CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

FORENSIC UK

FUSION VERSUS BEST CONSERVATIVE CARE

Full Study Title:

The clinical and cost-effectiveness of lumbar fusion surgery for patients with persistent, severe low back pain: FusiOn veRsus bEst coNServatIve Care

(the FORENSIC-UK trial)

Short Study Title:

FORENSIC-UK: Fusion versus Best Conservative Care

Version 2.0 14 Mar 2025

Study website: https://forensic.octru.ox.ac.uk/

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1. RESEARCH REFERENCE NUMBERS

Sponsor Protocol Number:	PID: 18505
Clinical Trials Unit (CTU) Reference:	OCTRU375
Funder Reference:	NIHR134859
Ethics Reference Number:	25/EE/0040
IRAS Number:	343826
Registry:	International Standard Randomised Controlled Trial Number (ISRCTN): tbc

2. ORGANISATIONAL INFORMATION

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Conflict of Interest statement:	The following conflicts of interest have been declared by the protocol authors/contributors: Mr. Almas Khan was consulted during the commissioning brief development process by NIHR HTA regarding this question and commissioned call.

Confidentiality Statement:	In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all.

3. KEY STUDY CONTACTS

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Data and Safety Monitoring Committee (DSMC) Chair:	Prof. Deborah Stocken Director Surgical Interventions, Diagnostics and Devices Division University of Leeds D.D.Stocken@leeds.ac.uk Other members of the DSMC are detailed within a study-specific DMC charter.
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4. PROTOCOL APPROVAL/SIGNATORIES

This protocol has been approved by the Sponsor, Chief Investigator and Lead Statistician. Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures.

All parties confirm that findings of the study will be made publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any important deviations and serious breaches of GCP from the study as planned in this protocol will be explained.

5. LAY SUMMARY/PLAIN ENGLISH SUMMARY

Why are we doing this research?

Low back pain is common and often improves without specific treatment. Where it doesn't, painkillers and physiotherapy can be successful and previous research has shown this is the best initial treatment. However, this approach does not work for everyone, and some people are left with persistent, severe low back pain impacting their health, daily activities and work. The cause of more persistent low back pain is thought to be 'wear-and-tear' (degeneration) of the spinal joints in the lower back. Spinal fusion, an operation that surgically fixes the spinal bones together in that area, may help. This type of fusion operation has been used successfully for degenerative conditions in the ankle and wrist, but its benefit remains less clear for patients with low back pain and degeneration.

We want to find out if spinal fusion surgery for a carefully selected group of patients with persistent severe low back pain, and who have already undergone non-surgical treatment, is more beneficial than continuing with best conservative (non-surgical) care. Best conservative care is an agreed patient focused treatment plan combining the use of medication, exercise, and pain control strategies. We also want to find out if the surgery is good value for money for the NHS.

How will the research be done?

A special type of study called a randomised controlled trial is needed to answer this question. This involves assigning participants to different treatments using a process called randomisation so the effects of each treatment can be compared fairly. After giving consent, 270 participants will be included and will have an equal chance of being allocated to receive either fusion surgery or best conservative (non-surgical) care (135 per group). Participants allocated to best conservative care will have some "tailoring" of their care (to make it the very best possible). Over a 24-month period we will ask participants about their physical function, pain, mental health, general health, quality of life, days off work and healthcare use. We also plan longer-term follow-up (at 5 years) if funding can be secured.

Who has been involved in the design of the project?

A PPI (Patient and Public Involvement) group of 8 patients has helped the study team shape the study, including having had five specific PPI meetings. A trial specific PPI group continue to input in the delivery of this study, this includes patients with experience of long-term, severe low back pain and fusion surgery. One is also a co-applicant on the study. Two other patient representatives sit on the Trial Steering Committee, which is a key oversight group for the study.

How will the results of this research be used?

At present lumbar spine fusion for low back pain is used rarely within the NHS. This study will provide evidence to guide decisions for patients and doctors about whether such surgery should be offered in the future to carefully selected patients with ongoing and severe low back pain. The findings will be made available to patients and the public, clinicians, healthcare managers, commissioners and national bodies (via spinal healthcare organisations, charities and policy-making such as the National Back Pain Pathway and NICE guidelines).

Who are the research team?

FORENSIC-UK has been designed by a team of spinal surgeons, physiotherapists, patients, pain specialists, researchers, statisticians, and health economists from several universities and hospitals, including Oxford, Cardiff, Keele, Sheffield, Birmingham, Bristol, Leeds, Southampton, Frimley, and

University College London. An Australian research group is also involved and conducting a very similar study to the same protocol (a 'sister' study known as FORENSIC-Australia).

6. STUDY SYNOPSIS

Full Study Title:	The clinical and cost-effectiveness of lumbar fusion surgery for patients with persistent, severe low back pain (LBP)
Short Title:	FusiOn veRsus bEst coNServatIve Care (the FORENSIC-UK trial)
Study Acronym:	FORENSIC-UK
Study Design:	A multicentre, 2 arm superiority RCT with internal pilot, integrated QRI and health economic analysis. Participants will be randomised (1:1) to either Lumbar Fusion Surgery (LFS) or continued Best Conservative Care (BCC).
Study Participants/Target Population:	Adults aged 18 to 65 with persistent severe Lower Back Pain (LBP) with recent imaging evidence of lumbar degeneration who have already undergone previous conservative treatment.

Eligibility criteria	**Inclusion:**
	• Aged 18 to 65.
	• Episode of Low Back Pain (lasting ≥6 months).
	• Low Back Pain is ≥6 on a 0-10 Numerical Rating Score (NRS).
	• Have undergone previous non-surgery treatment that aligns with best practice guidelines, (*National Institute of Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management (Clinical Guideline [NG59]) London 2016. Sect. 1.9*)[54] e.g.
	  • a course of physical therapy
	  • a course of psychological therapy
	  • a course of treatment from a multi-disciplinary team
	  • a course of treatment from specialist medical care
	  • Medial branch blocks/radiofrequency denervation
	  • Analgesia
	• Willing and able to provide informed consent.
	• Recent evidence (within the last 12 months) of lumbar degenerative disease using appropriate imaging (Magnetic Resonance Imaging [MRI] +/- Single Photon Emission Computed Tomography/Computed Tomography [SPECT/CT), +/- previous discectomy/decompression.
	• Suitable for both lumbar fusion surgery (LFS) at 1 or 2 lumbar spine levels and best conservative care (BCC).
	
	Exclusion:
	• Has low-back related leg pain more severe than low back pain e.g.: Claudication.
	• Pain in any other body region more severe than low back pain

<table>
<tr><td></td><td colspan="2">Previous (or attempted) LFS.
Has psychiatric disorders (e.g. diagnosed personality disorders, post-traumatic stress disorder, drug or alcohol abuse/addiction, diagnosis of severe depression).
Radiculopathy or claudication or clinical signs of nerve decompression where the treatment plan includes offering a direct or indirect decompression along with the fusion.
Any other reasons indicated for lumbar fusion surgery (LFS) e.g. deformity, infection, tumours, instability (due to spondylolisthesis of grade 2 or above), spinal fracture, systematic inflammatory disease.</td></tr>
<tr><td>No. of study arms</td><td colspan="2">Two</td></tr>
<tr><td>Intervention</td><td colspan="2">Lumbar Fusion Surgery [LFS] (& post-operative care)</td></tr>
<tr><td>Comparator</td><td colspan="2">Best Conservative Care (BCC)</td></tr>
<tr><td>Planned Sample Size:</td><td colspan="2">270 participants (135 per arm)</td></tr>
<tr><td>Target no. of centres:</td><td colspan="2">Approximately 20 UK NHS Hospitals</td></tr>
<tr><td>Planned recruitment duration:</td><td colspan="2">Recruitment is expected to last for 24 months</td></tr>
<tr><td>Duration of intervention/treatment:</td><td colspan="2">Intervention: Lumbar Fusion Surgery [LFS] and inpatient stay (& post-operative care and physiotherapy)

Comparator: Best Conservative Care (BCC)</td></tr>
<tr><td>Follow-up duration:</td><td colspan="2">Each participant will be followed up for 24 months from randomisation.</td></tr>
<tr><td></td><td>Objectives</td><td>Outcome Measures</td></tr>
<tr><td>Primary objective and outcome measure:</td><td>1) To test for superiority of lumbar fusion surgery versus continued best conservative (non-surgical) care on disability (physical function) in patients with severe persistent LBP and lumbar degenerative disease.</td><td>LBP-related physical function using the Oswestry Disability Index (ODI) at 24 months post randomisation.</td></tr>
<tr><td>Secondary objectives and outcome measures:</td><td>2) To investigate the cost-effectiveness of lumbar fusion surgery compared with continued best conservative care.</td><td>LBP severity (Numerical Rating Scale) monthly – post randomisation.</td></tr>
<tr><td></td><td colspan="2">Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main protocol for full study objectives and outcome measures.</td></tr>
<tr><td>QuinteT Recruitment Intervention (QRI/Information Study</td><td>1. To understand the recruitment process in the FORENSIC-UK Study (Phase 1).</td><td>The QRI team will present a summary of anonymised findings emerging from the QRI, based upon:</td></tr>
</table>

in patient facing documents)	2. To develop strategies to optimise recruitment and informed consent (Phase 2).	1(a). Analysis of screening log data, audio recordings of recruitment appointments and interviews with the TMG, recruiters and potential participants for FORENSIC-UK. 1(b). Results from the mapping of recruitment processes at FORENSIC-UK study sites. 2(a). Suggestions will be made to change aspects of design, conduct, organisation or training.

7. ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
AE	Adverse Event
AR	Adverse Reaction/Response
AX Hub	Axial Spondylarthritis Clinic
BAME	Black and Asian Minority Ethnic
BCC	Best Conservative Care
BMP	Bone Morphogenic Protein
BSR	British Spine Registry
CA	Conversation Analysis
CAG	Clinical Advisory Group
CATS	Clinical Assessment and Triage Services
CI	Chief Investigator
CMATS	Clinical Musculoskeletal Assessment and Treatment Service
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTU	Clinical Trials Unit
DSMC	Data and Safety Monitoring Committee
DVT	Deep Vein Thrombosis
EQ-5D-5L	European Quality of Life- 5 Dimensions - 5 Level version
FORENSIC	FusiOn veRsus bEst coNServatIve Care
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPE	Global Perceived Effects
GP	General Practitioner
HCP	Health Care Professional
HEAP	Health Economic Analysis Plan
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRG	Healthcare Resource Group
iCAT	Integrated Clinical Assessment and Treatment
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IMD	Index of Multiple Deprivation
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LBP	Lower Back Pain
LFS	Lumbar Fusion Surgery
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MDT	Multi-Disciplinary Team
MSK	Musculoskeletal Service
NG59 GDG	NICE Guidelines – Guideline Development Group
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health and Care Research
NLBRPP	National Low Back Pain and Radicular Pain Pathway
NRS	Numerical Rating Score
MCAT	Musculoskeletal Clinical Assessment and Triage
OCTRU	Oxford Clinical Trials Research Unit
ODI	Oswestry Disability Index
PE	Pulmonary Embolism
PI	Principal Investigator
PIC	Participant Identification Centres
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
PSEQ	Pain Self Efficacy Questionnaire
PHQ 8	Patient Health Questionnaire 8-item
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
RDSF	Research Data Storage Facility
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SEAR	The Screened, Eligible, Approached, Randomised Framework
SAP	Statistical Analysis Plan
SDM	Shared Decision Making
SDV	Source Data Verification
SITU	Surgical Intervention Trials Unit
SMS	Short Message Service
SOC	System Organ Class
SOP	Standard Operating Procedure
SPECT	Single-Photon Emission Computerised Tomography
SPIRIT	Standard protocol Items: Recommendations for Interventional Trials
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSK	Tampa Scale of Kinesiophobia
UKSSB	United Kingdom Spine Societies Board

8. BACKGROUND INFORMATION AND RATIONALE

Lumbar fusion is an operation to fix vertebrae and use bone graft to achieve fusion. It is included in the National Institute for Health and Care Excellence (NICE) guidelines [1] and the National Low Back and Radicular Pain Pathway (NLBRPP).[2] However, its effectiveness for lower back pain (LBP) associated with lumbar degenerative changes compared to conservative care is unclear,[3-6] leading to NICE [1] stating in 2016 that it should only be used in a randomised controlled trial (RCT). There were 4000 fusions in the NHS in 2009/10 reducing to < 1000 in 2018/19 (Hospital Episode Statistics (HES) data)[55]. In the NLBRPP, spinal fusion is included only as an option if patients have failed non-surgical treatments (currently, given NICE's statement, fusion surgery is not an option for these patients in the UK). We do not know if this surgery is beneficial or cost effective for this patient group because previous studies[3-6] have weaknesses which include high cross-over rates, heterogeneous populations, and varied approaches to conservative care.

Worldwide, LBP is the leading cause of disability[7] with highest burden from persistent, severe LBP.[8] Whilst the Lancet LBP Series highlighted past errors of over-reliance on medications and surgery [9, 10] the current UK situation (lack of quality rehabilitation programmes and the decommissioning of LFS) has left a substantial cohort of patients in difficulty. The NIHR has identified that LFS may be an option but requires evaluation as it is expensive and has risks. LFS may be better than continued best conservative care (BCC) [non-surgical] for these patients who have failed to improve with previous conservative treatments and who are considered appropriate patients for lumbar fusion surgery. It is crucial that patients have tried recommended conservative treatments before they are considered for spinal fusion, thereby reserving LFS for patients who have not had good response from previous conservative care. LFS may be better than BCC for appropriate patients with specific characteristics.

The few RCTs that have compared LFS to non-surgical care for LBP [10-15] are limited by small samples, cross-over, selection bias and widely varying non-surgical care. Studies [5, 6, 16-19] conclude no clear advantage of fusion but show modest benefits for function, pain and general health. The only previous UK trial [14] concluded there was no clear evidence that LFS was better than intensive rehabilitation although the trial included a mix of patients with chronic LBP, including those with spondylolisthesis and previous laminectomy surgery. That trial changed practice, and better quality conservative treatment pathways now exist (but are not always readily available), and no work has examined the more contemporary issue of whether LFS has a place in treating patients who have not responded to recommended conservative care interventions.[1, 18] The most recent systematic review [20] and meta-analysis of 6 RCTs concluded LFS is no better than non-operative care for pain and disability at short, or long term follow-up. It also concluded that previous RCTs had relatively 'lax' patient inclusion criteria and advised future RCTs to better define their selection criteria.

9. OBJECTIVES AND OUTCOME MEASURES

9.1. Aim

The aim of the FORENSIC-UK study is to assess if lumbar fusion surgery (LFS) is more clinically and cost effective than continued best conservative care (BCC) for people with persistent lower back pain (LBP) and lumbar degenerative disease as measured by a validated LBP disability score (Oswestry Disability Index) at 24 months follow-up.

Our objectives are:

1) To test for superiority of LFS versus BCC on disability (physical function) in patients with persistent LBP.

2) To investigate the cost-effectiveness of LFS compared with BCC.

A Quintet Recruitment Intervention (QRI) is also included with the following objectives:

1) To understand the recruitment process in the FORENSIC-UK study
2) To develop strategies to optimise recruitment and informed consent

9.2. Primary and secondary objectives and outcome measures

The primary outcome is the Oswestry Disability Index (ODI), a validated LBP physical function disability score, at 24 months (also measured at 6 & 12 months). The ODI is well validated and a commonly used outcome measure in LBP RCTs including surgery and contains 10 items that assess domains including personal care, walking, standing and sleeping.

Secondary outcomes include LBP severity (Numerical Rating Scale), measured using monthly SMS data or by email or paper options dependant on participant preference (over 24 months). We will also collect participant reported outcome measures reported via questionnaires at 6, 12 and 24 months. The participant questionnaires include: quality of life (EQ-5D-5L), depression (PHQ8), fear avoidance beliefs (TSK), pain self-efficacy (PSEQ), work outcomes (days-off-work), comparison of back pain from entering the study to timepoint of questionnaire using Global Perceived Effect Scale (GPE), healthcare use (NHS and non-NHS including concurrent treatments ie: analgesia) and treatment satisfaction measured at 24 months follow-up with scoring 0-10 (with 10 being very satisfied with treatment).

Further secondary outcome measures will be collected throughout the 24 months using specially designed CRF's to be completed by clinicians and researchers regarding surgery, Best Conservative Care (BCC), Surgery complications (intra and post operative), further surgery including re-admission, Fusion Failure (LFS participants only), BCC complications.

Objective	**Outcome measure**	**Time point(s) of evaluation of this outcome measure (if applicable)**
1. To test for superiority of lumber fusion surgery (LFS) versus BCC on disability (physical function) in patients with persistent lower back pain (LBP) 2. To investigate the cost-effectiveness of LFS compared with best conservative care (BCC)	**Primary:** LBP-related physical function using the Oswestry Disability Index (ODI version 2.1b) **Secondary:** LBP severity (Numerical Rating Scale) monthly – post randomisation Participant reported outcomes	24 months (also measured at 6 & 12 months)

	measured at 6m, 12m and 24m post randomisation: 1. Quality of Life: EQ-5D-5L 2. Pain Self-efficacy Questionnaire (PSEQ) 3. Patient Health Questionnaire (PHQ8) 4. Tampa Scale of Kinesiophobia (TSK) 5. Global Perceived Effect Scale (GPE) 6. Healthcare Resources Use 7. Work status 8. Treatment Satisfaction at 24m Follow up only Additional outcome measures: 9. Complications Data (inc. re-admissions)	
QuinteT Recruitment Intervention (QRI) Objectives		
QuinteT Recruitment Intervention (QRI or Information Study in patient facing documents)	1. To understand the recruitment process in the FORENSIC-UK Study (Phase 1). 2. To develop strategies to optimise recruitment and informed consent (Phase 2).	The QRI team will present a summary of anonymised findings emerging from the QRI, based upon: 1(a). Analysis of screening log data, audio recordings of recruitment appointments and interviews with the TMG, recruiters and potential participants for FORENSIC-UK. 1(b). Results from the mapping of recruitment processes at FORENSIC-UK study sites. 2(a). Suggestions will be made to change aspects of design, conduct, organisation or training.

9.3. Choice of primary outcome

The Oswestry Disability Index (ODI) is a well validated and commonly used outcome measure in low back pain (LBP) RCTs including surgery, contains 10 items that assess domains including personal care, walking, standing and sleeping.

Follow-up at 24 months after randomisation allows participants in both arms to reach at least 1 year follow-up after intervention taking into account treatment waiting lists.

9.4. Use of core outcome sets

The outcomes included in this trial reflect the core outcome sets for LBP RCTs,[21] and Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidance. [22]

9.5. Exploratory objectives/additional mechanistic objectives outcomes

There are no additional exploratory/mechanistic objectives/outcomes in this study.

10. STUDY DESIGN AND SETTING

The study is a multicentre, 2 parallel arm (lumber fusion surgery (LFS) versus best conservative care (BCC) [control]), superiority RCT with an internal pilot, integrated QuinteT Recruitment Intervention (QRI) and health economic analysis. The design is pragmatic and accounts for the main study purpose (to assess clinical and cost effectiveness of LFS in the contemporary NHS setting) whilst accounting for the current NICE guidance for persistent LBP.

270 participants (135 per arm) will be recruited from approximately 20 sites in the UK. Participants will be randomised to receive lumber fusion surgery or best conservative care.

A study flow chart is provided in APPENDIX 1 – study FLOW CHART.

Prior to study enrolment, all potential participants will have undergone core conservative therapies recommended in national guidance, such as exercise therapy, analgesia, and/or a psychologically informed LBP programme. Core therapies may have been delivered virtually, face to face, individually or in a group.

All participants will be suitable for both LFS and BCC. Patients with neurological symptoms for which a surgeon would rather consider decompression surgery due to lumbar spine deformity, lumbar spine infection, tumours, spondylolisthesis of grade 2 or above, spinal fracture, systemic inflammatory disease or previous fusion surgery, will be excluded. Those who have pain in multiple body sites, where the LBP is not the priority pain problem, will also be excluded.

Recruitment to the study will occur following discussion between a potential participant and review of the eligibility criteria by a participating surgeon at an outpatient clinic appointment in secondary care. As outlined earlier in Section 8, as LFS in not available as a treatment option for this group in the NHS apart from when used in an RCT, patients will not currently be routinely referred to secondary care for surgeon review for LFS. Therefore, potential eligible participants will need to be identified in various other parts of the patient pathways e.g. Musculoskeletal Clinical Assessment and Triage/ Integrated Clinical Assessment and Treatment (MCAT/iCAT) services, community physiotherapy centres, GP's and Primary Care and be referred through where appropriate to secondary care. We will also recruit from Orthopaedic centres and Neurosurgery centres in secondary care.

If eligible participants wish to participate in the study and provide written consent, following baseline data collection they will then be randomised to either: (1) Lumbar Fusion Surgery (LFS & usual post-operative care) or (2) Best Conservative Care (BCC).

Participants randomised to LFS will be listed and undergo spinal fusion surgery at one or two lumbar spine levels as determined by the opinion of the surgeon performing the operation. Any standard accepted fusion method/graft option is allowed, except the use of bone morphogenic protein (BMP), to maximise external validity.

BCC will commence with a review by a senior spinal practitioner or pain physician (usually a musculoskeletal physiotherapist) experienced in assessing and treating LBP with links to a wider multidisciplinary team. Following this review, participants will be offered a package of personalised BCC, based on the participant's individual goals, abilities, and expectations. The content of BCC includes non-surgical interventions recommended by NICE,[1] the National Low Back and Radicular Pain Pathway (NLBRPP),[23] and approved by our Clinical Advisory Group (CAG) (see Section 13).

10.1. Internal pilot/Decision points

The embedded pilot phase will take place in 10 sites with staggered initiation over a period of 10 months. The overall participant recruitment target for this period will be 45 (site recruitment target rate of 1-2 participants per month). The aim of the pilot will be to assess the recruitment strategy, modifying as appropriate. The internal pilot phase will use progression criteria (stop/amend/go). Each item will be assigned red, amber, or green to represent performance. The Trial Management Group (TMG) and Trial Steering Committee (TSC) will review the results of the pilot phase to determine further trial progression (stop/amend/go) and need for further site support or protocol amendments.

The internal pilot phase will mirror the procedures and logistics undertaken in the main definitive trial. It is intended that the trial will progress seamlessly into the main phase, with internal pilot phase participants included in the final analysis. This pilot phase will also confirm the expected rate of recruitment for the main trial phase. Following this internal pilot phase, additional sites (anticipate being up to 20 in total) across the UK will then be opened to recruitment to reach the overall target sample size of 270 participants.

Table 1 : Progression criteria (stop/amend/go criteria) for the internal pilot phase

Progression criteria	Red	Amber	Green
Trial recruitment % complete of total for internal pilot (n=45)	<60%	60%-99%	100%
Total number of participants recruited	<27	27-45	>45
Recruitment rate/site/month*	0.5	0.5-0.75	>0.75
Number of sites opened in 10 months	<6	6-9	10

NB: * = individual sites will vary, and figures are means across sites. The values are given in the metrics requested by the funder, viz. rate of participants per site per month.

10.2. QuinteT Recruitment Intervention (QRI or 'Information Study' in participant facing information)

Recruitment challenges may result from difficulties identifying and /or approaching eligible participants or overcoming their possible preferences for surgery, given that LFS is unavailable outside RCTs in the NHS.

The QuinteT Recruitment Intervention (QRI) aims to optimise recruitment and safeguard informed consent.[24] It identifies organisational barriers, difficulties with clinician equipoise, patient preferences and appropriate terminology. It has strong evidence of effectiveness in complex RCTs,[25] including orthopaedic surgery.[26] The QRI team will lead an intensive investigation to understand recruitment challenges and provide training and support to optimise recruitment.

The QRI comprises two iterative and overlapping phases.[24] Phase 1 combines analysis of screening log data with qualitative research undertaken with patient and professional groups to gain a detailed understanding of the recruitment process. Phase 2 involves detailed feedback of findings to the Chief Investigator and TMG, and tailored interventions formulated to improve study recruitment and informed consent.

QRI Phase 1

We will investigate what could influence recruitment during study set-up. We will aim to train Health and Research Professionals before recruitment begins by using evidence from previous QRIs, [27, 28] training programmes [29, 30] and data collected from patient and professional groups involved in FORENSIC-UK. Recruitment processes will be investigated in-depth at study sites as they open. The QRI researcher will use a multi-faceted, flexible, five-pronged approach (see below), using triangulation of data collected [31] to investigate site-specific and general recruitment obstacles:

1. The QRI researcher will observe TMG meetings during which the more detailed trial protocol is developed, with a focus on discussions and presentation of equipoise, eligibility criteria and the component parts of the intervention and comparator arms. The FORENSIC-UK Patient and Public Involvement and Engagement (PPIE) panel views on equipoise and study development will be investigated concurrently and in parallel during regular trial PPI meetings. Health Care Professionals' views will be explored in site training workshops involving relevant clinical co-applicants and study recruiters at all collaborating sites. Discussions will centre around potential participant screening and the identification pathway, the study eligibility criteria and equipoise.

2. Investigators and research teams will collect details of patients at each recruiting site who are screened (S), eligible (E), approached to take part (A), and randomised (R) for analysis using the SEAR framework.[32] Analysis will identify points in the recruitment pathway at which patients continue with recruitment to the trial or drop out.

3. Audio-recording of study discussion visits. Recruitment appointments where patients are screened for eligibility and participation in the trial are discussed will be audio-recorded with consent. These appointments provide insight into actual presentation of information to patients, identify recruitment difficulties and provide the basis for rapid feedback to sites and/or training as required. Recordings will be sought from a range of recruiting sites to ensure maximum variation and analysed by the QRI researcher (target minimum 50 recordings across at least 10 sites). All Health Research Professional's (HRP) at each participating site will be approached during the initial site training and site set-up and be

invited to take part in the Information study. Written consent will be required before the HRP can undertake any audio recordings. Consent to participate in the Information Study will be recorded on the site Delegation Log and a copy of the consent form will be filed in the site file or within QRI secure storage.

4. In-depth interviews. In-depth interviews will be conducted and audio-recorded by the QRI researcher with (i) members of the TMG (n=4-8), (ii) healthcare professionals (surgeons, physiotherapists etc.) involved in trial recruitment (n=15-20), and (iii) a sample of eligible patients who have been approached to take part in the trial (n=15-20). Interviews will investigate acceptability of the study design, views about eligibility criteria in practice intentions in relation to and variation in application of the protocol in clinical sites and patient preferences thus identifying recruitment barriers.

5. Study documentation review: Study documentation, including the participant information sheets and informed consent forms will be scrutinised to ensure the optimisation of presentation of the study and its arms, applying experience from previous surgical QRIs and also the specific insights gained when mapping recruitment pathways, interviewing patients and clinicians, and recording recruitment conversations (components 1-4).

QRI Phase 2

Findings from the investigation of recruitment within FORENSIC-UK (QRI phase 1) will be fed back iteratively to the Chief Investigator and the TMG to determine a joint plan of actions to optimise recruitment. Actions may include feedback to individuals or in groups as appropriate and will include template patient pathways, individualised or generic 'tips' sheets for recruiters and delivery of recruiter training.

Training of recruiters will raise awareness of key 'hidden' challenges when recruiting participants to trials comparing surgery versus conservative care and how these can be addressed, [30, 33] as well as including insights into particular issues identified as relevant to the FORENSIC-UK trial in how to deal with preferences and convey equipoise between fusion surgery and best conservative care. The QRI researcher will analyse data using the SEAR framework to observe whether recruitment changes following feedback and training as new sites open.[32] The QRI in the main trial will be informed by the pilot phase findings. QRI actions will be evaluated throughout, using screening log and qualitative data from interviews and audio-recordings.

QRI data analysis: Interview data will be transcribed with identifying data removed wherever possible. Audio-recorded recruitment consultation data will be subject to targeted transcription [31] with relevant sections first identified then transcribed for fuller analysis and again identifying data removed. Analyses of interview and audio-recorded data will combine content and thematic analysis, some elements of conversation analysis (CA) and some simple quantification as described in detail in Rooshenas et al. 2019.[25] Screening log data will be analysed to report simple descriptive values for total numbers screened, approached, eligible and randomised at individual sites and across the trial as a whole, with reasons why patients were not eligible, approached or randomised presented for individual sites and trial wide. These data will be reported monthly to the TMG. [32]

10.3. Recruiting sites/site types

Participants will be recruited from secondary care outpatient clinics at approximately 20 NHS hospital sites and linked spinal services. Patients will be identified from UK NHS musculoskeletal / spinal clinics including Musculoskeletal Clinical Assessment and Triage/ Integrated Clinical Assessment and Treatment (MCAT/iCAT) services, community physiotherapy centres, GP's and Primary Care and be referred where appropriate to secondary care. We will also recruit from Orthopaedic centres and Neurosurgery centres in secondary care.

10.4. Participant Identification Centres

Community services (e.g. physiotherapy) may act as Participant Identification Centres (PICs) to identify potentially eligible participants, depending on the set up of local services.

10.5. Collection of outcome data and follow-up assessments

Participants will be asked to complete a baseline questionnaire and receive communications from the FORENSIC-UK team to collect follow-up questionnaire outcome data at 6-, 12- and 24-months following randomisation. We will also collect a monthly pain score from participants via SMS text messaging, by email or by post using a paper form (participant preference) using the Numerical Rating Score (NRS).

Refer to section 17 for full details of outcome data collection and follow-up assessments.

10.6. Countries of recruitment

It is not anticipated that this study will open in non-UK sites. However, it is planned that a parallel Australian trial conducted to the same protocol will be led by co-applicant Professor Foster and an Australian team of clinicians and methodologists (the FORENSIC-Australia trial [FORENSIC-AUS]).

10.7. Duration of participant involvement

Participants will be in the study for approximately 24 months from randomisation to last protocol follow-up questionnaire completion.

10.8. Post-study treatment/care and follow-up

Following a participant's final follow-up questionnaire, should they require further healthcare, this will follow standard care pathways.

10.9. Central review procedures

Not applicable for this study.

10.10. Use of NHS Digital data (including data from registries)

We will consent all participants for long-term follow-up and access to their routine NHS records (British Spine Registry (BSR) and Hospital Episode Statistics (HES) data linkage) to facilitate assessment of long-term outcomes.

We will consent all participants for their digital records from the study to be shared with the British Spinal Registry (BSR).

The results of follow-up beyond 24 months is anticipated to be funded separately and reported at a later time-point, separate to the final report to the funder. We will request consent for this follow-up during the main study consent process.

10.11. Expected recruitment rate.

The anticipated monthly recruitment rate is 1 participant per month per site after the initial pilot. There will be a phased introduction to the opening of sites, and it is expected that all sites will be open within 15 months of starting recruitment. Each of the 20 NHS Trusts (and community partners) planned to take part in the FORENSIC-UK study currently manage patients in Clinical Musculoskeletal Assessment and Treatment Service CMATS clinics, pain clinics, spine clinics, primary care clinics, via GP surgeries or with first contact practitioners. The recruitment rate for the study was conservatively estimated to allow for the implementation of the trial into current pathways and pressures on resources within the NHS.

10.12. Equality, diversity and inclusion for study participants

As the trial is embedded in normal NHS care it is intended to be inclusive (all patients who meet our selection criteria at participating sites are candidates). We will endeavour to include under-served groups and use the published toolkit for increasing participation of Black and Asian minority ethnic (BAME) groups [38] in health and care research monitoring their inclusion using the QRI screening log data. There are no concerns about equality, diversity or inclusion/exclusion from a research perspective. There are no exclusions for geographical location, disability, gender reassignment, marriage and civil partnership. We have set age exclusions for patients older than 65 years because of issues surrounding spinal stenosis seen in an older population, i.e. a change in pathology involving neurological compression requiring a different surgery.

Translation materials and capability will reflect what is available at local NHS sites. Sites with dual language are accommodated as routine. Post intervention delivery interviews (via the process evaluation) will be carried out in line with the same principles. We are keen to be as inclusive and as representative of the studied population as possible in line with current NIHR guidelines and advice.

In addition to study participants, we intend to include a representative sample of clinicians and trial personnel in line with The Royal College of Surgeons recommendations[52] there is a particular emphasis on Associate Principal Investigators and an enthusiasm to introduce surgeons previously inexperienced in trials conduct to this study as part of the management and recruitment process.

10.13. End of study

The end of study is the point at which all the data has been entered and all queries resolved.

The sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

11. PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator and has been assigned the responsibility on the site delegation log.

11.1. Timing of eligibility assessment

Potentially eligible participants will be identified from various sources e.g. e.g. Musculoskeletal Clinical Assessment and Triage/ Integrated Clinical Assessment and Treatment (MCAT/iCAT) services

and referred through to secondary care for an outpatient appointment with a recruiting surgeon where eligibility will be assessed.

11.2. Overall description of study participants

Participants will be adults aged 18 to 65 with persistent, severe LBP with recent imaging evidence of lumbar degenerative disease. Prior to study enrolment, all potential participants will have undergone core conservative therapies recommended in national guidance, such as exercise therapy or analgesia and a locally available 'elevated' element, such as a psychologically informed LBP programme or review by a pain team. Conservative therapies may have been delivered virtually, face to face, individually or in a group.

All participants will be suitable for both LFS and BCC. Patients with neurological symptoms for whom a surgeon considers decompression is needed, lumbar spine deformity, infection, tumours, spondylolisthesis of grade 2 or above, spinal fracture), systemic inflammatory disease or previous fusion surgery, will be excluded. Those who have pain in multiple body sites, where the LBP is not the priority pain problem, will also be excluded.

Written informed consent must be obtained before any study specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI) based on the following criteria:

11.3. Inclusion Criteria

A patient will be eligible for inclusion in this study if all of the following criteria apply:

- Aged 18 to 65.
- Episode of Low Back Pain (lasting ≥6 months).
- Low Back Pain is ≥6 on a 0-10 Numerical Rating Score (NRS).
- Have undergone previous non-surgery treatment that aligns with best practice guidelines (*National Institute of Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management (Clinical Guideline [NG59]) London 2016. Sect. 1.9*)
  e.g.
    - a course of physical therapy
    - a course of psychological therapy
    - a course of treatment from a multi-disciplinary team
    - a course of treatment from specialist medical care
    - Medial branch blocks/Radiofrequency denervation
    - Analgesia

- Willing and able to provide informed consent
- Recent evidence (within the last 12 months) of lumbar degenerative disease using appropriate imaging (Magnetic Resonance Imaging [MRI] +/- Single Photon Emission Computed Tomography/Computed Tomography [SPECT/CT), +/- previous discectomy/decompression.
- Suitable for both lumbar fusion surgery (LFS) at 1 or 2 lumbar spine levels and best conservative care (BCC).

Exclusion:

- Has low-back related leg pain more severe than low back pain e.g. Claudication.
- Pain in any other body region more severe than low back pain.
- Previous (or attempted) LFS.

- Has psychiatric disorders (e.g. diagnosed personality disorders, post-traumatic stress disorder, drug or alcohol abuse/addiction, diagnosis of severe depression).
- Radiculopathy or claudication or clinical signs of nerve decompression where the treatment plan includes offering a direct or indirect decompression along with the fusion.
- Any other reasons indicated for lumbar fusion surgery (LFS) e.g. deformity, infection, tumours, instability (due to spondylolisthesis of grade 2 or above), spinal fracture, systematic inflammatory disease.

Potential eligible participants will have routine imaging under standard NHS care which will be assessed during eligibility and screening. If no recent imaging (within the previous 12 months) is available, they may be referred back to their NHS provider for imaging to be taken.

Potential participants will have expected to have undergone previous non-surgery treatment for at least 6 months and would have undertaken at least one of the treatments listed in the inclusion criteria. Assessment of each patient for their eligibility following non-surgery treatments will be made by the treating clinician as each site will have localised treatment options for non-surgery treatments in low back pain.

11.4. Rationale for inclusion and exclusion criteria

Patient characterisation and selection is a challenging element of this trial, highlighted by a recent UK spinal surgeon survey.[34] Being able to identify the group of patients who have undergone sufficient conservative care to justify eligibility for LFS, yet remain able to benefit from (and willing to try) additional treatment options in a BCC control arm, is key.

In addition, the most recent systematic review of LFS versus non-operative management highlighted that stricter selection criteria are needed in future RCTs.[20] Therefore, eligible patients are more tightly defined in this trial, compared to the 6 previous RCTs.

Participants must be potential candidates for 1 or 2 level LFS as confirmed by a participating spinal surgeon.[23] They must also have undergone previous conservative care that is recommended in national guidelines (recommended by NICE and the NLBRPP).[2, 23]

Prior to study enrolment, all potential participants will have undergone core therapy (assessment, simple analgesia, individualised or group exercise). Potential participants must also have trialled another 'elevated' locally available conservative therapy (combined physical and psychological rehabilitation, recommended injections, or review with a local pain management service).

We will exclude patients with spondylolisthesis of Grade 2 or above. These selection criteria differentiate the FORENSIC trial from the 6 previous RCTs including the only previous UK RCT.[19]

For surgery, NICE Guideline – Guideline Development Group (NG59 [GDG]) identified 3 systematic reviews of patient characteristics potentially predicting successful outcome from surgery [35-37]; their findings have helped guide the eligibility criteria.

11.5. Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a research study. There will be no waivers regarding eligibility i.e. each participant must satisfy all the eligibility criteria. Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient onto the study the Principal Investigator or designee will confirm eligibility. If unsure whether the patient satisfies all the entry criteria and to clarify matters of clinical discretion investigators must contact the Study Office, who will contact the Chief Investigator or designated

clinicians as necessary. If in any doubt the Chief Investigator must be consulted before entering the patient. Details of the query and outcome of the decision must be documented in the TMF.

11.6. Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the Study Office for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the Study Office. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all study investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see Urgent safety measures section.

12. SCREENING AND RECRUITMENT

12.1. Participant Identification

The research team will work with the staff in each participating site to optimise the local screening and recruitment processes, which is likely to vary due to local services available and current pathway. Patients will be identified from various sources e.g. UK NHS musculoskeletal / spinal clinics including Musculoskeletal Clinical Assessment and Triage/ Integrated Clinical Assessment and Treatment (MCAT/iCAT) services, community physiotherapy centres, GP's and Primary Care and be referred through where appropriate to secondary care. We will also recruit from Orthopaedic centres and Neurosurgery centres in secondary care.

As outlined earlier, community services (e.g. physiotherapy) may act as Participant Identification Centres (PICs) to identify potentially eligible participants, depending on the set up of local services.

Potential participants identified from these services, or secondary care will be referred to an outpatient appointment in secondary care with a participating surgeon for further discussion and assessment of their eligibility. A summary participant information sheet with links to further information will be available. Details of patients screened, assessed for eligibility, approached about the study will be collected using the SEAR framework[32] during the recruitment process in secondary care.

The following methods will be used to identify potentially eligible participants:

- Searching of clinic records/hospital databases/waiting lists by the healthcare team or site research staff to identify individuals that may be eligible to enter the study where verbal consent has been obtained from individuals
- Identification during routine clinic visits, physiotherapy and pain service treatments.

12.1.1. Identification of participants during routine clinic visits

Potentially eligible participants identified will be provided with a Participant Information Sheet (PIS). The PIS information will concurrently be available on-line in digital format.

Depending upon the site, the resources available, and most importantly how the participant is dealing with their diagnosis, the recruitment process and approach may vary across and within sites. Where their usual care clinician is not a member of the research team potential participants will be asked if they verbally consent for their name and contact details to be passed to their NHS site research team who will make contact at a later time point (this may be in person in a clinic or via telephone or video call in accordance with local site practice). Alternatively, potential participants

may be given the PIS either as a paper copy or a link to access electronically and asked to call the number on it if they wish to find out more about the study.

When a potential participant is approached for permission for their details to be passed onto the local research team – if this permission is given this should be recorded in their clinical notes.

12.2. Use of screening logs

A screening log must be kept for all potential participants screened for eligibility, including any that are identified as ineligible, with the reason for being ineligible recorded; ii) all patients approached for a discussion about the trial, including reasons why eligible patients are not approached; iii) all patients accepting or declining participation including reasons for declining if given. For those identified as eligible, their ethnicity, gender and IMD score will be recorded.

12.3. Pre-study screening tests or investigations

There are no pre-study screening tests for inclusion in the study.

12.4. Re-screening if patient does not meet inclusion/exclusion criteria first time round.

If a patient does not meet the list of key inclusion/exclusion criteria first time round, they can be re-screened. Re-screening will be done on a patient-to-patient basis with clinical assessment as to suitability of the potential participant for the study. Due to the nature of the study a person can be re-screened a number of times if appropriate. Each time this occurs a new study record will be completed for that individual.

12.5. Use of social media

Social media feeds e.g. X (previously Twitter) or Blue Sky may be utilised to promote the study and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment at a site etc.). Also, it is anticipated that patient representative bodies may either create their own social media feeds regarding the study and its achievements. There will also be a trial website that participants can access for information about the study, and study progress.

13. STUDY INTERVENTION AND COMPARATOR

13.1. Lumbar Fusion Surgery [LFS] & post-operative care (intervention)

For participants randomised to LFS all commonly accepted fusion methods and graft options within the NHS will be permitted as; 1) there is no evidence of superiority for one method of LFS over another; 2) the approach will enable greater generalisability and external validity for change in practice should LFS be superior, and 3) it will facilitate recruitment of sites/surgeons (and therefore participants) to the trial, many of whom may undertake varying approaches to LFS. All methods permitted for the trial have been reviewed and agreed by the FORENSIC-UK Clinical Advisory Group (FORENSIC-UK CAG) and approved at the British Association of Spinal Surgeons (BASS) conference 2024.

The FORENSIC-UK CAG felt strongly that bone morphogenetic protein (BMP)which may be used in spinal fusion procedures is a confounder and should be excluded. Reflecting the pragmatic nature of this trial, overall level of experience of the operating surgeon will not be an inclusion factor but all surgeons performing LFS in the trial will be required to be familiar with the techniques and equipment used at their respective site. Inter-operative data will be collected on the surgical

approach to the LFS (anterior, posterior, lateral, level(s)) and the types of implants and bone graft used.

For Lumbar fusion surgery (LFS), i.e. 1 or 2 level LFS, either posterolateral or interbody, (other than excluding BMP and mixed fusion procedures [i.e. fusion with decompression, fusion with disc replacement at the same of different levels]), there are no limitations (within accepted methods) for implants, bone grafts or surgical approach, given the evidence that none are superior. LFS also includes intra/postoperative x-rays, usual review appointment (which may be via telehealth) for example at 6-8 weeks and usual post-operative care. All participants undertaking LFS will have a CT Scan at 24 months follow-up to establish fused/not fused. We will finalise mandatory/optional/prohibited components, including how to record, and check fidelity of the LFS in the internal pilot phase.[40] We will also collect data on the operation specifics i.e. date of surgery and any intraoperative complications.

Participants randomised to LFS will be placed on the relevant NHS Trust routine wait list with monitoring for symptomatic changes. If the wait list is lengthy from date of randomisation to proposed date of surgery, it is expected the treating surgeon will reassess the participant and follow the NHS Trust standard of care for surgical patients.

Investigation of the post-operative care after LFS is not the aim of this pragmatic trial, but in keeping with the pragmatic approach, post-operative care will follow usual practice at participating sites.

13.2. Best Conservative Care (BCC) (usual care/ comparator)

All participants randomised to the BCC control arm will be reviewed by a senior spinal practitioner or pain physician, (usually a senior MSK physiotherapist), with experience in delivering personalised spinal care utilising shared decision making (SDM) with links to a wider Multi-Disciplinary Team (MDT). This will include a clinical evaluation of imaging findings,[41] a formulation of the participants case and a review of previous treatment effectiveness. An individually tailored package of care based on the participant's goals and expectations will be agreed through Shared Decision Making (SDM) and labelled as 'Personalised Spinal Care'. In this way the BCC will be personalised and attractive to potential participants.

Treatment options within BCC will be aligned with national guidance (NICE and the NLBRPP) and include at least one of the following:

1. Advice (active self-management, pacing, diagnosis, aetiology, return to work etc.)
2. Analgesia
3. Exercise
4. Manual Therapy (manipulation, joint/soft tissue mobilisation)
5. Combined Physical & Psychological Programme
6. Pain Management Programme
7. Psychological Therapy (e.g. Psychologist, Cognitive Behaviour Therapy, ACT, Behavioural Therapist, Counselling)
8. Interventional Pain Management for low back pain (e.g. medial branch block/radiofrequency denervation)
9. Signposting to other health material or interventions (e.g. Dietician, smoking cessation, social prescribing)

Complex healthcare interventions such as those utilised for the conservative care of those with persistent LBP are frequently composed of multiple independent and interdependent elements. Therefore, slight variations from those listed above but within the accepted framework are

acceptable to reflect local service provision. We have worked with the FORENSIC-UK CAG to closely define essential and preferred treatment components.

If the participant randomised to BCC is placed on a long wait list for BCC treatment options they will continue with the relevant NHS Trust routine care with monitoring until they can commence their BCC treatments.

13.3. Change of Management

Change of allocated intervention from BCC to LFS is not possible as LFS is not a commissioned intervention in the NHS. However, it is possible that a limited number of participants allocated to LFS may not undergo the surgery during the trial (in line with usual surgical care more generally) and some may not take up the offer of BCC. These changes of management will be investigated in the QRI, and our aim is to keep these to a minimum. Change of management for both arms will be monitored and accounted for in the secondary analysis.

13.4. Intervention Fidelity

Assessment of the fidelity of interventions is key for both arms of the FORENSIC-UK trial. The two arms of the trial present different types of fidelity and adherence issues. We will collect high level process data throughout the trial to record intervention fidelity (on the part of healthcare providers) and adherence (on the part of trial participants).

Fidelity of the BCC arm

We will collect data on both intervention adherence (on the part of participants) and intervention fidelity (on the part of clinicians). Firstly, collection methods for adherence data from all participants in the BCC arm have been shaped by our PPIE group and CAG. Specifically, this data will consist of; a) attendance data from bespoke case report forms (CRFs) and completed by BCC delivery personnel, and b) BCC outcome statement at the end of the BCC intervention. Treatment satisfaction questionnaire will also be asked at 24m follow-up.

Fidelity of the LFS arm

Issues of adherence and fidelity are more straightforward for LFS (there are no grades of adherence to the surgery), but a different set of fidelity issues exist. A surgical procedure CRF will be included to record what was done at operation. It is also important to ascertain whether lumbar bony fusion has occurred or not, especially for interpretation of trial results. A follow-up CT scan for those who have LFS in the trial, at 24 months post-date of randomisation, will provide these data.

The assessed fidelity will be fed back to sites for the duration of the trial, including evaluation of whether intervention fidelity changes during the trial. This is in keeping with the revised guidelines from MRC on complex healthcare interventions and similar approaches have been utilised elsewhere.[46]

14. INFORMED CONSENT

14.1. Pre-study screening consent procedure

Not applicable. No pre-study screening tests/assessments are required for this study. See section 12.

14.2. Consent to participate in the FORENSIC-UK trial

Informed consent will be sought and if a person approached is willing and capable to provide informed consent it will be collected by a member of the site research team listed on the delegation

log from each potential participant before they undergo any study-related procedures or interventions related to the study.

A member of the site research team will explain the details of the study in addition to the already presented Participant Information Sheet, ensuring that the potential participant has sufficient time to consider participating or not. A member of the site research team (authorised to do so on the delegation log) will answer any questions that the potential participant has concerning study participation.

14.3. Time allowed to decide to take part

Potential participants will be given as much time as they wish to consider the information and will have the opportunity to ask any questions to the site research team (authorised to do so on the delegation log), Investigator, their GP or other independent parties to decide whether they wish to take part in the study and completion of the Informed Consent Form

The participant and the Investigator (or authorised designee) must personally sign and date the current approved version of the informed consent form. A copy of the fully signed consent form will be given to the participant and a further copy given to the CTU study team if the participant has agreed to any of the four optional aspects of consent.

The Informed Consent Form will usually be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on the study database, REDCap), however, paper consent forms will also be made available for use in situations where electronic consent is not possible or suitable. Where it is not possible for a consent form to be completed in clinic (for example, if a participant has only had telephone appointments), remote electronic consent may also be used.

If a potential participant wishes to have more time to consider participating in the study following their initial discussion in clinic, they will be offered the opportunity to complete the consent remotely at a later time using the remote electronic consent form.

Where consent forms are completed electronically signatures will be either achieved by a finger tracing across a tablet device or using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen.

Where electronic consent is used and the participant has an email address, they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have/does not provide an email address the site research team will be able to print a copy of the signed ICF and provide this to the participant. A copy of the electronic consent form downloaded from the study database should be placed in the Investigator Site File and a copy in the participant's medical record.

Remote eConsent (using REDCap) will be obtained in accordance with OCTRU's standard operating procedure for obtaining consent. Where remote consent will be used following the potential participants initial clinic visit and consultation, they will be asked to provide an e-mail address for receiving consent documents prior to obtaining written informed consent. Potential participants will receive a unique link via e-mail to an electronic consent form which may then be completed remotely. Once completed this form will be countersigned by a member of the site research team authorised to do so and then sent, via e-mail, to the participant as a PDF document. A member of the site research team will be required to countersign all consent forms completed remotely, in the same way as for paper forms, and verify the identity of the participant.

The potential participant's e-mail address will not be retained within any study systems once this e-mail has been sent, ensuring that patients who decide not to consent will not have their e-mail address retained by the central study team. Patients that do consent to study participation will receive a copy of the fully completed consent form via e-mail once this has been countersigned.

14.4. Patients lacking capacity to consent.

Not applicable. Patients lacking capacity to consent to study participation will not be eligible to enter the study.

14.5. Participants who lose capacity during the study

Participants who lose capacity during the study will be withdrawn. Data collected up to the point of withdrawal will be used in the study analysis.

14.6. GP notification

Permission from the participant will also be obtained to inform their GP of their inclusion in the study. An approved GP letter will be sent by the FORENSIC central study team together with the study information to the participant's GP informing them of their participation and allocation in the study. We will also inform the GP of the requirement for their patient to have a CT scan at 24months follow-up if they were allocated to the surgery arm.

14.7. Re-consenting

Should there be any subsequent amendment to the approved protocol, which might affect a participant's participation in the study, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

14.8. Consent to the QRI Information Study

All eligible patients who are approached to take part in the FORENSIC study will be invited to take part in an interview with the QRI researcher about their experiences of being invited to join.

All pilot study centres, and some main phase sites will also be involved in audio-recording appointments where eligibility for and participation in the trial is discussed (including conversations held in person and by remote methods). At these sites, where possible potential participants attending the eligibility assessment outpatient clinic will be sent the FORENSIC-UK PIS in advance, which explains rationale and processes of the QRI/Information study. Where this is not possible, they will be given the FORENSIC-UK PIS to read on arrival.

Potential participants will be invited to give verbal consent to their conversations being audio-recorded, at the start of their screening and eligibility appointment before discussion of the trial begins and have opportunity to confirm this with written consent at the end of the appointment. It will be clearly stated in the FORENSIC-UK PIS that participants are free to withdraw from the QRI/Information study at any time and without giving a reason. A copy of the signed Information Study written Informed Consent Form will be given to the participant.

The original signed Informed Consent Form for the QRI will be retained at the study site, a copy will be filed in the patient medical record, a copy will be given to the participant and the participant consent will also be recorded in the FORENSIC-UK study database.

Written consent to audio-recordings will cover all future recruitment discussions. Participation in audio-recordings of recruitment discussions is optional.

If written consent to record discussions is given, the recordings will be transferred to the University of Bristol for analysis (see section 24). If initial spoken consent is not confirmed with written consent, all recordings for that participant will be deleted, no further recordings will be made and no invitation to interview extended. Missed recordings of recruitment conversations are not required to be recorded as protocol deviations.

Consent to be contacted for an interview exploring reasons for declining participation.

Patients who decline participation in FORENSIC-UK trial will be invited to consent to take part in an optional interview with the QRI researcher, exploring their experiences of being approached and invited to take part in the trial. Written consent to an interview will be given using the Information Study written Informed Consent Form and recorded in the FORENSIC-UK database and following this consent the patient's contact details will be made available to the QRI research team to arrange an interview.

Consent from health care professionals (HCPs):

Consent from healthcare professionals to audio record their consultations with potential participants will be discussed and sought as part of the site set up processes. Staff may consent to an interview only, to audio-record the recruitment discussion only, to both or to neither. Where the recruiting member of staff has not consented to participate in the QRI audio-recordings, their patients will not be invited to take part in the Information Study. It will be clearly stated in the Information Study PIS for HCPs that they are free to withdraw from the study at any time and without giving a reason. Consent to take part will be documented as verbal consent and/or written consent. Consent forms can be signed then witnessed by a colleague at a study site or given verbally and witnessed by the central study team/QRI researcher if given remotely. A copy of the signed Information Study Informed Consent Form for HCPs will be given to the participating HCP. The original signed form will be retained at the study site or University of Bristol, depending on who witnesses the consent

15. RANDOMISATION

15.1. Timing of randomisation

Randomisation will take place once eligibility has been assessed by a participating surgeon during an outpatient clinic appointment in secondary care, informed consent has been given by participants and baseline questionnaires completed. In the unlikely event the participant will not be present at a clinic appointment to give consent (participant has chosen to opt for remote consent and remote completion of their baseline questionnaire) randomisation will take place only after the baseline questionnaire has been completed and returned back to the site research team. It is essential that the completed Baseline questionnaire has been recorded on REDCap before randomisation can take place.

Randomisation is not time sensitive and the participant, if required, may take as much time as they require to consider participation in the study before consent, baseline and randomisation

15.2. Randomisation procedure

Participants will be randomised by the site research team using the REDCap randomisation system, a centralised validated computer randomisation program, accessed within the FORENSIC-UK REDCap study database.

Upon randomisation of a participant, the FORENSIC study office and a member of the site research team will be notified by an automated email. If the participant is not present in the clinic for their screening, consent and randomisation, a member of the site research team will contact the participant to inform them of their randomisation result.

It is expected that most participants that attend their screening/eligibility assessment appointment in clinic and will go on to complete baseline, informed consent and on to be randomised in the same appointment.

Full details of the randomisation procedure will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the TMF.

15.3. Randomisation methodology

Consenting participants will be allocated randomly (1:1) to either lumber fusion surgery (LFS) or best conservative care (BCC).

Randomisation will be performed using a minimisation algorithm (or randomisation schedules) to ensure balance between the two treatment groups using stratification factors:

- site
- number of lumbar spine levels indicated for spinal fusion (1 or 2 levels)

Participants will be randomly allocated to the treatment options via automated, secure (encrypted), web-based randomisation provided by the Oxford Clinical Trials Research Unit (OCTRU) using a REDCap platform. Minimisation will be implemented with a 1:1 allocation ratio using the REDCap-Minimization module.[53]

The minimisation algorithm will include a non-deterministic probabilistic element to prevent predictability of treatment allocation. The first few participants will be randomised using a simple randomisation schedule to seed the minimisation algorithm. The constraints for the randomisation schedule will be determined by the OCTRU study statistician and full details will be detailed in a randomisation and blinding plan.

15.3.1. Justification for stratification factors

Number of lumbar spine levels indicated for spinal fusion is used as a randomisation factor as it is an important prognostic factor associated with the outcomes.

Similar, randomisation is stratified by recruiting site as site is expected to be confounded with other known or unknown prognostic factors including the available interventions options within BCC and will therefore increase balance between the treatment arms.

15.4. Back-up randomisation procedure

There is no back-up randomisation procedure for this study as randomisation is not time critical.

16. SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

There are currently no planned sub-studies/translational studies/mechanistic studies.

17. STUDY ASSESSMENTS/PROCEDURES

17.1. Overview

The study flow chart outlining the study assessments/time points can be found in Appendix 1 of this protocol.

Table 2 shows scheduled assessments/outcome collection for the study.

17.2. Data Collection

17.2.1. Baseline

A baseline questionnaire will be completed by participants at a face-to-face appointment, over the telephone, videoconference or via the post. The questionnaire will include the following outcome measures: Oswestry Disability Index (ODI), Quality of life (EQ-5D-5L) only, we have omitted the EQ-VAS scale for this study, Pain Self-efficacy Questionnaire (PSEQ), Patient Health Questionnaire (PHQ8), Tampa Scale of Kinesiophobia (TSK), Work status/work type.

In order to include variables that may be potential moderators of outcome from the treatments offered in the trial, to support future secondary trial analyses of the combined trial datasets from the UK and Australia, we will collect data on the following: smoking, workers' compensation claim, heavy physical demands at work, medication use for LBP, body mass index (Hayden JA et al 2020)[56] via Participant height and weight collected data, duration of LBP, co-morbidities which may include: diabetes, heart problems, high blood pressure, anxiety, depression, stress, neurological conditions, chronic fatigue (ME, Fibromyalgia), COPD, asthma, breathing problems. We will also ask about education, pain following movement, use of a pain mannequin diagram to identify area of pain, low back pain characteristic, severity of low back pain on movement, effects of changing position on low back pain, ethnicity, work status and type.

Information will also be collected if the participant has previously had a discectomy or decompression.

17.2.2. Intervention

An intervention case report form (CRF) will be used to document the interventions and monitor compliance with the intervention guidelines. For the Lumbar Fusion Surgery (LFS) group, information will be collected on type of surgery undertaken and length of stay post-operation and will be used to attach the relevant Healthcare Resource Group (HRG) code from the most recent NHS reference costs. Any additional post-operative resource use will be collected via the participant completed follow-up questionnaires.

For the Best Conservative Care (BCC) group the package of care will be recorded, including types of care (e.g. a course of physiotherapy, multidisciplinary pain management programme, medial branch block, facet ablation, self-management, signpost to other health related services etc), and number of sessions. See section 13: Best Conservative Care (BCC).

17.2.3. Follow-up assessments/subsequent visits

Follow-up will involve:

- Participant questionnaires at 6-, 12- and 24-months post randomisation
- Medical notes check (local sites) to record complications
- Appointment for a follow-up CT scan at 24 months post-randomisation for participants who have had LFS only.

Participant questionnaires

A study questionnaire will be sent to participants for completion at 6-, 12- and 24-months post randomisation. These will be sent by the central study team and can be completed by post or online. The questionnaire will include the following:

- LBP-related physical function using the Oswestry Disability Index (ODI)
- Quality of life (EQ-5D-5L)
- Pain Self Efficacy Questionnaire (PSEQ)
- Change to back pain measure using Global Perceived Effect (GPE)
- Patient Health Questionnaire (PHQ8)
- Fear of movement (fear avoidance) beliefs (TSK)
- Healthcare resources use (NHS and non-NHS) including surgery, conservative care, concurrent treatments (including analgesia)
- Work Status (days off work)
- Participant Intervention Adherence
- Treatment Satisfaction at 24m only

In addition, LBP severity (Numerical Rating Scale) will be collected using monthly SMS messages which will contain a link to enter a score or by email or by paper version via the post (participant preference) to capture data on low back pain severity. A reminder email/SMS message will be sent 2 days after the initial message, sent from the central study team to participants over the 24 months follow-up period. We will follow up with a postal reminder by post (for participants wishing to complete the LBP pain severity on paper) two weeks after the initial postal form was sent to accommodate postal delivery.

All postal questionnaires including LBP pain severity will be accompanied with a self-addressed stamped return envelope.

17.3. Communication with study participants by the central study team

At 6-, 12- and 24-months participants will be sent either a postal questionnaire or an email from the central study team with a personalised link asking them to complete the electronic questionnaire, depending on their stated preference. If the paper-based version of the questionnaire is requested, this will be sent to participants to complete and return to the Trial Office in a prepaid envelope.

Reminders will be sent to participants who do not respond to the initial follow up questionnaires by post or email with an electronic link (dependant on participant preference) at 2 weeks and a further 2 weeks later if there is no response. This data would be entered onto the trial database by the data entry personnel at the Trial Office.

Telephone follow-up will be used (2 weeks after), as applicable, to contact those who do not respond to either the initial or reminder questionnaire. Telephone and email follow-up will also be used to collect a core set of questionnaire items for the Oswestry Disability Index questionnaire

(primary outcome), and other outcome data, if these have not been fully completed on the returned questionnaire.

Participants will be contacted with regular newsletters (by email or post) to disseminate study progress and maintain engagement in the study.

Table 2: Scheduled assessments/outcome collection for the study

Assessments	Screening	Baseline	Intervention LFS/BCC	6months	12months	24months (Primary outcome timepoint)
Eligibility	X					
Informed Consent		X				
QRI Consent *		X*				
Demographics		X				
Randomisation		X				
Intervention Details			X			
Participant Completed Questionnaires:						
Oswestry Disability Index (ODI)		X		X	X	X
Quality of life (EQ-5D-5L)		X		X	X	X
Depression (PHQ8)		X		X	X	X
Fear of movement beliefs (TSK)		X		X	X	X
Pain Self-efficacy (PSEQ)		X		X	X	X
Global Perceived Effect Scale (GPE)		X		X	X	X
Healthcare Resource Use				X	X	X
Treatment Satisfaction						X
Work Status		X		X	X	X
LBP severity (NRS) [over 24 months]		X		X	X	X
Safety reporting				X	X	X
Complication data				X	X	X
CT Scan at 24months post randomisation						X
Participant interviews **		X**				

*Optional for integrated information study

** Optional for integrated Information Study

Medical notes check

The central study team will follow up any complications reported by participants with the local research team at participating sites. Details will be collected and recorded on a complications form.

In addition, a final readmission checklist will be undertaken by the research staff on participating site records at 24 months post-randomisation to ensure that all complications data are collected from all participants (i.e. those who had not returned a questionnaire). Data from any readmission events e.g. revision/further surgery identified will be recorded on the Complications Form.

CT scan appointment

For participants who have undergone lumbar fusion surgery an appointment for a follow-up CT scan will be planned at the 24 months follow-up timepoint as part of the fidelity assessment of the LSF (to determine if there is evidence of bony fusion in the lumbar spine).

17.4. Qualitative assessments

Previous studies have shown that qualitative work on outcomes can be helpful in interpreting trial findings from a participant's point of view.[48] During FORENSIC-UK follow-up, interviews will be undertaken by the QRI researcher with up to 25 participants who consent to the Information Study, purposively sampled to include those reporting good and poor outcomes based on the ODI score from each trial arm to provide participant perspectives to understand nuances of outcomes.[48]

17.5. Withdrawal of participants

Withdrawal of consent by the participant

Withdrawal of consent means that a participant has expressed a wish to withdraw from the study altogether or from certain aspects of the study only. The type of withdrawal will be collected on the CRF labelled 'Withdrawal'. It is important that every effort is made to encourage participants, including those participants who do not receive/complete their allocated treatment, to complete follow-up questionnaires, and attend for their CT scan (in those who have LFS) to avoid bias in the analysis of the results.

Participants may also be withdrawn from the study (or aspects of the study) by their clinician if they believe the participant needs to be withdrawn.

The Withdrawal CRF should be completed to document the reasons for withdrawal and state who the decision to withdraw was made by. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow- up any SAEs and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant expresses a wish to withdraw from the study, the research team will determine which aspect(s) of the study the participant wishes to withdraw from.

The aspects of the study that the participant may request to withdraw from are as follows:

- No longer willing to receive study intervention.
- No longer willing to complete study questionnaires.
- No longer willing to take part in the qualitative interviews as part of the Information Study.
- No longer willing to receive study-related communications.
- No longer willing to attend study visits.
- No longer willing to have study CT scans.
- No longer willing to be contacted by the research team to obtain CRF data
- No longer willing to be contacted by research team to obtain outcome data.
- No longer willing for routine data from health data providers e.g. NHS England, to be provided to the study.
- No longer willing for trial data to be shared with the British Spine Registry
- No longer willing to participate in any of the above aspects (full withdrawal)

Where a participant wishes to withdraw from all aspects of study participation detailed above this will be recorded on the Withdrawal CRF as full withdrawal.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from trial treatment for clinical reasons. Participants will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the study withdrawal case report form. Withdrawn participants will not be replaced as we have allowed for possible withdrawals and loss to follow-up in the estimated sample size.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the Study Office. Appropriate action will be taken by the study teams (centrally at the CTU and by the site research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used/analysed as explained in the PIS, unless the participant specifically requests otherwise.

BLINDING AND CODE BREAKING

Participants and clinicians delivering the interventions will not be blinded to intervention allocation due to the nature of the interventions.

Table 3: provides an overview of the blinding status of all individuals involved in the conduct and management of the study.

Table 3: Blinding status of those involved in study conduct and management.

Role in study	Blinding status	Additional information
Participants	Not blinded	It is not possible to blind due to the nature of the interventions. Participants will be told their treatment allocation immediately after randomisation.
Site clinical and research staff including Principal Investigator	Not blinded	It is not possible to blind due to the nature of the interventions. Following randomisation, an email will be sent to the members of the site research team, as applicable, performing the randomisation (as delegated) confirming treatment allocation.
Chief Investigator(s)	Blinded, except for any SAE causality assessment.	The Chief investigator will remain blinded to treatment allocation overall (knowledge of treatment allocation is limited to participants at their own site). In instances where serious adverse events are reported, the CIs will become unblinded to complete the full causality assessment.
Database programmer	Not blinded	The database programmer is responsible for the management of RRAMP randomisation system and the REDCAP database and will have access to all unblinded datasets within both systems.
FORENSIC-UK Study Management staff within FORENSIC-UK study team	Not blinded	Study Management staff within FORENSIC-UK study team will not be blinded to treatment allocations as site staff may require support for randomisation, or participants may contact the study team directly. Serious Adverse Event reports will also be handled by the study management team which will contain allocation information.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the study randomisation system and database to ensure data quality and undertake central monitoring activities.

Study statistician and Senior Study Statistician	Not blinded	The study statistician and senior study statisticians will have access to treatment allocations or data needed for generating the Data Monitoring Committee (DMC) closed reports and the final analysis.
Health Economist	Not blinded	The costs of the two interventions in this trial are considerably different and thus it will not be possible to blind the health economist.
TSC	Blinded	Will review accruing data and safety overall only, not separated by treatment groups. Full details will be specified in the TSC charter.
DSMC	Not Blinded	DSMC will review accruing data and safety by treatment groups. Allocation may be blinded (arm A or B). Full details will be specified in the DSMC charter and DSMC Report template

17.6. Code break/ unblinding.

Not applicable for this study.

18. SAMPLES

The study protocol does not require any samples to be taken from study participants.

19. IMAGING

Data will be collected on any MRI, SPECT CT, standing X-Rays and other imaging that has been undertaken in the 12m pre-randomisation.

For participants randomised to the surgery arm they will undergo Image intensification during the surgical procedure.

Standard Computed Tomography (CT) scans for patients randomised to surgery will be carried out at the 24-month follow-up time point as part of the fidelity assessment. The clinical team at the local site will review and complete a CRF to indicate whether spinal fusion was achieved.

20. SAFETY REPORTING

20.1. Safety reporting period

Safety reporting for each participant will begin from the first point of administration of the intervention i.e. lumbar fusion surgery or best conservative care and will end when the participant has reached their final main follow-up time point, at 24 months post-randomisation (including period for CT scan at 24 months for participants who have undergone Lumbar Fusion Surgery).

20.2. Definitions

These are listed in Table 4.

Table 4: Safety reporting definitions

An adverse event (AE)	Any untoward occurrence in a trial participant. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with study procedures, whether or not considered related to the procedures.
Related Adverse Event	An event that resulted from administration of any of the research procedures
Serious Adverse Event (SAE)	An AE that: • results in death • is life-threatening[1] • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • is otherwise considered medically significant by the Investigator[2]
Unexpected Related Serious Adverse Event	A serious adverse event related to the study (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence).

[1] Participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

20.3. Expected adverse events

Expected events from LFS include intra-operative, early post-operative and post-operative complications. Intra-operative expected events can include excessive bleeding/blood loss, vascular injury, peritoneal tear, dural tear, nerve injury, damage to nerve root, damage to spinal cord, Cauda Equina, visceral injury, bowel injury, screw misplacement, implant malposition, loss of swab, bone fracture, loss of purchase of fixation, wrong level surgery as well any other complications associated with the surgical approach. In addition, General Anaesthetic expected events can include additional intra-operative complications i.e. Anaesthetic complications (aspiration, myocardial infarction, air embolism, cardiac problems and death) .[14] Further complication can be systemic such as haemorrhage or the need for further surgery over the 24-month period.[14]

Expected early post-operative and post-operative complications include wound infection, thromboses (DVT and PE), bleeding that requires transfusion, CSF Leak, hematoma or clot formation around the nerve or spinal cord, pseudarthrosis, cage or implant movement or migration, malposition of screws, screw cut out, breakage of screws or rods, construct failure i.e. Implant pull-out, Junctional problems i.e.: adjacent segment issues, Cauda Equina syndrome, damage to spinal cord, sympathetic nerve damage, damage to nerve root, damage to major blood vessels, scarring around the nerve, loss of bladder/bowel, paralytic ileus, loss of sensations/motor power to legs, warm legs, worsening pain or symptoms, retrograde ejaculation (men only), sexual dysfunction (male and female). In addition, early post-operative and post-operative risk of complications

include: stroke, heart attack, death. General Anaesthetic complications include. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage.

Expected event from BCC include significant unexpected increase in pain due to unaccustomed new exercise programmes, adverse events associated with prescribed medications, damage to the sciatic nerve, allergic reaction (e.g. to medications), infection.

Any expected adverse events related to the procedures will be collected as complication data on a CRF. The central study team will follow up any complications reported by participants with the local research team at participating sites.

In addition, a final readmission checklist will be undertaken by the research staff on participating site records at 24 months post-randomisation to ensure that all complications data are collected from all participants (i.e. those who had not returned a questionnaire). Data from any readmission events (e.g. evacuation of haematoma, revision of metal work (e.g. implant failure, malposition of screws, cage migration), exploration and wash out for suspected infection), which may result in further surgery will be recorded in the Complications Form

20.4. Reporting of SAEs from sites to the CTU study team

Only serious adverse events considered by the site investigator to be related (possibly, probably, or definitely) to the study intervention will be reported immediately to the central study team. Such events will be reported immediately to the Study Office as follows:

SAEs will be reported by the local site research team using the SAE form within the REDCap study database, within 24 hours of becoming aware of the event. The CTU is automatically notified of the SAE report through the database. A paper SAE form should be used as a back-up if the SAE form is not available electronically. This should be e-mailed to forensic@ndorms.ox.ac.uk within 24 hours of becoming aware of the event. The central CTU study team will acknowledge receipt of any SAEs reported via e-mail within one working day and provide the site with a unique SAE Log number.

20.5. Assessment of SAEs by the Principal Investigator (or delegate)

The site Principal Investigator (PI) (or delegated individual) is responsible for assessing all reported serious adverse events for reason for seriousness, causality and expectedness.

Relatedness/causality

The assessment of “relatedness” to the study intervention is the responsibility of the PI at site or an agreed designee according to the following definitions (Table 5):

For the purpose of safety reporting the intervention is defined as lumbar fusion surgery (LFS) or best conservative care (BCC).

Table 5: Adverse event causality reporting

Relationship to intervention	Attribution (Causality)	Description
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possibly	The AE may be related to the intervention

	Probably	The AE is likely related to the intervention
	Definitely	The AE is clearly related to the intervention

20.6. Review of SAEs by the Sponsor/CTU Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the study procedures/intervention. The site will be encouraged to respond and if a response is not provided the CI will be consulted by the CTU and the CTU will complete the sponsor part of the SAE form.

20.7. Reporting of SAEs to the Research Ethics Committee (REC)

All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event.

20.8. Unblinding of SAEs for reporting to the REC

Not applicable. There is no blinding in this study.

20.9. Follow-up of Serious Adverse Events

If the SAE is an Unexpected Serious Adverse Event, then follow up information must be provided as requested by the study office. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

21. PREGNANCY

If a participant does become pregnant during this study, it does not need to be reported due to the nature of the intervention of this study as concluded in the risk assessment of the study.

22. STATISTICAL CONSIDERATIONS

22.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP) that will be drafted early in the study and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Study Statistician in accordance with the current OCTRU SOPs. The SAP will be reviewed and will receive input from the TSC and DSMC.

22.2. Sample Size/Power calculations

A total of 270 participants (135 per arm) will be recruited. The sample size estimate is based on a between arm target difference of 8 points on the ODI with a standard deviation of 18, as observed in similar populations [20] using a 2-sided 5% significance level, 90% power and allowing for up to 20% loss to follow-up. The target difference is considered important by our PPI group, is smaller than the commonly accepted MCID of 10 points, [48] to allow for some dilution of the treatment effect due to protocol deviation (including some modest crossover from LFS to BCC) and corresponds to a moderate effect size of 0.44.

In this trial, we expect to observe a zero cross-over rate compared to other surgical intervention trials. LFS is not currently offered on the standard NHS pathway, and we expect only those participants randomised to LFS to progress to this surgery within the trial, so the surgical intervention (i.e. LFS) is not, and will not be, accessible to those randomised to BCC. We expect that only a low number of participants randomised to LFS may not undergo their randomised procedure, but we will keep this under review as part of trial monitoring.

22.3. Description of Statistical Methods

Standard descriptive statistics will be used to summarise the baseline characteristics by treatment group using means and standard deviation or median and interquartile range for continuous variables, as appropriate, and numbers and percentages for binary or categorical variables.

Unless stated otherwise, analyses and summaries will be based on the as-randomised population, whereby participants will be analysed in line with their randomisation allocation regardless of adherence to the study protocol.

Results will be reported in line with the CONSORT statement and any appropriate extensions and will be described fully in a separate Statistical Analysis Plan. A single final unblinded statistical analysis will take place after all follow-up has been completed, and sufficient time has been allowed for data collection and cleaning.

It is anticipated that all statistical analyses will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages.

Primary Outcome

The primary outcome measure is the ODI, which will be summarised descriptively by trial arm at baseline and all follow-up time-points. Differences between the trial arms will be estimated using multilevel mixed effects regression model, allowing for repeated measures clustered within participants. The model will be adjusted for the number of levels indicated for spinal fusion (1 or 2 levels), baseline ODI (fixed factors), randomising site (random factor) and other important prognostic factors as appropriate. All covariates will be pre-specified in the statistical analysis plan. A treatment by time interaction will be included. Time will be used as a categorical variable, indicating the protocol stipulated follow-up time point for assessment.

Adjusted mean differences between the groups will be presented together with 95% confidence intervals and p-values, with focus on the between intervention effect at 24 months (primary follow-up time-point).

A number of sensitivity analyses will be performed:

Complier average-causal effect analysis [49] will be used to evaluate the counterfactual causal effect of LFS, the treatment effect based on time from intervention, area under the curve analysis,[50] and the per-protocol population and consider the type of conservative care received in BCC.

Sensitivity analyses will investigate the effect of missing data on results, including analyses for informative drop-out, whereby participants with missing outcomes will be assumed to have worse outcomes than participants with available data. These sensitivity analyses will be implemented using pattern mixture models using Stata's 'rctmiss' command or similar.

Secondary outcomes

Secondary outcomes will be analysed using multilevel mixed effects regression models in line with the primary analysis.

Adverse events will be presented descriptively.

22.4. Inclusion in analysis

All analyses will be on an intention-to-treat basis. This means that participants will be analysed as they are randomised irrespective of the treatment actually received. The intention-to-treat population will include participants who have given their informed consent, for whom there is confirmation of successful allocation of a randomisation number, and for whom at least one follow-up assessment is available. The principal analyses will not include imputation for missing data.

A per protocol population will exclude participants who did not receive their randomised intervention. Details of additional exclusions from this analysis population will be defined in the statistical analysis plan.

22.5. Subgroup analysis

Consistency of the treatment effects for important subgroups (including the number of levels indicated for spinal fusion (1 or 2 levels) and baseline ODI categories) will be explored. A full list of subgroups to be explored will be provided in the statistical analysis plan. Subgroup effects with 95% CIs will be obtained from linear regression models for the 24-month primary outcome, adjusted in line with the principal analysis and an interaction between randomised intervention and subgroup. We will also explore the effect of delayed intervention (both LFS and BCC) on the observed ODI outcomes. Findings will be presented graphically and viewed as exploratory.

22.6. Interim analyses

The main outcomes will be analysed as stated in the analysis plan once the study follow-up has been completed. No formal interim analyses of treatment effect are planned for any of the study outcomes.

22.7. Stopping rules

As no formal interim analyses are planned, no stopping rules have been incorporated into the study design. An independent Data and Safety Monitoring Committee (DSMC) will review the accumulating data at regular intervals and may recommend pausing or stopping the study in the event of safety concerns, as specified in the DSMC Charter. The TSC will make any final decision to terminate the study if appropriate.

22.8. Level of Statistical Significance

All treatment comparisons will be reported with 95% confidence intervals and a significance level of 5% will be used to test statistical significance.

22.9. Procedure for accounting for missing data

The procedure for handling spurious or missing data will be described in the Statistical Analysis Plan, and the Data Monitoring and Sharing Plan. The study will attempt to collect data as completely as possible.

Missing data will be minimised by careful data management, information provided to participants and training of study staff. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by intervention arm. All data collected on the database will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

The primary analysis will utilise all available data, and participants with at least one follow-up data point will be included in analyses. No imputation for missing data is planned, and sensitivity analyses will investigate the effect of missing data on the results, including analyses for informative drop-out.

22.10. Procedures for reporting any deviation(s) from the original statistical analysis plan

Any changes or deviations to the original SAP will be described and justified in the protocol, final statistical report and/or publications, as appropriate to the timing of the changes.

23. HEALTH ECONOMICS

The health economics aspects of the study are summarised here, and full details will be described in a Health Economic Analysis Plan (HEAP) that will be drafted and finalised prior to the final analysis data lock. The HEAP will be written by the study lead Health Economist and will be reviewed and will receive input from the TSC.

23.1. Within trial economic evaluation

An economic evaluation will be undertaken alongside the trial to estimate the cost effectiveness of LFS versus BCC. This will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY) and incremental net benefit at 24 months follow-up, using patient level data on costs and outcomes from the trial. The base-case analysis will be from an NHS perspective, with an additional analysis from a societal perspective taking into account out of pocket expenditure and productivity losses. In order to calculate QALYs, the EQ-5D-5L will be included in the questionnaires to participants at baseline, 6, 12 and 24 months. The UK mapping value [51] set will be applied to participant responses to obtain utility scores, in line with current NICE recommendations.

Data will be collected within the trial to calculate the cost of each LFS undertaken. Information will be collected via the surgery CRF on the type of surgery undertaken and length of stay post-operation and will be used to attach the relevant Healthcare Resource Group (HRG) code from the most recent NHS reference costs. Any additional post-operative resource use will be collected via the participant completed follow-up questionnaires. For each participant allocated to BCC, their package of care will be recorded, including types of care (e.g. a course of physiotherapy, multidisciplinary pain management programme), mode and number of sessions. The per-person cost of BCC will then be calculated.

Information on all other LBP-related resource use will be collected via participant questionnaires at 6, 12 and 24 months. Questions will request information regarding primary and secondary care visits (e.g. GP, nurse, physiotherapy, consultant, specialist, outpatient clinic), visits to other healthcare professionals including non-NHS, prescribed analgesics, tests and investigations, further treatment including surgery and injections. The recall period in each questionnaire will be the previous 6 or 12 months. Unit costs from standard UK sources will be sought for all healthcare resource use items.

Data on broader costs will also be collected, related to both out of pocket expenditure (e.g. private health care or pain relief items such back supports, TENS machines) and time off work to calculate productivity losses. Information on occupation group and the nature of their employment (full time or part time) will be sought. The average wage for each respondent will be identified using UK Standard Occupational Classification coding and annual earnings data for each broad job type.

23.2. Health economics analysis

QALYs will be calculated using responses to the EQ-5D-5L, using the "area under the curve" approach. Unit costs will be applied to all healthcare resource use items, and mean resource use (for each category of healthcare usage) and mean total costs will be calculated for all trial participants. The per participant cost of each surgical procedure will also be determined, with the mean cost per type of LFS also estimated. Analysis of productivity losses will use the human capital approach, and the self-reported days of absence will be multiplied by the respondent-specific wage rate. The human capital approach assumes that the value of lost work is equal to the amount of resources an individual would have been paid to do that work, and values productivity losses as a result of morbidity (or mortality) by measuring time lost from work and multiplying this with the gross wage of the person.

The final statistical model for analysis will be selected following data examination and measures of model fit. Multiple imputation will be used to impute all missing values for the EQ-5D-5L and total cost estimates for non-responders. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences (across the full range of clinical outcomes). Incremental cost-utility analysis will then be undertaken to estimate the incremental cost per QALY gained, adjusting for baseline covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial-based data itself, the methods employed to analyse the data, the population and the generalisability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability that LFS is cost-effective at different cost per QALY willingness to pay thresholds, compared to BCC.

Model-based analysis

If the trial shows a positive clinical result for surgical intervention, preliminary decision modelling will also be undertaken to enable extension of the within-trial results beyond 24 months follow-up. The purpose of the model is to extrapolate costs and QALYs over a lifetime time horizon to calculate the long-term cost-effectiveness (cost per QALY) of LFS compared to BCC, from an NHS perspective, with discounting of costs and outcomes at 3.5%. This will be a Markov model which allows the representation of health states related to the condition, recurrence of symptoms and new clinical events e.g. surgery. Full details will be provided in the HEAP.

24. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the study-specific Data Management Plan. See section 28 Participant Confidentiality for information on management of personal data.

24.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. For this study, source data will include the following:

- Hospital records (from which data will be summarised into the CRF)
- Trial specific intervention CRFs
- CT scans
- Participant-reported outcome measures that are submitted directly to the coordinating centre

24.2. Location of source data

The location of source data in the study is listed with the tables within the section OBJECTIVES AND OUTCOME MEASURES.

24.3. Case report forms (CRFs)

The Investigator and study site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. All appropriate data will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Source data to be recorded directly on the CRFs

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data).

24.4. Non-CRF data

All study data will be recorded on the CRF. No additional data will be held outside of the CRF.

24.5. Access to Data

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit study-related monitoring, audits and inspections. The data submitted by study participants directly via the clinical database REDCap (i.e. electronic participant reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

Members of the study team will only be able to access data that they need to, based on their roles and responsibilities within the study.

24.6. Data Recording and Record Keeping

The case report forms will be designed by members of the study management team which will include the Chief Investigator, study statisticians and study manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the study database by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic participant-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford.

The database and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the study participant information sheet.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required.

Data captured during phone calls to participants or from paper-based study questionnaires returned to the study office will be entered into the study database by suitably trained central study office staff. Full details of this process will be recorded in the Data Management Plan. Identifiable data will only be accessible by members of the research team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. for study sending follow-up reminders for online form completion or telephone follow-up).

Refer to section 28 for details about retention of participant identifiable data.

24.7. Electronic transfer of data

Any electronic transfer of data during the course of the study will be strictly controlled in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for Secure Information/Data Transfer.

24.8. QRI data

Audio files, made using encrypted audio-recorders, will be saved by those involved in taking consent from participants or a member of the site research team directly on to the local Trust secure servers. Electronic data (audio files) will then be transferred to the University of Bristol servers via an encrypted electronic data transfer method approved by sponsor, to ensure safe and secure transfer. Data sent via this method is encrypted via a HTTPS link preventing any third party to read the exchanged data; folders will also benefit from the added security of password protection. Pseudo-anonymised transcripts of audio recorded recruitment discussions data will be retained on the Bristol University's secure Research Data Storage Facility (RDSF) for 20 years in line with the study's ethical approval.

Patient contact details of participants in the Information Study (with consent) will be stored on a password-protected spreadsheet on the University of Bristol servers and will be destroyed within 12 months of being used.

Audio files, transferred from the Trust, will be uploaded onto the University of Bristol secure severs, where they will be stored for at least 10 years after the end of the study before they will be destroyed. All files will be labelled under participants' unique ID numbers and secured in password protected files. Oxford will retain a links document containing personal identifiers. This will not be shared with the University of Bristol. Interview data will be transcribed in-house by University of Bristol employees or by a University of Bristol approved transcription service that meets data security protocols

Although the transcripts can be pseudo-anonymised, there may be aspects of the audio-recordings that contain personal/identifiable information (such as participants' voices in the recordings). Only authorised members of staff involved in the research will be able to access the data. University of Bristol may use this data as part of publications, teaching and presentations at academic meetings. All quotes will be completely anonymised. If a section of audio is played (i.e. for training), voices will be modified, and any personal information will be removed. Information about how the data is stored and used is provided in the FORENSIC-UK PIS, and participants will confirm they consent for their data to be used in this manner in the Information Study informed consent form.

Pseudo-anonymised transcriptions of interviews and audio recorded recruitment discussions will be made "Controlled Access" at the end of the study. This means that transcripts will be stored in an

online database for 20 years, which can be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to apply for permission to do this, and applications will be assessed by an independent committee. We will therefore have no control over how these data are used in future. However, all data will have identifiable information removed before they are made available, and there will be no way to identify individuals mentioned in interviews/discussions.

25. QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The study management group will be responsible for ensuring adherence to the study protocols at the study sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of eligibility screening, randomisation, study entry procedures and data collection. The OCTRU has a QA team who will monitor this study by conducting audits of the Trial Master File. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the Central CTU study team. Additionally, the study may be monitored or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A study-specific data management and monitoring plan will be in place prior to the start of the study.

25.1. Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the study opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the study or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

25.2. Study monitoring

Monitoring will be performed by the central CTU study team according to a study-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report form data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner (within no more than 7 working days of the data query unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the study site for resolution.

Study sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the study. Study Office staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in accordance with OCTRU SOPs and the study monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

25.3. Audit and regulatory inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this study must inform the Study Office without delay.

25.4. Study committees

Trial Management Group (TMG)

A Trial Management Group (TMG) will be established for the study and operate in accordance with a study specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities/ individuals will be invited as required for specific items/issues.

Data and Safety Monitoring Committee (DSMC)

An independent Data & Safety Monitoring Committee (DSMC) will be established for this study made up of independent experts external to the study who will assess the progress, conduct and critical outcomes of the study. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the study. The DSMC will meet regularly throughout the study at time-points agreed by the Chair of the Committee and the Chief Investigator. At a minimum this will be on an annual basis. The DSMC will review study progress, accruing interim data and `all safety aspects of the study and make recommendations as to whether any changes to the study should be undertaken, including stopping early for safety reasons. Full details of responsibilities are included in the DSMC Charter. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. Its terms of reference will be agreed with the NIHR and will be drawn up in a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the study towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the study

The TSC will consider, and act, as appropriate, upon the recommendations of the DMC.

FORENSIC Clinical Advisory Group (CAG)

The design and implementation of FORENSIC has been overseen and guided by a dedicated FORENSIC Clinical Advisory Group of consultant physiotherapists, spinal surgeons and pain specialists. The FORENSIC CAG will continue to assist with the delivery and oversight of the study.

26. IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

26.1. Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the study. Potential sites will be invited to complete a site feasibility questionnaire (SFQ) which will be used by the Trial Management Group/Coordinating Centre to assess suitability of the site for the study; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

26.2. Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for conduct of the study but may delegate responsibility where appropriate to suitably experienced and trained members of the study site team. All members of the study site team must complete a delegation log provided by the central study team prior to undertaking any study duties. The PI must countersign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

26.3. Study site set up and activation

The Principal Investigator at each site is responsible to ensure the provision of all required core documentation. Mandatory Site Training which is organised by the study office (usually carried out as a tele- or video- conference call or personal visit) must be completed before the site can be activated. Training in the study processes will be administered at site initiation visits (SIVs) delivered either in-person or online by the Central Study team. The Study Office will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the study database and are able to begin recruiting participants.

26.4. Training

Training in the study processes will be administered at site initiation visits (delivered face to face or online) by the Central Study team.

26.5. Study documentation

The study office will provide an electronic Investigator File to each investigational site containing the documents needed to initiate and conduct the study. The study office must review and approve any local changes made to any study documentation including participant information and consent forms prior to use. Additional documentation generated during the course of the study, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the study.

26.6. Arrangements for sites outside the UK

It is not anticipated that this study will open in non-UK sites. However, it is planned that a parallel Australian trial conducted to the same protocol will be led by co-applicant Professor Foster and an Australian team of clinicians and methodologists (the FORENSIC-AUS trial). The completion of two trials to the same protocol, will provide pooled data for potential future moderator analyses, to investigate whether there are subgroups of patients who are more likely to benefit from lumbar spinal fusion or best conservative care. This pooled dataset is intended to available for future secondary data analyses.

27. ETHICAL AND REGULATORY CONSIDERATIONS

27.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

27.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

27.3. Ethical conduct of the study and ethical approvals

The protocol, participant information sheet, informed consent form and any other information that will be presented to potential study participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC).

27.4. NHS Research Governance

Once HRA & HCRW approval is in place for the study, sites will confirm capability and capacity to participate in the study.

27.5. Protocol amendments

All amendments will be generated and managed according to the study office standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study participants (see below).

It is the Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the study. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

27.6. Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A study related deviation is a departure from the ethically approved study protocol or other study document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be captured within the study database either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from the study database and reviewed regularly by the Trial Management Group (TMG). Deviations will be handled and reviewed in a timely manner in accordance with a study-specific Data Management and Monitoring Plan.

The investigator must promptly report any important deviation from Good Clinical Practice or protocol to the study office. Examples of important deviations are those that might impact participant safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see section28).

27.7. Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The study may continue with the urgent safety measures in place. **The Investigator must inform the study office IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure.
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the study office to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The Study Office will follow written procedures to implement the changes accordingly.

27.8. Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined a formal decision to:

- interrupt the treatment of participants already in the study for safety reasons.
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the study in a timely manner.

The Study Office will report the temporary halt via an expedited substantial amendment procedure. The study may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the study this will be reported as an early termination.

27.9. Serious Breaches

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

Investigators must notify the Study Office within one working day if any serious breach of GCP is suspected. The Study Office will review the event and, if appropriate will report a serious breach to the REC and the NHS host organisation within 7 days of the Study Office becoming aware of the breach.

27.10. Study Reports

This protocol will comply with all current applicable HRA, Research Ethics Committee, and Sponsor reporting requirements.

27.11. Transparency in Research

Prior to the recruitment of the first participant, the study will have been registered on a publicly accessible database (ISRCTN), which will be kept up to date during the study, and results will be uploaded to the registry within 12 months of the end of the study declaration. A Final Report will be submitted to the REC containing a lay summary of the study results which will be published on the HRA website.

The results of the study will be published and disseminated in accordance with the PUBLICATION AND DISSEMINATION section.

27.12. Use of social media

Social media (e.g. X (previously Twitter) or Blue Sky may be utilised to make general announcements about the study and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment by a site etc).

28. PARTICIPANT CONFIDENTIALITY

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which will require data to be de-identified as soon as it is practical to do so. Personal data on all documents will be regarded as confidential. The processing of the personal data of participants will be minimised by making use of a unique participant study number on all study documents and any electronic databases). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participant's personal data. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. See section DATA MANAGEMENT for more details.

28.1. Collection and use of personal identifiable information

Contact details (e-mail addresses/postal addresses/phone number) will be collected in this study for the following purposes, and where an activity is optional, only with the specific consent of the participant:

- Sending/contacting regarding follow-up questionnaires and any reminder messages
- Contact about future research
- Contact to take part in a QRI interview
- Sending a copy of the completed consent form by e-mail (for any participants that consent electronically and wish to receive a copy by e-mail)

Where remote eConsent is used, participants will be asked to give their permission verbally for a link to the consent documentation to be sent to their email address or an email address they provide.

The participant information sheet explains what contact details will be collected and how these will be used; explicit consent will be obtained for this.

Permission will also be requested from trial participants to retain the participant's NHS/HIC number for long-term follow-up (up to five years), using routinely collected NHS and BSR data, from baseline (i.e. from the time of consent/randomisation). This is subject to additional funding.

28.2. Use of audio /visual recording devices

See section 24 above for details of how QRI data (audio-recordings) will be captured on digitally encrypted audio recorders and transferred using secure data transfer processes to the University of Bristol, where these data will be held on a secure drive, accessible only to members of the QRI team. Audio recordings of QRI interviews will be captured on digitally encrypted audio recorders and transferred to the same University of Bristol approved secure data storage facility likewise accessible only to members of the QRI team.

28.3. Storage and use of personal data

During the study personal data will be stored and used in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for confidentiality, protection and breach of personal data in relation to research subjects. This ensures that all personal data collected during the study is recorded, handled and stored in accordance with the requirements of the UK General Data Protection Regulation.

If a Participant decides to claim travel expenses for their additional clinic visits due to taking part in FORENSIC-UK, their bank details will be held securely with the University of Oxford for 7years and in accordance with the University of Oxford Financial Policy.

All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with participant-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible by the use of a unique participant study number on study documents and any electronic systems.

Personal data on all documents will be regarded as confidential. The study staff will safeguard the privacy of participant's personal data.

The use of all personal data in the study will be documented in a study-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

The Investigator site will maintain the participant's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

28.4. Access to participants' personal identifiable data during the study

Access to participants personal identifiable data will be restricted to individuals authorised to have access. This includes a) members of the research team at participating study sites with delegated responsibility by the site Principal Investigator and b) members of the central CTU study team involved in the conduct/management of the study where this is necessary for their role and c) members of the QRI team conducting interviews with potential or actual participants.

Research staff that are not part of the participant's direct healthcare team will not have access to personal identifiable data until the participant has given their consent to take part in the study or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site research team – permission for this will be recorded in the participant's medical notes.

The participant information sheet clearly describes who will have access to the participants personal identifiable data during the study and explicit consent is obtained from study participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to their taking part in this study; only authorised individuals will be granted access where this is necessary for their role.

28.5. Destruction of personal identifiable data

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the study data management plan and is in accordance with OCTRU standard operating procedures which comply with the UK GDPR.

Personal identifiable data may be retained longer than the duration of study – please refer to section 24 for details.

28.6. Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

29. PUBLIC AND PATIENT INVOLVEMENT

29.1. Impact of PPI on study design and protocol development

The advice and input from eight people with lived experience has been a vital part of the development of this study and will be key to the study's success including recruitment and retention of participants.

This public involvement has ensured that key decisions about the design of the study design and how patients will participate in the study has remained patient centred. Any uncertainties about how the research will be delivered with participants were informed by the views of patients.

Public contributors were a mix of males and females, ages, locations (Keele and Cardiff) and back-grounds, including ethnic minorities. Patients' insights were based on a range of experience of low back pain - some with severe problems for many (20+) years, and some with experience of surgery for related problems. Public contributors were involved in three group discussions with the research team, plus an advisory meeting with other clinical trials specialists. Additionally, our public co-applicant (ST) has been in multiple proposal development meetings.

Public contributors shaped the study by:

• Confirming the importance of conducting a study about spinal surgery from a patients' viewpoint as some people just learn to "live with the [back] pain". Non-surgical care was seen as preferable for some but "it comes to a point when what else can you do"

• Acknowledging that participant recruitment could be challenging. Public contributors advised that the information to potential participants should be balanced regarding both the surgical and non-surgical care. The potential benefits of either treatment arm and the potential waiting times should be highlighted, and include stories of patients who have undergone fusion surgery to help reassure those patients with concerns about surgery

• Helping the thinking around participant eligibility to the study by describing the different reasons why patients may have “unsuccessful non-surgical care”

• Advising that pain severity should not be a criterion for entry into the trial because patients may “exaggerate their pain” to get into the study. This recommendation was considered by the FORENSIC-UK Clinical Advisory Group but felt a cut-off level for pain severity would be required for eligibility to the study and agreed for a pain severity measure of ≥ 6 using the Numerical Rating score (NRS) of 0-10 to be used.

• Suggesting that the Conservative Care arm needs to offer care that is better than they may have received before (or at least different to). They also recommended that the conservative care is “personalised” to their needs and lifestyles and described in a way that is clearer and easier to understand

• Confirming that cross-over from the conservative care arm to the surgical arm was unlikely due to the current unavailability of surgery on the NHS, but highlighted the possibility of participants going private for surgery

• Highlighting that some participants in the non-surgical care arm may need encouragement and support to keep them in the study and suggested the use of regular information (e.g. newsletter) about the progress of the trial and their part in it

• Agreeing that pain severity was main important outcome but suggested that a measure of global change should also be included

•Reviewing and improving the clarity of the plain English summary

• Suggesting preference for the study name acronym: FORENSIC

• Reviewing and commenting on the funding application, including co-writing the sections on public involvement (ST).

29.2. PPI during the study

People with lived experience of low back pain will be involved throughout the study to ensure it remains focused on participant needs. The PI Lead (SB) will coordinate activities. For this study, PI will be delivered using the UK Standards as follows:

Inclusive opportunities:

• Our existing public contributors have agreed to be involved during the study as part of a patient advisory group. We will seek to increase diversity of the group, by reaching out to patients and community groups via regional public involvement networks, NIHR People in Research, social media and clinical contacts through the research team.

• Public involvement activities will take place virtually but other ways of being involved (e.g. telephone calls, email) will be offered.

Working together:

• Public contributors will work as part of an advisory group to inform specific aspects of the study. We will agree when and how they will meet.

• Public co-applicant (ST) will attend Trial Management Group and provide the link between the patient advisory group and the research team.

• All public contributors will be given a role description.

Support and learning:

• Public contributors will be offered payment, in line with national guidelines.

• Patient advisory group meetings will be co-chaired by the PPI Lead (SB) and Public Co-applicant (ST). Public contributors will be given a plain English Glossary of research terms, and guides about PI and research methods.

• We will work with public contributors to address any training needs identified, as required and/or signpost to existing training resources (e.g. NIHR Learning for Involvement).

Communication:

• Meetings and information provided will be in plain language, with terminology explained clearly.

• Regular and timely updates and feedback will be provided as agreed with the patient advisory group.

Governance

• The public co-applicant (ST) contributes to study decision-making as part of the Trial Management Group and two public contributors are involved in the Trial Steering Group.

Summary of public involvement activities:

• Informing approaches to recruitment

• Developing participant documentation, such as the participant information sheet study questionnaire pack

• Informing qualitative interviews for the QRI

• Reviewing ethics application

• Interpreting findings from a patient perspective, including informing QRI results and recommendations

• Co-creating dissemination resources, including developing plain English summaries of the findings

• Study management and oversight, including public involvement in Trial Management and Steering Group

29.3. Dissemination of study results

Findings of the study will be made available to participants via the CTU study website and social media.

30. EXPENSES/PAYMENTS TO PARTICIPANTS

Reasonable travel expenses for any visits to NHS clinics or for imaging, that are made in addition to normal clinical care [e.g. additional research visits for eligibility assessment, giving consent if done in clinic, visit for CT scan at 24 months (participants randomised to LFS only)] will be reimbursed on production of receipts or a mileage allowance provided as appropriate.

Expense claim forms will be supplied together with information on how to complete and submit to the central study team. In addition, vouchers for participants, as a thank you for study participation in their follow-up completion of questionnaires will be given.

31. SPONSORSHIP, FINANCE AND INSURANCE

31.1. Sponsorship

The Sponsor of this study is the University of Oxford and will provide written confirmation of Sponsorship.

31.2. Funding and support in kind

The table below provides detail of all funding and support in kind for the study.

Funder(s)	**Financial and non-financial support given**
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme	NIHR (project **NIHR 134859**) /research costs/NHS support costs (NIHR CRN Portfolio adoption)

31.3. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

32. CONTRACTUAL ARRANGEMENTS

Appropriate contractual arrangements will be put in place with all third parties.

This study is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the study as appropriate.

33. PUBLICATION AND DISSEMINATION

The sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results and associated study publications (e.g. the study protocol, statistical analysis plan (SAP), health economics analysis plan (HEAP) and secondary analyses) will be in accordance with the OCTRU Standard Operating Procedure and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research and will include reference to the integrated QRI. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

33.1. Dissemination of study results

All data will be presented such that no individual participants can be identified.

Where there is publication of direct quotations from participants, explicit consent will have been obtained for the use of any quotations used.

A summary of the study results for study participants will be written collaboratively with clinicians and patient representatives and distributed accordingly. The PIS includes a link to the study website where participants will be advised that the results will be published. Newsletters, social media etc. will also be used to ensure the results of the study are communicated to the wider community once they are available.

A Dissemination Plan will be developed for the UK trial and in collaboration with the Australian team. Dissemination of results will include the following methods:

Conference: The results of this study will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders. It is expected that findings from this project will be presented at national and international conferences.

Publications: Results will be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper, along with links to other digital media on the study website to explain the study result in an accessible format – i.e. an explainer video and/or infographic.

Public Dissemination: We will work with our PPI group and relevant organisations (e.g. Versus Arthritis & Back Care) to ensure good dissemination to the public. To ensure a broad campaign we will target a range of social media outlets (e.g. X or Blue Sky) with the explainer video and infographic. We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal'.

All participants will be asked at the time of recruitment if they would like to receive a copy of the study results. This document will be written collaboratively with clinicians and patient representatives and distributed accordingly. Newsletters, Facebook, Twitter etc. will be used to ensure the results of FORENSIC-UK are communicated to the wider community once they are available.

The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. Moreover, the University of Oxford and Oxford University Hospitals NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, we will agree upon effective communication strategies including co-ordinated press releases, interviews etc.

33.2. Implementation into national and international guidelines

Wide dissemination of the results is planned on completion of the trial to policy makers such as United Kingdom Spine Societies Board (UKSSB), National Institute for Health and Care Excellence (NICE) and the NLBLBP, as appropriate. The results will have high impact and substantially change or confirm current practice. Should lumbar fusion surgery show little benefit over best conservative care then fusion surgery should remain a non-commissioned treatment option. Should spinal fusion surgery be shown to be superior to best conservative care then this option should then be offered under NICE guidelines for appropriate patients.

33.3. Authorship

Authorship of any publications arising from the study will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from FORENSIC-UK must acknowledge the funder, SITU study group, OCTRU, Quintet group, and the Sponsor.

34. DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Ownership of IP generated by employees of the University vests in the University. It is not anticipated that any new IP will be generated from this study, but the University will ensure appropriate arrangements are in place.

35. ARCHIVING

Minimum Mandatory archiving period

It is the University of Oxford's policy to store data for a minimum of 3 years following publication. Investigators may not archive or destroy study essential documents without written instruction from the study office.

Anonymised research data will be kept by the University of Oxford for 5years after the end of the study.

The minimum mandatory archiving period for essential study documents for this study is 3 years following publication. In addition, we will store certain documents as listed below for a longer time period.

Retention of documents/information beyond the mandatory archiving

The following documents will be retained longer; explicit consent for this retention will be obtained from participants:

- Informed consent forms and contact details for the purpose of contacting participants about future research
    - These will be stored on Oxford University's secure server area for 5 years after the end of the study. The contact details will be maintained and backed up to the required standard of the University of Oxford.
- Digital data from audio recorded recruitment discussions, transferred from the Trust, will be uploaded onto the University of Bristol secure severs, where they will be stored for at least 10 years after the end of the study before they will be destroyed.
- Pseudoanonymised transcripts of audio recorded recruitment discussions data will be retained on the Bristol University's secure Research Data Storage Facility (RDSF) for 20 years.

35.1. Archiving responsibilities/procedure

During the study and after study closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical study and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period as specified above.

35.2. CTU Trial Master File

All paper and electronic data including the Trial Master File and study data collection system will be archived in accordance with the OCTRU standard operating procedures which are compliant with the UK GDPR.

35.3. Investigator Site File and participant medical records.

The Investigator Site Files will be archived at the participating site. The medical files of study participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period of time permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the study Sponsor.

35.4. Retention of data sets

Study data and associated metadata electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

36. DATA SHARING

The study statistician and health economist may retain copies of anonymised datasets for the purpose of data sharing in accordance with the study data sharing plan.

36.1. Retention of anonymised datasets

Upon completion of the study, and with appropriate participant consent, anonymised research data may be shared with other organisations on request to the Chief Investigator and in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s).

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VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the protocol

APPENDIX 1 – STUDY FLOW CHART