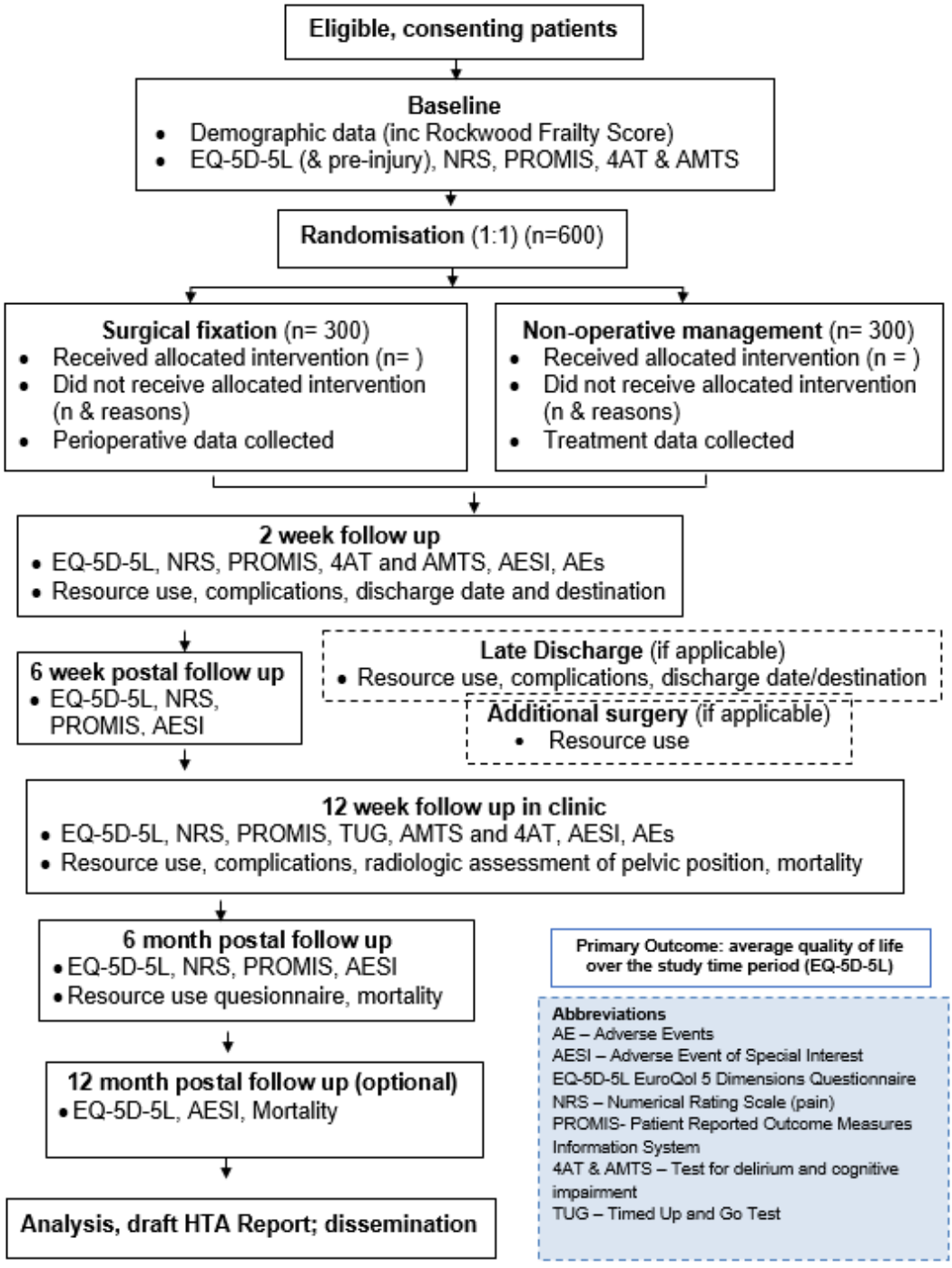

Figure 2: Flowchart of follow up and data collection

10. Data management

Study data will be recorded in a number of files for both the administration of the study and collection of patient data. All data will be completely anonymised for

purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, once randomised, individual patients will only be identified by Participant ID numbers.

10.1 Data entry

The data collected by sites using paper CRFs, will be mailed (original paper CRFs) to YTU to be entered/scanned into a secure web-based interface, specifically developed for this study. When necessary, a site can securely return the CRF electronically.

The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards.

Data will be checked according to procedures detailed in the trial specific Data Management Plan.

10.2 Data storage

Each site will hold data according to the General Data Protection Regulations (2018) and data will be collated in CRFs identified by a unique identification number (i.e. the Participant ID number) only. A Trial Enrolment Log at the sites will list the ID numbers. YTU will maintain a list of Participant ID numbers for all trial patients at each site.

All data recorded electronically at YTU will be held in a secure environment with permissions for access as detailed in the delegation log. The Department of Health Sciences, in which YTU is based at the University of York, has a backup procedure approved by auditors for disaster recovery. Full data backups are performed nightly using rotational tapes, to provide five years' worth of recoverable data. The tape backup sessions are encrypted and password protected, with tapes stored in a locked fire-proof safe in a separate secured and alarmed location. All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All essential documents, including source documents, will be retained for a minimum period of five years after study completion. The separate archival of electronic data will performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory

requirements. All work will be conducted following the University of York's data protection policy which is publically available (www.york.ac.uk/records-management/dp/policy).

10.2.1 Proposed time period for retention of relevant trial documentation

Essential trial documentation will be kept with the Trial Master File and Investigator Site Files. The Sponsor (Barts Health NHS Tust) will ensure that this documentation will be retained for a minimum of 20 years after the conclusion of the trial to comply with standards of Good Clinical Practice and the sponsor's Standard Operating Procedures (SOPs). CRFs will be will be stored up to 20 years after the conclusion of the trial as paper records; and a minimum of 20 years in electronic format in accordance with guidelines on Good Research Practice (57). All paper records will be stored in a secure storage facility at York Trials Unit and in the longer term transferred to a secure off-site storage facility as described in the SOPs provided by Barts Health NHS Trust. The research data will be archived for 20 years according to Queen Mary University of London/ Barts Health NHS Trust policy. The data will be archived in the Modern Records Facility, 9 Prescot Street, Aldgate, London, E1 8PR. All electronic records will be stored on a password protected server.

10.3 Quality Assurance and Quality Control

Barts Health NHS Trust is the sponsor for this project and takes overall responsibility for the quality of study conduct. This study will be fully compliant with the UK Policy Framework for Health and Social Care research (2017) and Medical Research Council (MRC) Good Clinical Practice Guidance. A trial specific data management plan agreed by the Chief Investigator, Sponsor, YTU and other study investigators will be drafted to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

A rigorous programme of quality control will be undertaken. The day-to-day management of the trial will be the responsibility of the Trial Co-ordinator based at York Trials Unit. Regular meetings with the Trial Management Group will be held and the trial team will monitor adherence to the trial protocols at the trial sites. Quality

assurance checks will be undertaken by York Trials Unit to ensure integrity of randomisation, study entry procedures and data collection.

10.4 Statistical methods

10.4.1 Statistical Analysis Plan

Full analyses will be detailed in a statistical analysis plan (SAP), which will be finalised prior to the end of data collection and which will be reviewed and approved by the independent data monitoring committee. Any exploratory analyses of sub-groups that are of clinical interest will be pre-specified in the SAP. This trial will be reported according to the CONSORT guidelines for clinical trials (Consolidated Standards Of Reporting Trials statement).

10.4.2 Internal pilot

The recruitment rate will be reported by month by hospital site and overall from the data collected. A CONSORT diagram will be constructed to show the flow of participants through the study and the following outcomes calculated: number of eligible patients; proportion of eligible patients approached for consent; proportion of eligible patients not approached and reasons why; proportion of patients approached who provide consent; proportion of patients approached who do not provide consent; proportion of patients providing consent who are randomised; proportion of patients randomised who do not receive the randomly allocated treatment; and proportion of patients dropping out between randomisation and follow-up. Data will be summarised on the reasons why eligible patients were not approached, reasons for patients declining to participate in the study; reasons why randomised patients did not receive their allocated treatment and reasons for drop-out, if available. Results will be compared against the study's recruitment assumptions and progression targets, and continuation of the trial or relevant modifications will be decided by the funding body.

10.4.3 Statistical analysis main trial

Statistical analyses will be on intention to treat (ITT) basis with patients being analysed in the groups to which they were randomised. Analyses will be conducted using 2-sided significance tests at the 5 % significance level (unless otherwise stated in the SAP).

A CONSORT flow diagram will be provided to display the flow of participants through the study. The number of participants withdrawing from the trial will be summarised with reasons where available. Baseline characteristics will be presented by trial arm. All trial outcomes will be reported descriptively by trial arm at all time points at which they were collected. Continuous baseline and outcome data will be summarised as means, standard deviations, medians and ranges, whereas categorical data will be summarised as frequencies and percentages.

The primary analysis will be a mixed effects linear regression model, with EQ-5D-5L scores at 2, 6 and 12 weeks and 6 months follow-up as the dependent variable, adjusting for baseline EQ-5D-5L, randomised group and other pertinent baseline characteristics as fixed effects. Potential clustering at hospital site level will be controlled for by including it in the model as a random effect. The model will account for the correlation of scores within patients over time by means of an appropriate covariance structure. The estimated treatment group differences across all time points will be reported as the primary endpoint with 95% confidence interval (CI) and associated p-value. Secondary analyses will include an estimate of treatment group differences at each time point from the same model.

The secondary outcomes PROMIS: Lower Extremity Function score, TUG score, AMTS score, 4AT score, PROMIS Scale v1.2: Global Health Mental 2a score and Pain NRS will be analysed by similar mixed effects linear regression models.

Subgroup analysis

A subgroup analysis will be performed to explore the potential effect of patients' knowledge of which treatment they received (allocation cannot be blinded) and their experience of this treatment on the results of the trial. This will be for the primary outcome only and the interaction term between preference and treatment group will be included in the primary analysis model as described in the previous section.

Optional 12 Months follow-up

For patients who are eligible to complete the 12 month follow-up questionnaire, the primary analysis model will be repeated and the treatment effect with associated 95% CI reported for the 12 month follow-up time point.

Safety Reporting

The summary of complications, deaths, AEs and SAEs experienced by the participants will be reported by treatment group. Mortality will be analysed as a secondary outcome using a logistic regression model.

10.4.4 Economic evaluation

The analysis will be conducted from the recommended NHS and personal social services (PSS) perspective according to NICE guidance (58). Data will be collected on the costs and outcomes of each trial participant during the period between randomisation and 6 months post-randomisation as well as an optional 12 month time point. There will be an internal pilot phase that will permit testing of the data collection forms to be used in the economic analyses in terms of validity, consistency, reliability and response rate (e.g. missing data). Trial participants will be asked to complete economic resource use questionnaires at 12 weeks and 6 months as well as at the optional 12 month time point. These will report hospital (e.g. inpatient, outpatient, A&E) and community and social care resource used; and for the purposes of secondary analysis, costs associated with lost productivity and out-of-pocket costs. Hospital forms will be specifically designed to collect information on the cost of surgery (e.g. time in theatre, staff time, consumables and devices, nights in hospital after the procedure), complications, physiotherapy and removal of devices. Relevant UK unit costs, such as NHS Reference costs and Personal Social Services Research Unit (PSSRU) Unit costs of health and social care, will be applied to each resource item to value total resource use in each group.

The raw EQ-5D-5L scores at baseline (today and one week prior to injury), 2 weeks, 6 weeks, 12 weeks and 6 months post-randomisation according to domain will be displayed, in order to examine the movements between levels for each domain according to group. The overall difference in EQ-5D-5L index scores between the two groups will be examined through regression methods, consistent with the model selected in the statistical analysis. The EQ-5D-5L health states will be valued using the mapping function developed by van Hout et al (2012) in accordance with NICE recent recommendation (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf).Qualityadjusted life years (QALYs) will be calculated by plotting the utility scores at each of the four time points and

estimating the area under the curve (59). For the analysis, regression methods will be used to express the incremental cost per QALYs gained. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. The pattern of missing data will be analysed and handled by means of multiple imputation (MI) methods (60). A range of sensitivity analyses will be conducted to test the robustness of the results using different scenarios, including probabilistic sensitivity analysis. We propose to undertake longer term modelling if this is appropriate (i.e. there is a non-dominant situation in the trial based evaluation). To do this we will undertake a secondary analysis to explore how the differences observed during the trial evolve beyond the study. For this projection, we will use a decision-modelling approach to extrapolate the cost-effectiveness data observed in the study to a lifetime horizon. The analysis will be based on a combination of observed in-trial cost and HRQoL and projections of life expectancy.

Full analyses will be detailed in a pre-specified health economics analysis plan (HEAP) that will be signed off by the trial management team and oversight committees.

10.5 Data monitoring

The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial Sponsor. Data monitoring will be undertaken by the Trial Management Group (TMG), Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC), on behalf of the Sponsor and Funder. The project will also be monitored by the Sponsor for whom a representative will be invited to attend the Trial Management Group and Trial Steering Committee meetings and we will submit regular progress reports to the Funding Body.

10.5.1 Trial Management Group (TMG)

A TMG has been established to oversee the day-to-day management of L1FE, and is chaired by the Chief Investigator. Other members include the trial statisticians, trial manager, trial coordinators, health economist, and other co-applicants. The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly by teleconference, with quarterly face-to-face meetings where feasible, from the start of the study until the

end of the pilot. The TMG will meet more frequently if there is a need to monitor recruitment more closely. The TMG will then meet quarterly.

10.5.2 Trial Steering committee (TSC)

An independent TSC has been established to provide overall supervision for L1FE on behalf of the Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. This committee comprises of an Independent Chair who is a Professor of Clinical Trials, a consultant orthopaedic surgeon with expertise in the procedure, a public contributor, Consultant Physiotherapist, representative from the sponsor, the Chief Investigator and Trial Coordinator/Manager. Other study collaborators may also attend the meeting with the agreement of the Chair. The TSC will meet at least annually and will work to a Charter which has been agreed.

10.5.3 Data monitoring and ethics committee (DMEC)

The role of the DMEC is to review accumulating data in L1FE and advise the sponsor (directly or indirectly) on the future management of the trial. The DMEC is Chaired by a statistician, with other members comprising of experts in the clinical area: Prof of trauma & orthopaedics, Senior Lecturer in Physiotherapy, and the Chief Investigator. The DMEC will review safety and efficacy data as well as quality and compliance data. The DMEC will review all serious adverse events which are thought to be treatment related and unexpected. The independent members of the DMEC committee will be allowed to see unblinded data. The DMEC will meet at least annually or more frequently if the committee requests. A DMEC Charter has been agreed which they will work to.

11. Harms

11.1 Risks and anticipated benefits

In the context of the lack of robust evidence to determine the best intervention for patients with these injuries, the risks are not increased through trial participation. However, there are risks associated with this study, which are associated with both treatment groups.

Surgical risks in this population include the following reported complications: wound infection 2%-4% (61), hardware loosening 5.3% (62), hardware (screw/strut) revision 7% (61), temporary lesions of the lateral femoral cutaneous nerve (changes in sensation) 30%-37% (61, 62) and heterotrophic ossification (bone growth in soft tissue) in 25%-35% of patients (61) of which >50%, correlated with increased age (only one case symptomatic) (63). Importantly, the more common complications (heterotopic ossification and sensory changes over the thigh) are generally either asymptomatic or not bothersome. Haematoma is an established risk of all orthopaedic surgery and also applies to this population, although treatment is usually non-operative and symptoms are both minor and short-lived. Some patients will request to have their metalwork removed, either because of persistent infection (2-4%) or because of discomfort around prominent metalwork. Based on clinical experience, in total, we anticipate a metalwork removal rate of about 20%, although the majority will keep their hardware in place. INFIX is usually well-tolerated.

Patients will be formally examined at the 3-month follow-up appointment. If removal of metal is indicated, they will be scheduled to a routine day-case operating list to have it done. Removal of metalwork carries the normal risks of wound infection and haematoma.

Risks associated with anaesthetic are generic to all elderly patients undergoing surgery. These include pulmonary complications associated with a reduced cough reflex following surgery, cardiac events and post-operative delirium (64). Post-operative delirium is a common and significant challenge in the elderly post operatively and is associated with increased mortality, morbidity and length of stay (65).

Outcomes of conservative management are poor, with decreased mobility, severe pain, increased physical and social dependency, high mortality and increased economic burden following a fragility fracture of the pelvis (5, 66). Surgery has the potential to allow immediate weight-bearing, thus limiting the adverse events associated with immobility and decreasing the acute and chronic pain associated with these fractures (5). This has potential to reduce the need for prolonged hospital stay, extensive social services input and prolonged rehabilitation. As such the benefits could potentially be far reaching in terms of individual and economical gains.

Measures taken by us, such as our emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. We will adhere to the Research Governance Framework/ UK Policy Framework for Health and Social Care Research and MRC Good Clinical Practice Guidance (67, 68) (69). The participant information sheet for the study will be developed with the involvement of service users and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants as described in section 12.2 after they have had sufficient time to read the study materials and ask questions.

The trial will be subject to DMEC and TSC oversight.

11.2 Informing potential trial participants of possible benefits and known risks

Informed consent will be obtained by the trained local research nurse or clinician using a patient information leaflet developed with the help of service users, which explains the risks and benefits clearly. In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the TSC for addition to the patient information leaflet. A revised consent form will also be completed if necessary.

11.3 Adverse event management

Adverse events (AE) are defined as any untoward medical occurrence in a clinical trial participant and do not necessarily have a causal relationship with the treatment. We will only collect adverse event data for the Adverse Event of Special Interest (AESI) (which is lateral cutaneous nerve injury) and any unexpected adverse events that are related to treatment for the original injury. We will collect adverse event data from the point of randomisation to 6 months post randomisation for all patients and up to 12 months post randomisation for patients that agree to this additional timepoint.. All AEs will be listed on the appropriate AE CRF for routine return to York Trials Unit. Data for expected AEs (other than the AESI) will be collected as complications in the investigator CRFs at 2 weeks, 12 weeks and at discharge (if after 2 weeks). Complications (or expected AEs) listed in table 2 are expected as part

of the intervention, they will be reported as complications in the hospital CRFs and do not need to be reported to the main REC. Although lateral cutaneous nerve injury is an expected adverse event, it is considered an adverse event of special interest (AESI) therefore an AE CRF will be completed.

Serious adverse events are defined as any untoward and unexpected medical occurrence that:

1) Results in death;

2) Is life-threatening (that is places the participant, in the view of the Investigator, at immediate risk of death);

3) Requires unplanned hospitalisation or prolongation of existing hospitalisation (unplanned refers to emergency hospitalisations resulting in an inpatient stay. Prolonged hospitalisation is deemed to be where a patient's stay is longer than expected. For the purposes of this trial prolonged hospitalisation will be defined as a stay in hospital beyond 30 days post operation);

4) Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);

5) Results in a congenital anomaly or birth defect;

6) Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed. A list of expected adverse events is given in Table 2.

Important medical events that may not be immediately life-threatening, result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition of an SAE will also be considered serious.

In the context of this trial, SAEs will only be reported if they appear to be related to an aspect of taking part in the study and within 6 months of randomisation for all patients and up to 12 months post randomisation for patients that agree to this additional timepoint..

All Serious Adverse Events (SAE) will be entered onto the SAE reporting form and forwarded to York Trials Unit within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings. Follow up reports a month later may be requested by the CI for their review to ensure that adequate action has been taken and progress made. All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

Complications
Injury to blood vessels or nerves
Wound complications (including infection)
Thromboembolic events
Delayed union/ Non-union
Peri-prosthetic fracture; or for symptoms related to the metalwork
Further surgery to remove or replace metalwork
Loosening/mechanical failure of prosthesis
Surgical site infection
Haematoma
Neurovascular injury
Delayed wound healing and/or wound dehiscence
Intraoperative fracture
Skin problems such as pressure sores
Adverse events associated with anaesthetic such as DVT, pulmonary embolism, and respiratory tract infection

Table 2: Expected adverse events

12. Research ethics approval

As the study is led from England, approval from a Research Ethics Committee (REC) in England was sought and this study has been reviewed and given favourable opinion by London - Harrow REC (Ref: 19/LO/0555). The Health Research Authority

(HRA) has also given governance approval. A separate application for REC approval in Scotland will be made.

Local R&D will confirm the capacity and capability of centres to participate.

12.1 Protocol amendments

Any amendments to the protocol during the course of the trial will be submitted for approval by the REC and the HRA as necessary. Any amendments that affect patients who lack capacity will also be submitted for approval by the REC in Scotland.

12.2 Consent

Responsibility for recording and dating both oral and written informed consent or agreement will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log.

Given the age of the population it is expected that some potential participants will have a cognitive problem such as dementia which may affect their ability to process information and make informed decisions about both their care and involvement in the trial. There may also be a range of other factors which temporarily prevent patients from being able to give informed consent through delirium. In our consultation with patients about the study, the view was that individuals with cognitive impairment should be included as it would be discriminatory to exclude them, and that consultee declaration or consent should be sought on their behalf if they lacked capacity. This would be in the form of a nominated or personal consultee declaration in England, Wales and Northern Ireland and consent from a relative, guardian or welfare attorney in Scotland. In clinical practice, it is also routine to treat patients with cognitive impairment surgically.

Each centre routinely looks after patients who lack mental capacity and are experienced in assessing such patients, and delivering information that is appropriate to their level of understanding. The clinical team will make an assessment of the patient's capacity according to their usual procedures for securing consent for surgery and advise the research team whether the individual has the capacity to consent and consult with their local orthogeriatrician as required.

The process for seeking consultee declaration for patients lacking capacity in England and Wales will be approved by the Research Ethics Committee in England and will be in accordance with the Mental Capacity Act 2005. The process for seeking consultee declaration for patients lacking capacity in Northern Ireland will be approved by the Research Ethics Committee in Northern Ireland and will be in accordance with the Mental Capacity Act (NI) 2016. The process for seeking consent for patients who lack capacity in Scotland will be in accordance with the Adults with Incapacity Act (Scotland) 2000 and approved by the Research Ethics Committee in Scotland. The Mental Capacity Act 2005, the Mental Capacity Act (NI) 2016 and the Adults with Incapacity Act (Scotland) 2000 establish a framework for the protection of the rights of people who lack the capacity to make a decision themselves. They are designed to ensure that the interests and rights of people who lack capacity are protected and that their current and previously expressed wishes are respected.

Before a person with diminished capacity in England, Wales or Northern Ireland is recruited into the trial, the research team must take reasonable steps to identify a suitable person who can act as a consultee and advise the researcher on whether the person who lacks capacity would want to be involved in the project. For potentially eligible patients that lack mental capacity, a personal consultee should be identified and approached. If this is not possible, then a nominated consultee should be identified who is not connected with the trial.

Personal Consultee: Someone who knows the person lacking capacity and is able to give advice about the person's wishes and feelings in relation to the study. This could be a family member, friend or carer, but should not be someone who is acting in a professional or paid capacity. Should a potential consultee feel unable to take on this role, they may suggest someone else to take on this role, or ask that a nominated consultee is approached.

Nominated Consultee: A nominated consultee should be approached in a situation where either no personal consultee is available, the personal consulteeis unwilling to undertake this role, or a nominated consultee is requested. The nominated consultee must have no connection with the study. The nominated consultee must be a health care professional who will consider how the wishes and interests of the patient would incline them to decide if they had capacity to make the decision.

The personal or nominated consultee will be informed about the trial by the responsible clinician or a member of the research team and they will be provided with a Consultee Information Sheet along with the Patient Information Sheet and given the opportunity to ask questions and discuss the study. They will be asked to advise on whether the patient would be agreeable to taking part in such research or if they would have objections. If the personal or nominated consultee decides that the patient would have no objection to participating in the research; a Consultee Declaration Form will be completed.

In Scotland, before a person with diminished capacity is recruited into the trial, the research team must take reasonable steps to identify a suitable person who can give consent on the patient's behalf. This could be the nearest relative or Guardian or a Welfare Attorney. This person will be informed about the trial by the responsible clinician or a member of the research team and they will be provided with a Guardian, Welfare Attorney or Nearest Relative Information Sheet along with the Patient Information Sheet and given the opportunity to ask questions and discuss the study. They will be asked to advise on whether the patient would be agreeable to taking part in such research or if they would have objections. If the Guardian, Welfare Attorney or nearest relative decides that the patient would have no objection to participating in the research; a Guardian, Welfare Attorney or nearest relative Consent Form will be completed.

Capacity will be formally reassessed at the 2 week (if still in hospital), and 12 week time points. If the patient initially gave consent but has since lost the capacity to provide informed consent, a Personal or Nominated Consultee should be sought if in England, Wales or Northern Ireland and a Guardian, Welfare Attorney or Nearest Relative should be sought if in Scotland (as outlined above). If a participant regains capacity, their informed consent should be sought for continued involvement in the trial. As capacity will not be formally assessed at 6 weeks, 6 months, and 12 months (when postal questionnaires are used) capacity status will be assumed to be the same as the most recent formal assessment.

We anticipate that there will be four groups of people, in terms of their ability to provide consent: 1) those who have capacity to provide consent throughout the trial; 2) those who have capacity to give consent initially but loose it during the course of the trial; 3) those who do not have capacity at the start of the trial but regain it during the trial; 4) those who are unable to provide consent and do not regain capacity to do so within the trial.

12.2.1 Patients who have capacity to consent throughout the trial

Research Nurses or the attending clinician will invite the patient to consider joining the study. They will be provided with a participant information sheet and have the opportunity to ask questions of the surgeon and the local research team. They will also have the opportunity to discuss the study with their friends or family before reaching a decision.

12.2.2 Patients who have capacity to consent but lose it during the course of the trial

In England, Wales or Northern Ireland, if a participant loses capacity or experiences diminishing or fluctuating capacity before the study ends then the research team should consult either a personal or nominated consultee as appropriate. Their role will be to advise on the whether the participant would want to continue participating in the study and to complete a Consultee Declaration Form.

In Scotland if a participant loses capacity or experiences diminishing or fluctuating capacity before the study ends then the research team should consult either a nearest relative, a guardian or a welfare attorney as appropriate to give consent for the participant to continue in the trial.

12.2.3 Participants who do not have capacity when enrolled to the trial but regain it during follow up

If a participant with temporary loss of capacity (e.g. delirium) regains capacity during the course of the trial, a member of the research team will fully inform them about the trial. They will be asked for their consent to continue in the study and sign a Participant Consent to Continue in Trial Form. Participants may decline to continue their participation without prejudice.

12.2.4 Patients without capacity to consent throughout the duration of the trial

For patients that lack mental capacity, the procedure outlined above should be followed. In England, Wales and Northern Ireland, a personal or nominated consultee should be identified and approached to give consultee declaration. In Scotland, a nearest relative or guardian or a welfare attorney should be identified and approached to give consent on the patients' behalf.

12.2.5 Documenting consent

The original signed consent form or declaration form will be kept in the investigator site file. Three additional copies of the consent or declaration forms will be made; one held in the patient's medical notes, one for the patient, and one copy to be returned to YTU. Throughout the whole study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion.

12.2.6 Withdrawal of Consent or consultee declaration

A trial participant can entirely withdraw from the study at any time for any reason but any data collected up to that point will be included in the analysis. The participant can also agree to being withdrawn from only postal questionnaire collection and/or only hospital CRF collection.

12.3 Patient confidentiality

The researchers and clinical care teams must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a Participant ID number and this will be used on CRFs; patients will not be identified by their name in order to maintain confidentiality.

All records will be kept in locked locations. All consent and consultee declaration forms will be secured safely in a separate compartment of a locked cabinet. Clinical information will only be looked at by responsible individuals from the study team, the Sponsor, the NHS Trust, or from regulatory authorities; where it is relevant to the patient taking part in this research as he/she would have agreed to at the time of consent or consultee declaration.

12.4 Proposed action to comply with the medicines for human use (clinical trials) regulations 2004

The devices used in this study are CE marked medical devices which are widely used for spinal surgery. In L1FE these devices will be used to stabilise LC-1 pelvic fractures which although technically considered off label, is now a well described technique in pelvic fracture surgery, with a number of peer-reviewed series confirming safety and efficacy of the technique (23). It is therefore a widely-practiced, rather than 'novel' technique and is technically straightforward to carry out. The procedure is not being evaluated for commercial purposes and the study would not be subsidised by a manufacturer. We do not therefore require prior authorisation by the UK Competent Authority, the MHRA, under the Medical Devices Regulations (2002). This has been confirmed by the trial sponsor.

13. Plan of investigation and timetable

The L1FE study is proposed to run from 1st October 2018 to 30th Sept 2022. The internal pilot will take place from months 7 to 18. The summarised project plan is provided below.

Oct18 to Mar19	Apr19 to Sep19	Oct19 to Mar20	Apr20 to Sep20	Oct20 to Mar21	Apr21 to Sep21	Oct21 to Mar22	Apr22 to Sep22	Oct22 to Mar23
Set-up								
	Internal pilot							
	Recruitment							
		6 month follow-up						
								Write up

14. Declaration of interests

- Mr Peter Bates: No conflict of interest declared
- Dr Dhanupriya Sivapathasuntharam: No conflict of interest declared

- Prof David Torgerson: No conflict of interest declared
- Dr Catriona McDaid: Is a member of the NIHR HTA and EME Editorial boards
- Prof Catherine Hewitt: Is a member of the NIHR HTA commissioning board
- Mr Mehoolo (Mez) Acharya: No conflict of interest declared
- Mr Daren Forward: No conflict of interest declared
- Mr Peter Hull: No conflict of interest declared
- Ms Jamila Kassam: No conflict of interest declared
- Ms Belen Corbacho: No conflict of interest declared
- Ms Coleen Colechin: No conflict of interest declared
- Mr Joshua Lee: No conflict of interest declared
- Mrs Liz Cook: No conflict of interest declared
- Dr Joanne Laycock: No conflict of interest declared
- Ms Camila Maturana: No conflict of interest declared
- Ms Jenny Roche: No conflict of interest declared

15. Access to data

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the consent and consultee declaration forms with explicit explanation as part of the consent/consultee process and Participant Information Sheet. Once YTU has completed the analysis and published all intended papers in scientific journals, the data will be made available for other researchers.

In principle, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and study Sponsor.

The Investigator(s)/Institutions will permit monitoring, audits, and REC review (as applicable) and provide direct access to source data and documents.

16. Indemnity

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

This study will be sponsored by Barts Health NHS Trust. If there is negligent harm during the trial, when the NHS Trust owes a duty of care to the person harmed, NHS Indemnity covers NHS staff and medical academic staff with honorary contracts only when the trial has been approved by the R&D department. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

17. Finance

The financial arrangements for the study will be as contractually agreed between the funder (HTA), the University of York and the Sponsor (Barts Health NHS Trust).

18. Dissemination and projected outputs

Through the planned outputs, the study is expected to play a key role in enhancing the evidence base on the effectiveness and cost-effectiveness of surgical fixation for the management of pelvic fractures. The economic component will help us to identify the most efficient provision of future care and thus savings to the NHS and society.

The executive summary and copy of the trial report will be sent to NICE and other relevant bodies, including Clinical Commissioning Groups, so that study findings can inform their deliberations and be translated into clinical practice nationally. We will work with the relevant Specialty Advisory Committees (SAC) to incorporate the findings into the training curriculum for clinicians who will undertake treatment for pelvic fractures. We will use a number of dissemination channels to ensure that patients and the public are also informed about the results of the study. We will produce the following outputs:

- The study protocol will be published in a peer-reviewed, open access journal.
- A HTA research monograph will be produced.
- In conjunction with patient members of the team, we will generate patient information for “Shared Decision Making” based on findings from this trial and

update the entry on Wikipedia (70) and write the Map of Medicine (71) entry on pelvic fractures.

- The results of the study will be presented at national and international surgical meetings such as the British Orthopaedic Association Annual Congress, the UK Orthopaedic Trauma Society meeting, the North American Orthopaedic Trauma Association the European Federation of National Associations of Orthopaedics and Traumatology (EFFORT), Société Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT), and the American Academy of Orthopaedic Surgeons.
- The findings will be published in peer reviewed high impact general medical and orthopaedic journals such as Lancet, the BMJ or similar.
- A summary of the study report, written in lay language will be produced and made available to participants, members of our user group and relevant patient-focused websites.
- We will seek to raise the profile of the trial via social media including a dedicated Twitter account. This will be aimed at participating site staff and focus on trial progress, trial related events, and publicising research outputs.
- If found to be effective, the Major Trauma Centre pelvic specialist surgeon co-applicants will explore ways of cascading training in the technique to orthopaedic surgeons in NHS hospital Trauma Units to ensure consistency of best practice across the NHS.

A full dissemination strategy will be produced for the trial.

19. Trial management

The Trial Co-ordinators will be based at YTU and will co-ordinate recruitment across the UK, supported by a senior Trial Manager.

19.1 Expertise of trial team

The multidisciplinary team includes expertise in the management of pelvic fractures in both techniques being tested; experience of receiving treatment for a pelvic fracture; physiotherapy; and design, delivery and statistical analysis of randomised controlled trials.

20. Public Involvement

PPI input has played a large part in shaping this study and will continue to be at the heart of the trial going forward. We have established a PPI group of people who have had an LC-1 fracture and continue to recruit new members to this group. We will consult with this PPI group regularly and PPI members will be invited to sit on the TMG. The PPI groupwill include representation from the Age UK hub within Barts to provide a level of continuity should PPI members decide they no longer want or are able to attend meetings.

21. Funding acknowledgement

This research is funded by the NIHR Health Technology Assessment Programme (project number HTA - 16/167/57).

22. Department of Health disclaimer

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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This protocol is based on JRMO Protocol template for Interventional Studies; version 1.0, February 2018.

Appendix 1 SWAT Protocol

Do courtesy telephone calls or postcards to trial participants following enrolment increase future retention rates? Study Within A Trial (SWAT) protocol

Name and title of SWAT lead applicant

Mrs Elizabeth Cook (EC)

Names and titles of SWAT Co-applicants

Dr Michael Backhouse (MB), Dr Catriona McDaid (CM), Mrs Saleema Rex (SR), Dr Adwoa Parker (AP)

Applicant affiliations

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SWAT Registration

This SWAT will be registered on the MRC SWAT Repository.

Host trial Registration

ISRCTN 16478561; IRAS ID: 255609, 263397

Background: the courtesy telephone call intervention

Randomised controlled trials (RCTs) are the bedrock of testing the effectiveness of healthcare treatments. Achieving high retention of participants in RCTs can be difficult. Trial teams often experience difficulties with maintaining follow-up and questionnaire response rates from participants, which can introduce bias, reduce the sample size and statistical power and affect the validity, reliability and generalisability of findings (52-56).

There is therefore a need to develop and test interventions to improve retention of participants. One method is to 'embed' trials of retention interventions in ongoing randomised trials. Testing interventions in ongoing trials ensures causality of intervention effectiveness is assessed [4] and avoids limitations associated with testing in a quasi-randomised controlled trial, or non-randomised setting such as the feasibility of intervention implementation.

In the UK as of 2017, 89 percent of households owned a landline telephone (72), whilst 95 percent of households owned a mobile telephone (73). With wide prevalence of telephone use, courtesy telephone calls are routinely used in commercial and service settings to engage customers and are perceived to be 'good customer service'. Courtesy calls are perceived to be a good method by which to remind customers of upcoming appointments or to check on the arrival of products.

In clinical research settings there is evidence that telephone calls offer an effective method of data collection (74). Advantages of speaking with research participants on the telephone include developing positive relationships between research teams and participants (74). Some trial teams also routinely telephone newly recruited participants as a courtesy or introduction to thank them for participating in the trial, and to remind them that they will be followed up at pre-specified times. It is unclear however what impact these courtesy telephone calls make, whether they are cost effective and how they compare with a written thank you card with a reminder about subsequent follow-ups.

Objective of this SWAT

The objective of this SWAT is to evaluate the impact of making a courtesy introductory telephone call to newly recruited trial participants on response rates to follow-up questionnaires compared with a written card with equivalent information, or nothing.

Background: the host trial

The SWAT will be hosted in the 'Lateral compression Type-1 fracture fixation in the elderly, a randomised controlled trial' (L1FE). L1FE aims to investigate the clinical and cost effectiveness of surgical fixation (with an anterior internal surgical fixation device such as INFIX) compared with non-surgical management of LC-1 fragility

fractures in older adults. L1FE is a multi-centre, randomised controlled superiority trial, with an internal pilot phase to assess the assumptions about recruitment and provide guidance on optimising the trial processes. The trial will be undertaken in NHS hospitals with orthopaedic surgeons specialising in pelvic injuries. Participants will be adult patients (60 years or older) with LC-1 fractures who meet the eligibility criteria specified by the L1FE trial protocol. Approximately 600 eligible and consenting patients will be randomly allocated to either surgical fixation or non-operative management. The primary outcome measure is average patient quality of life, over the study time period, assessed by the patient-reported outcome measure, EuroQol 5 Dimensions (5L) utility score (EQ-5D-5L). Follow up will be at 2 weeks, 6 weeks, 12 weeks, and 6 months post randomisation. Follow-up data will be collected at recruiting sites or by post from patients, then returned to the coordinating centre at York Trials Unit for scanning and processing. The L1FE trial will use the following methods to minimise attrition for all participants: pre-notification letters sent in advance of the postal questionnaires, text message reminders, postal and telephone reminders. This is described in section 9.8 of the L1FE Trial Protocol.

Methods

Interventions and comparators

Participants will be randomised in a 1:1:1 ratio to receive one of the following:

A courtesy introductory telephone call will be made, where possible within one month of being enrolled into L1FE, if unable to contact (for example patient is still in hospital) further attempts will be made in due course. This telephone call will include the following content: 1) Participants will be thanked for taking part in the L1FE trial; 2) Participants will be reminded how valuable their contribution to the L1FE trial is; 3) Participants will be reminded that they will be asked to complete postal questionnaires at 6 weeks, and 6 months following enrolment, completion of these is important to help answer the trial question, even if they are feeling better. They will also be asked to attend a clinic visit at 12 weeks where they will be asked to complete another questionnaire; 4) Participants will be informed when the trial results are expected; 5) participants are asked to contact the L1FE team if they have any queries or asked if they would like L1FE team to contact them?.

A postcard-sized written card, with the similar content as above, signed by the Chief Investigator and Trial manager posted in an envelope to participants' homes, where possible this will be within one month of being randomised.

Participants will receive neither of the above.

Eligibility criteria for the SWAT

The L1FE trial includes patients with capacity as well as those who lack capacity, a lack of capacity in this cohort may be temporary therefore will be reassessed throughout the trial. Participants who lack capacity at the 2 week time point will be excluded from the SWAT. All participants recruited into the L1FE trial who have capacity at the 2 week time point and consent to being contacted by telephone will be eligible for the SWAT. There are no additional inclusion or exclusion criteria.

Method for allocating to intervention or comparator

We will use block randomisation stratified by the host trial's treatment arm to avoid imbalance between the SWAT intervention arms. The allocation ratio will be 1:1:1. A researcher (e.g. trial statistician) not involved with making the telephone calls or the mail out of the postcards will undertake generation of the allocation sequence independently.

Outcome measures

The primary outcome is the questionnaire response rate, defined as the proportions of participants in each intervention group who complete and return the questionnaire at the, 6 weeks, 12 weeks, and 6 month-time points. **Secondary outcomes:**

Time to response (length of time taken to return the questionnaires)

Completeness of response (average percentage of questions completed for all applicable questionnaires) at the 6 month timepoint

Whether a reminder notice is required (number of participants requiring a reminder mailing divided by the number of participants who were sent a questionnaire) at the 6 month timepoint.

Cost of SWAT intervention per participant retained.

Sample size calculations

As is common with SWATs, the sample size is limited by the host trial sample size. L1FE aims to recruit 600 participants. Assuming that 70% of these participants will consent to receive telephone calls[1], we expect an analysable sample size of approximately 420 participants for the SWAT (140 per group). Analysed independently, this sample would give 80% power to detect differences in retention rates of approximately 11.65% or more (increase from 80% to 91.65%).

Analysis plans

All eligible participants will be included in the analysis on an intention-to-treat basis, using two-sided statistical significance at the 5% level. All statistical analyses will be conducted using Stata (StataCorp). We will summarise baseline characteristics of participants by SWAT blinded intervention allocation (e.g. using codes like A, B & C for intervention groups).

Primary Outcome

For the primary outcomes of questionnaire response rates, a logistic regression will be performed and the effect of the SWAT intervention reported as adjusted Odds Ratio (OR) with its associated 95% Confidence Interval (CI) and p-values.

For secondary outcomes:

The secondary outcome of 'time to 6 month questionnaire return' will be assessed by a Kaplan Meier curve. Cox regression will be applied and the effect of the interventions reported. Completeness of response will be analysed using linear regression and reported. The requirement for any questionnaire return reminder will be analysed and reported using logistic regression.

A Statistical analysis plan (SAP) detailing these analyses will be finalised prior to the end of data collection. Analyses will be undertaken by a statistician blind to this SWAT group allocation.Project timetable

[1] 70% consent rate assumption is based on experience from a previous trial 'KrebS' in which 70% of the participants provided mobile numbers to receive SMS messages

Date	Action
December 2018	Peer review of SWAT protocol
December 2018	Documentation for the SWAT agreed & signed off
December 2018	Submission to REC of application
April 2019	Recruitment to the SWAT begins
March 2022	Recruitment to the SWAT ends
October 2022	Data cleaning and submission of data set to PROMETHEUS team
January 2023	Collation of results and analysis, begin write up of trial level paper

Level of funding required

We estimate the proposed SWAT will cost £4500. This includes cost of printing and sending postcards, data management time to make phone calls and conference attendance.

Expertise of team

EC is a Trial Manager, with extensive experience in delivery of orthopaedic surgical trials and SWATs. MB has over a decade of experience in applied health research; this includes an interest in recruitment and retention trials, having published two SWATs previously. SR is an experienced statistician. CM is a Reader in Trials with extensive experience in trial design and evaluation.

They are supported by an experienced team of Data Management and administrative staff that are experienced in the practical implementation of SWATs.

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