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The ASSERT (Acute Sacral insufficiency fracture augmentation) Randomised Controlled, Feasibility in Older People Trial: study protocol.

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Manuscripts

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3 **The ASSERT (Acute Sacral insufficiency fracture augmentation) Randomised**
4 **Controlled, Feasibility in Older People Trial: study protocol**
5

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ABSTRACT

Introduction Pelvic fragility fractures (PFF) are common in older people and are associated with a significant burden of mortality and morbidity. This is related to the challenges of appropriate pain control and early mobilisation. The current standard for treatment of PFF is non-surgical management. Minimally invasive surgical techniques for sacral fracture stabilisation have been shown to improve outcomes in terms of pain control and mobility, and are safe. Randomised controlled trials are required before recommendations can be made for surgical management of PFF to become the new standard of care. Several uncertainties around conducting such a trial will be explored in this feasibility study.

Methods and analysis The ASSERT study is a single-site randomised controlled, parallel-arm, feasibility trial of surgical stabilisation versus non-surgical management of acute sacral fragility fractures in people aged 70 years and over. Patients will be randomised to either surgical or non-surgical group on a 1:1 ratio. Follow-up of participants will occur at 2, 4 and 12 weeks with safety data collected at 52 weeks. Primary objectives are to determine feasibility and design of a future trial, including outcomes on recruitment, adherence to randomisation and safety. This will be supplemented with an embedded qualitative interview study of participants and clinicians. Secondary objectives will inform study design procedures to determine clinical and economic outcomes between groups, including scored questionnaires, analgesia requirements, resource use and quality of life data. Data analysis will be largely descriptive to inform outcomes and inform future sample size.

Ethics and dissemination Ethical approval was granted by the North East Newcastle and North Tyneside 2 Research Ethics Committee (reference 18/NE/0212) and it was approved and sponsored by Nottingham University Hospitals NHS Trust (reference 18HC001) and the Health Research Authority (reference IRAS 232791). Recruitment is currently ongoing.

Trial registration number ISRCTN16719542

ARTICLE SUMMARY (Strengths and limitations of this study)

- Descriptive analysis on effectiveness of outcomes will inform hypothesis testing in a future definitive trial, including levels of variability in order to power the trial appropriately.
- Nested semi-structured interview study will provide valuable qualitative data to inform future definitive trial acceptability and processes.
- Determines the feasibility of economic measures including detailed resource use collection and quality of life data within the two arms, to aid the design of more comprehensive economic evaluation in a future definitive trial.
- The intervention is a proven safe surgical intervention, already used in existing healthcare practice, but further safety data in this cohort of patients will also be collected.
- A pragmatic trial set in an existing healthcare setting that may lead to a number of limitations on trial processes, including recruitment, adherence to randomisation and ease of data collection.

INTRODUCTION

Pelvic fragility fractures (PFF) are common in older people, as they are a frequent presentation of osteoporosis, a condition characterised by low bone mass and structural deterioration of bone tissue, leading to bone fragility.[1] Thus, PFF can occur as a result of low-energy trauma, typically following a fall from standing height or less.[2] The reported overall incidence of PFF is variable, between 25 to 92 per 100'000 persons-years, with the highest frequency reported in females over the age of 75 years.[3-8] Epidemiology studies worldwide have consistently shown a sustained increase in the age-adjusted incidence of PFF, with numbers expected to continue to rise exponentially over the next 10 years.[3-4,6-7,9-11] These patients are also increasingly requiring inpatient admission for management of their PFF, representing a considerable on-going burden to hospital services.[3-4,6,12]

The pelvis is a complex ring like structure composed of three principal bones; the paired innominate bones and the sacrum. Fractures of the pelvis are a heterogenous group of fractures and are most commonly described by the Young-Burgess classification, which relates to the predominant direction of the vector force at the time of injury.[13-14] Within this, Lateral Compression (LC) fractures are the most common and are further subtyped based on the resulting degree of displacement of the pelvic ring:[13]

- Type I Oblique or transverse ramus fracture and ipsilateral sacral compression fracture
- Type II Rami fracture and ipsilateral posterior ilium fracture dislocation (crescent fracture)
- Type III Ipsilateral lateral compression and contralateral anterior-posterior compression (windswept pelvis)

The most commonly identified PFF presenting to hospital is that of the anterior ring in the form of fractures of the pubic rami.[12,15-16] Sixty to ninety percent of these patients will also have a concomitant posterior ring fracture in the form of an insufficiency fracture of the sacrum.[2,17-19] Type 1 LC is therefore the most common subtype of PFF.[17,20] Whilst anterior pelvic ring fractures can be identified on plain x-ray, those fractures of the posterior pelvic ring are most typically identified on computerised tomography (CT) or magnetic resonance imaging (MRI), which now has a much wider availability on emergency admission to hospital.[17,19,21] From a bio-mechanical point of view, an undisplaced anterior pelvic ring is more stable than a posterior pelvic ring fracture, with the posterior ring providing the majority of structure and stabilisation of the pelvis on load-bearing.[2]

PFF, especially those involving the sacrum within the load-bearing posterior pelvic ring, result in pain related immobilisation and increased care dependency.[21-23] PFF have been shown to confer poor outcomes like those reported extensively in hip fractures but covets much less attention.[24] Inpatient 30-day mortality sits at up to 11%, with a 12-month mortality up to 27%. [5,9,12,15-17,20,24-26] This may be related to the demographics of patients admitted to hospital with PFF. This patient group commonly have significant co-morbidities and over third exhibit cognitive impairment, leaving them more susceptible to the medical complications of pain-dependant immobility and associated prolonged hospital stay.[5,17,25] Inpatient mortality is often attributed to exacerbation of pre-existing co-morbidity.[12] Around half of the patients admitted with PFF develop hospital and immobility related complications including pressure sores, infection, renal injury, venous thromboembolism and delirium.[9,16-17,25-28] The majority are unable to return home at their baseline level of mobility or independence upon discharge.[5,25,27] In excess of this, those with confirmed combined anterior and posterior ring insufficiency fractures have hospital stays 2 weeks longer than those with isolated anterior ring fractures, higher

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3 complication rates, 30% more chance of losing previous independence and higher rates of
4 institutionalisation.[17,20,22,29]
5

6 Current standard care for PFF is conservative, consisting of systemic analgesia and
7 mobilisation as tolerated.[30] As a response to the high level of associated morbidity,
8 management of PFF needs to be targeted at good early pain control in order to allow early
9 mobilisation, return of independence and discharge.[22,31] Currently standard pain
10 management consists of the use of systemic analgesia, especially opioids, but pain control
11 adequate to allow early mobilisation is difficult to achieve in this cohort.[23] Barriers to
12 adequate pain management in PFF can include under-reporting of symptoms due to
13 cognitive impairment, susceptibility to side-effects of opioids in the elderly and
14 undertreatment due to perceived prescriber fear of opioid side-effects.[32]
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17 Development of minimally invasive surgical techniques targeting fractures of posterior ring-
18 sacral fractures may provide an alternative to improve adequate pain control in this
19 significant subset of PFF.[21] Minimally invasive keyhole surgery techniques involving
20 percutaneous cement augmentation with or without trans-sacral screw are increasingly being
21 performed in order to stabilise sacral fractures.[21-22,31] For those patients who have failed
22 to progress with conservative management, these procedures have been shown to reduce
23 pain and the amount of analgesia required post-operatively.[30,33-34] This in turns allows
24 increased patient mobility with a quicker return to baseline function and shorted length of
25 stay, as well as having an established safety profile.[9,22,30,33-39] However, there are no
26 randomised controlled trials that compare efficacy of sacral fracture surgery compared with
27 conservative management in the early stages of recovery.[21,22,33]
28
29

30 **METHODS and ANALYSIS**

31 **Aims**

32 The aim of this study is to determine the feasibility and design of a future randomised
33 controlled clinical trial to evaluate the clinical and cost effectiveness of keyhole spinal sacral
34 fixation (cement augmentation +/- screw fixation) compared to current standard practice of
35 non-surgical management in older people presenting in the early stages to hospital with a
36 Type 1 Lateral Compression (LC) pelvic fragility fracture (PFF).
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40 **Objectives**

41 The feasibility and final design of a definitive trial will be determined by fulfilment of the
42 objectives outlined below. These are to:
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44

- 45 • Determine the number of patients who meet the eligibility criteria in addition to
46 recruitment (including willingness to be randomised) and retention rates of eligible
47 patients.
- 48 • Explore the adherence of clinicians to the randomisation of patients within the trial.
- 49 • To collect outcome measure data for the assessment of mobility, pain and quality of
50 life (face to face and self-reported measures), for potential use in a future definitive
51 trial; estimate the mean and standard deviation (SD) of these quantitative measures
52 for hypotheses testing purposes.
- 53 • Evaluate ease of access and availability of information from current primary and
54 secondary care databases, to determine the most efficient way of measuring
55 associated patient level resource use.
- 56 • Use a qualitative nested interview study to assess participants' and clinicians' views
57 on trial acceptability and processes to inform the design and conduct of a future
58 definitive trial.
59
60

- Evaluate long term safety of the intervention.

Study Design

The primary study design is a parallel, two-arm randomised controlled feasibility trial with participants allocated to either surgical or non-surgical intervention on a 1:1 ratio. A preliminary economic evaluation and a qualitative nested interview study will also be embedded within the feasibility study.

Participants will be recruited from a single site, Queens Medical Centre, Nottingham University Hospitals NHS Trust (NUH); a university teaching hospital serving a population of 700,000 and offering a tertiary spinal surgical unit.

Participants

Participants presenting to NUH with a Type 1 LC PFF who fulfil the eligibility criteria, outlined below, will be approached for possible recruitment into the study. A fragility fracture is defined as a fracture sustained after low level trauma, usually a fall from standing height or less.

Inclusion criteria

- Aged 70 years and over
- Ambulatory with/without walking aids prior to injury
- Injury sustained within 28 days of presenting to hospital

Exclusion criteria

- Complex pelvic fractures (e.g. fractures involving/or close to the hip joint) requiring urgent surgery or progressive weight bearing exercises
- Pathological fracture in the context of known or unknown malignancy
- Previous surgery of the pelvis with metal obstructing the planned paths of the ilio-sacral screws
- Condition that precludes surgery or general/spinal anaesthesia
- Bedbound prior injury
- Receiving palliative care
- Moribund on admission

Recruitment

All patients admitted with a Type 1 LC PFF as identified on imaging (CT or MRI), will be invited to participate. The research team will be notified of the potential participant and will confirm eligibility with their clinical care team. The process for obtaining participant informed consent will be in accordance with Good Clinical Practice guidance and will include consent for potential inclusion in the qualitative interview nested study.

An Abbreviated Mental Test (AMT) will be used as a screening tool for capacity assessment. If the admission AMT completed by the clinical team is documented as 5-6/10 then it will be repeated by the research team at the time of screening. A participant will be assumed to have capacity if their AMT $\geq 7/10$ at either point of assessment. An AMT $< 7/10$ will prompt a

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3 capacity assessment based on the principles of the Mental Capacity Act 2005 in relation to
4 research.
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6 Relatives or carers of potential participants who are unable to provide consent
7 independently, will be approached as the participants' personal consultee. If there is more
8 than one relative or carer willing to act as the patient's consultee, then they must all agree on
9 the decision for the participant to be included in the study.
10

11 For patients or consultees who decline to take part, they will be asked if they would be willing
12 to share their reasons this. It will be made clear this is in order to help us improve the design
13 and acceptability of the study and there is no obligation to do this. The findings will be
14 tabulated into the final results.
15
16

17 **Randomisation**

18
19 Consented participants will be randomly allocated to either surgical intervention or
20 conservative non-surgical care on the day they consent via a secure web-based system
21 (Sealed Envelope Ltd) by a member of the research team, ensuring allocation concealment.
22 In order to minimise bias, participant baseline enrolment data will be entered into the
23 randomisation system to be stratified prior to intervention allocation. Randomisation to the
24 intervention groups will be on a 1:1 basis.
25
26

27 **Interventions**

28
29 *Intervention group* will receive surgical intervention by key-hole spinal sacral fixation as
30 determined by the treating spinal surgeon based on the participant's general condition,
31 morphology of the fracture and surgeon's experience. The surgery will be completed within 7
32 days of randomisation. Cement augmentation of the sacral ala will be undertaken in
33 participants with unilateral or bilateral sacral fractures with minimal cortical comminution.
34 Additional sacroiliac screw fixation will be offered to participants with extensive fracture
35 patterns which affect both sacral ala with significant cortical comminution. Usual post-
36 operative care, monitoring and rehabilitation will follow.
37

38
39 *Control group* will receive usual hospital care. Participants will be treated with appropriate
40 analgesia and have regular input from the ward therapy team. Participants may be referred
41 for surgical intervention if it is indicated by their clinical team. This will be recorded, and data
42 collected and followed up with intention to treat.
43

44 **Outcomes**

45
46 The study procedures undertaken are directly related to the outcomes used in order to
47 address the objectives of this feasibility study.
48

49 *Feasibility study outcomes*

50 Primary outcomes:

- 51 • Number of eligible patients;
- 52 • Number of patients willing to be randomised and adherence to randomisation;
- 53 • Number of clinicians willing to randomise and adherence to randomisation.
- 54
- 55

56 Secondary outcomes:

- 57 • Rate of participant recruitment and retention;
- 58
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- Data on the completeness and variability of proposed definitive trial outcome measures;
- Failure of non-surgical conservative care and adverse events in both arms.

Outcomes measures for the subsequent definitive trial

Primary outcome measures:

- Timed Up and Go test (TUG)[40] as a measure of mobility requiring both static and dynamic balance;
- Roland Morris Disability Questionnaire (RMDQ)[41] as a self-rated measure of physical disability caused by low back pain.

Secondary outcome measures:

- Abbreviated Mental Test (AMT) as an assessment of cognition[42];
- Montreal Cognitive Assessment (MoCA)[43] as an assessment of cognition;
- Functional Independence Measure (FIM)[44] as a measure of disability severity;
- Clinical Frailty Scale (CFS)[45] as an assessment of frailty;
- Charlson Co-morbidity Index[46] as a prediction of one-year mortality based on co-morbid conditions;
- Numeric 0-10 Pain Rating Scale[47] as a measure of average pain on mobilising;
- EuroQol 5 Dimensions (EQ-5D-3L) Score[48] as an assessment of quality of life;
- Barthel Activities of Daily Living (ADL) Index[49] as an assessment of care dependency;
- Fracture details/classification;
- Analgesia requirements;
- Surgery details;
- Health and Social Care resource use;
- Adverse events and readmissions (as part of the long-term safety review).

Analgesia requirement

Analgesia requirement will be recorded as follows: each medication will be classified as a strong opioid (including oxycodone, morphine, fentanyl, pethidine, hydromorphone, buprenorphine and tramadol), mild opioid (including medications containing codeine or dextropropoxyphene) or non-opioid medications (including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)). The participant will be given a score of 0, 1 or 2 in each of these three categories depending on the number of concurrent different medications being taken within each category. Opioid medication will also include a calculation of the oral Morphine Equivalent Daily Dose using the Opioid Dose Equivalence score.[50]

Study Procedures

Participant flow through the trial is summarised in Figure 1. Face to face contact with participants and/or carer will be required at baseline (considered Day 0), week 2 and a limited number of participants at week 12. Telephone interviews will be conducted with participants at week 4 and for the majority of participants at week 12. Week 12 marks end of trial for the participant, with further contact made at week 52 as part of the long-term safety analysis.

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5 Figure 2 shows the schedule of data collection, outlining which study procedures will be
6 undertaken at what time point in the study period, measured from the point of randomisation.
7 In addition, follow-up data at each time point will include participant still living, hospital length
8 of stay, unplanned hospital readmission (within the first 28 days and 91 days post discharge)
9 and all adverse events, including surgical complications. For those participants that lack
10 capacity, only clinically assessed questionnaires will be used. Participant contact will be
11 conducted in the location the participant is residing at the time of the respective follow up.
12

13 **Economic Evaluation**

14
15 Information about a participant's treatment (including recorded resource use of the surgical
16 procedure if applicable), hospital stay, emergency department, out-patient, readmission and
17 primary care attendances (if related to ongoing management of the fracture), and social care
18 needs, will be gathered through discussion with participants, as well as hospital and primary
19 care databases. An assessment of total resource use will be made at baseline, week 12 and
20 week 52 in order to inform an economic analysis between the two treatment groups.
21
22

23 Individual prices of these health resources will be based on information from national tariffs,
24 such as the Unit Costs of Health and Social Care[51] for primary care resources, NHS
25 Reference Costs[52] for secondary care resources and the British National Formulae
26 (BNF)[53] for prescriptions. If the price for a resource cannot be found from the references
27 above, a suitable estimate will be identified from consultation with the hospital finance
28 department. Prices will be estimated at 2018-2018 prices.
29
30

31 **Qualitative Assessment**

32
33 Using maximum variation sampling, up to ten participants will be chosen to undertake a
34 semi-structured face-to-face interview 7-10 days after randomisation. An interview topic
35 guide will explore their views on the trial and recruitment process, the presentation of study
36 information, study documentation and reasons for agreeing to randomisation. A smaller
37 selection of five participants who complete the trial will have another shorter follow-up
38 interview at week 12. The aim will be to further explore their experience of the trial, data
39 collection processes, and overall perception of participating. Further specific consent for this
40 qualitative interview nested study will be taken in addition to that agreed at the point of trial
41 recruitment.
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45 A number of clinicians will also be asked to partake in a semi-structured interview to explore
46 their experiences of the study. These interviews will consider participant recruitment
47 (eligibility and randomisation) as well as the process of integrating the research with the
48 clinical team. All participating clinicians will complete informed consent for interview,
49 recording and transcription.
50
51

52 **Sample Size Calculation**

53
54 This feasibility study will aim to provide estimates of recruitment and retention rates, and the
55 variability of important outcomes, in order to generate appropriate power calculations for the
56 definitive trial. It is estimated that sample sizes between 24 and 50 are required for a
57 feasibility study.[54-57] Therefore, we propose to recruit for a ten-month period, from which
58 we expect to screen approximately 100 patients. Our estimates are based on data from
59 Gateshead Health Foundation Trust, who screened 67 patients with a similar eligibility
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3 criterion over a 12 month period within a smaller acute trust catchment population.[17] We
4 assume in this feasibility study that 20% of patients screened are not eligible and a 60%
5 recruitment rate, so we expect to recruit 48 participants. By recruiting 48 patients the
6 estimated recruitment rate has a standard error (SE) of 5.5% (95% CI 48.4%; 70.8%). Given
7 the short active follow-up period we are allowing for a lower 10% three-month attrition rate.
8 This estimates that 43 participants will complete the study, thus estimating the 90% retention
9 rate with a SE of 4.4% (95% CI 77.3%; 96.5%). Completed follow-up on 43 patients will
10 allow an estimated SE for the TUG of 1.2 seconds assuming the SD is about 8 seconds
11 (95% CI 6.6; 10.2), and an SE of 0.9 for the RMDQ, assuming the SD is about 6 (95% CI
12 4.9; 7.6).
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15 **Data Analysis**

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18 Data analysis will primarily be descriptive to address the aims of the feasibility study. A
19 statistical analysis plan will be agreed prior to database lock and a CONSORT flow diagram
20 produced. Data analysis overall will inform future trial feasibility and the hypothesis analysis
21 plan for a definitive trial.
22

23
24 Characteristics of participants recruited will be summarised using appropriate descriptive
25 statistics and compared with patients who were eligible but not randomised. Completeness
26 of data collection will be reported by intervention group and overall.
27

28
29 Descriptive summaries of outcome data at each follow up time point will be presented by
30 intervention group and overall. Outcome distributions for suggested floor and ceiling effects
31 will be checked. Confidence intervals will be presented for the proportion of patients
32 consented, randomised, and retained in the trial completing assessment at 12 weeks, both
33 overall and by treatment group. Confidence intervals for the SD of the secondary outcomes
34 will also be calculated where appropriate.
35

36
37 Exploratory analysis of continuous outcomes for the subsequent definitive trial will be
38 performed to investigate potential treatment effects. Differences in mean values between
39 baseline and 12 weeks will be presented, with 95% confidence intervals. This feasibility trial
40 is not powered to perform hypotheses testing, however, descriptive statistics of the
41 difference between randomised groups will inform the design of the main definitive trial. No
42 sub-group analyses are planned, and no interim analyses will be performed aside from
43 routine checks of safety data.
44

45 **Health economic analysis**

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47
48 The within-trial economic evaluation will determine the cost-effectiveness of the surgical
49 intervention compared to non-surgical (standard) treatment from an NHS and Personal
50 Social Services perspective. The evaluation will follow the reference case guidance for
51 technology appraisals as set out by NICE.[58] Effectiveness will be captured using Quality
52 Adjusted Life Years (QALYs) as assessed by the EQ-5D-3L.[48] The primary outcome of the
53 evaluation will be the incremental cost-effectiveness ratio (ICER) per additional QALY
54 (ICER) gained from surgical fixation compared to standard care. Sensitivity analyses will be
55 performed to control for uncertainty, which will include one- and two-way sensitivity analyses
56 on (but not exclusively) age, gender and baseline scores, with a probabilistic sensitivity
57 analysis to control for all uncertainty. Results of the sensitivity analyses will be presented as
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3 tornado plots, 95% confidence interval for the ICER and cost-effectiveness acceptability
4 curves.
5

6 **Qualitative analysis**

7
8 Qualitative interview data will be handled using the NVivo 12 software package and
9 analysed using a framework approach informed by the literature about the challenges of
10 clinical trial methodology.[59-63] Initial thematic tables are likely to include elements such as
11 randomisation and outcome measures. Table summaries will be used to generate
12 recommendations about the nature and form of the subsequent trial; specific detail will also
13 be used to inform recruitment strategies, data collection regimes, and participant information
14 resources.
15
16

17 **ETHICS and DISSEMINATION**

18 **Patient & Public Involvement**

19
20 Two members of the Royal Osteoporosis Society's Nottingham support group represent the
21 Patient and Public Involvement (PPI) for this study. Two focus groups have been held to inform
22 the research, design and specific study outcomes. The PPI representatives have provided input
23 into the grant application, study design and reviewing all participant facing documents. They will
24 continue to provide input into trial conduct, as members of the Trial Management Group (TMG).
25 They will assist with dissemination of study findings through their Royal Osteoporosis Society
26 local communications as well as national contacts, and support writing of the definitive future
27 trial research grant application.
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30

31 **Study Registration and Approvals**

32
33 All study material has received approval from the Research Ethics Committee (REC - North
34 East; Newcastle & North Tyneside 2, reference number 18/NE/0212), Health Research
35 Authority (HRA) and the Nottingham Queens Medical Centre Research & Innovation
36 department. Nottingham University Hospitals NHS Trust will act as sponsor to this study.
37 The study has been registered on a clinical trials database (<https://www.isrctn.com>,
38 reference number ISRCTN16719542).
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42 **DISCUSSION**

43
44 The growing older person population confers a large group of potential patients with complex
45 medical and social needs, both in terms of medical co-morbidities, susceptibility to hospital
46 acquired complications and dependency. With the numbers of pelvic fragility fractures (PFF)
47 set to exponentially increase in the coming years, the potential healthcare resource burden
48 within this group of patients is alarming. A recent systematic review concluded that
49 randomised controlled trials were required to develop evidence-based protocols to reduce
50 morbidity and mortality in older people with PFF.[22,33,64] Given that keyhole spinal sacral
51 fixation is already an established treatment option with a sound safety record, we propose
52 that surgical management should be considered earlier in the treatment of PFF in older
53 people admitted to hospital. This is to maximise early pain management with the aim of
54 preventing pain-related immobilisation and its short- and long-term consequences.
55
56

57 This burden of patient care will fall to our existing national healthcare service. In order to
58 ensure that the outcome of a clinical trial in this area has a high level of validity, it must be
59 delivered within the constraints of the existing healthcare service. This feasibility trial,
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3 delivered within this existing healthcare service, will analyse the outcomes posed by some of
4 these constraints, to ensure that a future definitive trial is able to answer the clinical question
5 efficiently. The inclusion of an economic evaluation will also demonstrate whether surgical
6 fixation offers value for money as well as clinical effectiveness, an important consideration
7 for existing healthcare services.
8

9
10 Potential limitations of delivering a clinical trial of this kind within an active healthcare service
11 include identification of the sacral fractures themselves. Any patient presenting with an
12 anterior pelvic ring fracture would need to be referred for further imaging in order to identify
13 sacral fractures and thus be considered within the eligibility criteria for this trial. However, as
14 standard care for patients presenting with PFF is currently conservative care, clinicians may
15 feel that further imaging would not change a patient's treatment course and thus be an
16 unnecessary expense. As an identified sacral fracture is a key requirement for the eligibility
17 criteria, this clinician assessment may significantly affect recruitment.
18

19
20 The target cohort in question may also provide further recruitment barrier. Cognitive
21 impairment is common (up to 67%) in older patients presenting to hospital with PFF.[5,17,25]
22 As these patients confer such a large proportion of the real world PFF cohort, it would
23 severely affect the validity of the trial to exclude them. Therefore, we have included a
24 consent process for those patients that lack capacity. Identification is by AMT as a surrogate
25 marker of capacity, which is completed as part of the clinical assessment of all admitted
26 patients and therefore does not add any unnecessary burden prior to recruitment. Patients
27 without capacity are reliant on the presence of relatives or carers to act as personal
28 consultees, which may add a logistic barrier and reduce the recruitment of this subset of
29 participants. Participants with cognitive impairment that are recruited may also be less likely
30 to complete data collection due to difficulty with engagement, introduce detection bias due to
31 issues with recall and may be more likely to be lost to follow-up.
32
33

34
35 Even once randomised, our participants remain under the existing healthcare service's care
36 for the entirety of the trial and are therefore at risk of protocol deviations due to the
37 pragmatic setting of the study. The final decision to receive any intervention remains the
38 responsibility of the patient's clinical team. For participants in the surgical intervention group,
39 the decision remains with the surgical team and may be susceptible to influence from factors
40 such as surgeon experience and preference, belief in the clinical equipoise and theatre
41 availability. Participants in the non-surgical (standard care) group may still be reviewed for
42 surgical intervention based on clinical need identified by their clinical team, as determined by
43 current practice. In order to assess the effect of this limitation, quantification and analysis of
44 adherence to randomisation is an important outcome of this feasibility study.
45

46
47 An area of confounding not specifically assessed in this feasibility trial is the possibility of
48 variation in the usual care received by all participants in both groups. This is not set by the
49 protocol and whilst minimised by using a single site setting, where staff are working from the
50 same local guidelines, resources and practices, variation is likely inevitable due to the non-
51 regimented workings of a real-world healthcare service. The effect of these innate
52 differences could be further minimised by using analysis of variation in outcome measures
53 from this feasibility trial in order to power a future definitive trial appropriately
54

55
56 This study is not powered to test the hypotheses, but the data collected will be able to
57 provide a descriptive analysis on effectiveness of outcomes in order to inform analysis in a
58 future definitive trial. The key outcomes address questions posed by the possible limitations
59 of conducting such a trial within an existing public health service, specifically to recruitment
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3 and adherence to randomisation. The future aim is that the feasibility trial will advise a valid
4 and fully powered randomised controlled trial to test the hypothesis that surgical intervention
5 in PFF is of clinical benefit to patients, as well as being cost effective and safe.
6

7
8 **Trial Status** The study has been open for recruitment since October 2018 at QMC, with a
9 current total of 9 recruited patients, and is ongoing. Estimated study duration is 30 months
10 for a completion date of March 2021.

11
12 **Author's Contributions** DVB wrote the manuscript draft. TO and OS contributed to editing
13 the manuscript. OS, TO, AD, PH, PL, MJ, CT, KS, NQ and MP are all key protocol
14 contributors providing expertise on specific aspects. OS is the Chief Investigator of the
15 study. SE is the Senior Trial Manager, CB the lead statistician and ASDP the trial statistician.
16 All authors have read and approved the final manuscript.
17

18
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22
23 **Disclaimer** The views expressed in this publication are those of the authors and not
24 necessarily those of the NHS, the National Institute for Health Research or the Department
25 of Health.

26
27 **Competing Interests Statement** None declared.

28
29 **Patient consent** Obtained.

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LEGENDS

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31 *Figure 1: Participant flow through the trial including timings of data collection.*

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33 *Figure 2: Schedule of enrolment, interventions and assessments.*

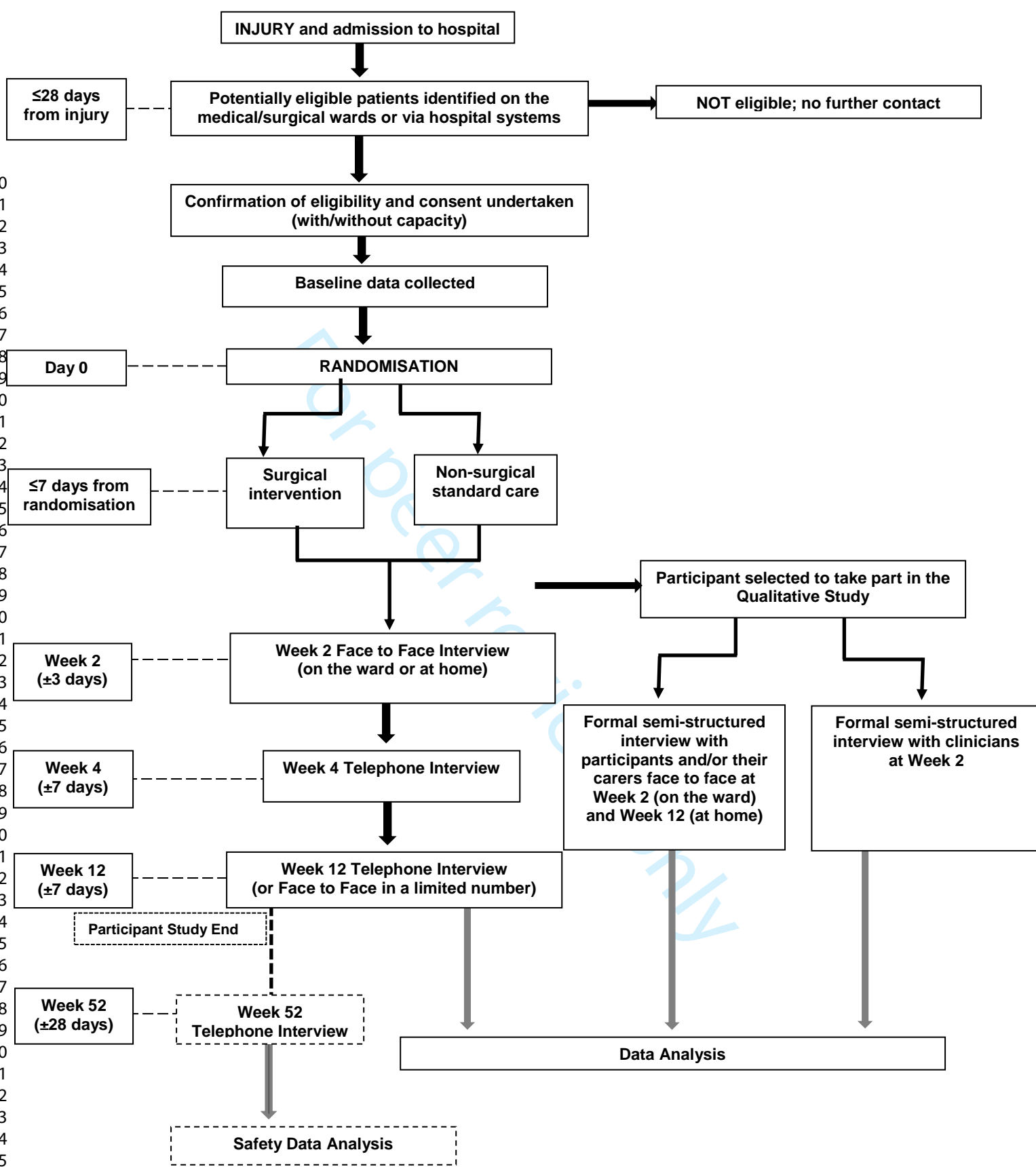
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Data Collected	Timing of Data Collection (from randomisation)	STUDY PERIOD							
		ENROLMENT	ALLOCATION	POST ALLOCATION					CLOSE-OUT
		Screening	Baseline (Face to face)	Day of surgery	Week 2 (Face-to-face)	At Discharge	Week 4 (Telephone)	Week 12 (Face to face OR Telephone)	Week 52 (Telephone)
		≤28 days from injury	Day 0	≤ 7 days	14 ±3 days (or post-surgery)	Any (may occur prior to Week 2)	28 ±7 days	84 ±7 days	365 ±28 days
ENROLMENT:	<u>Sociodemographics</u>	x	x					x	
	Fracture Details	x	x						
	Eligibility Assessment	x	x	x	x		x	x	x
	Abbreviated Mental Test (AMT) ^[a] [f]	x ^[a]			x			x ^[a]	
	Informed Consent ^[b]		x		x ^[b]		x ^[b]	x ^[b]	x ^[b]
	Allocation		x						
INTERVENTION:	Surgery Details ^[c]			x ^[c]					
ASSESSMENTS:	Healthcare Services Usage ^[d]		x ^[d]	x		x	x	x ^[d]	x
	Pain Management		x		x		x	x	
	Ambulatory Status				x			x	
	Clinical Frailty Scale (CFS)		x						
	Functional Independence Measure (FIM)		x		x			x	
	<u>Charlson Co-Morbidity Assessment</u>		x		x				
	<u>Barthel Index</u>		x		x		x	x	
	Montreal Cognitive Assessment (MOCA)		x						
	Numeric Pain Rating Scale		x		x		x	x	
	EQ-5D-3L		x		x		x	x	
	Timed Up and Go Test (TUG) ^[e]				x			x ^[e]	
	Roland Morris Disability Questionnaire (RMDQ)						x	x	
	Adverse Events			x	x	x	x	x	x
	Qualitative Study Interviews ^[f]					x ^[f]		x ^[f]	

[a] AMT will be assessed at the point of hospital admission as part of routine care. This is to be repeated by the study team on the ward if score was 5 to 6.

[b] Continued consent checked at every point of participant contact

[c] Only applicable if in surgical intervention group

[d] Includes Travel Costs when assessed at Baseline and includes Care Aids when assessed at Week 12

[e] TUG and AMT repeated at Week 12 only if face-to-face visit (omitted if telephone follow-up at Week 12)

[f] Applicable to a randomly selected group of 10 patients at Week 2 and 5 patients at Week 12



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A (not included in publication version for succinctness)
Protocol version	3	Date and version identifier	N/A (not included in publication version for succinctness)
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12

1 5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint
 2 adjudication committee, data management team, and other individuals or groups overseeing the trial, if
 3 applicable (see Item 21a for data monitoring committee) N/A (not included
 4 in publication
 5 version for
 6 succinctness)
 7

9 **Introduction**

10 **Background and** 6a Description of research question and justification for undertaking the trial, including summary of relevant 3-4
 11 **rationale** studies (published and unpublished) examining benefits and harms for each intervention
 12
 13 6b Explanation for choice of comparators 3-4
 14
 15 **Objectives** 7 Specific objectives or hypotheses 4-5
 16
 17 **Trial design** 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
 18 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 5
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22 **Methods: Participants, interventions, and outcomes**

23 **Study setting** 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 5
 24 be collected. Reference to where list of study sites can be obtained
 25
 26 **Eligibility criteria** 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 5
 27 individuals who will perform the interventions (eg, surgeons, psychotherapists)
 28
 29 **Interventions** 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 6
 30 administered
 31
 32 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 11
 33 change in response to harms, participant request, or improving/worsening disease)
 34
 35 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence N/A
 36 (eg, drug tablet return, laboratory tests)
 37
 38 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 6
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1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
6	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8+Fig 1+Fig 2
10	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6

Methods: Assignment of interventions (for controlled trials)

Allocation:

19	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
33	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
36		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

1	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	6-8
2	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
3			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
4			Reference to where data collection forms can be found, if not in the protocol	
5				
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	9
7			collected for participants who discontinue or deviate from intervention protocols	
8				
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	N/A (not included
10			(eg, double data entry; range checks for data values). Reference to where details of data management	in publication
11			procedures can be found, if not in the protocol	version for
12				succinctness)
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15	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	9-10
16			statistical analysis plan can be found, if not in the protocol	
17				
18		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
19				
20		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
21			statistical methods to handle missing data (eg, multiple imputation)	9-10
22				
23				
24	Methods: Monitoring			
25				
26	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	N/A (not included
27			whether it is independent from the sponsor and competing interests; and reference to where further details	in publication
28			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	version for
29			needed	succinctness)
30				
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32		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	9
33			results and make the final decision to terminate the trial	
34				
35	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	N/A (not included
36			events and other unintended effects of trial interventions or trial conduct	in publication
37				version for
38				succinctness)
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1	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A (not included in publication version for succinctness)
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7	Ethics and dissemination			
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9	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
10				
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12	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A (not included in publication version for succinctness)
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18	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-6
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21		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
22				
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24	Confidentiality	27	How personal information about potential and enrolled participants will be collected, stored, and maintained in order to protect confidentiality before, during, and after the trial	N/A (not included in publication version for succinctness)
25				
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30	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
31				
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33	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A (not included in publication version for succinctness)
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39	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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1	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A (not included in publication version for succinctness)
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5				
6		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A (not included in publication version for succinctness)
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12		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A (not included in publication version for succinctness)
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18	Appendices			
19				
20	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A (not included in publication version for succinctness)
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25				
26	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
27				
28				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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The ASSERT (Acute Sacral insufficiency fracture augmentation) Randomised Controlled, Feasibility in Older People Trial: study protocol.

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3 **The ASSERT (Acute Sacral insufficiency fracture augmentation) Randomised**
4 **Controlled, Feasibility in Older People Trial: study protocol**
5

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ABSTRACT

Introduction Pelvic fragility fractures (PFF) are common in older people and associated with a significant burden of mortality and morbidity. This is related to the challenges of appropriate pain control and early mobilisation. The current standard for treatment of PFF is non-surgical management. Minimally invasive surgical techniques for sacral fracture stabilisation have been shown to improve outcomes in terms of pain control and mobility, and are safe. Randomised controlled trials are required before recommendations can be made for surgical management of PFF to become the new standard of care. This feasibility study will explore several uncertainties around conducting such a trial.

Methods and analysis ASSERT is a single-site randomised controlled, parallel-arm, feasibility trial of surgical stabilisation versus non-surgical management of acute sacral fragility fractures in people aged 70 years and over. Patients will be randomised to either surgical or non-surgical group on a 1:1 ratio. Follow-up of participants will occur at 2, 4 and 12 weeks with safety data collected at 52 weeks. Primary objectives are to determine feasibility and design of a future trial, including outcomes on recruitment, adherence to randomisation and safety. This will be supplemented with a qualitative interview study of participants and clinicians. Secondary objectives will inform study design procedures to determine clinical and economic outcomes between groups, including scored questionnaires, analgesia requirements, resource use and quality of life data. Data analysis will be largely descriptive to inform outcomes and future sample size.

Ethics and dissemination Ethical approval was granted by the North East Newcastle and North Tyneside 2 Research Ethics Committee (reference 18/NE/0212). ASSERT was approved and sponsored by Nottingham University Hospitals NHS Trust (reference 18HC001) and the Health Research Authority (reference IRAS 232791). Recruitment is ongoing. Results will be presented at relevant conferences and submitted to appropriate journals on study completion.

Trial registration number ISRCTN16719542

ARTICLE SUMMARY (Strengths and limitations of this study)

- Descriptive analysis on effectiveness of outcomes will inform hypothesis testing in a future definitive trial, including levels of variability in order to power the trial appropriately.
- Nested semi-structured interview study will provide valuable qualitative data to inform future definitive trial acceptability and processes.
- Determines the feasibility of economic measures including detailed resource use collection and quality of life data within the two arms, to aid the design of more comprehensive economic evaluation in a future definitive trial.
- The intervention is a proven safe surgical intervention, already used in existing healthcare practice, but further safety data in this cohort of patients will also be collected.
- A pragmatic trial set in an existing healthcare setting that may lead to a number of limitations on trial processes, including recruitment, adherence to randomisation and ease of data collection.

INTRODUCTION

Pelvic fragility fractures (PFF) are common in older people, as they are a frequent presentation of osteoporosis, a condition characterised by low bone mass and structural deterioration of bone tissue, leading to bone fragility.[1] Thus, PFF can occur as a result of low-energy trauma, typically following a fall from standing height or less.[2] The reported overall incidence of PFF is variable, between 25 to 92 per 100'000 persons-years, with the highest frequency reported in females over the age of 75 years.[3-8] Epidemiology studies worldwide have consistently shown a sustained increase in the age-adjusted incidence of PFF, with numbers expected to continue to rise exponentially over the next 10 years.[3-4,6-7,9-11] These patients are also increasingly requiring inpatient admission for management of their PFF, representing a considerable on-going burden to hospital services.[3-4,6,12]

The pelvis is a complex ring like structure composed of three principal bones; the paired innominate bones and the sacrum. Fractures of the pelvis are a heterogenous group of fractures and are most commonly described by the Young-Burgess classification, which relates to the predominant direction of the vector force at the time of injury.[13-14] Within this, Lateral Compression (LC) fractures are the most common and are further subtyped based on the resulting degree of displacement of the pelvic ring:[13]

- Type I Oblique or transverse ramus fracture and ipsilateral sacral compression fracture
- Type II Rami fracture and ipsilateral posterior ilium fracture dislocation (crescent fracture)
- Type III Ipsilateral lateral compression and contralateral anterior-posterior compression (windswept pelvis)

The most commonly identified PFF presenting to hospital is that of the anterior ring in the form of fractures of the pubic rami.[12,15-16] Sixty to ninety percent of these patients will also have a concomitant posterior ring fracture in the form of an insufficiency fracture of the sacrum.[2,17-19] Type 1 LC is therefore the most common subtype of PFF.[17,20] Whilst anterior pelvic ring fractures can be identified on plain x-ray, those fractures of the posterior pelvic ring are most typically identified on computerised tomography (CT) or magnetic resonance imaging (MRI), which now has a much wider availability on emergency admission to hospital.[17,19,21] From a bio-mechanical point of view, an undisplaced anterior pelvic ring is more stable than a posterior pelvic ring fracture, with the posterior ring providing the majority of structure and stabilisation of the pelvis on load-bearing.[2]

PFF, especially those involving the sacrum within the load-bearing posterior pelvic ring, result in pain related immobilisation and increased care dependency.[21-23] PFF have been shown to confer poor outcomes like those reported extensively in hip fractures but covets much less attention.[24] Inpatient 30-day mortality sits at up to 11%, with a 12-month mortality up to 27%. [5,9,12,15-17,20,24-26] This may be related to the demographics of patients admitted to hospital with PFF. This patient group commonly have significant co-morbidities and over third exhibit cognitive impairment, leaving them more susceptible to the medical complications of pain-dependant immobility and associated prolonged hospital stay.[5,17,25] Inpatient mortality is often attributed to exacerbation of pre-existing co-morbidity.[12] Around half of the patients admitted with PFF develop hospital and immobility related complications including pressure sores, infection, renal injury, venous thromboembolism and delirium.[9,16-17,25-28] The majority are unable to return home at their baseline level of mobility or independence upon discharge.[5,25,27] In excess of this,

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3 those with confirmed combined anterior and posterior ring insufficiency fractures have
4 hospital stays 2 weeks longer than those with isolated anterior ring fractures, higher
5 complication rates, 30% more chance of losing previous independence and higher rates of
6 institutionalisation.[17,20,22,29]
7

8 Current standard care for PFF is conservative, consisting of systemic analgesia and
9 mobilisation as tolerated.[30] As a response to the high level of associated morbidity,
10 management of PFF needs to be targeted at good early pain control in order to allow early
11 mobilisation, return of independence and discharge.[22,31] Currently standard pain
12 management consists of the use of systemic analgesia, especially opioids, but pain control
13 adequate to allow early mobilisation is difficult to achieve in this cohort.[23] Barriers to
14 adequate pain management in PFF can include under-reporting of symptoms due to
15 cognitive impairment, susceptibility to side-effects of opioids in the elderly and
16 undertreatment due to perceived prescriber fear of opioid side-effects.[32]
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19 Development of minimally invasive surgical techniques targeting fractures of posterior ring-
20 sacral fractures may provide an alternative to improve adequate pain control in this
21 significant subset of PFF.[21] Minimally invasive keyhole surgery techniques involving
22 percutaneous cement augmentation with or without trans-sacral screw are increasingly being
23 performed in order to stabilise sacral fractures.[21-22,31] For those patients who have failed
24 to progress with conservative management, these procedures have been shown to reduce
25 pain and the amount of analgesia required post-operatively.[30,33-34] This in turns allows
26 increased patient mobility with a quicker return to baseline function and shorted length of
27 stay, as well as having an established safety profile.[9,22,30,33-39] However, there are no
28 randomised controlled trials that compare efficacy of sacral fracture surgery compared with
29 conservative management in the early stages of recovery.[21,22,33]
30
31

32 **METHODS and ANALYSIS**

33 **Aims**

34 The aim of this study is to determine the feasibility and design of a future randomised
35 controlled clinical trial to evaluate the clinical and cost effectiveness of keyhole spinal sacral
36 fixation (cement augmentation +/- screw fixation) compared to current standard practice of
37 non-surgical management in older people presenting in the early stages to hospital with a
38 Type 1 Lateral Compression (LC) pelvic fragility fracture (PFF).
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42 **Objectives**

43 The feasibility and final design of a definitive trial will be determined by fulfilment of the
44 objectives outlined below. These are to:
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46

- 47 • Determine the number of patients who meet the eligibility criteria in addition to
48 recruitment (including willingness to be randomised) and retention rates of eligible
49 patients.
- 50 • Explore the adherence of clinicians to the randomisation of patients within the trial.
- 51 • To collect outcome measure data for the assessment of mobility, pain and quality of
52 life (face to face and self-reported measures), for potential use in a future definitive
53 trial; estimate the mean and standard deviation (SD) of these quantitative measures
54 for hypotheses testing purposes.
- 55 • Evaluate ease of access and availability of information from current primary and
56 secondary care databases, to determine the most efficient way of measuring
57 associated patient level resource use.
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- Use a qualitative nested interview study to assess participants' and clinicians' views on trial acceptability and processes to inform the design and conduct of a future definitive trial.
- Evaluate long term safety of the intervention.

Study Design

The primary study design is a parallel, two-arm randomised controlled feasibility trial with participants allocated to either surgical or non-surgical intervention on a 1:1 ratio. A preliminary economic evaluation and a qualitative nested interview study will also be embedded within the feasibility study.

Participants will be recruited from a single site, Queens Medical Centre, Nottingham University Hospitals NHS Trust (NUH); a university teaching hospital serving a population of 700,000 and offering a tertiary spinal surgical unit.

Participants

Participants presenting to NUH with a Type 1 LC PFF who fulfil the eligibility criteria, outlined below, will be approached for possible recruitment into the study. A fragility fracture is defined as a fracture sustained after low level trauma, usually a fall from standing height or less.

Inclusion criteria

- Aged 70 years and over
- Ambulatory with/without walking aids prior to injury
- Injury sustained within 28 days of presenting to hospital

Exclusion criteria

- Complex pelvic fractures (e.g. fractures involving/or close to the hip joint) requiring urgent surgery or progressive weight bearing exercises
- Pathological fracture in the context of known or unknown malignancy
- Previous surgery of the pelvis with metal obstructing the planned paths of the ilio-sacral screws
- Condition that precludes surgery or general/spinal anaesthesia
- Bedbound prior injury
- Receiving palliative care
- Moribund on admission

Recruitment

All patients admitted with a Type 1 LC PFF as identified on imaging (CT or MRI), will be invited to participate. The research team will be notified of the potential participant and will confirm eligibility with their clinical care team. The process for obtaining participant informed consent will be in accordance with Good Clinical Practice guidance and will include consent for potential inclusion in the qualitative interview nested study.

An Abbreviated Mental Test (AMT) will be used as a screening tool for capacity assessment. If the admission AMT completed by the clinical team is documented as 5-6/10 then it will be

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3 repeated by the research team at the time of screening. A participant will be assumed to
4 have capacity if their AMT $\geq 7/10$ at either point of assessment. An AMT $< 7/10$ will prompt a
5 capacity assessment based on the principles of the Mental Capacity Act 2005 in relation to
6 research.
7

8
9 Relatives or carers of potential participants who are unable to provide consent
10 independently, will be approached as the participants' personal consultee. If there is more
11 than one relative or carer willing to act as the patient's consultee, then they must all agree on
12 the decision for the participant to be included in the study.
13

14 For patients or consultees who decline to take part, they will be asked if they would be willing
15 to share their reasons this. It will be made clear this is in order to help us improve the design
16 and acceptability of the study and there is no obligation to do this. The findings will be
17 tabulated into the final results.
18

19 20 **Randomisation**

21 Consented participants will be randomly allocated to either surgical intervention or
22 conservative non-surgical care on the day they consent via a secure web-based system
23 (Sealed Envelope Ltd) by a member of the research team, ensuring allocation concealment.
24 In order to minimise bias, participant baseline enrolment data will be entered into the
25 randomisation system to be stratified prior to intervention allocation. Randomisation to the
26 intervention groups will be on a 1:1 basis.
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29 30 **Interventions**

31 *Intervention group* will receive surgical intervention by key-hole spinal sacral fixation as
32 determined by the treating spinal surgeon based on the participant's general condition,
33 morphology of the fracture and surgeon's experience. The surgery will be completed within 7
34 days of randomisation. Cement augmentation of the sacral ala will be undertaken in
35 participants with unilateral or bilateral sacral fractures with minimal cortical comminution.
36 Additional sacroiliac screw fixation will be offered to participants with extensive fracture
37 patterns which affect both sacral ala with significant cortical comminution. Usual post-
38 operative care, monitoring and rehabilitation will follow.
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41 *Control group* will receive usual hospital care. Participants will be treated with appropriate
42 analgesia and have regular input from the ward therapy team. Participants may be referred
43 for surgical intervention if it is indicated by their clinical team. This will be recorded, and data
44 collected and followed up with intention to treat.
45

46 47 **Outcomes**

48 The study procedures undertaken are directly related to the outcomes used in order to
49 address the objectives of this feasibility study.
50

51 *Feasibility study outcomes*

52 Primary outcomes:

- 53 • Number of eligible patients;
- 54 • Number of patients willing to be randomised and adherence to randomisation;
- 55 • Number of clinicians willing to randomise and adherence to randomisation.
- 56
- 57
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59 Secondary outcomes:
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- Rate of participant recruitment and retention;
- Data on the completeness and variability of proposed definitive trial outcome measures;
- Failure of non-surgical conservative care and adverse events in both arms.

Outcomes measures for the subsequent definitive trial

Primary outcome measures:

- Timed Up and Go test (TUG)[40] as a measure of mobility requiring both static and dynamic balance;
- Roland Morris Disability Questionnaire (RMDQ)[41] as a self-rated measure of physical disability caused by low back pain.

Secondary outcome measures:

- Abbreviated Mental Test (AMT) as an assessment of cognition[42];
- Montreal Cognitive Assessment (MoCA)[43] as an assessment of cognition;
- Functional Independence Measure (FIM)[44] as a measure of disability severity;
- Clinical Frailty Scale (CFS)[45] as an assessment of frailty;
- Charlson Co-morbidity Index[46] as a prediction of one-year mortality based on co-morbid conditions;
- Numeric 0-10 Pain Rating Scale[47] as a measure of average pain on mobilising;
- EuroQol 5 Dimensions (EQ-5D-3L) Score[48] as an assessment of quality of life;
- Barthel Activities of Daily Living (ADL) Index[49] as an assessment of care dependency;
- Fracture details/classification;
- Analgesia requirements;
- Surgery details;
- Health and Social Care resource use;
- Adverse events and readmissions (as part of the long-term safety review).

Analgesia requirement

Analgesia requirement will be recorded as follows: each medication will be classified as a strong opioid (including oxycodone, morphine, fentanyl, pethidine, hydromorphone, buprenorphine and tramadol), mild opioid (including medications containing codeine or dextropropoxyphene) or non-opioid medications (including paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)). The participant will be given a score of 0, 1 or 2 in each of these three categories depending on the number of concurrent different medications being taken within each category. Opioid medication will also include a calculation of the oral Morphine Equivalent Daily Dose using the Opioid Dose Equivalence score.[50]

Study Procedures

Participant flow through the trial is summarised in Figure 1. Face to face contact with participants and/or carer will be required at baseline (considered Day 0), week 2 and a limited number of participants at week 12. Telephone interviews will be conducted with participants at week 4 and for the majority of participants at week 12. Week 12 marks end of trial for the participant, with further contact made at week 52 as part of the long-term safety analysis.

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Figure 2 shows the schedule of data collection, outlining which study procedures will be undertaken at what time point in the study period, measured from the point of randomisation. In addition, follow-up data at each time point will include participant still living, hospital length of stay, unplanned hospital readmission (within the first 28 days and 91 days post discharge) and all adverse events, including surgical complications. For those participants that lack capacity, only clinically assessed questionnaires will be used. Participant contact will be conducted in the location the participant is residing at the time of the respective follow up.

Economic Evaluation

Information about a participant's treatment (including recorded resource use of the surgical procedure if applicable), hospital stay, emergency department, out-patient, readmission and primary care attendances (if related to ongoing management of the fracture), and social care needs, will be gathered through discussion with participants, as well as hospital and primary care databases. An assessment of total resource use will be made at baseline, week 12 and week 52 in order to inform an economic analysis between the two treatment groups.

Individual prices of these health resources will be based on information from national tariffs, such as the Unit Costs of Health and Social Care[51] for primary care resources, NHS Reference Costs[52] for secondary care resources and the British National Formulae (BNF)[53] for prescriptions. If the price for a resource cannot be found from the references above, a suitable estimate will be identified from consultation with the hospital finance department. Prices will be estimated at 2018-2018 prices.

Qualitative Assessment

Using maximum variation sampling, up to ten participants will be chosen to undertake a semi-structured face-to-face interview 7-10 days after randomisation. An interview topic guide will explore their views on the trial and recruitment process, the presentation of study information, study documentation and reasons for agreeing to randomisation. A smaller selection of five participants who complete the trial will have another shorter follow-up interview at week 12. The aim will be to further explore their experience of the trial, data collection processes, and overall perception of participating. Further specific consent for this qualitative interview nested study will be taken in addition to that agreed at the point of trial recruitment.

A number of clinicians will also be asked to partake in a semi-structured interview to explore their experiences of the study. These interviews will consider participant recruitment (eligibility and randomisation) as well as the process of integrating the research with the clinical team. All participating clinicians will complete informed consent for interview, recording and transcription.

Sample Size Calculation

This feasibility study will aim to provide estimates of recruitment and retention rates, and the variability of important outcomes, in order to generate appropriate power calculations for the definitive trial. It is estimated that sample sizes between 24 and 50 are required for a feasibility study.[54-57] Therefore, we propose to recruit for a ten-month period, from which

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3 we expect to screen approximately 100 patients. Our estimates are based on data from
4 Gateshead Health Foundation Trust, who screened 67 patients with a similar eligibility
5 criterion over a 12 month period within a smaller acute trust catchment population.[17] We
6 assume in this feasibility study that 20% of patients screened are not eligible and a 60%
7 recruitment rate, so we expect to recruit 48 participants. By recruiting 48 patients the
8 estimated recruitment rate has a standard error (SE) of 5.5% (95% CI 48.4%; 70.8%). Given
9 the short active follow-up period we are allowing for a lower 10% three-month attrition rate.
10 This estimates that 43 participants will complete the study, thus estimating the 90% retention
11 rate with a SE of 4.4% (95% CI 77.3%; 96.5%). Completed follow-up on 43 patients will
12 allow an estimated SE for the TUG of 1.2 seconds assuming the SD is about 8 seconds
13 (95% CI 6.6; 10.2), and an SE of 0.9 for the RMDQ, assuming the SD is about 6 (95% CI
14 4.9; 7.6).

17 **Data Analysis**

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20 Data analysis will primarily be descriptive to address the aims of the feasibility study. A
21 statistical analysis plan will be agreed prior to database lock and a CONSORT flow diagram
22 produced. Data analysis overall will inform future trial feasibility and the hypothesis analysis
23 plan for a definitive trial.

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26 Characteristics of participants recruited will be summarised using appropriate descriptive
27 statistics and compared with patients who were eligible but not randomised. Completeness
28 of data collection will be reported by intervention group and overall.

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31 Descriptive summaries of outcome data at each follow up time point will be presented by
32 intervention group and overall. Outcome distributions for suggested floor and ceiling effects
33 will be checked. Confidence intervals will be presented for the proportion of patients
34 consented, randomised, and retained in the trial completing assessment at 12 weeks, both
35 overall and by treatment group. Confidence intervals for the SD of the secondary outcomes
36 will also be calculated where appropriate.

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39 Exploratory analysis of continuous outcomes for the subsequent definitive trial will be
40 performed to investigate potential treatment effects. Differences in mean values between
41 baseline and 12 weeks will be presented, with 95% confidence intervals. This feasibility trial
42 is not powered to perform hypotheses testing, however, descriptive statistics of the
43 difference between randomised groups will inform the design of the main definitive trial. No
44 sub-group analyses are planned, and no interim analyses will be performed aside from
45 routine checks of safety data.

46 **Health economic analysis**

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49 The within-trial economic evaluation will determine the cost-effectiveness of the surgical
50 intervention compared to non-surgical (standard) treatment from an NHS and Personal
51 Social Services perspective. The evaluation will follow the reference case guidance for
52 technology appraisals as set out by NICE.[58] Effectiveness will be captured using Quality
53 Adjusted Life Years (QALYs) as assessed by the EQ-5D-3L.[48] The primary outcome of the
54 evaluation will be the incremental cost-effectiveness ratio (ICER) per additional QALY
55 (ICER) gained from surgical fixation compared to standard care. Sensitivity analyses will be
56 performed to control for uncertainty, which will include one- and two-way sensitivity analyses
57 on (but not exclusively) age, gender and baseline scores, with a probabilistic sensitivity
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3 analysis to control for all uncertainty. Results of the sensitivity analyses will be presented as
4 tornado plots, 95% confidence interval for the ICER and cost-effectiveness acceptability
5 curves.
6

7 **Qualitative analysis**

8
9 Qualitative interview data will be handled using the NVivo 12 software package and
10 analysed using a framework approach informed by the literature about the challenges of
11 clinical trial methodology.[59-63] Initial thematic tables are likely to include elements such as
12 randomisation and outcome measures. Table summaries will be used to generate
13 recommendations about the nature and form of the subsequent trial; specific detail will also
14 be used to inform recruitment strategies, data collection regimes, and participant information
15 resources.
16
17

18 **Data Management and Monitoring**

19 Electronic data records will be stored in a SQL Server database, stored on a restricted access,
20 secure server maintained by the University of Leicester, with access permission allocated by
21 the LCTU IT team. Data monitoring for quality and completeness, including source data
22 verification on a sample of documents, will be conducted by LCTU staff. The study documents
23 shall be archived at secure archive facilities subcontracted to NUH. Data will be stored for 5
24 years.
25
26

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28 Given this is a feasibility trial, the Data Monitoring Committee (DMC) is included as part of
29 the majority independent TSC, comprising 2 clinical experts and a statistician. The TSC will
30 review trial progress, addressing study-related problems, assessing the safety of participants
31 and ensuring timely publication of the study findings.
32

33 **Harms**

34 All adverse events (AEs) will be reviewed by the Chief Investigator (CI) and recorded as
35 part of the study outcome measures with an assessment of severity, relation and
36 expectation. All deaths occurring up to the final study visit and serious adverse events,
37 other than expected surgical complications, will be recorded on the Sponsor SAE Form
38 and faxed/e-mailed to the Sponsor and LCTU within 3 days of a researcher becoming
39 aware of the event. Those related to the study and unexpected will be reported to the
40 REC within 15 days. Events will be followed up until resolved or a final outcome has
41 been reached.
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45 The intervention in this trial is not testing a new surgical treatment. Therefore, serious expected
46 sacroplasty surgical complications including wound infection, cement leakage causing nerve
47 root damage and rarely pulmonary embolus will be captured in the CRF, but do not require
48 expedited reporting.
49

50 **ETHICS and DISSEMINATION**

51 **Patient & Public Involvement**

52
53 Two members of the Royal Osteoporosis Society's Nottingham support group represent the
54 Patient and Public Involvement (PPI) for this study. Two focus groups have been held to inform
55 the research, design and specific study outcomes. The PPI representatives have provided input
56 into the grant application, study design and reviewing all participant facing documents. They will
57 continue to provide input into trial conduct, as members of the Trial Management Group (TMG).
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3 They will assist with dissemination of study findings through their Royal Osteoporosis Society
4 local communications as well as national contacts, and support writing of the definitive future
5 trial research grant application.
6

7 8 **Dissemination Policy**

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10 Dissemination will include publication of the protocol methodology, with results being
11 submitted for presentation at scientific meetings and conferences aimed at clinicians working
12 with older people, trauma and spinal surgery (as well as being available on the NIHR RfPB
13 website). Relevant patient groups and policy makers will be informed of the results,
14 supported by our PPI engagement strategies.
15

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17 If the findings indicate that a full-scale definitive trial is feasible, the data will be used to
18 prepare an application for funding a large-scale definitive clinical and cost effectiveness
19 RCT, with the aim to change standard practise for the benefit of patient outcomes.
20

21 22 **Study Registration and Approvals**

23 All study material has received approval from the Research Ethics Committee (REC - North
24 East; Newcastle & North Tyneside 2, reference number 18/NE/0212), Health Research
25 Authority (HRA) and the Nottingham Queens Medical Centre Research & Innovation
26 department. Nottingham University Hospitals NHS Trust will act as sponsor to this study.
27 The study has been registered on a clinical trials database (<https://www.isrctn.com>,
28 reference number ISRCTN16719542).
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31 32 **DISCUSSION**

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34 The growing older person population confers a large group of potential patients with complex
35 medical and social needs, both in terms of medical co-morbidities, susceptibility to hospital
36 acquired complications and dependency. With the numbers of pelvic fragility fractures (PFF)
37 set to exponentially increase in the coming years, the potential healthcare resource burden
38 within this group of patients is alarming. A recent systematic review concluded that
39 randomised controlled trials were required to develop evidence-based protocols to reduce
40 morbidity and mortality in older people with PFF.[22,33,64] Given that keyhole spinal sacral
41 fixation is already an established treatment option with a sound safety record, we propose
42 that surgical management should be considered earlier in the treatment of PFF in older
43 people admitted to hospital. This is to maximise early pain management with the aim of
44 preventing pain-related immobilisation and it's short- and long-term consequences.
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47 This burden of patient care will fall to our existing national healthcare service. In order to
48 ensure that the outcome of a clinical trial in this area has a high level of validity, in must be
49 delivered within the constraints of the existing healthcare service. This feasibility trial,
50 delivered within this existing healthcare service, will analyse the outcomes posed by some of
51 these constraints, to ensure that a future definitive trial is able to answer the clinical question
52 efficiently. The inclusion of an economic evaluation will also demonstrate whether surgical
53 fixation offers value for money as well as clinical effectiveness, an important consideration
54 for existing healthcare services.
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57 Potential limitations of delivering a clinical trial of this kind within an active healthcare service
58 include identification of the sacral fractures themselves. Any patient presenting with an
59 anterior pelvic ring fracture would need to be referred for further imaging in order to identify
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sacral fractures and thus be considered within the eligibility criteria for this trial. However, as standard care for patients presenting with PFF is currently conservative care, clinicians may feel that further imaging would not change a patient's treatment course and thus be an unnecessary expense. As an identified sacral fracture is a key requirement for the eligibility criteria, this clinician assessment may significantly affect recruitment.

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The target cohort in question may also provide further recruitment barrier. Cognitive impairment is common (up to 67%) in older patients presenting to hospital with PFF.[5,17,25] As these patients confer such a large proportion of the real world PFF cohort, it would severely affect the validity of the trial to exclude them. Therefore, we have included a consent process for those patients that lack capacity. Identification is by AMT as a surrogate marker of capacity, which is completed as part of the clinical assessment of all admitted patients and therefore does not add any unnecessary burden prior to recruitment. Patients without capacity are reliant on the presence of relatives or carers to act as personal consultees, which may add a logistic barrier and reduce the recruitment of this subset of participants. Participants with cognitive impairment that are recruited may also be less likely to complete data collection due to difficulty with engagement, introduce detection bias due to issues with recall and may be more likely to be lost to follow-up.

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Even once randomised, our participants remain under the existing healthcare service's care for the entirety of the trial and are therefore at risk of protocol deviations due to the pragmatic setting of the study. The final decision to receive any intervention remains the responsibility of the patient's clinical team. For participants in the surgical intervention group, the decision remains with the surgical team and may be susceptible to influence from factors such as surgeon experience and preference, belief in the clinical equipoise and theatre availability. Participants in the non-surgical (standard care) group may still be reviewed for surgical intervention based on clinical need identified by their clinical team, as determined by current practice. In order to assess the effect of this limitation, quantification and analysis of adherence to randomisation is an important outcome of this feasibility study.

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An area of confounding not specifically assessed in this feasibility trial is the possibility of variation in the usual care received by all participants in both groups. This is not set by the protocol and whilst minimised by using a single site setting, where staff are working from the same local guidelines, resources and practices, variation is likely inevitable due to the non-regimented workings of a real-world healthcare service. The effect of these innate differences could be further minimised by using analysis of variation in outcome measures from this feasibility trial in order to power a future definitive trial appropriately

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This study is not powered to test the hypotheses, but the data collected will be able to provide a descriptive analysis on effectiveness of outcomes in order to inform analysis in a future definitive trial. The key outcomes address questions posed by the possible limitations of conducting such a trial within an existing public health service, specifically to recruitment and adherence to randomisation. The future aim is that the feasibility trial will advise a valid and fully powered randomised controlled trial to test the hypothesis that surgical intervention in PFF is of clinical benefit to patients, as well as being cost effective and safe.

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Trial Status The study has been open for recruitment since October 2018 at QMC, with a current total of 9 recruited patients, and is ongoing. Estimated study duration is 30 months for a completion date of March 2021.

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Acknowledgments Our thanks go to our two PPI representatives for their contribution to the original protocol and the NIHR RfPB for funding this study.

Author's Contributions DVB wrote the manuscript. OS, TO, AD, PH, PL, MJ, KS and NQ are all key protocol contributors providing expertise on specific aspects. OS is the Chief Investigator of the study. SE is the Senior Trial Manager, CB the lead statistician and ASDP the trial statistician. All authors have read, contributed amendments to and approved the final manuscript.

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Disclaimer The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Competing Interests Statement None declared.

Patient consent Obtained.

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19 LEGENDS

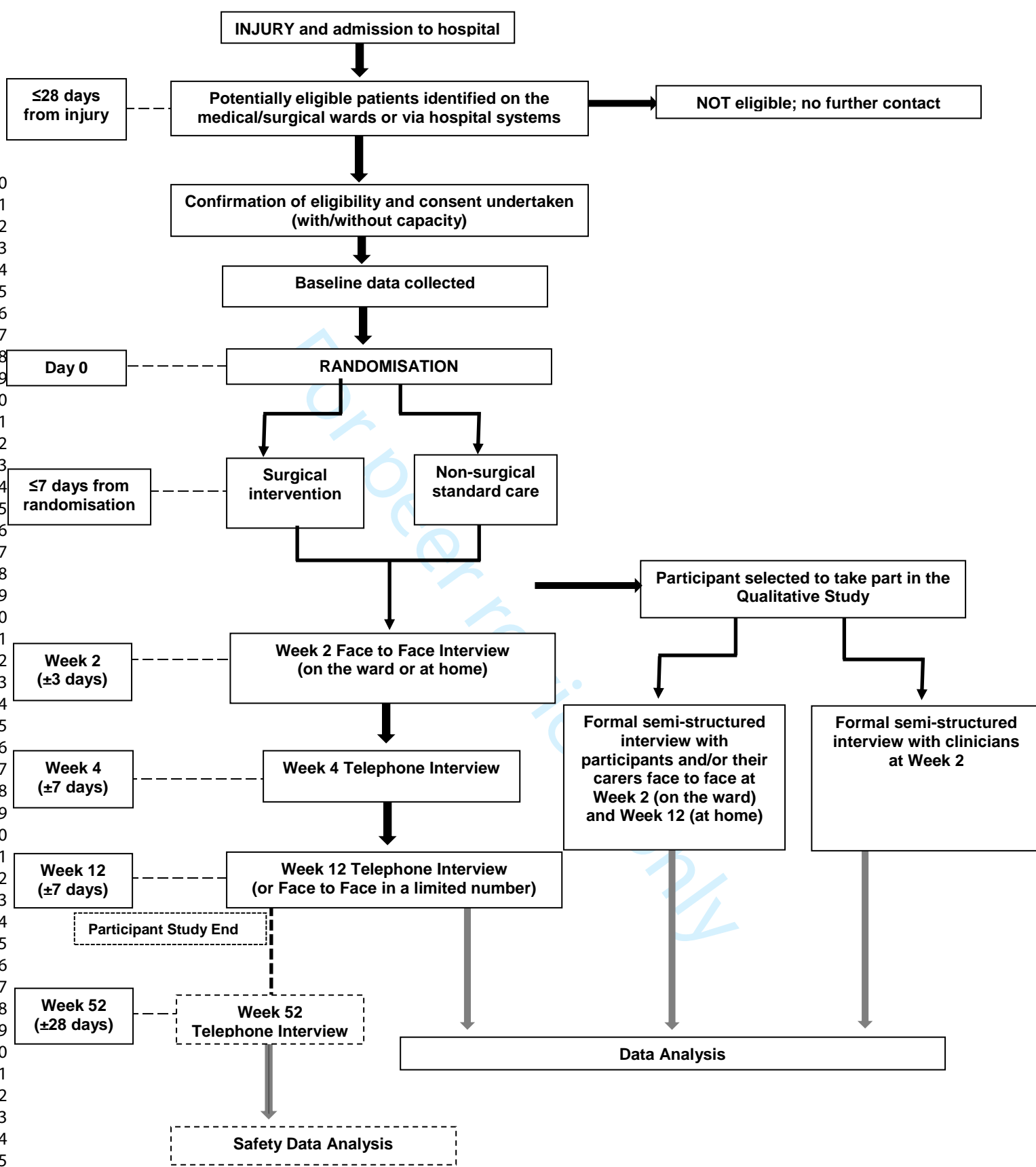
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22 *Figure 1:* Participant flow through the trial including timings of data collection.
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24 *Figure 2:* Schedule of enrolment, interventions and assessments.
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Data Collected	Timing of Data Collection (from randomisation)	STUDY PERIOD							
		ENROLMENT	ALLOCATION	POST ALLOCATION					CLOSE-OUT
		Screening	Baseline (Face to face)	Day of surgery	Week 2 (Face-to-face)	At Discharge	Week 4 (Telephone)	Week 12 (Face to face OR Telephone)	Week 52 (Telephone)
		≤28 days from injury	Day 0	≤ 7 days	14 ±3 days (or post-surgery)	Any (may occur prior to Week 2)	28 ±7 days	84 ±7 days	365 ±28 days
ENROLMENT:	<u>Sociodemographics</u>	x	x					x	
	Fracture Details	x	x						
	Eligibility Assessment	x	x	x	x		x	x	x
	Abbreviated Mental Test (AMT) ^[a] [f]	x ^[a]			x			x ^[a]	
	Informed Consent ^[b]		x		x ^[b]		x ^[b]	x ^[b]	x ^[b]
	Allocation		x						
INTERVENTION:	Surgery Details ^[c]			x ^[c]					
ASSESSMENTS:	Healthcare Services Usage ^[d]		x ^[d]	x		x	x	x ^[d]	x
	Pain Management		x		x		x	x	
	Ambulatory Status				x			x	
	Clinical Frailty Scale (CFS)		x						
	Functional Independence Measure (FIM)		x		x			x	
	<u>Charlson Co-Morbidity Assessment</u>		x		x				
	<u>Barthel Index</u>		x		x		x	x	
	Montreal Cognitive Assessment (MOCA)		x						
	Numeric Pain Rating Scale		x		x		x	x	
	EQ-5D-3L		x		x		x	x	
	Timed Up and Go Test (TUG) ^[e]				x			x ^[e]	
	Roland Morris Disability Questionnaire (RMDQ)						x	x	
	Adverse Events			x	x	x	x	x	x
	Qualitative Study Interviews ^[f]					x ^[f]		x ^[f]	

[a] AMT will be assessed at the point of hospital admission as part of routine care. This is to be repeated by the study team on the ward if score was 5 to 6.

[b] Continued consent checked at every point of participant contact

[c] Only applicable if in surgical intervention group

[d] Includes Travel Costs when assessed at Baseline and includes Care Aids when assessed at Week 12

[e] TUG and AMT repeated at Week 12 only if face-to-face visit (omitted if telephone follow-up at Week 12)

[f] Applicable to a randomly selected group of 10 patients at Week 2 and 5 patients at Week 12



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A (not included in publication version for succinctness)
Protocol version	3	Date and version identifier	N/A (not included in publication version for succinctness)
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12

1		5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A (not included in publication version for succinctness)
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9	Introduction			
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11	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
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13		6b	Explanation for choice of comparators	3-4
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15	Objectives	7	Specific objectives or hypotheses	4-5
16				
17	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
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22	Methods: Participants, interventions, and outcomes			
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24	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
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27	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
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30	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
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32		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
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34		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
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37		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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1	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-7
6	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8+Fig 1+Fig 2
10	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
13	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6

Methods: Assignment of interventions (for controlled trials)

Allocation:

19	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
25	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
30	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
33	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
36		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

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1	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	6-8
2	methods		processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of	
3			study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	
4			Reference to where data collection forms can be found, if not in the protocol	
5				
6		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	9
7			collected for participants who discontinue or deviate from intervention protocols	
8				
9	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	10
10			(eg, double data entry; range checks for data values). Reference to where details of data management	
11			procedures can be found, if not in the protocol	
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14	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the	9-10
15			statistical analysis plan can be found, if not in the protocol	
16				
17		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
18				
19		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any	
20			statistical methods to handle missing data (eg, multiple imputation)	9-10
21				
22				
23	Methods: Monitoring			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of	10
26			whether it is independent from the sponsor and competing interests; and reference to where further details	
27			about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not	
28			needed	
29				
30				
31		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim	9
32			results and make the final decision to terminate the trial	
33				
34	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse	10
35			events and other unintended effects of trial interventions or trial conduct	
36				
37	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent	10
38			from investigators and the sponsor	
39				
40				
41	Ethics and dissemination			
42				
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1	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
2				
3				
4	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A (not included in publication version for succinctness)
5				
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8				
9	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-6
10				
11				
12		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
13				
14				
15				
16	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
17				
18				
19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
20				
21				
22	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
23				
24				
25				
26	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
27				
28				
29	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
30				
31				
32				
33		31b	Authorship eligibility guidelines and any intended use of professional writers	12-13
34				
35		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
36				

Appendices

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1	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A (not included in publication version for succinctness)
2				
3				
4				
5				
6	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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8				

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10 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.

11 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons

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