Radiofrequency denervation for chronic and moderate to severe low back pain

Trial protocol

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Abbreviations

A&E	Accident and Emergency
AE	Adverse event
AR	Adverse reaction
BPS	British Pain Society
BTC	Bristol Trials Centre
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
DMSC	Data monitoring and safety committee
ED	Emergency Department
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ITT	Intention to treat
LBP	Low back pain
MBB	Medial branch block
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NBT	North Bristol NHS Trust
NLBRPP	NHS England National Low Back and Radicular Pain Pathway
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS	Numeric Rating Scale
PEP-R	Patient Experience Partnership in Research
PI	Principal Investigator
PIL	Patient information leaflet
PP	Per protocol
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REC	Research ethics committee
RF	Radiofrequency
RFD	Radiofrequency denervation
SAE	Serious adverse event

SAP	Statistical analysis plan
SF-12	12-Item Short Form Survey
SMS	Short message service
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SWAT	Study within a trial
TMG	Trial management group
TSC	Trial steering committee
UKCRC	UK Clinical Research Collaboration
WPAI	Work Productivity and Activity Impairment

1. Protocol synopsis

Primary aim	Evaluate the effectiveness and cost-effectiveness of RFD for moderate-severe chronic localised LBP
Trial design	Pragmatic, double-blind, parallel group, superiority RCT with 12 month internal pilot, qualitative research and health economic analysis
Setting	Pain clinics and spinal clinics providing RFD to NHS patients
Target population	Adults with localised moderate to severe chronic LBP, with the main source of pain from structures supplied by the medial branch nerve
Inclusion criteria	Adults with chronic moderate to severe LBP (>3 months duration, pain NRS ≥5); primary pain complaint is LBP; listed for RFD following a positive response to a single diagnostic MBB.
Exclusion criteria	Pregnancy; severe depression; previous RFD; pacemaker or implantable cardioverter defibrillator
Randomisation and blinding	1:1 randomisation stratified by operator (within site). Participants, RFD operators and all members of the research team will be masked to allocation.
Interventions	RFD of the lumbar medial branches of the dorsal rami. Placebo treatment will follow the same protocol, but the electrode tip temperature will not be raised. Participants who do not experience a clinically meaningful improvement in pain 3 months after randomisation will be offered “repeat RFD” but with the alternative intervention to the one provided at the outset without

	disclosing the original allocation. All other aspects of care will be the same as the usual care provided by the hospital.
Primary outcome	Pain severity, measured using a 0-10 pain NRS, at 3 months after randomisation
Secondary outcomes	Functional disability, health-related quality of life, psychological distress, time to pain recovery, satisfaction with the outcome of treatment, adverse events, work outcomes and healthcare utilisation
Follow-up	Pain severity (assessed on a NRS) and adverse events will be collected at 2 weeks and 6 weeks (serious adverse events only) after randomisation via a telephone call. The EQ-5D-5L will also be collected over the telephone at 6 weeks. Paper/online questionnaires, assessing all outcomes, will be administered before randomisation and at 3 months after randomisation for all patients. Further questionnaires will be administered at 6, 12, 18 and 24 months after randomisation, for all patients who reach those time points within the study period.
Number of patients	206 (103 per group) to detect a target difference in pain NRS of 0.84, allowing for 10% attrition at 3 months
Duration of study	79 months comprising 31 month set up, 39 months recruitment (including 12 month internal pilot; extended set up due to Covid-19 pandemic), up to 24 months follow-up (3 months for all patients), and 6 months data analyses and reporting.
Statistical analysis	The analyses will be by intention-to-treat, adjusted for operator, fitted as a random effect. The primary outcome will be analysed using a linear mixed effects model, using all available repeated pain measurements up to 3 months, and reported as a mean difference in pain at 3 months.
Cost effectiveness analysis	The primary economic evaluation will take an NHS and social services perspective and estimate the discounted cost per quality adjusted life year and incremental net benefit of RFD up to 24 months follow up .
Nested qualitative study	During the internal pilot, recruitment consultations for 20 patients will be audio-recorded. Telephone interviews will be conducted with 20 participants, 15 clinicians and 10 recruiters.

2. Plain English summary

Background

Long-term low back pain (LBP) is common, affecting 10-15% of adults. It can significantly impair the health, mood, and daily lives of people who have it. One type of low back pain is caused by the small joints between the bones in the lower back. Treatments include painkillers, exercise and talking therapies. However, if people do not get better with these treatments, they can be offered radiofrequency "denervation" (RFD). Denervation involves placing a needle in the nerve to the painful joint, which is heated up to cause a break in the nerve. The purpose of this is to stop the nerve sending pain messages to the brain. Denervation is low risk and is used widely in the National Health Service (NHS) but we do not know if this procedure definitely reduces pain or is a good way to spend NHS money. This study aims to find out if denervation reduces low back pain and is good value for money.

Design and methods

For health professionals to provide the best care for patients, randomised studies are needed to find out if treatments work. A randomised study involves assigning patients by chance to the treatment of interest, or to usual care, so that the effect of the treatment can be compared fairly. In some studies, a treatment is compared to a placebo treatment.

This study will involve 206 NHS patients who are eligible for the denervation treatment in up to 25 pain management centres and spinal clinics across the UK. Half will have the denervation and half will have a placebo treatment involving placement of the needle in the nerve but without heating it up, so the nerve is not affected. The treatment offered will be decided by chance. All other aspects of care will be the same as the usual care provided by the hospital. Patients, clinicians and researchers will not know which treatment has been given. This is to make sure that no one can influence the results. Patients whose symptoms do not improve after 3 months will be offered the chance to receive the other treatment but without disclosing to the patient or the doctor what treatment was given either the first or second time. This means that patients who had no improvement because they had the placebo treatment first would have the opportunity for denervation the second time.

We will ask all patients questions about their low back pain, ability to carry out daily tasks including their work, their general health, and mental well-being over the next 2 years. We will compare the answers of people who had denervation to those who had placebo treatment to find out if denervation improves symptoms. We will also collect information so that we can find out if denervation is good value for money.

Patient and public involvement (PPI)

This study has been developed with our musculoskeletal PPI group. To make sure the views of patients are central to the way the study is done, we will set up a new PPI group for this trial, involving patients with experience of denervation. Regular meetings will be held to discuss

design, management and dissemination. Two patient representatives will sit on the Trial Steering Committee (TSC).

Dissemination
We will make sure that the findings reach all the people who can benefit from them in a suitable format. This includes plain English summaries for the public and customised material for other people such as health professionals or NHS Trusts. Team members have links with relevant patient support organisations and will ensure the findings are considered by experts responsible for the National Back Pain Pathway. Details of the study results and publications will also be made available on the ISRCTN registry.

3. Background

3.1 What is the problem being addressed?

LBP is the leading global cause of years lived with disability(1), and the lifetime incidence of LBP is 58-84%(2). It is associated with high personal, societal and economic burden(3). It can impact on many aspects of patients' lives, and in some cases dominate patients' lives with life-changing psychological and social consequences including disengagement in meaningful activities, changed identity, psychological problems, damaged relationships and inability to work(4, 5). Disability from LBP is highest in people of working age(1), accounts for more lost workdays than any other musculoskeletal condition in the USA(6) and is associated with high costs due to productivity losses(7). LBP is the most common musculoskeletal reason for General Practitioner (GP) appointments, accounting for 417 consultations per year per 10 000 registered persons(8). Approximately a third of the direct health care costs associated with LBP are incurred in the hospital sector(7).

LBP is now understood as a persisting or recurrent condition with a variable course, and many patients who report an episode of LBP will experience further LBP(9). Non-surgical interventions for LBP recommended by the National Institute for Health and Care Excellence (NICE) are self-management, exercise, psychological therapy, combined physical and psychological programmes, and non-steroidal anti-inflammatory drugs. Most LBP is non-specific, with no known patho-anatomical cause(10), and invasive interventions are not recommended. However, in some cases LBP can be localised and arise from the facet joints and periarticular structures supplied by the medial branches of the primary dorsal rami. Clinical features suggestive of pain with a facet joint component include increased pain unilaterally or bilaterally on lumbar para-spinal palpation; increased back pain with extension, rotation, extension/side flexion or extension/rotation; no radicular symptoms; and no sacroiliac joint pain elicited using a provocation test(11). NICE guidelines recommend that patients with these clinical features who have moderate to severe pain and have not experienced an improvement in symptoms with conservative management can be offered a diagnostic Medial Branch Block (MBB) with local anaesthetic, and patients who respond positively can undergo RFD.

RFD is a minimally invasive outpatient procedure which aims to reduce pain by interrupting the pain signal from the medial branch nerves in the spine to the brain, by destroying the nerves. RFD is performed under local anaesthetic, with sedation as needed. The electrode is placed parallel to the nerve, which is confirmed by fluoroscopy. An oscillating electrical current at a very high frequency is used to heat up a small area of nerve tissue, thereby causing localised destruction of nerve tissue and reduction in sensory information along that nerve from that specific area. It is possible the nerve will regrow through the burned lesion that was created by radiofrequency ablation. The duration of effect is mediated by the length of time taken for coagulated nerves to regenerate. If the nerve regrows, it is usually >12 months after the procedure, after which RFD can be repeated if needed.

Based on Hospital Episode Statistics (HES) data, there were 13,046 RFDs of the lumbar facet joints performed in 2017-18 (12). The NHS 2017-18 reference costs for RFD, including the initial outpatient appointment, diagnostic MBB, RFD procedure and follow up appointment, were £1,667. Therefore, RFD costs the NHS nearly £22 million per year. However, there is uncertainty regarding the effectiveness of RFD due to a lack of high quality evidence(13). The recent MINT trial from the Netherlands concluded that RFD combined with an exercise program was not superior to an exercise program alone(14). This trial was criticised for the following reasons: patients could only have RFD if they agreed to participate in the trial and therefore some questioned whether this might have led to an overestimation of benefit from diagnostic MBB; there was wide variation in RFD operator protocols; true RFD was not compared to a placebo treatment; and it was underpowered to detect the pre-specified target difference due to 34% of patients in the control group receiving RFD (15-19). High quality evidence on the clinical and cost-effectiveness of RFD compared to a placebo treatment in the NHS is needed to inform clinical practice guidelines and commissioning of care.

3.2 Why is the research important?

The burden from LBP is high and is increasing due to the ageing and growing population(1). A global challenge in the management of LBP is preventing the use of harmful or wasteful interventions and ensuring the availability of effective and cost-effective healthcare for those in need(20). RFD is endorsed by NICE, and implemented into clinical practice through inclusion in the NHS England National Low Back and Radicular Pain Pathway (NLBRPP) and the British Pain Society (BPS) Low Back and Radicular Pain Pathway(11, 21). However, NICE recommends that further research is needed to evaluate the long-term effectiveness of RFD in the NHS. This would contribute to the development of evidence-based care pathways to enable people to receive appropriate, effective treatments. If RFD is not effective, then removing provision of this intervention would save the NHS nearly £22 million per year, which could be redirected into the provision of other effective services for people with LBP. If RFD is found to be effective and cost-effective, then this could impact on commissioning and availability of this intervention.

3.3 Rationale

A number of systematic reviews on the effectiveness of RFD have been published with conflicting findings and interpretation(22-26). A Cochrane review, published in 2015, concluded that there was no high-quality evidence that RFD provides pain relief for patients with chronic LBP(13). Despite this, RFD is endorsed in the 2016 NICE guideline on low back pain and sciatica, based on the intervention being cost-effective if the duration of pain relief exceeds 16 months. RFD is also included in the NLBRPP and BPS pathway(27), which implement NICE recommendations. Subsequent to the publication of the NICE guidelines, the MINT trial in the Netherlands challenged the NICE recommendations as it found that RFD combined with an exercise program was not superior to an exercise programme alone. Based on the findings of this trial, RFD is no longer covered in the Netherlands public health insurance package. However, the use of an exercise programme as a comparator in the unblinded MINT trial has received criticism(15, 16), and the exercise programme was also more intensive than patients receive in the NHS (comprising 8 to 12 hours of physiotherapy over 3 months with referral to psychological care if needed compared to usual NHS physiotherapy care comprising 3 to 4 sessions typically lasting 30 to 40 minutes). The lack of evidence to inform provision of this procedure is acknowledged, and NICE have recommended research is needed to evaluate the long-term clinical and cost-effectiveness of RFD in the NHS(28). The recent call to action on LBP in the *Lancet r*ecommends that research to evaluate treatments without supporting evidence should be commissioned (20). Our RADICAL trial will provide definitive evidence on the clinical and cost-effectiveness of RFD to inform NHS service provision to ensure that patients are offered effective and appropriate treatments for LBP.

4. Aims and objectives

The RADICAL pragmatic trial will evaluate the effectiveness and cost-effectiveness of RFD for moderate-severe chronic localised LBP. Specific objectives are:

A. To estimate the difference between RFD and placebo treatment in mean pain severity measured using a pain Numeric Rating Scale (NRS) score at 3 months after randomisation, testing the superiority of RFD to placebo treatment.

B. To estimate the differences between RFD and placebo treatment in secondary outcomes up to 2 years: back-specific disability, health-related quality of life (HRQoL), psychological distress, time to pain recovery, satisfaction with treatment outcome, frequency of uptake of offer of repeat RFD, adverse events, work outcomes and further healthcare use.

C. To estimate the cost-effectiveness of RFD compared to placebo treatment at 3 months and up to 24 months follow-up.

5. Plan of investigation

5.1 Participant flow chart

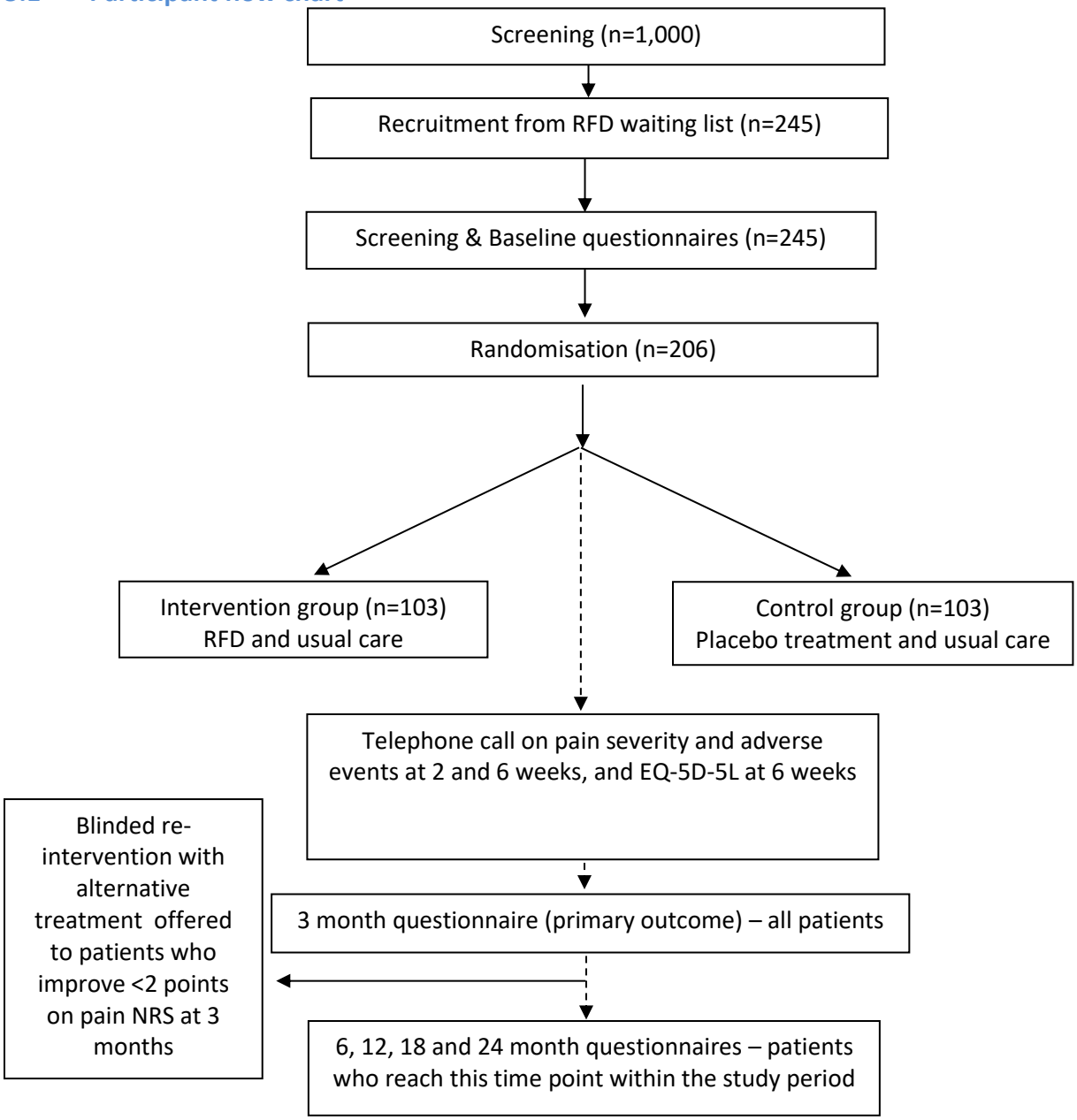


Figure 1 Participant flow chart

5.2 Trial design and setting

The study design is a pragmatic, double-blind, parallel group, superiority randomised controlled trial (RCT) with 12 month internal pilot, qualitative research and health economic analysis. The control group will receive a placebo treatment, and all participants will receive concurrent usual care. Participants, RFD operators and all members of the research team will be masked to allocation. The internal pilot will establish processes for, and test the feasibility of, recruitment.

The full trial will test the hypothesis that RFD compared to a placebo treatment reduces the severity of pain at 3 months after intervention.

This study will recruit 206 patients from up to 25 multidisciplinary pain clinics and spinal clinics which provide RFD to NHS patients. No trial-specific RFD equipment is required, as radiofrequency (RF) machines used as part of usual practice can be used for the trial if they meet the trial criteria for RF machines (see section 5.5.1). Clinicians delivering the intervention at trial sites must be experienced consultants who perform RFD as part of their usual practice or junior doctors supervised by an experienced consultant. Sites must have the staff and theatre capacity for performing blinded re-intervention for participants who do not experience a clinically important improvement in pain by 3 months after randomisation (see Section 5.5.4).

5.3 Key design features to minimise bias

Selection bias/allocation bias (systematic differences between baseline characteristics of the groups that are compared). This bias is ruled out by concealed randomisation (see Section 6.3).

Performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest). This bias will be minimised by:

- Blinding all participants and personnel and assessing the success of blinding using the Bang Blinding Index (see Section 6.4);
- Defining procedures for participant follow-up (see Section 6.6);
- Monitoring adherence to protocol (see section 6.6)

Detection bias (systematic differences between groups in how outcomes are determined). This bias will be minimised by blinding individuals providing outcomes and research staff collecting minimum datasets from participants by telephone (see Section 6.4).

Attrition bias (systematic differences between groups in withdrawals from a study).
This bias will be minimised by:

- Implementing measures to promote trial acceptability, including the offer of the alternative treatment at 3 months to patients who do not experience a clinically important improvement in pain (see Section 5.5.4);
- Using established Bristol Trials Centre (BTC) methods to maximise the proportion of participants for whom all outcome data are available (see Section 6.6);
- Conducting a SWAT to evaluate whether inclusion of a branded pen can improve response rates to follow-up questionnaires compared to a non branded pen (see section 6.10)
- Documenting non-adherence to random allocations (see section 6.6);
- Using intention to treat (ITT) analysis and investigating sensitivity to attrition bias in statistical analysis (see Section 8);
- Investigating sensitivity to attrition bias in the statistical analysis, implementing appropriate imputations for missing data (see Section 8).

Reporting bias will be minimised by having pre-specified outcomes (see Section 5.6) and pre-specified Statistical and Health Economics Analysis Plans, which will be finalised before the database is locked (see Section 8).

5.4 Trial population

In line with NICE guidance, the target population will be adults with localised moderate to severe chronic LBP who have experienced insufficient improvement despite conservative management, evidenced by referral to a pain or spinal clinic, and have had a positive response to a single diagnostic MBB, indicating that the main source of pain is originating from structures supplied by the medial branch nerve.

5.4.1 Inclusion criteria

Patients will be eligible for the trial if ALL of the following apply:

- 18 years of age or older
- LBP is the primary source of pain[1]
- Positive response to a single diagnostic MBB with no steroids administered(11). Based on the outcome of a meeting of RADICAL clinicians, a positive response is defined as ≥60% pain relief in the first 24 hours, based on patient reported assessment. Final eligibility will be met if a patient's pain returns to ≥5 (NRS score) at baseline and they are listed for RFD.
- Chronic LBP (>3 months duration), assumed due to the fact patient was listed for MBB
- Moderate to severe LBP (pain NRS score ≥5 on Baseline Questionnaire)
- Listed for RFD by their clinical care team

5.4.2 Exclusion criteria

Patients may not participate in the study if ANY of the following apply:

- Known pregnancy
- Severe depression (Hospital Anxiety and Depression Scale (HADS) depression score ≥15(29))[2]
- Known previous RFD
- Known previous back surgery where metal-work has been used in the lumbar spine
- Pacemaker or implantable cardioverter defibrillator
- Clinical suspicion that an alternative diagnosis is the reason for low back pain (as defined by NICE (28), including, but not limited to: metastatic spinal cord compression, spinal injury, spondyloarthritis, or cancer)[3, 4]
- Prisoner
- Patient lacks capacity to consent[5]
- Existing co-enrolment in another clinical study[6] if: i) the intervention in the other study is expected to influence the primary outcome (this will be considered by a senior clinician on a case-by-case basis); ii) it is considered too burdensome for the patient; or iii) it is not permitted by the other study

[1]This is based on the BPS expert consensus panel which recommended that patients undergoing RFD should have localised LBP to ensure appropriate patient selection and maximise the chance of a good outcome. However, we will include patients with widespread pain that appear to be managing their other areas of pain well but specifically need intervention for their LBP.
[2]This is a contraindication to RFD in the BPS pathway of care for low back and radicular pain because severe depression can be a psychological barrier to recovery and engagement in rehabilitation.
[3]This may be based on review of a recent magnetic resonance imaging (MRI) scan report, if available.
[4]If the patient is having investigations to exclude malignancy as the reason for their LBP then the patient should not be included until malignancy is excluded.
[5]A formal assessment of capacity is not required. The person taking consent should use their judgement to assess if there is capacity to consent, based on known medical history and other information, such as information from other members of the direct care team.
[6]Co-enrolment with another study will be considered by a member(s) of the RADICAL TMG on a case-by-case basis.

5.5 Trial interventions

5.5.1 Radiofrequency denervation

There is considerable variation in RFD technique (30) and this was a key criticism of the MINT trials. In order to ensure that the RFD procedure in the trial is delivered in a way that is acceptable to clinicians and reflects how the procedure is performed within the NHS, we held a meeting in November 2019 with 10 clinicians from 10 different potential trial sites, 2 academics and 2 patient representatives to refine the clinical protocol. The meeting allowed us to understand how RFD is performed at potential trial sites and discuss any variations in protocols. As this is a pragmatic trial, we aim to avoid artificially constraining practice as much as possible while adhering to best practice.

Pre-requisites for clinicians and sites participating in RADICAL

- All clinicians who are unfamiliar with the RFD technique used within trial will be asked to complete training. This will include an online video and/or attendance at cadaver workshops.
- Participating sites must have a RF machine that meets the criteria of the RADICAL trial – ability to deliver RF lesion at 80º Celsius for 90 seconds and an appropriate solution in place to maintain blinding of the clinical team and the patient.

Additional quality assurance measures

- Images (X-rays) from at least three views for each lesion, from each clinicians' first case, to be shared with the study Clinical Lead or other clinical expert on the Trial Management Group (TMG; if unavailable), so that needle placement can be checked as

soon as possible after the first case. Placement quality will be recorded and feedback given to the clinician.

- If needle placement is poor, the study Clinical Lead and the study Clinical expert will agree on a way forward, discuss with the TMG, and feedback to the clinician on a case by case basis.
- Images (X-rays) from at least three views for each lesion, for every participant procedure will be saved by the site, for potential future monitoring, by either the study clinical lead and/or other clinical expert on the TMG, as required.

RFD procedure

RFD will be performed as a day procedure. RFD of the lumbar medial branches of the dorsal rami will be performed under local anaesthetic, with sedation if needed. The following items will be considered mandatory:

- The number and laterality of medial branches to be lesioned should be based on response to the MBB.
- Each lesion is to be carried out at 80^{o} Celsius for 90 seconds with two lesions per medial branch, unless a multipronged needle is used (only one lesion required in this case).
- For the second lesion (if required), the position of the RF cannula tip will be adjusted.
- Images (X-rays) from at least three views should be saved so that needle placement can be evaluated (as required).

The following items are recommended, but not mandatory:

- A maximum of eight medial branches at a maximum of four vertebral levels may be lesioned in a single sitting, participants with unilateral pain to receive unilateral treatment.
- Chlorhexidine is to be applied for skin preparation unless the patient is allergic; the concentration utilised will depend upon local trust guidance.
- A full aseptic technique including hand scrub, use of mask, gown and gloves should be used.
- Lignocaine is the local anaesthetic that should be used for skin infiltration.
- A curved 18 G RF cannula with a 10mm active tip should be used for targeting the medial branch (multi-pronged versions of this cannula are permitted).
- The position of the RF cannula will be confirmed with inferior (cranial), superior (caudal) and oblique views.
- Once the needle position is confirmed, routine motor testing can be carried out, however this is optional and depends on technique and use of local anaesthetic.
- Local anaesthetic is to be infiltrated before the lesion in order to minimise discomfort. Lignocaine 20mg/mL in 0.5mL boluses should be used.

5.5.2 Placebo treatment

Participants randomised to the control group will receive the same RFD protocol as the intervention group, but the temperature of the electrode tip will not be raised but maintained at 37^{o} Celsius.

5.5.3 Interventions available as part of the usual care pathway

The NLBRPP recommends RFD as a stand-alone procedure after conservative care has failed (including combined physical and psychological programmes) whereas the BPS guidelines place RFD alongside other interventions, including cognitive behavioural therapy, complex medication and specialist spinal input. To ensure we can deliver a trial within current NHS services that is acceptable to sites, we will take a pragmatic approach to participants' uptake of other interventions that may be offered or sought out. Rather than asking sites to develop or withhold services, we will collect information from the sites about their usual care pathways so that the care offered to patients at the different sites can be described. Since randomisation will be stratified by operator (within site), and assignment to RFD or placebo will be blinded, variations in usual care should be balanced across RFD and placebo treatment groups.

5.5.4 Blinded re-intervention with alternative treatment

The current widespread availability of RFD in the NHS is a challenge to this study, and patients with chronic LBP are unlikely to participate in a trial that asks them to accept a 50% chance of not having RFD for up to 2 years. Therefore, to increase acceptability and optimise recruitment in the RADICAL trial, participants will be offered the alternative treatment if symptom gain is below the minimal clinically important difference at 3 months (<2 on the pain NRS, determined from responses to the 3 month questionnaire). The "repeat RFD" will be the alternative intervention to the one provided at the outset without disclosing the original allocation to maintain blinding of allocation and all outcomes up to 2 years. This design feature means that a participant will receive a maximum of one RFD and one placebo treatment as trial interventions, i.e. participants will not be treated twice with the same intervention as part of the trial protocol. Therefore, participants have the potential to be exposed to risk twice; once for RFD and once for the placebo treatment. However, RFD is a minimally invasive procedure and serious complications are rare (see Section 7.1) (31, 32).

In line with standard NHS practice, patients may be offered unblinded RFD as part of usual NHS care if the first trial intervention provides benefit for 16 months or more but subsequently the benefit is lost. This would be provided outside of the trial, and any further request for RFD will be at the discretion of a participant's consultant, taking into account a participant's circumstances and national and local NHS policies. If any usual care RFD interventions do occur, they will be documented from medical records as part of trial follow-up. Methods of analysing longer-term outcomes, taking into account that some participants will have had a repeated RFD, are described in Section 8.

5.6 Primary and secondary outcomes

Primary and secondary outcomes are based on the core outcome set for trials in the field of LBP(33), and recommendations from the Initiative on Methods, Measurement, and Pain

Assessment in Clinical Trials (IMMPACT)(34) and NLBRPP. A schedule of data collection is provided in Section 6.6.

5.6.1 Primary outcome

The primary outcome is patient-reported LBP pain severity over the past week, measured using a 0-10 pain NRS, at 3 months post-randomisation. This was chosen as the primary outcome as the primary aim of RFD is to reduce the severity of LBP.

5.6.2 Secondary outcomes

Secondary outcomes will include:

a) Patient-reported LBP pain severity over the past week, measured using a 0-10 pain NRS, at 6, 12, 18 and 24 months post-randomisation
b) Functional disability: Oswestry Disability Index (ODI) version 2.1b (35)
c) Health-related quality of life (HRQoL): EQ-5D-5L(36)
d) General health: 12-Item Short Form Survey (SF-12) Physical Component Score(37)
e) Mental health: SF-12 Mental Component Score (37)
f) Time to pain recovery: time from randomisation until the first timepoint at which the patient reports a pain reduction of ≥60% that remains at ≥60% lower than baseline at their subsequent timepoint
g) Uptake of offer for repeat RFD
h) Satisfaction with treatment outcome: Likert scale
i) Adverse events: Active capture of adverse events (see Section 7)
j) Work outcomes: Work status and days lost from work and usual activities due to LBP using the Work Productivity and Activity Impairment (WPAI) questionnaire(38)
k) Healthcare utilisation, including medications, from a patient-reported resource use questionnaire and medical records

5.7 Sample size calculation

The original sample size calculation was based on the following assumptions:
The trial will be powered to detect a 1-point difference in the pain severity NRS (scored 0-10) between trial arms at 3 months after randomisation. The standard deviation for the pain NRS is assumed to be 2.0 (14). However, to take uncertainty in the estimate of the difference of 1-point into account, we will recruit a sample size that allows a difference of 0.84 to be detected. Assuming that scores at 3 months will be adjusted for baseline scores, with a correlation of 0.3 between scores (based on data from the MINT trials provided by collaborator Professor Raymond Ostelo), a sample size of 226 participants is required to detect a target difference of at least 0.84 in the NRS with 90% power and 5% 2-tailed significance (standardised difference=0.42). Allowing for up to 10% attrition at 3 months gives a total of 250 participants (125 per group).

The sample size calculation was revisited in March 2024 reducing the power to 85% due to the lower than anticipated recruitment rate. All other assumptions remained unchanged. This

results in a total sample size of 206 participants (103 per group). This change was approved by the funder.

6. Trial Methods

6.1 Participant screening recruitment

Initial identification and preliminary screening

Clinical lists/diaries of participating staff performing RFD will be screened weekly by a member of the local care team, to identify consecutive patients who are scheduled for RFD, having had a positive response to a single diagnostic MBB (defined as ≥60% pain relief in the first 24 hours for this study). A member of the local care team will provide a study information pack, comprising a cover letter, patient information leaflet (PIL) and accessible PIL. The PIL will contain a web link where patients can access a video to supplement the information they have received in the PIL if they wish. A member of the local care team, trained in the trial protocol, will then follow-up with a conversation/phone call to discuss the study further and answer any questions they may have. Patients who are telephoned and do not want to find out more about the study will be asked if they would be willing to briefly give their reasons. They will also be asked if they are happy to answer a few questions so that we can find out about the population screened (see section 6.6b.). Patients who are interested in the study will be asked some initial eligibility screening questions. They will also be made aware that eligibility will depend on some further checks which will take place after consent (if the patient is willing to participate), primarily: their answers to a questionnaire (depressive symptoms will be screened using the HADS questionnaire) and some further questions about their back pain history.

Recruitment consultation

If a patient appears to meet the eligibility criteria and is interested in taking part in the study, the local care team will either approach the patient for consent at the time, or arrange a further recruitment consultation at a time and place that is more convenient for the patient. The recruitment consultation may take place in person (e.g. at the hospital), or it may be via an online video call or telephone call.

Patients who are willing to participate will be asked to give informed, written consent (patients who have their recruitment consultation via online video call or telephone call will either be posted a consent form in advance or asked to complete an electronic consent (e-consent) form) but they will not be randomised at this stage. Reasons for declining participation will be recorded on the patient case report form (CRF) and will inform any changes to recruitment procedures if needed.

Questionnaire

Participants will be asked to complete the HADS questionnaire and asked some further questions about their back pain history. Responses to these assessments will indicate whether participants are eligible to proceed. Patients who are eligible after completing the

questionnaire will be contacted by a member of the local research team to confirm that they are eligible for randomisation. Final eligibility will only be met if a patient's pain is ≥5 (NRS score) at baseline. There may be a time lag between consent and receiving RFD (and therefore randomisation). If this is the case patients will be asked to reaffirm consent to the study verbally immediately prior to the RFD procedure and this will be documented in the medical records. With patients' consent, a letter will be sent to inform their GP about their participation in the study once they have been randomised.

6.2 Qualitative research

Qualitative research will be conducted in the internal pilot to evaluate trial acceptability and equipoise and facilitate improvements in communication about the trial to optimise recruitment.

6.2.1 Audio-recording of recruitment consultations

During the pilot phase patients will be approached for written consent to audio-recording of their recruitment consultation(s), but if a patient declines to be audio-recorded the recruitment consultation will still take place. With patient consent, up to 20 recruitment consultations will be audio-recorded.

6.2.2 Patient interviews

Audio-recorded telephone interviews, with an experienced qualitative researcher from the University of Bristol, will be conducted with around 20 participants in the pilot phase to elicit patient equipoise and understanding of trial procedures, acceptability of trial recruitment pathways, and the quality of patient information. As part of the approach for consent to the main trial during the pilot phase, patients will be asked to indicate whether they are willing to take part in an audio-recorded 30-minute telephone interview. If they agree, then 1-4 weeks after they are listed for RFD a qualitative researcher will telephone them and arrange to speak at a time and date convenient to them. In addition to providing written consent on the main trial consent form, the researcher will reiterate the study information and ask participants to re-affirm their consent verbally prior to commencing the interview. The interview topic guides have been developed in collaboration with PPI members and clinicians.

6.2.3 Clinician and recruiter interviews

Audio-recorded telephone interviews will also be conducted with up to 15 clinicians (including PIs at the sites) and 10 recruiters across the trial sites. This will allow understanding of trial personnel's position of equipoise and their perspectives of the trial design and protocol, recruitment pathways and any challenges to recruitment. Clinicians and recruiters will be given/sent a participant information leaflet and consent form when they first become involved in the trial. The participant information leaflet will include contact details of the researcher should the participant wish to discuss any aspect of the study before deciding whether or not to participate. If they consent to take part in an interview the qualitative researcher will contact them to arrange a mutually convenient time for this to take place. At the beginning of the

interview, participants will be asked if they have any questions before to verbally reaffirming their consent.

6.2.4 Analysis and reporting of qualitative research

All audio-recordings of recruitment consultations (including both those who agreed or declined to take part in the trial) will be transcribed by a University approved transcription company, then anonymised and subjected to rapid descriptive analysis by an experienced qualitative researcher. Analysis will focus on identifying interactions related to issues such as trial interventions, randomisation processes, how information about the trial is conveyed, patients' questions, requests for extra information/clarification and any misconceptions or notable comments. Audio-recordings of patient and clinician / recruiter interviews will be transcribed and anonymised in the same way, and then subjected to thematic analysis (39) by a qualitative researcher. A sample of transcripts will be double-coded by another member of the research team. Findings from the rapid analysis of the qualitative work will be regularly reported to and discussed by the Trial Executive Group, TMG, TSC and PPI group. This will ensure that any issues relating to participant equipoise, trial information, or the acceptability of recruitment and randomisation are reviewed in a timely fashion to ensure smooth implementation of any necessary improvements in trial processes. Reports will also be used to inform and update training sessions for recruiters.

6.3 Randomisation

Randomisation will be carried out immediately before the patient enters the treatment room for RFD. Randomisation will be performed by a member of the staff not involved in participant follow-up, using their personal login details to access a secure internet-based randomisation system ensuring allocation concealment (the RADICAL database will include the randomisation system). Participants will be allocated in a 1:1 ratio to RFD or placebo treatment. The allocation, prepared by a statistician independent of the trial team, will be computer-generated and blocked with varying block sizes. Randomisation will be stratified by operator to ensure that any operator effect is distributed equally across groups.

Instructions on how to perform a manual randomisation will be provided to the research team, for any event in which the online randomisation system should fail.

6.4 Blinding

Participants, the research team and the RFD operator will all be blinded to the allocation. The member of staff, who has randomised the participant, or another member of staff who is also unblinded, will control the electrode temperature via the radiofrequency machine, and the machine display (showing the temperature) will not be visible to the clinician performing the treatment. This same member of staff will record the treatment that the patient received on a study CRF, which will be concealed from the research team. This member of staff will have no other role in the trial.

The main potential mechanism by which RFD operators could become unblinded is because of the sound omitted by the RF machine when the maximum electrode temperature is reached. RF machines to be used in the trial will have to meet key checklist criteria, including having an appropriate solution in place to maintain blinding of the clinical team and the patient (so the team and patient would not know, from any sound emitted, or other factor, which treatment is being given). Patients who have previously received RFD will be excluded because some patients may be aware of the heat of the electrode despite local anaesthetic and may therefore become unblinded. To assess blinding, the Bang Blinding Index (40) will be administered to the clinician performing the procedure, immediately after the procedure, and to all participants via the 3 month questionnaire and 2 year questionnaire. The PIL and the process of obtaining informed consent will describe the potential effects of RFD. Therefore, in the event of inadvertent unblinding of a participant, he or she should not have a strong expectation that one or other method should lead to a more favourable result.

During the recruitment consultation participants will be asked if they would like to know their treatment allocation at the end of the trial. For those that do, we will provide this information at the same time as we send a plain English summary of findings, after the results have been analysed and a report of the primary results accepted for publication.

If clinically indicated (i.e. in the event of a serious adverse event requiring knowledge of the allocation for treatment) the treatment allocation will be unblinded. For example, unblinding would be clinically indicated if deafferentation pain was suspected (due to burning a nerve root); however, this complication is very rare.

During the recruitment consultation and consent process, the recruiter will explain to patients the importance of remaining blinded for the duration of the trial. It will be made clear that that unblinding will only occur if required clinically, i.e. that subsequent treatment would depend on knowing what treatment the patient has received.

The BTC should be contacted for requests to unblind. Any request for unblinding will be fully documented, which will include who requested the unblinding and the reason. Instances of unblinding will be monitored throughout the trial and reviewed by the Data monitoring and safety committee (DMSC). For the statistical analysis, all data up to two years after RFD will be valid and included in the analysis. We expect almost all participants to remain blinded until the end of the study.

6.5 Timing and frequency of follow-up

Participants will be followed-up for up to 24 months after randomisation. Participants will complete outcomes assessments at up to 8 timepoints: baseline (within 6 weeks prior to randomisation), 2 weeks, 6 weeks and 3 months after randomisation for everyone, and 6 months, 12 months, 18 months and 24 months after randomisation for all participants that reach those timepoints within the study period.

Pain severity at 2 and 6 weeks will be assessed using a NRS administered by a member of the local research team over the telephone. Adverse events at 2 weeks and serious adverse events only at 6 weeks, and EQ-5D-5L at 6 weeks will also be collected over the telephone by a member of the local research team. Assessments at 3, 6, 12, 18 and 24 months will be by study questionnaires which will be completed online or on paper, depending on patient preference. Postal/email reminders will be sent approximately 2 weeks after the initial contact if no reply has been received. Participants can also opt to receive SMS text message reminders (maximum of 3 texts per time point). The SMS service will be provided by Three Cherries Limited, a third party vendor, contracted by the University of Bristol under a long-standing agreement to provide an SMS for research purposes. Telephone data collection will be carried out for non-responders. We will aim to complete follow up within one month of the relevant time point where possible but will not exclude data collected after this point. The Bang Blinding Index (40) will be administered to all participants as the final question on the 3 month questionnaire and 2 year questionnaire to evaluate blinding.

As well as sending reminders, participant newsletters, and a Study within a trial (SWAT; see section 6.10), will be used as strategies to maximise the proportion of participants for whom all outcome data are available. If, following several reminders, questionnaires have not been completed, the BTC team may also try to contact the participant by telephone to collect this information, if felt appropriate. We have accounted for a 10% loss to follow-up by 3 months in our sample size calculation.

6.6 Data collection

Data collection will include the following elements:

a.) A log of patients listed for RFD and those who are sent/given a study information pack. Reasons for ineligibility and declining participation (when provided) will be recorded
b.) Consent to participate in the trial, as well as the following characteristics from participants and non-participants, as far as possible, to characterise the population and in order that an analysis of the generalisability of the patient population in the trial can be carried out: age, sex, deprivation index, pain severity (NRS) and duration of current LBP episode. Patients who choose to consent using electronic consent methods will provide their email address to the local care team to receive a link to the electronic consent form.
c.) Eligibility for the trial after post-consent screening checks
d.) Baseline characteristics, including sociodemographics, co-morbidities, and previous back surgery.
e.) Further baseline data collected via participant questionnaire completed within 6 weeks prior to randomisation. This will include measures of pain severity (NRS), risk of persistent disabling pain and psychological distress (STarT Back tool (41)), functional disability (ODI), HRQoL (EQ-5D-5L and SF-12), mental health, current opioid use, and work status and work loss (WPAI questionnaire).
f.) Pain severity (NRS) at 2 and 6 weeks, and 3, 6, 12, 18 and 24 months

g.) Functional disability (ODI) at 3, 6, 12, 18 and 24 months
h.) Adverse events from randomisation to 2 years post-randomisation (see section 7)
i.) Response to HRQoL questionnaires (EQ-5D-5L and SF-12) at 6 weeks, 3, 6, 12, 18 and 24 months
j.) Bang Blinding Index from operators and patients
k.) Allocation and key details of the RFD procedure, to monitor protocol adherence (42), and also including procedure start/end time, staff, equipment and consumables, depth of local anaesthetic injection, recovery and discharge time
l.) Images (X-rays) from at least three views so that needle placement can be evaluated (these will be saved at site, and shared with the study Clinical Lead or other clinical expert on the TMG if necessary, but not saved centrally)
m.) Offer and uptake of repeat RFD
n.) Patient satisfaction with treatment outcome (Likert scale)
o.) Linked HES for outpatient, inpatient and emergency department (ED) care and mortality data during follow up.
p.) Resource and health service use from randomisation to 2 years post randomisation using bespoke questionnaires
q.) Work status and outcomes (WPAI questionnaire) at 3, 6, 12, 18 and 24 months
r.) Information from sites about their usual care pathways
s.) Training and experience in RFD of participating clinicians, including years of experience using RFD and number of previous RFDs conducted
t.) Number of RFDs that each clinician has conducted using the standardised technique prior to participation in the study
u.) For less experienced clinicians (conducted less than 20 using the standardised technique), the number that each study participant RFD is in their learning curve until they have done enough to be considered competent (20 using the standardised technique)

Consent will also be sought from participants to obtain copies of a recent MRI scan/report (where available) if this is deemed of potential interest when it comes to interpretation of study results.

A schedule of data collection is provided in Table 1.

Table 1 Data collection

	Screening & recruitment		Eligibility confirmed	Randomisation & intervention	Post-randomisation***									
	Initial screening & consent	Post consent	Baseline	0	2		6			3	6	12	18	24
					weeks					months				
Initial screening data	X													
Consent	X													
HADS, LBP history and pain location questionnaires		X												
Baseline data e.g. demography, medical history, psychological distress			X											
Pain severity			X		X		X			X	X	X	X	X
HRQoL			X				X			X	X	X	X	X
Functional disability, general health, mental health, work outcomes			X							X	X	X	X	X
Allocation, procedural and post-procedural data				X										
Bang blinding index				X*						X**				X**
Blinded re-intervention offered										X				
Uptake of blinded re-intervention										X	X	X	X	X
Satisfaction with treatment outcome										X	X	X	X	X
Adverse events					X		X			X	X	X	X	X
Resource and health service use questionnaire										X	X	X	X	X

*Administered to clinician performing the procedure

**Administered to patient

*** Data collection up to and including 3 months post-randomisation will be completed for all participants. Data collection at 6, 12, 18 and 24 months post-randomisation will be completed for participants who reach those timepoints within the study period

6.7 Source data

Source data will be the patient's medical records and patient-reported questionnaires and where information is not recorded anywhere else, the CRFs are the source data.

6.8 Planned recruitment rate

We plan to recruit patients from 25 sites, with a recruitment rate of 0.4 patients/site/month (allowing for no recruitment in the first 3 months after opening for new sites). We estimate that 50% of patients listed for RFD will meet our eligibility criteria and 50% will agree to participate. Therefore we anticipate approaching 1,000 patients to recruit and randomise 206 patients.

6.9 Internal pilot

A 12-month internal pilot with embedded qualitative research will be conducted. All participants in the internal pilot will continue with follow-up and be retained in the full analysis. The relevant progress report to the National Institute for Health Research (NIHR) will report on the progression criteria based on data up to month 12 of recruitment. We anticipate that the NIHR decision to progress to the main trial will be made by month 15 of recruitment to the trial.

6.9.1 Progression criteria

A slower pace of recruitment is anticipated during the pilot phase due to a phased start across all sites during set up. Progression from the pilot phase to the main trial will depend on satisfying the following criteria by month 12 of the pilot recruitment phase:

- 13 sites opened to recruitment
- 79 patients consented
- 25 patients randomized

6.10 Study within a trial (SWAT)

There is little evidence of how best to retain patients after interventions cease and follow-up is conducted remotely. We will evaluate whether including a trial-branded pen can improve response rates to follow-up questionnaires within a trial compared to an unbranded pen. The addition of a pen has been shown to improve response rates to questionnaire follow-ups in a previous studies (45), however, it is unclear if it makes a difference whether the pen is branded with the study logo or is an unbranded pen. Sites will be randomised to the intervention or the comparator group. Participants at sites in the intervention group will receive a pen branded with the study logo with each follow-up questionnaire. Participants at sites in the comparator group will receive an unbranded pen with each follow-up questionnaire. All infection control guidelines will be followed. The primary analysis will be a comparison of the number of

questionnaires issued and returned between the comparator and intervention groups. We will also explore other outcomes as described by Bell et al(46).

6.11 Discontinuation/withdrawal of participants

Participants are free to withdraw from the study at any time. It is unlikely for this study that there would be any reason for the investigator/treating clinician to withdraw the participant from their allocated treatment arm especially as they are blinded to participant allocation. All withdrawals, including reasons (where given), will be recorded. If a participant wishes to withdraw, data collected up until that point will be included in the analyses. Passive data collection (e.g. from medical records) will also continue, unless the participant expresses a wish for this to stop. This is explained in the PIL.

6.12 End of trial

When patient follow up has been completed, all data entry has been completed, all data queries cleared, and the database has been locked and analyses completed. The trial may be terminated early on the instruction of the DMSC or the results of another study supersede the necessity for completion of this study.

Study results will be publicly available within 12 months of the last patient last visit.

7. Safety reporting

Serious and other adverse events (AEs) will be recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy (see Figure 3 below).

With radiofrequency denervation, some procedural and post-procedural complications are not unexpected. See section 7.1 for a list of AEs that are 'expected' for patients undergoing this procedure.

Details of all 'expected' AEs, including a description of the event, the date it started and estimated duration, will be recorded in the study CRFs, from the time of randomisation and for all events that started within a two week period post randomisation. After this period, only those which meet the serious criteria (serious adverse events; SAEs) will be recorded.

From the time of randomisation up until 3 months post-randomisation for each study participant, centres will be required to report all fatal and 'unexpected' non-fatal SAEs to the BTC within 24 hours of becoming aware of the event. The participant will be followed-up by the research team until the event resolves or until the end of the trial if the event is ongoing. The BTC will report all of these SAEs to the trial Sponsor within 24 hours of becoming aware of the

event. 'Expected' SAEs will not need expedited reporting to the Sponsor, unless they result in death, and will be reported periodically instead.

Further to this, BTC will report suspected unexpected serious adverse reactions (SUSARs) to the research ethics committee (REC), the DMSC and the clinical lead, and copy all reports to the Sponsor within 15 days (or 7 days, if fatal) of becoming aware of the event.

All SAEs will be reviewed by the Clinical Lead, DMSC and Sponsor as required.

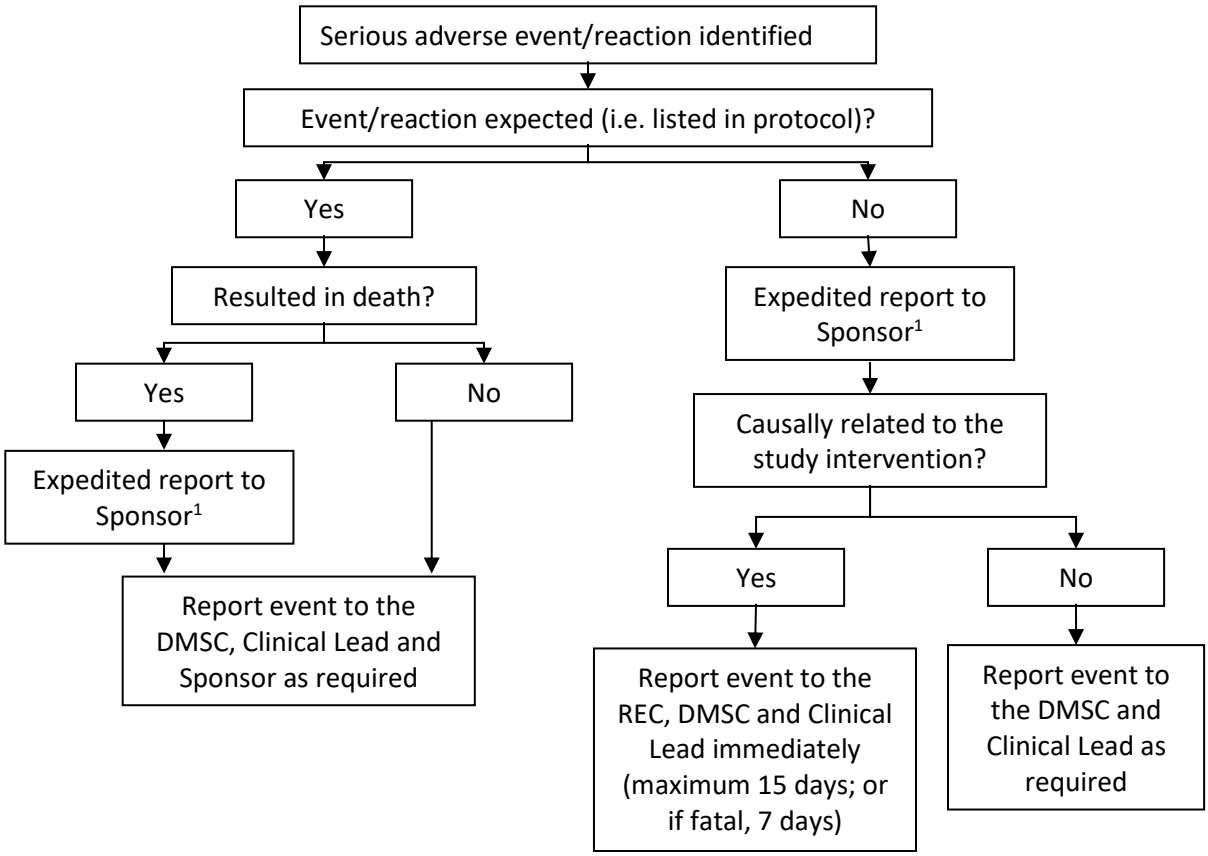
7.1 Expected adverse events

The following AEs are 'expected' after the procedure and therefore do not require expedited reporting to the Sponsor unless they result in death:

- Bruising around the site of needle insertion
- Temporary numbness and/or weakness in legs, due to local anaesthetic spread
- Discomfort (e.g. pain, tingling, burning sensation) in the back
- Infection around the site of needle insertion
- Neuritis in the back
- Allergic reaction to injection of local anaesthetic
- Deafferentation pain in the back (very rare, similar to neuritis but fails to settle).
- Damage to the sciatic nerve

Note: The following will also not be considered as 'unexpected' SAEs:

- Pre-existing conditions (i.e. conditions that were diagnosed prior to randomisation) unless symptoms worsen
- Elective procedures that were planned prior to randomisation
- Planned inpatient hospitalization immediately after RFD



[1]After 3 months post-randomisation these events do not need reporting to the Sponsor immediately but will be reported periodically, as required.

Figure 3: Serious adverse event reporting flow chart for the coordinating centre (BTC)

8. Statistics and data analysis

8.1 Statistical analysis

A detailed statistical analysis plan (SAP) will be written, including detail of all analyses that will be conducted. The data will be analysed according to ITT and follow Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

All formal comparative analysis models will be mixed effect models adjusted for treatment allocation, timepoint, and the treatment*timepoint interaction as fixed effects, and adjusted for operator and participant as random effects, where treatment differences will be reported with 95% confidence intervals. Model assumptions will be tested using standard methods and if not met, alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate.

The analysis of the primary outcome will be a linear mixed effect model, using all available repeated pain measurements up to 3 months, reported as a mean difference (and 95% confidence interval) in pain between the treatments at 3 months. In addition to this primary analysis according to ITT, a per-protocol (PP) secondary analysis will be considered if there are a substantial number of protocol deviators. Another secondary responder analysis of the primary outcome at 3 months will be carried out, i.e. between-group difference in the proportion of participants achieving ≥30% improvement in pain from baseline as recommended by IMMPACT (34, 47), and the number needed to treat will be calculated based on this analysis (48-50).

Secondary outcomes at 3 months will be compared using linear regression models. Secondary outcomes after 3 months will be described. Time to pain recovery, uptake of offer for repeat RFD will be analysed using survival methods. Frequencies of adverse events will be described and time to first adverse event compared using survival methods

Exploratory analyses will assess the effect of re-intervention with the alternative treatment using methods developed to appropriately adjust for treatment switching (51). An exploratory analysis will also be undertaken to assess the learning effect of the intervention for those less experienced practitioners with fewer than 20 procedures by including procedure number in the model. Sub-group analyses for the primary outcome will be analysed by adding a treatment by subgroup interaction to the model. Sub-groups with no prior hypotheses regarding potential interactions include: younger vs older age (split at median), sex, lower vs higher (split at median) index of multiple deprivation. Additional, hypothesis-informed, subgroup analyses will be carried out: isolated (larger treatment effect) vs widespread pain; >=80% reduction in NRS (larger treatment effect) vs >=60-79% reduction in NRS in response to the MBB; low/medium risk of persistent disabling pain (larger treatment effect) vs high risk of persistent disabling pain based on the STarT Back tool. Sub-group analyses may, by chance, generate false negative or positive results and those carried out will be interpreted with caution and treated as hypothesis-generating.

Screening data will be compared descriptively between randomised and non-randomised patients, to ascertain generalisability of results in terms of age, sex, deprivation index, pain severity (NRS) and duration of current LBP episode.

Details of the analysis of the SWAT will also be included in the SAP and will be analysed according to ITT. The primary outcome of completion and return of questionnaires will be analysed via a logistic regression model adjusting for age, host trial treatment allocation, and whether they received a trial-branded or unbranded pen. The odds ratio, 95% confidence interval and p-value for the effect of the intervention type received will be presented. Other exploratory outcomes will be described in detail in the SAP.

The only analyses that will be conducted at the end of the internal pilot will be descriptive statistics to summarise eligibility and recruitment to decide whether the trial satisfies the progression criteria, and will not include formal comparative analyses.

No formal interim analysis is planned, but the DMSC may request one if deemed necessary. Safety data will be reported to the DMSC, together with any additional analyses the committee request.

8.2 Cost-effectiveness analysis

We will collect key details of the RFD procedure, including procedure start/end time, staff, equipment and consumables, recovery and discharge time on a CRF. This will allow us to estimate how activity-based costs of the procedure vary between and within centres. However, in our primary analysis we will use NHS reference costs to estimate the cost to NHS purchasers (i.e. clinical commissioning groups) of RFD. NHS (secondary, primary care, prescriptions), social service, informal care, and absenteeism due to LBP will be collected using resource use questionnaires and the Work Productivity and Activity Impairment questionnaire administered to patients throughout follow up, supplemented with linked HES for outpatient, inpatient and ED care during follow up. We will seek participant consent to use data linkage (using e.g. NHS number, date of birth) to access data on their hospital care. We will purchase NHS Digital admitted patient (day case and inpatient), outpatient and Accident and Emergency (A&E) HES datasets. HES datasets are typically available from NHS Digital 3 months after service use. Use of hospital, primary and community care will be costed using national unit costs (52, 53). Medication costs will be estimated from the British National Formulary. Informal care by family, friends, and other volunteers will be valued using a shadow price method. Absenteeism will be valued using age-specific values. All unit costs will be taken from or inflated to the most recent available cost year. Quality of life will be assessed using EQ-5D-5L(54) to calculate quality-adjusted life years (QALYs). EQ-5D-5L assesses quality of life in 5 domains. An index score will then be derived using the UK value set recommended by NICE at the time of analysis. QALYs will be estimated adjusting for baseline differences in utility scores and any mortality observed during follow up.

We aim to determine whether RFD is cost-effective for use in the NHS. The economic analysis will take an ITT approach with imputation of missing data. In the primary economic analysis we will estimate the cost per QALY gained of RFD up to 2 years (median follow up will be shorter due to curtailed follow up for patients recruited towards the end of the study period) from the perspective of NHS and social services (to aid comparison with NICE appraisals). Based on the current NICE willingness to pay thresholds for a QALY of £20,000-£30,000 we will calculate net benefit statistics for each patient and use net benefit regressions, adjusting for baseline EQ-5D-5L scores and baseline characteristics to estimate the incremental net benefit (and 95% confidence intervals) and determine whether RFD is cost-effective. Uncertainty will be explored using cost effectiveness acceptability curves to estimate the probability that RFD is cost-effective at a range of plausible cost-effectiveness thresholds.

If the offer of “repeat RFD” after 3 months is taken up by a high proportion of participants randomized to the control group, then these ITT estimates will be attenuated towards the null.

Essentially the analysis would be comparing immediate versus delayed RFD. Therefore, in secondary exploratory analyses we will use methods developed to appropriately adjust for treatment switching(51). In additional analyses we will also estimate the cost per QALY gained and cost per additional responder (>=30% improvement in pain) at 3 months. We will also expand the perspective (i.e. societal) of the analysis to include informal care and productivity costs. If the intervention has a sustained effect in reducing pain, but is not definitively cost-effective at 2 years, we will develop a simple extrapolation model to assess cost-effectiveness over a lifetime horizon. A detailed Health Economic Analysis Plan will be prepared.

9. Trial management

North Bristol NHS Trust will act as Sponsor. The trial will be managed by the Bristol Trials Centre (BTC). The BTC is a fully registered UK Clinical Research Collaboration (UKCRC) Unit. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the investigators.

9.1 Day-to-day management

An appropriately qualified person by training will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, collecting trial data and ensuring the trial protocol is adhered to.

Day-to-day management of the trial will be overseen by the Chief Investigator (CI) and BTC staff. The Trial Executive Group, consisting of the CI, Trial Manager and BTC staff, with other co-applicants and trial staff attending as needed, will meet approximately every 6 weeks (with smaller internal update meetings held on an ad hoc basis as needed). The Trial Executive Group will report to the TMG. The TMG will meet every 4-6 months, and more frequently if needed. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial. All co-applicants and core trial staff will be invited to attend the TMG meetings. Trial newsletters will be distributed at regular intervals to all members of the research team and staff at participating sites to provide an update on trial progress and news. Meetings will be held with use of teleconference facilities to reduce environmental impact where appropriate.

9.2 Monitoring of sites

9.2.1 Site initiation

Before the study commences training sessions will be organised by the BTC. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

9.2.2 Site monitoring

BTC will carry out central monitoring and audit of compliance of sites with the principles of GCP and data collection procedures. The study database will have extensive in-built validation and the Trial Executive Group will review the completeness and consistency of the data throughout the trial. BTC will not check CRFs against the data entered or against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem or as requested by the sponsor).

9.3 Trial Steering Committee and Data Monitoring and Safety Committee

An independent TSC will be established to oversee the conduct of the study. The TSC will comprise an independent chair (trial methodologist), two patient representatives, clinicians, a statistician and health economist. The CI, Trial Manager and other TMG members as appropriate will attend TSC meetings, and a representative from the Sponsor (North Bristol NHS Trust) and NIHR will also be invited to attend. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet regularly (at intervals to be agreed with the Committee) during the course of the trial.

An independent DMSC, comprising three members, will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (before or jointly with the TSC) before the trial begins and they will meet regularly thereafter (at intervals to be agreed with the Committee).

10. Patient and Public Involvement

A PPI group involving patients with experience of RFD will be convened for this study. The PPI group will play an integral part in steering the research, including recruitment, developing accessible documentation for participants, interpretation of results and dissemination. The research team and PPI group will work together to develop public dissemination strategies and material, including production of a short YouTube video, posters and plain English summaries. Two other patient representatives will join the TSC. The PPI coordinator will be responsible for the day-to-day running of the PPI group and provision of one-to-one support to patient representatives.

11. Ethical considerations

11.1 NHS Research Ethics Committee and HRA approval

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA), including any provisions of local site capacity and capability confirmation. Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent

amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

11.2 Risks and anticipated benefits

We do not anticipate any direct benefits to participants; however the research will benefit future patients and the NHS by providing evidence on the effectiveness and cost-effectiveness of RFD.

If participants in the trial do not experience a clinically meaningful improvement in pain by 3 months they will be offered blinded re-intervention. Therefore, there is the potential for participants in the trial to be exposed to the risks associated with RFD twice. However, RFD is a low risk procedure and serious complications are very rare. Possible adverse events associated with RFD include bruising and discomfort after the procedure, infection, neuritis, allergy and deafferentation pain (see Section 7.1).

In addition, participants will be exposed to ionising radiation during fluoroscopic guidance of RFD procedures. Some of the exposures required by the study are additional to routine clinical care. Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is 0.04 %. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

11.3 Co-enrolment

Co-enrolment with another study will be considered by a member(s) of the RADICAL TMG on a case-by-case basis. Generally, co-enrolment will be allowed if the intervention is not expected to influence the primary outcome and it is not considered too burdensome for the patient.

12. Research governance

This study will be conducted in accordance with:

- GCP guidelines
- UK Policy Framework for Health and Social Care Research

12.1 Sponsor approval

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC/HRA.

12.2 Confirmation of capacity and capability

Confirmation of capacity and capability from the local NHS Trust is required prior to the start of the study.

Any amendments to the study documents approved the REC and the HRA will be submitted to the study sites, as required by the HRA.

12.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities. Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC/HRA that they receive and ensure that the changes are complied with.

12.4 Monitoring

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. All study related documents will be made available on request for monitoring and audit by the Sponsor (or BTC if they have been delegated to monitor), the relevant REC/HRA and for inspection by the Medicines and Healthcare products Regulatory Agency (MHRA) or other licensing bodies.

12.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

12.6 Clinical Trial Authorisation

The MHRA have confirmed that the trial is not a Clinical Trial of an Investigational Medicinal Product as defined by the EU Directive 2001/20/EC and therefore no submission to the Clinical Trials Unit at the MHRA is required.

13. Data protection and participant confidentiality

13.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

13.2 Data handling, storage and sharing

13.2.1 Data handling

The majority of study data will be entered onto a purpose designed database hosted on the NHS network. Access to the database will be via a secure password-protected web-interface. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to RADICAL study staff. Information capable of identifying participants will not be made available in any form to those outside the study, unless participants give permission (e.g. use of mobile phone numbers by a texting service).

Within this main study database, participants will be identified using their name and unique study identifier. Other personal identifiers (address, postcode, contact number, NHS number) will also be held in order that study participants may be contacted during follow-up and provided with a summary of the results at the end of the trial. Data extracted from the database for analysis and reporting purposes, and transferred electronically between the NHS and the University of Bristol, will only be transferred via a secure network in an encrypted form, and will not include personal identifiers, with the exception of audio-recording data and mobile phone number (please see further details below). Participants will be identified by their study ID only.

A small amount of study data will be held on a separate database, not on the NHS network, but hosted on the University of Bristol server. However, personal identifiers will not be stored on this database and participants will be identified by their study ID only. This database will include the randomisation system, and a place for the person randomising to enter the unblinded intervention data. Quality of needle placement assessment data will also be recorded here.

Data will be entered promptly, and data validation and cleaning will be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

It will be necessary to hold some identifiable data outside of the main study database for specific reasons as follows:

- Patients will be given the option to consent online, using an e-consent form. The REDCap e-consent module will be hosted on the University of Bristol server and access to the module will be given to members of participating site staff who have been delegated responsibility for taking informed consent. Coordinating centre staff will also have access to the module. If patients would like to consent using the electronic method, the patient will verbally give their email address to a member of the local care team who will enter it into the REDCap e-consent module alongside the patient's study ID. The patient will then receive an email with the link to the e-consent form. A log of all email invitations will be retained in the REDCap system which can only be accessed by

the BTC IT team. Nothing will be electronically transferred from the e-consent module to main study database. The local research team will upload a copy of the final consent form PDF to the main study database (like they would with a scanned copy of a paper consent form).

If a patient gives their email but then decides not to consent, their email can be removed from the REDCap e-consent module. However, these details will remain in the system's audit logs and cannot be deleted.

- Recruitment consultation audio-recordings will be submitted to the study qualitative team (at the University of Bristol) either using encrypted USB sticks or via the study database and transferred onto the University server. Telephone interview audio-recordings will be saved onto the University server by the study qualitative team (who will be conducting the interviews). These recordings will be transcribed by a University of Bristol approved transcription company, and the transcriptions will be pseudonymised by the research team. Although sites will be instructed not to save these files using patient names or any other identifiers apart from study ID, it is possible that names and/or other identifiers may be used during the course of the conversations recorded.
- X-ray files (that may show patient identifiers) will be shared with the study clinical lead and/or another clinical expert on the TMG, as required, so that needle placement can be evaluated for quality assurance purposes. There will, however, be no transfer of image files. Sites will share X-ray images via secure video conferencing only.
- Patient mobile phone numbers will be transferred to an SMS messaging provider via the University of Bristol server and used to send text reminders to patients. The SMS messaging provider will not have access to participant names.

13.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. All audio-recording files will be retained in a secure location during the conduct of the study and for 12 months after the end of the study, when these files will be deleted. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial. In compliance with the Medical Research Council (MRC) Policy on Data Sharing, and with participant agreement, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique study identifier, will be held indefinitely. These will be retained because of the potential for the raw data to be used subsequently for secondary research and/or training.

13.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. Anonymised recruitment consultation and interview transcripts may also be used to support teaching of qualitative research methods.

14. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR Health Technology Assessment (HTA) programme) and through patient organisations and newsletters to patients, where available. Patients who state they would like to be updated on the results of the study will receive a summary of results at the end of the study.

15. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	**Previous version**	**Previous date**	**New version**	**New date**	**Brief summary of change**	**Date of HRA/ethical approval (or NA if non-substantial)**
Non-Substantial 01	No changes to protocol.					
Non-Substantial 02	No changes to protocol.					
Non-Substantial 03	No changes to protocol.					
Substantial 01	3.0	19 August 2021	4.0	01 November 2022	- Definition of a positive response to a single diagnostic MBB in the relevant inclusion criteria amended.	01 December 2022

					- Instead of being able to mute the sound, sites must have an alternative appropriate solution in place to maintain blinding. - Details regarding X-rays views that must be saved / shared, for quality assurance purposes, amended. - RFD procedure protocol details amended. - Pain severity in the first 10 weeks now to be assessed via a telephone call, instead of 2-way SMS text messaging.	
Non-Substantial 04	No changes to protocol.					
Non-Substantial 05	No changes to protocol.					
Non-Substantial 06	No changes to protocol.					
Substantial 02	4.0	01 November 2022	5.0	06 April 2023	- Recruitment pathway amended so that patients are recruited once they have had a positive response to the MBB. - Time period for assessing patients response to MBB amended. - Added flexibility regarding local anaesthetic given for MBB. - Removed requirement for two conversations with the	02 May 2023

					patient prior to approach for consent.	
Non-Substantial 07	No changes to protocol.					
Non-Substantial 08	No changes to protocol.					
Substantial 03	5.0	06 April 2023	6.0	17 May 2024	- Added pain severity at 6, 12, 18 and 24 months as secondary outcomes. - Reduced the early follow up time points from 2, 4, 6, 8 and 10 weeks, to 2 and 6 weeks only. - Added in that an estimated duration for the 'expected' (non-serious) adverse events experienced in the first 2 weeks of patient follow up will be recorded, to monitor whether these are persistent/long term events, or temporary. - Revised how data after unblinding will be used in analysis to be inline with an ITT analysis approach. - Removed specification that only data up to 3 months will be included in the primary analysis model. - Removed 10% significance level from the specification of treatment*time interaction in the analysis of secondary	28 May 2024

					outcomes. Details to be included in the statistical analysis plan.	
Non-Substantial 09	No changes to protocol.					
Non-Substantial 10	No changes to protocol.					
Substantial 04	No changes to protocol.					
Non-Substantial 11	No changes to protocol.					
Non-Substantial 12	No changes to protocol.					
Substantial 05	6.0	17 May 2024	7.0	20 December 2024	- Changes made to reflect the reduced sample size, designed to achieve 85% power instead of 90%; and to collect primary outcome data at 3 months post-randomisation for all participants, and secondary outcomes at 6, 12, 18 and 24 months after randomisation only for participants who reach the timepoints within the revised study period (follow up ending 3 months after randomisation of the last participant). - The period for expedited reporting of Unexpected SAEs and all deaths to Sponsor has been reduced from 6 months to 3 months post-randomisation. - Minor change to timing of Baseline questionnaire	TBC

					completion, so that this is within 6 weeks of randomisation rather than within 6 weeks of RFD. - Minor changes to sections 6.3 and 6.4 to reflect the fact that the unblinded member of staff does not necessarily need to be a member of theatre staff, as long as they have no role in the study other than to carry out the tasks outlined in these sections, and that the tasks can be carried out by different unblinded members of staff – it doesn't have to be the same person doing both. - Minor amendment to section 6.5 to clarify that if after several reminders follow up questionnaires have still not been completed, the BTC team may try to contact the participant to collect this information.	

16. References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.
2. Parson S, Ingram M, Clarke-Cornwell A, Symmons D. A Heavy Burden: The occurrence and impact of musculoskeletal conditions in the United Kingdom today. Arthritis Research UK Epidemiology Unit. https://www.escholar.manchester.ac.uk/uk-ac-man-scw:123774. 2011.
3. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. Lancet. 2018;391(10137):2356-67.
4. Froud R, Patterson S, Eldridge S, Seale C, Pincus T, Rajendran D, et al. A systematic review and meta-synthesis of the impact of low back pain on people's lives. BMC Musculoskelet Disord. 2014;15:50.
5. MacNeela P, Doyle C, O'Gorman D, Ruane N, McGuire BE. Experiences of chronic low back pain: a meta-ethnography of qualitative research. Health Psychol Rev. 2015;9(1):63-82.
6. US Bone & Joint Initiative. The Burden of Musculoskeletal Diseases in the United States http://www.boneandjointburden.org/about/rights (accessed December 2018). 2014.
7. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain. 2000;84(1):95-103.
8. Jordan KP, Kadam UT, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. BMC Musculoskelet Disord. 2010;11:144.
9. Kongsted A, Kent P, Axen I, Downie AS, Dunn KM. What have we learned from ten years of trajectory research in low back pain? BMC Musculoskelet Disord. 2016;17:220.
10. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet. 2017;389(10070):736-47.
11. NHS England. National Low Back and Radicular Pain Pathway (Second Edition). 2017 20th February 2017.
12. NHS Digital. Hospital Admitted Patient Care Activity; https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 2017-18 [
13. Maas ET, Ostelo RW, Niemisto L, Jousimaa J, Hurri H, Malmivaara A, et al. Radiofrequency denervation for chronic low back pain. The Cochrane database of systematic reviews. 2015(10):CD008572.
14. Juch JNS, Maas ET, Ostelo R, Groeneweg JG, Kallewaard JW, Koes BW, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. JAMA : the journal of the American Medical Association. 2017;318(1):68-81.
15. van Kuijk S, Van Zundert J, Hans G, Van Boxem K, Vissers K, van Kleef M, et al. Flawed Study Design and Incorrect Presentation of Data Negatively Impact Potentially Useful Interventional Treatments for Patients with Low Back Pain: A Critical Review of JAMA's MinT Study. Pain Practice. 2018;18(3):292-5.

16. McCormick Z, Vorobeychik Y, Gill J, Kao M, B D, W S, et al. Guidelines for Composing and Assessing a Paper on the Treatment of Pain: A Practical Application of Evidence-Based Medicine Principles to the Mint Randomized Clinical Trials. Pain medicine. 2018;0:1-11.
17. Provenzano D, Buvanendran A, de Leon-Casasola O, Narouze S, Cohen S. Interpeting the MINT randomised trials evaluating radiofrequency ablation for lumbar facet and sacroiliac joint pain. Regional anesthesia and pain medicine. 2018;43:68-71.
18. Kapural L, Provenzano D, Narouze S. RE: Juch JNS, et al. Effect of Radiofrequency Denervation on Pain Intensity Among Patients With Chronic Low Back Pain: The Mint Randomized Clinical Trials. JAMA. Neuromodulation. 2017;20:844.
19. Vorobeychik Y, Stojanovic M, McCormick Z. Radiofrequency Denervation for Chronic Low Back Pain. JAMA : the journal of the American Medical Association. 2017;318(22):2254-55.
20. Buchbinder R, van Tulder M, Oberg B, Costa LM, Woolf A, Schoene M, et al. Low back pain: a call for action. Lancet. 2018;391(10137):2384-8.
21. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management. 30 November 2016.
22. Al-Najjim M, Shah R, Rahuma M, Gabbar OA. Lumbar facet joint injection in treating low back pain: Radiofrequency denervation versus SHAM procedure. Systematic review. J Orthop. 2018;15(1):1-8.
23. Lee CH, Chung CK, Kim CH. The efficacy of conventional radiofrequency denervation in patients with chronic low back pain originating from the facet joints: a meta-analysis of randomized controlled trials. Spine J. 2017;17(11):1770-80.
24. Piso B, Reinsperger I, Rosian K. Radiofrequency denervation for sacroiliac and facet joint pain. Decision Support. Document No. 99; Vienna: Ludwig Boltzmann Institute for Health Technology Assessment. 2016.
25. Leggett LE, Soril LJ, Lorenzetti DL, Noseworthy T, Steadman R, Tiwana S, et al. Radiofrequency ablation for chronic low back pain: a systematic review of randomized controlled trials. Pain Res Manag. 2014;19(5):e146-53.
26. Poetscher AW, Gentil AF, Lenza M, Ferretti M. Radiofrequency denervation for facet joint low back pain: a systematic review. Spine (Phila Pa 1976). 2014;39(14):E842-9.
27. Lee J, Gupta S, Price C, Baranowski AP, British Pain S. Low back and radicular pain: a pathway for care developed by the British Pain Society. British journal of anaesthesia. 2013;111(1):112-20.
28. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16s: assessment and management, Invasive treatments, NICE guideline NG59: Methods, evidence and recommendations. 2016.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
30. Eldabe S, Tariq A, Nath S, Gulve A, Antrobus H, Baloch M, et al. Best practice in radiofrequency denervation of the lumbar facet joints: a consensus technique. British Jounral of Pain. in press.
31. Cohen S, Huang J, Brummett C. Facet joint pain—advances in patient selection and treatment. Nat Rev Rheumatol. 2013;9:101-16.

32. Kornick C, Kramarich S, Lamer T, Sitzman B. Complications of lumbar facet radiofrequency denervation. Spine (Phila Pa 1976). 2004;29(12):1352-4.
33. Chiarotto A, Deyo RA, Terwee CB, Boers M, Buchbinder R, Corbin TP, et al. Core outcome domains for clinical trials in non-specific low back pain. Eur Spine J. 2015;24(6):1127-42.
34. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.
35. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000;25(22):2940-52; discussion 52.
36. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2011;20(10):1727-36.
37. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.
38. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire--general health version in patients with rheumatoid arthritis. Arthritis Res Ther. 2010;12(5):R177.
39. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology. 2013;13:117.
40. Bang H, Ni L, Davids C. Assessment of blinding in clinical trials. Controlled Clinical Trials. 2004;25:143-56.
41. Hill JC, Dunn KM, Lewis M, Mullis R, Main CJ, Foster NE, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. Arthritis and rheumatism. 2008;59(5):632-41.
42. Blencowe NS, Mills N, Cook JA, Donovan JL, Rogers CA, Whiting P, et al. Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials. Br J Surg. 2016;103(10):1377-84.
43. Clarkson JE, Ramsay CR, Averley P, Bonetti D, Boyers D, Campbell L, et al. IQuaD dental trial; improving the quality of dentistry: a multicentre randomised controlled trial comparing oral hygiene advice and periodontal instrumentation for the prevention and management of periodontal disease in dentate adults attending dental primary care. BMC Oral Health. 2013;13:58.
44. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A, et al. Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33.
45. Trial Forge. TRIAL FORGE EVIDENCE PACK – RETENTION: ADDING A PEN (ID RET3). https://www.trialforge.org/resource/evidence-pack-retention-adding-a-pen-ret3/ [Accessed 30 October 2020].

46. Bell K, Clark L, Fairhurst C, Mitchell N, Lenaghan E, Blacklock J, et al. Enclosing a pen reduced time to response to questionnaire mailings. Journal of clinical epidemiology. 2016;74:144-50.
47. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. The journal of pain : official journal of the American Pain Society. 2008;9(2):105-21.
48. Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008;33(1):90-4.
49. Froud R, Eldridge S, Kovacs F, Breen A, Bolton J, Dunn K, et al. Reporting outcomes of back pain trials: a modified Delphi study. European journal of pain. 2011;15(10):1068-74.
50. Henschke N, van Enst A, Froud R, Ostelo RW. Responder analyses in randomised controlled trials for chronic low back pain: an overview of currently used methods. Eur Spine J. 2014;23(4):772-8.
51. Latimer N. Treatment switching in oncology trials and the acceptability of adjustment methods. Expert Rev Pharmacoecon Outcomes Res. 2015;15(4):561-4.
52. PSSRU. Unit Costs of Health and Social Care 2016 [Internet]. [cited 2017 Jan 17]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php [
53. NHS reference costs - GOV.UK [Internet]. [cited 2017 Jan 17]. Available from: https://www.gov.uk/government/collections/nhs-reference-costs [
54. Cheung P, Wong C, Cheung J. Differential Psychometric Properties of EuroQoL 5-Dimension 5-Level and Short-Form 6-Dimension Utility Measures in Low Back Pain. Spine (Phila Pa 1976). 2018;Nov 20. doi: 10.1097/BRS.0000000000002939. [Epub ahead of print].