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Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for chronic and moderate to severe low back pain: study protocol for the RADICAL randomised controlled trial

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Abstract

Introduction

Low back pain is the leading global cause of disability. Patients with moderate to severe LBP who respond positively to a diagnostic medial nerve branch block can be offered radiofrequency denervation (RFD). However, high-quality evidence on the effectiveness of RFD is lacking.

Methods and analysis

RADICAL is a double-blind, parallel group, superiority randomised controlled trial. A total of 250 adults listed for RFD will be recruited from approximately 20 NHS pain and spinal clinics. Recruitment processes will be optimised through qualitative research during a 12-month internal pilot phase. Participants will be randomised in theatre using a 1:1 allocation ratio to RFD or placebo. RFD technique will follow best practice guidelines developed for the trial. Placebo RFD 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 the alternative intervention to the one provided at the outset without disclosing the original allocation. The primary clinical outcome will be pain severity, measured using a pain Numeric Rating Scale, at 3 months after randomisation. Secondary outcomes will be assessed up to 2 years after randomisation and include disability, health-related quality of life, psychological distress, time to pain recovery, satisfaction, adverse events, work outcomes and healthcare utilisation. The primary statistical analyses will be by intention-to-treat and will follow a pre-specified analysis plan. 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 over the 2-year follow up period.

Ethics and dissemination

Ethics approval was obtained from the London - Fulham Research Ethics Committee (21/LO/0471). Results will be disseminated in open access publications and plain language summaries.

Registration: ISRCTN16473239

Article summary

Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- Guidelines for RFD technique were developed during a national workshop with pain clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and reflect best practice recommendations
- A training video has been developed to support clinicians in performing the RFD technique to be used in the trial
- Offering participants who do not experience an improvement in pain after 3 months the alternative intervention to which they were randomised may increase trial acceptability while maintaining blinding
- There is a time lag between consent (waiting list for RFD) and randomisation (in theatre), which may impact on participant engagement

INTRODUCTION

Low back pain (LBP) is the leading global cause of healthy life years lost due to disability[1], and between 58% and 84% of people in the UK will experience back pain in their lifetime[2]. LBP is associated with high personal, societal and economic burden[3]. It can impact on many aspects of patients' lives, and in some cases cause life-changing psychological and social consequences including disengagement from meaningful activities, changed identity, psychological problems, damaged relationships and inability to work[4 5]. LBP is the most common musculoskeletal reason for General Practitioner (GP) appointments, accounting for 417 consultations per year per 10,000 patients registered[6]; approximately a third of the direct health care costs associated with LBP are incurred in the hospital sector[7].

Non-surgical interventions recommended by the National Institute for Health and Care Excellence (NICE) for conservative management of LBP are: self-management, exercise, psychological therapy, combined physical and psychological programmes, and non-steroidal anti-inflammatory drugs[8]. NICE guidelines also recommend that patients with moderate to severe LBP, clinical features suggesting that a facet joint is the main source of pain and insufficient improvement in symptoms with conservative management, can be offered radiofrequency denervation (RFD) of the medial nerve to a facet joint, providing that they have a positive response to a diagnostic, local anaesthetic medial nerve branch block (MNBB). RFD is a minimally invasive outpatient procedure, where a needle is placed into the back and heated up to damage the nerve, thereby interrupting the pain signal. Approximately 13,000 RFDs of the lumbar facet joints are performed annually in the NHS, with a cost to the NHS of around £22 million per year[9].

Systematic reviews of the effectiveness of RFD have been published with conflicting conclusions[10-15]. A Cochrane review, published in 2015, concluded that there was no high-quality evidence that RFD provides pain relief for patients with chronic LBP[15]. In 2017, the MINT trial (published after the systematic reviews), concluded that RFD combined with an exercise programme was not superior to an exercise programme alone[16]. However, this trial received criticism on a number of methodological grounds, including, variation in RFD operator protocols, and high numbers of patients in the control group receiving RFD[17-21].

Hence, the effectiveness of RFD is uncertain due to a lack of high-quality evidence[15], and NICE recommends that further research is needed[8].

The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference between groups in pain severity 3 months after RFD; (ii) differences between groups in 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; and (iii) the cost-effectiveness of RFD compared to placebo.

METHODS AND ANALYSIS

Trial design

RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled, superiority randomised controlled trial. Patients will be recruited from approximately 20 multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure 1).

Eligibility criteria

Patients will be eligible for the study if all the following apply:

1. ≥18 years of age
2. LBP is the primary source of pain
3. Positive response to a single diagnostic MNBB with no steroids administered. Based on the outcome of a meeting of RADICAL clinicians[22], 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 on a 0-10 numerical rating scale (NRS) after MNBB.

4. Chronic LBP (>3 months duration), assumed due to the fact the patient was listed for MNBB
5. Moderate to severe LBP (NRS score ≥5)
6. Listed for RFD

Patients will be excluded if any of the following apply:

1. Known pregnancy
2. Severe depression (Hospital Anxiety and Depression Scale (HADS)[23] depression score ≥15) (assessed following consent)
3. Known previous RFD
4. Known previous back surgery where metal-work has been used in the lumbar spine
5. Pacemaker or implantable cardioverter defibrillator
6. Clinical suspicion that an alternative diagnosis is the reason for LBP (as defined by NICE[8], including, but not limited to: metastatic spinal cord compression, spinal injury, spondyloarthritis, or cancer)
7. Prisoners
8. Lacks capacity to consent
9. Existing co-enrolment in another clinical study if: i) the intervention in the other study is expected to influence the primary outcome; ii) it is considered too burdensome for the patient; or iii) it is not permitted by the other study

Patient recruitment

Potential patients will be identified from RFD waiting lists and those potentially eligible will receive a patient information leaflet (PIL). The PIL will contain a web address where patients can access an information video to supplement the PIL. The local research team will then contact the patient to discuss the study further and answer any questions they may have. If a patient meets the initial eligibility criteria and decides to participate, the research team will request informed consent. Eligibility for randomisation will depend on further (post-consent) eligibility checks.

Details of all patients approached and reasons for non-participation will be documented. Participants will also be given the option for their data to be stored for potential use in future research and/or training. Participants can withdraw at any time and will be treated according to standard hospital procedures. Data collected up until the point of withdrawal will be included in the analysis.

Randomisation and blinding

Randomisation of eligible participants will be performed using a secure internet-based randomisation system, ensuring allocation concealment. Participants will be allocated in a 1:1 ratio to either RFD or placebo. A computer-generated allocation sequence will be prepared by an independent statistician, using random permuted blocks of varying size and stratified by operator to ensure that any operator effect is distributed equally across groups.

Participants, their clinical care team and the local research team will not be informed of the allocation. Radiofrequency machines to be used in the trial will have to meet key criteria, including having an appropriate method for maintaining blinding of the clinical team and the participant. The trained operator will randomise the participant and then control the electrode temperature. The machine display (showing the temperature) will not be visible to the rest of the team in theatre. This operator will have no other role in the trial. Treatment allocation will only be unblinded on participant request or if clinically indicated; for example, in the event of a serious adverse event requiring knowledge of the allocation for treatment. The success of blinding will be assessed using the Bang Blinding Index[24].

Intervention

The intervention is RFD of the lumbar medial branches of the dorsal rami performed under local anaesthetic, with sedation if needed. Due to considerable variation in RFD technique across clinicians and centres[25], a national consensus meeting with clinicians, patients and academics was held to refine the RFD technique for the trial[22]. Components of the RFD procedure were classified as mandatory or recommended (see Supplementary file), based on existing best practice recommendations.

Placebo

The control is placebo treatment in which participants will receive the same RFD protocol as the intervention group, but the temperature of the electrode tip will not be raised.

Clinical training

Clinicians who are unfamiliar with the RFD technique used within the trial will complete training prior to delivering the trial intervention. This will include an online video (https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver workshops.

Quality assurance measures

X-rays from at least three views for each lesion, from each clinician's first case, will be shared with a clinical expert on the Trial Management Group (TMG), so that needle placement can be checked. Placement quality will be recorded, and feedback given. If needle placement is poor, the study clinical experts will agree on a way forward, discuss with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least three views for each lesion, for every participant procedure, will be saved locally, for potential future monitoring.

Adverse Events

Adverse events that are expected due to RFD will be recorded between randomisation and two weeks post-randomisation. Serious adverse events will be recorded between randomisation and the two-year follow up. Between randomisation and 6 months post-randomisation, all unexpected or fatal serious adverse events will be reported to the Sponsor.

Outcomes

The primary outcome is LBP severity (average intensity of LBP over the past week, assessed using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected up to 2 years after randomisation and include:

1. Functional disability measured using the Oswestry Disability Index (ODI)[26] version 2.1b
2. HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D-5L)[27]
3. General health measured using the 12-Item Short Form Survey (SF-12) Physical Component Score[28]
4. Mental health measured using the SF-12 Mental Component Score
5. Time to pain recovery: time from randomisation until the participant first reports a pain reduction of ≥60% that remains at ≥60% lower than baseline at their next assessment.
6. Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3 months.
7. Satisfaction with treatment outcome using a Likert scale
8. Adverse health events
9. Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire[29]
10. Resource use assessed via a patient-reported resource use questionnaire

Data collection

Screening data will be collected before consent to establish patient eligibility. Some demographic data (i.e. age, sex and deprivation index), information about pain severity and duration of current LBP episode will also be collected from participants and non-participants, as far as possible, at the time of screening, to characterise the population and to interpret the applicability of the trial findings to the reference population. The schedule of data collection outlined in Table 1 will take place after consent has been received. Data will either be collected on paper data collection forms and entered onto the study database, or entered directly onto the database. Data for the primary outcome and most secondary outcomes will be collected via patient-completed questionnaires. Participants will be followed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and adverse health events at 2 and 6 weeks. After this, participants will complete postal/online questionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end after they have completed follow-up at 24 months post-randomisation. The end of the study

as a whole will be after all participants have completed follow-up, all data queries have been resolved, the database locked and the analysis completed.

Sample size

A sample size of 250 participants (125 per group) is sufficient to detect a difference of at least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90% power and 5% 2-tailed significance, assuming:

a) The standard deviation for the pain NRS is 2.0[16].
b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the MINT trials provided by collaborator Professor Raymond Ostelo)
c) Allowing for up to 10% attrition at 3 months.

Statistical analyses

The data will be analysed on an intention-to-treat basis and will follow a pre-specified Statistical Analysis Plan.

The primary outcome (NRS) will be analysed using linear mixed effect models, including all available repeated pain measurements up to 3 months, adjusted for timepoint and the treatment*timepoint interaction as fixed effects, and operator and participant as random effects. Treatment effects at 3 months will be reported with 95% confidence intervals. Protocol deviations will be documented, and a per-protocol secondary analysis will be considered if there are a substantial number of protocol deviators. A secondary responder analysis of the primary outcome will be performed, exploring the between-group difference in the proportion of participants achieving ≥30% improvement in pain from baseline as recommended by IMMPACT [30 31], and the number needed to treat will be calculated based on this analysis [32-34].

Continuous and binary secondary outcomes will also be compared using mixed models; and if the treatment*timepoint interaction is significant at the 10% level, treatment effects at 3, 6, 9, 12, 18 and 24 months will be reported. Time to pain recovery will be analysed using survival methods. Frequencies of adverse events will be described.

Sub-group analyses for the primary outcome will be analysed by adding a treatment by subgroup interaction to the model. Sub-groups include: younger vs older age (split at median); sex; lower vs higher (split at median) index of multiple deprivation; isolated vs widespread pain; >=80% reduction in NRS vs >=60-79% reduction in NRS in response to the MNBB; low/medium vs high risk of persistent disabling pain based on the STarT Back tool[35].

Exploratory analyses will assess the effect of re-intervention with the alternative treatment using methods developed to appropriately adjust for treatment switching[36]. Exploratory analyses 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. Screening data will be compared descriptively between randomised and non-randomised patients, to ascertain generalisability of results. No formal interim analysis is planned.

Cost-effectiveness analyses

The analysis will follow a pre-specified Health Economic Analysis Plan. We will use NHS reference costs to estimate the cost to NHS purchasers 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 WPAI administered to participants throughout follow up. We will seek consent for data linkage to access Hospital Episode Statistics (HES) inpatient, day case, outpatient and emergency department datasets. Hospital, primary and community care will be costed using national unit costs[37 38]. Quality of life will be assessed using EQ-5D-5L[39] to calculate quality-adjusted life years (QALYs). An index score will 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.

The economic analysis will take an intention to treat approach with imputation of missing data. In the primary economic analysis we will estimate the cost per QALY gained of RFD at 2 years from the perspective of NHS and social services. Based on the current NICE willingness to pay thresholds for a QALY of £20,000-£30,000 we will 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 a cost-effective use of NHS funds. Uncertainty will be explored using cost effectiveness acceptability curves. In additional analyses we will also estimate the cost per QALY gained and cost per additional responder (>=30% improvement in pain) at 3 months and expand the perspective of the analysis to include informal care and productivity costs.

Internal pilot phase

RADICAL includes a 12-month internal pilot phase with embedded qualitative research. Progression from the pilot to the main study will be contingent on demonstrating that after 12 months of recruitment, enough patients are eligible for the trial and can be randomised. Progression criteria are:

1. 13 sites are open to recruitment
2. 79 patients consented
3. 25 patients randomised (this accounts for a 3-month time lag between consent and randomisation)
4. Consent rate of 1.5 patients/site/month

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. Up to 20 recruitment consultations will be audio-recorded, and telephone interviews with up to 20 participants will elicit patient understanding of trial procedures and interventions, equipoise, acceptability of recruitment pathways, and quality of patient

information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow understanding of trial personnel's equipoise and perspectives on the protocol, usual care, and recruitment pathways. Data will be subjected to rapid thematic framework analysis[40 41] to ensure findings are reported and implemented in a timely fashion.

Data handling, storage and sharing

Most data will be stored in a bespoke database hosted on the NHS network. Some data items will be held on a separate database, hosted on the University of Bristol server, comprising the randomisation system, information about the intervention delivered and the quality of needle placement. Access to both databases will be via secure password-protected web-interfaces.

All study documentation will be retained in a secure location during the conduct of the study and for five years afterwards, when all participant 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 afterwards, 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 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.

Patient and public involvement (PPI)

RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of Bristol. A PPI group involving patients with experience of RFD has also been convened specifically for this study. This group has played an integral part in designing the research,

including development of accessible participant documents. They will continue to co-work with the research team on all aspects of the study, including interpretation of results and development of public dissemination strategies and material. The Trial Steering Committee (TSC) also includes two patient members.

Ethics and dissemination

The study received Research Ethics Committee (REC) approval from London - Fulham REC in July 2021 and Health Research Authority (HRA) approval in September 2021. The study is sponsored by North Bristol NHS Trust (https://www.nbt.nhs.uk/research-innovation) who are responsible for the oversight of the study and ensuring it is managed appropriately. The study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data Monitoring and Safety Committee (DMSC) (see Supplementary file).

Changes to the protocol since REC/HRA approval

Following REC and HRA approval the following changes have been made to the study protocol: i) two amendments to the time frame for assessing response to the MNBB; ii) increase in number of x-ray images to be saved for quality assurance purposes; iii) increased flexibility introduced within the RFD procedure protocol to match usual variability in standard practice, whilst still adhering to the same technique, and to reflect advances in equipment; iv) muting the sound of the radiofrequency machine (the original proposed method to maintain blinding) was found not to be an option due to safety factors, therefore it was mandated that sites must have an alternative appropriate solution in place; v) telephone calls instead of two-way text messages for assessment of pain severity over the first 10 weeks after randomisation ; vi) recruitment pathway shortened so that patients are recruited once listed for RFD rather than after listing for MNBB; vii) added flexibility regarding protocol for MNBB. Protocol version 5.0 (dated 6th April 2023) is currently in use. All relevant parties are informed of protocol amendments.

Dissemination of findings

Findings will be presented at conferences and published open access in peer-review journals. Impact on clinical practice will be through engagement with relevant organisation such as NICE, British Pain Society, Clinical Reference Group for Spinal Services, and UK Spine Societies Board. We will work with our PPI group and relevant charities on public dissemination.

Discussion

Findings from the RADICAL trial will contribute to shaping clinical guidelines and service provision for patients living with chronic LBP. Study training resources, developed in line with the consensus-based best practice guidelines for RFD produced by the RADICAL team[22], have been positively received and taken up by clinicians across the country, demonstrating that the trial is already impacting on RFD provision by improving standards. The study opened to recruitment on 27th May 2022 and is currently recruiting across 13 centres. To date, 46 patients have been recruited and 14 randomised.

During the internal pilot phase (ongoing at the time of manuscript submission), RADICAL has experienced three substantial challenges to delivery: delays in site opening, complex screening processes limiting sites capacity to recruit patients and long NHS waiting times for RFD. Opening sites has been an ongoing issue due to the continuing impact of the COVID-19 pandemic on research infrastructure; we have experienced delays of up to two years from feasibility assessment to site opening due to research and development departments' limited capacity to process local approvals. However, we have recently seen an improvement in site opening timelines, with a recent site opening in 4 months. Identification of sites with the necessary clinical expertise and engagement, alongside the research infrastructure to deliver the trial, has been key, and we have achieved this through a combination of national calls for sites through the National Institute for Health Research (NIHR) Clinical Research Network and one-to-one discussions with clinicians.

During our internal pilot phase, we identified that recruitment was slower than anticipated. To understand site-level barriers to recruitment, we held three recruitment training meetings with 17 staff members from seven sites. Feedback from local delivery teams was that patients were willing to participate but our screening processes were complex, and that the workload associated with our recruitment processes was limiting their capacity to recruit patients. Our original recruitment process was to screen patients listed for a MNBB and then recruit patients prior to their MNBB. Patients who had ≥60% pain relief from the MNBB (approximately 40% of patients) were then eligible to proceed in the trial and were listed for RFD and randomised in theatre. This process meant there was a significant time lag (often 18 months or more since the pandemic) between recruitment and randomisation due to NHS waiting lists for MNBB and RFD. Our original pathway also meant that 625 patients needed to be consented into the trial for us to randomise 250. We designed the trial this way to optimise acceptability to patients, as we were concerned that once they are on an established pathway to RFD, they would find randomisation (including the possibility of receiving a placebo) unacceptable. However, the feedback from sites was that patients are willing to participate and are motivated by the desire to help future patients. In particular, they are reassured by a feature we included in the design to promote recruitment, namely the offer of blinded reintervention with the alternative treatment if they do not experience a clinically important improvement in pain after 3 months. In light of this feedback from sites, we simplified our screening and recruitment processes by recruiting patients after they are listed for RFD. This approach substantially reduces the screening and recruitment workload to sites, reduces the time lag between consent and randomisation, and means that we no longer need to consent many more patients than will be randomised.

In summary, our internal pilot phase identified some challenges to trial delivery. We have been proactive in understanding how best to address these challenges and adapting our trial design to optimise delivery.

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Table 1 Schedule of data collection

	Baseline	Randomisation & intervention	Post-randomisation									
			2	4	6	8	10	3	6	12	18	24
			weeks					months				
Sociodemographic details	X											
HADS	X											
Medical history including pain location	X											
Psychological distress	X											
NRS pain score	X		X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	X				X			X	X	X	X	X
SF-12	X							X	X	X	X	X
ODI	X							X	X	X	X	X
WPAI	X							X	X	X	X	X
Procedural data		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

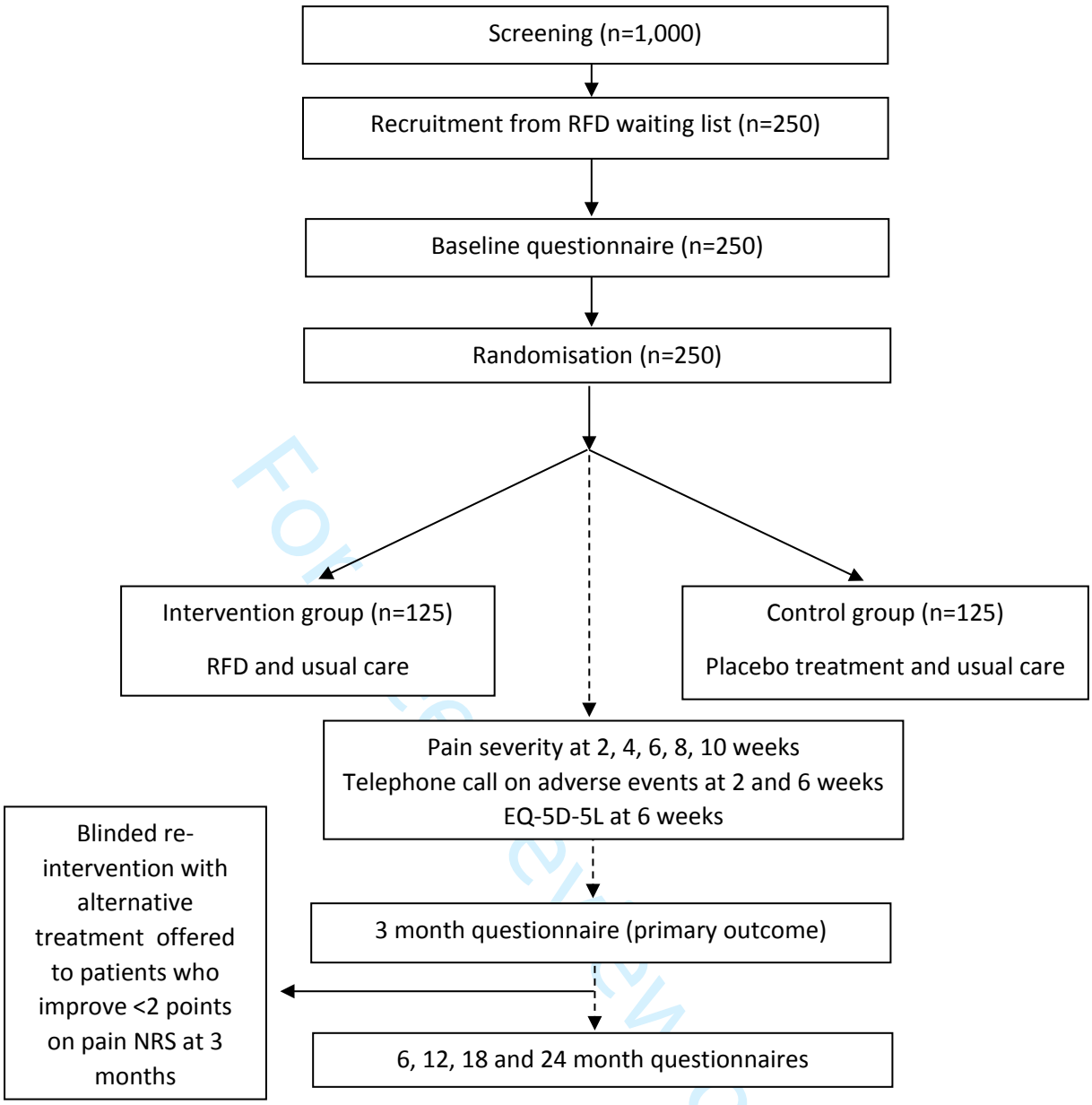

Figure 1 Trial schema

Author contributions

KA is involved in conducting the trial and assembled the manuscript from the trial protocol. VW is the chief investigator, identified the funding opportunity and co-designed the trial. CPr is the clinical pain lead for the trial. BR and CR, respectively, lead on methodology and statistics for the trial. RE drafted the statistical analysis plan. AM and CPa carry out qualitative research within the trial. LF has assisted with set up and delivery of the trial. WH

is the health economics lead and NJ the health economist working on the trial. LC provides senior trial management oversight and advice. NF, NO and AB provide clinical advice as part of the Trial Management Group. CJ coordinates the PPI involvement in the trial. VW, CPr, AB, BR, LC, CR, NF, NO, WH and AM all co-designed the trial and obtained funding. All authors have been involved in preparation of the study protocol and have read and approved the final manuscript.

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Competing interests statement

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No other conflicts were reported.

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Supplementary Information

Mandatory and recommended components of the RFD procedure

Mandatory components include that the numbers and laterality of medial branches to be lesioned should be based on response to the MNBB; lesions to be carried out at 80° Celsius for 90 seconds with two lesions per medial branch, unless a multipronged needle is used (only one lesion required in this case); the position of the RF cannula tip should be adjusted for the second lesion (if required); and x-rays from at least three views should be saved so that needle placement can be evaluated (as required).

Recommended, but not mandatory, components include: a maximum of eight medial branches at a maximum of four vertebral levels lesioned in a single sitting, and participants with unilateral pain to receive unilateral treatment; Chlorhexidine applied for skin preparation, unless the patient is allergic; full aseptic technique used; Lignocaine (local anaesthetic) used for skin infiltration; a curved 18 G RF cannula with a 10mm active tip used for targeting the medial branch (multi-pronged versions permitted); position of RF cannula confirmed with inferior, superior and oblique views; once the needle position is confirmed, optional routine motor testing can be carried out; and local anaesthetic (Lignocaine 20mg/mL in 0.5mL boluses recommended) is infiltrated before the lesion in order to minimise discomfort.

TSC and DMSC details

The TSC is made up of representatives from the RADICAL study team and independent members approved by the funder. The DMSC consists of an independent medical statistician and medical experts in this field approved by the funder. The TSC and DMSC meet as frequently as they feel is necessary, usually at least once a year.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 20-21
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7

	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Figure 1
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request: radical-study@bristol.ac.uk
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for chronic and moderate to severe low back pain: study protocol for the RADICAL randomised controlled trial

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Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for chronic and moderate to severe low back pain: study protocol for the RADICAL randomised controlled trial

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Abstract

Introduction

Low back pain (LBP) is the leading global cause of disability. Patients with moderate to severe LBP who respond positively to a diagnostic medial nerve branch block can be offered radiofrequency denervation (RFD). However, high-quality evidence on the effectiveness of RFD is lacking.

Methods and analysis

RADICAL is a double-blind, parallel group, superiority randomised controlled trial. A total of 250 adults listed for RFD will be recruited from approximately 20 National Health Service (NHS) pain and spinal clinics. Recruitment processes will be optimised through qualitative research during a 12-month internal pilot phase. Participants will be randomised in theatre using a 1:1 allocation ratio to RFD or placebo. RFD technique will follow best practice guidelines developed for the trial. Placebo RFD 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 the alternative intervention to the one provided at the outset without disclosing the original allocation. The primary clinical outcome will be pain severity, measured using a pain Numeric Rating Scale, at 3 months after randomisation. Secondary outcomes will be assessed up to 2 years after randomisation and include disability, health-related quality of life, psychological distress, time to pain recovery, satisfaction, adverse events, work outcomes and healthcare utilisation. The primary statistical analyses will be by intention-to-treat and will follow a pre-specified analysis plan. 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 over the 2-year follow up period.

Ethics and dissemination

Ethics approval was obtained from the London - Fulham Research Ethics Committee (21/LO/0471). Results will be disseminated in open access publications and plain language summaries.

Registration: ISRCTN registration number: ISRCTN16473239

Article summary

Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- Guidelines for RFD technique were developed during a national workshop with pain clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and reflect best practice recommendations
- A training video has been developed to support clinicians in performing the RFD technique to be used in the trial
- Offering participants who do not experience an improvement in pain after 3 months the alternative intervention to which they were randomised may increase trial acceptability while maintaining blinding
- There is a time lag between consent (waiting list for RFD) and randomisation (in theatre), which may impact on participant engagement

INTRODUCTION

Low back pain (LBP) is the leading global cause of healthy life years lost due to disability(1), and between 58% and 84% of people in the UK will experience back pain in their lifetime(2). LBP is associated with high personal, societal and economic burden(3). It can impact on many aspects of patients' lives, and in some cases cause life-changing psychological and social consequences including disengagement from meaningful activities, changed identity, psychological problems, damaged relationships and inability to work(4, 5). LBP is the most common musculoskeletal reason for General Practitioner (GP) appointments, accounting for 417 consultations per year per 10,000 patients registered(6); approximately a third of the direct health care costs associated with LBP are incurred in the hospital sector(7).

Non-surgical interventions recommended by the National Institute for Health and Care Excellence (NICE) for conservative management of LBP are: self-management, exercise, psychological therapy, combined physical and psychological programmes, and non-steroidal anti-inflammatory drugs(8). NICE guidelines also recommend that patients with moderate to severe LBP, clinical features suggesting that a facet joint is the main source of pain and insufficient improvement in symptoms with conservative management, can be offered radiofrequency denervation (RFD) of the medial nerve to a facet joint, providing that they have a positive response to a diagnostic, local anaesthetic medial nerve branch block (MNBB). RFD is a minimally invasive outpatient procedure, where a needle is placed into the back and heated up to damage the nerve, thereby interrupting the pain signal. Approximately 13,000 RFDs of the lumbar facet joints are performed annually in the NHS, with a cost to the NHS of around £22 million per year(9).

Systematic and narrative reviews of the effectiveness of RFD have been published with conflicting conclusions(10-16). A Cochrane review, published in 2015, concluded that there was no high-quality evidence that RFD provides pain relief for patients with chronic LBP(15). In 2017, the MINT trial (published after the systematic reviews), concluded that RFD combined with an exercise programme was not superior to an exercise programme alone(17). However, this trial received criticism on a number of methodological grounds, including, variation in RFD operator protocols, and high numbers of patients in the control

group receiving RFD(18-22). Hence, the effectiveness of RFD is uncertain due to a lack of high-quality evidence(15), and NICE recommends that further research is needed(8).

The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference between groups in pain severity 3 months after RFD; (ii) differences between groups in 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; and (iii) the cost-effectiveness of RFD compared to placebo.

METHODS AND ANALYSIS

Trial design

RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled, superiority randomised controlled trial. Patients will be recruited from approximately 20 multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure 1).

Eligibility criteria

Patients will be eligible for the study if all the following apply:

1. ≥18 years of age
2. LBP is the primary source of pain
3. Positive response to a single diagnostic MNBB with no steroids administered. Based on the outcome of a meeting of RADICAL clinicians(23), 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 on a 0-10 numerical rating scale (NRS) after MNBB.

4. Chronic LBP (>3 months duration), assumed due to the fact the patient was listed for MNBB
5. Moderate to severe LBP (NRS score ≥5)
6. Listed for RFD

Patients will be excluded if any of the following apply:

1. Known pregnancy
2. Severe depression (Hospital Anxiety and Depression Scale (HADS)(24) depression score ≥15) (assessed following consent)
3. Known previous RFD
4. Known previous back surgery where metal-work has been used in the lumbar spine
5. Pacemaker or implantable cardioverter defibrillator
6. Clinical suspicion that an alternative diagnosis is the reason for LBP (as defined by NICE(8), including, but not limited to: metastatic spinal cord compression, spinal injury, spondyloarthritis, or cancer)
7. Prisoners
8. Lacks capacity to consent
9. Existing co-enrolment in another clinical study if: i) the intervention in the other study is expected to influence the primary outcome; ii) it is considered too burdensome for the patient; or iii) it is not permitted by the other study

No restrictions will be placed on usual care, and all co-interventions are permitted to reflect usual NHS practice.

Patient recruitment

Potential patients will be identified from RFD waiting lists and those potentially eligible will receive a patient information leaflet (PIL). The PIL will contain a web address where patients can access an information video to supplement the PIL. The local research team will then contact the patient to discuss the study further and answer any questions they may have. If a patient meets the initial eligibility criteria and decides to participate, the research team

will request informed consent. Eligibility for randomisation will depend on further (post-consent) eligibility checks.

Details of all patients approached and reasons for non-participation will be documented. Participants will also be given the option for their data to be stored for potential use in future research and/or training. Participants can withdraw at any time and will be treated according to standard hospital procedures. Data collected up until the point of withdrawal will be included in the analysis.

Randomisation and blinding

Randomisation of eligible participants will be performed using a secure internet-based randomisation system, ensuring allocation concealment. Participants will be allocated in a 1:1 ratio to either RFD or placebo. A computer-generated allocation sequence will be prepared by an independent statistician, using random permuted blocks of varying size and stratified by operator to ensure that any operator effect is distributed equally across groups.

Participants, their clinical care team and the local research team will not be informed of the allocation. Radiofrequency machines to be used in the trial will have to meet key criteria, including having an appropriate method for maintaining blinding of the clinical team and the participant. The trained randomiser will randomise the participant and then control the electrode temperature. The machine display (showing the temperature) will not be visible to the rest of the team in theatre. This person will have no other role in the trial. Treatment allocation will only be unblinded on participant request or if clinically indicated; for example, in the event of a serious adverse event requiring knowledge of the allocation for treatment. The success of blinding will be assessed using the Bang Blinding Index(25).

Intervention

The intervention is RFD of the lumbar medial branches of the dorsal rami performed under local anaesthetic, with sedation if needed. Although there are international consensus practice guidelines for performing RFD(26), there is considerable variation in RFD technique across clinicians and centres in the UK(27). To refine the RFD technique for the trial, a national consensus meeting was held with clinicians, patients and academics(23).

Components of the RFD procedure were classified as mandatory or recommended (see Supplementary file), based on existing best practice recommendations.

Placebo

A placebo control will be used to minimise bias, which is important as the primary outcome is patient-reported. The placebo treatment will follow the same RFD protocol as the intervention group, but the temperature of the electrode tip will not be raised.

Clinical training

Clinicians who are unfamiliar with the RFD technique used within the trial will complete training prior to delivering the trial intervention. This will include an online video (https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver workshops.

Quality assurance measures

X-rays from at least three views for each lesion, from each clinician's first case, will be shared with a clinical expert on the Trial Management Group (TMG), so that needle placement can be checked. Placement quality will be recorded, and feedback given. If needle placement is poor, the study clinical experts will agree on a way forward, discuss with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least three views for each lesion, for every participant procedure, will be saved locally, for potential future monitoring.

Adverse Events

Adverse events that are expected due to RFD will be recorded between randomisation and two weeks post-randomisation. Serious adverse events will be recorded between randomisation and the two-year follow up. Between randomisation and 6 months post-randomisation, all unexpected or fatal serious adverse events will be reported to the Sponsor.

Outcomes

The primary outcome is LBP severity (average intensity of LBP over the past week, assessed using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected up to 2 years after randomisation and include:

1. Functional disability measured using the Oswestry Disability Index (ODI)(28) version 2.1b
2. HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D-5L)(29)
3. General health measured using the 12-Item Short Form Survey (SF-12) Physical Component Score(30)
4. Mental health measured using the SF-12 Mental Component Score
5. Time to pain recovery: time from randomisation until the participant first reports a pain reduction of ≥60% that remains at ≥60% lower than baseline at their next assessment.
6. Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3 months.
7. Satisfaction with treatment outcome using a Likert scale
8. Adverse health events
9. Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire(31)
10. Resource use assessed via a patient-reported resource use questionnaire

Data collection

Screening data will be collected before consent to establish patient eligibility. Some demographic data (see Supplementary file), information about pain severity and duration of current LBP episode will also be collected from participants and non-participants, as far as possible, at the time of screening, to characterise the population and to interpret the applicability of the trial findings to the reference population. The schedule of data collection outlined in Supplementary Table 1 will take place after consent has been received. Data will

either be collected on paper data collection forms and entered onto the study database, or entered directly onto the database. Data for the primary outcome and most secondary outcomes will be collected via patient-completed questionnaires. Participants will be followed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and adverse health events at 2 and 6 weeks. After this, participants will complete postal/online questionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end after they have completed follow-up at 24 months post-randomisation. The end of the study as a whole will be after all participants have completed follow-up, all data queries have been resolved, the database locked and the analysis completed.

Sample size

A sample size of 250 participants (125 per group) is sufficient to detect a difference of at least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90% power and 5% 2-tailed significance, assuming:

a) The standard deviation for the pain NRS is 2.0(17).
b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the MINT trials provided by collaborator Professor Raymond Ostelo)
c) Allowing for up to 10% attrition at 3 months.

The trial will therefore have sufficient power to detect the target difference used by NICE (1-point difference) and reflects a moderate effect size.

Statistical analyses

The data will be analysed on an intention-to-treat basis and will follow a pre-specified Statistical Analysis Plan.

The primary outcome (NRS) will be analysed using linear mixed effect models, including all available repeated pain measurements up to 3 months, adjusted for timepoint and the

treatment*timepoint interaction as fixed effects, and operator and participant as random effects. Treatment effects at 3 months will be reported with 95% confidence intervals. Protocol deviations will be documented, and a per-protocol secondary analysis will be considered if there are a substantial number of protocol deviators. A secondary responder analysis of the primary outcome will be performed, exploring the between-group difference in the proportion of participants achieving ≥30% improvement in pain from baseline as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)(32, 33), and the number needed to treat will be calculated based on this analysis(34-36).

Continuous and binary secondary outcomes will also be compared using mixed models; and if the treatment*timepoint interaction is significant at the 10% level, treatment effects at 3, 6, 9, 12, 18 and 24 months will be reported. Time to pain recovery will be analysed using survival methods. Frequencies of adverse events will be described. Missing data on patient questionnaires will be dealt with according to the scoring manuals. Imputation methods e.g. multiple imputation, will be considered if the proportion of missing data is >5%, otherwise complete case analysis will be undertaken.

Sub-group analyses for the primary outcome will be analysed by adding a treatment by subgroup interaction to the model. Sub-groups include: younger vs older age (split at median); sex; lower vs higher (split at median) index of multiple deprivation; isolated vs widespread pain; >=80% reduction in NRS vs >=60-79% reduction in NRS in response to the MNBB; low/medium vs high risk of persistent disabling pain based on the STarT Back tool(37).

Exploratory analyses will assess the effect of re-intervention with the alternative treatment using methods developed to appropriately adjust for treatment switching(38). Exploratory analyses 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. Screening data will be compared descriptively between randomised and non-randomised patients, to ascertain generalisability of results. No formal interim analysis is planned.

Cost-effectiveness analyses

The analysis will follow a pre-specified Health Economic Analysis Plan. We will use NHS reference costs to estimate the cost to NHS purchasers 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 WPAI administered to participants throughout follow up. We will seek consent for data linkage to access Hospital Episode Statistics (HES) inpatient, day case, outpatient and emergency department datasets. Hospital, primary and community care will be costed using national unit costs(39, 40). Quality of life will be assessed using EQ-5D-5L(41) to calculate quality-adjusted life years (QALYs). An index score will 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.

The economic analysis will take an intention to treat approach with imputation of missing data (e.g. using multiple imputations). In the primary economic analysis we will estimate the cost per QALY gained of RFD at 2 years from the perspective of NHS and social services. Based on the current NICE willingness to pay thresholds for a QALY of £20,000-£30,000 we will 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 a cost-effective use of NHS funds. Uncertainty will be explored using cost effectiveness acceptability curves. In additional analyses we will also estimate the cost per QALY gained and cost per additional responder (>=30% improvement in pain) at 3 months and expand the perspective of the analysis to include informal care and productivity costs.

Internal pilot phase

RADICAL includes a 12-month internal pilot phase with embedded qualitative research. Progression from the pilot to the main study will be contingent on demonstrating that after

12 months of recruitment, enough patients are eligible for the trial and can be randomised. Progression criteria are:

1. 13 sites are open to recruitment
2. 79 patients consented
3. 25 patients randomised (this accounts for a 3-month time lag between consent and randomisation)
4. Consent rate of 1.5 patients/site/month

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. Up to 20 recruitment consultations will be audio-recorded, and telephone interviews with up to 20 participants will elicit patient understanding of trial procedures and interventions, equipoise, acceptability of recruitment pathways, and quality of patient information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow understanding of trial personnel's equipoise and perspectives on the protocol, usual care, and recruitment pathways. Data will be subjected to rapid thematic framework analysis(42, 43) to ensure findings are reported and implemented in a timely fashion.

Data handling, storage and sharing

Most data will be stored in a bespoke database hosted on the NHS network. Some data items will be held on a separate database, hosted on the University of Bristol server, comprising the randomisation system, information about the intervention delivered and the quality of needle placement. Access to both databases will be via secure password-protected web-interfaces.

All study documentation will be retained in a secure location during the conduct of the study and for five years afterwards, when all participant 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 afterwards, 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 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.

Patient and public involvement (PPI)

RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of Bristol. A PPI group involving patients with experience of RFD has also been convened specifically for this study. This group has played an integral part in designing the research, including development of accessible participant documents. They will continue to co-work with the research team on all aspects of the study, including interpretation of results and development of public dissemination strategies and material. The Trial Steering Committee (TSC) also includes two patient members.

Ethics and dissemination

The study received Research Ethics Committee (REC) approval from London - Fulham REC in July 2021 and Health Research Authority (HRA) approval in September 2021. The study is sponsored by North Bristol NHS Trust (https://www.nbt.nhs.uk/research-innovation) who are responsible for the oversight of the study and ensuring it is managed appropriately. The study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data Monitoring and Safety Committee (DMSC) (see Supplementary file).

Changes to the protocol since REC/HRA approval

Following REC and HRA approval the following changes have been made to the study protocol: i) two amendments to the time frame for assessing response to the MNBB; ii) increase in number of x-ray images to be saved for quality assurance purposes; iii) clarification regarding the mandatory and recommended components of the RFD procedure protocol, to match usual variability in standard practice, whilst still adhering to the same technique, and to reflect advances in equipment; iv) muting the sound of the radiofrequency machine (the original proposed method to maintain blinding) was found not to be an option due to safety factors, therefore it was mandated that sites must have an alternative appropriate solution in place (further details are provided in the Supplementary file); v) telephone calls instead of two-way text messages for assessment of pain severity over the first 10 weeks after randomisation ; vi) recruitment pathway shortened so that patients are recruited once listed for RFD rather than after listing for MNBB; vii) added flexibility regarding protocol for MNBB. Protocol version 5.0 (dated 6th April 2023) is currently in use. All relevant parties are informed of protocol amendments.

Dissemination of findings

Findings will be presented at conferences and published open access in peer-review journals. Impact on clinical practice will be through engagement with relevant organisation such as NICE, British Pain Society, Clinical Reference Group for Spinal Services, and UK Spine Societies Board. We will work with our PPI group and relevant charities on public dissemination.

Discussion

Findings from the RADICAL trial will contribute to shaping clinical guidelines and service provision for patients living with chronic LBP. Study training resources, developed in line with the consensus-based best practice guidelines for RFD produced by the RADICAL

team(23), have been positively received and taken up by clinicians across the country, demonstrating that the trial is already impacting on RFD provision by improving standards. The study opened to recruitment on 27th May 2022 and is currently recruiting across 17 centres. As of the 8th February 2024 , 83 patients have been recruited and 47 randomised.

During the internal pilot phase, RADICAL experienced three substantial challenges to delivery: delays in site opening, complex screening processes limiting sites capacity to recruit patients and long NHS waiting times for RFD. Opening sites has been an ongoing issue due to the continuing impact of the COVID-19 pandemic on research infrastructure; we have experienced delays of up to two years from feasibility assessment to site opening due to research and development departments' limited capacity to process local approvals. However, we have recently seen an improvement in site opening timelines, with a recent site opening in 4 months. Identification of sites with the necessary clinical expertise and engagement, alongside the research infrastructure to deliver the trial, has been key, and we have achieved this through a combination of national calls for sites through the National Institute for Health Research (NIHR) Clinical Research Network and one-to-one discussions with clinicians.

During our internal pilot phase, we identified that recruitment was slower than anticipated. To understand site-level barriers to recruitment, we held three recruitment training meetings with 17 staff members from seven sites. Feedback from local delivery teams was that patients were willing to participate but our screening processes were complex, and that the workload associated with our recruitment processes was limiting their capacity to recruit patients. Our original recruitment process was to screen patients listed for a MNBB and then recruit patients prior to their MNBB. Patients who had ≥60% pain relief from the MNBB (approximately 40% of patients(44)) were then eligible to proceed in the trial and were listed for RFD and randomised in theatre. This process meant there was a significant time lag (often 18 months or more since the pandemic) between recruitment and randomisation due to NHS waiting lists for MNBB and RFD. Our original pathway also meant that 625 patients needed to be consented into the trial for us to randomise 250. We designed the trial this way to optimise acceptability to patients, as we were concerned that

once they are on an established pathway to RFD, they would find randomisation (including the possibility of receiving a placebo) unacceptable. However, the feedback from sites was that patients are willing to participate and are motivated by the desire to help future patients. In particular, they are reassured by a feature we included in the design to promote recruitment, namely the offer of blinded reintervention with the alternative treatment if they do not experience a clinically important improvement in pain after 3 months. In light of this feedback from sites, we simplified our screening and recruitment processes by recruiting patients after they are listed for RFD. This approach substantially reduces the screening and recruitment workload to sites, reduces the time lag between consent and randomisation, and means that we no longer need to consent many more patients than will be randomised.

In summary, our internal pilot phase identified some challenges to trial delivery. We have been proactive in understanding how best to address these challenges and adapting our trial design to optimise delivery.

Author contributions

KA is involved in conducting the trial and assembled the manuscript from the trial protocol. VW is the chief investigator, identified the funding opportunity and co-designed the trial. CPr is the clinical pain lead for the trial. BR and CR, respectively, lead on methodology and statistics for the trial. RE drafted the statistical analysis plan. AM and CPa carry out qualitative research within the trial. LF has assisted with set up and delivery of the trial. WH is the health economics lead and NJ the health economist working on the trial. LC provides senior trial management oversight and advice. NF, NO and AB provide clinical advice as part of the Trial Management Group. CJ coordinates the PPI involvement in the trial. VW, CPr, AB, BR, LC, CR, NF, NO, WH and AM all co-designed the trial and obtained funding. All authors have been involved in preparation of the study protocol and have read and approved the final manuscript.

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Competing interests statement

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No other conflicts were reported.

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Figure Legend:

Figure 1 – Trial schema

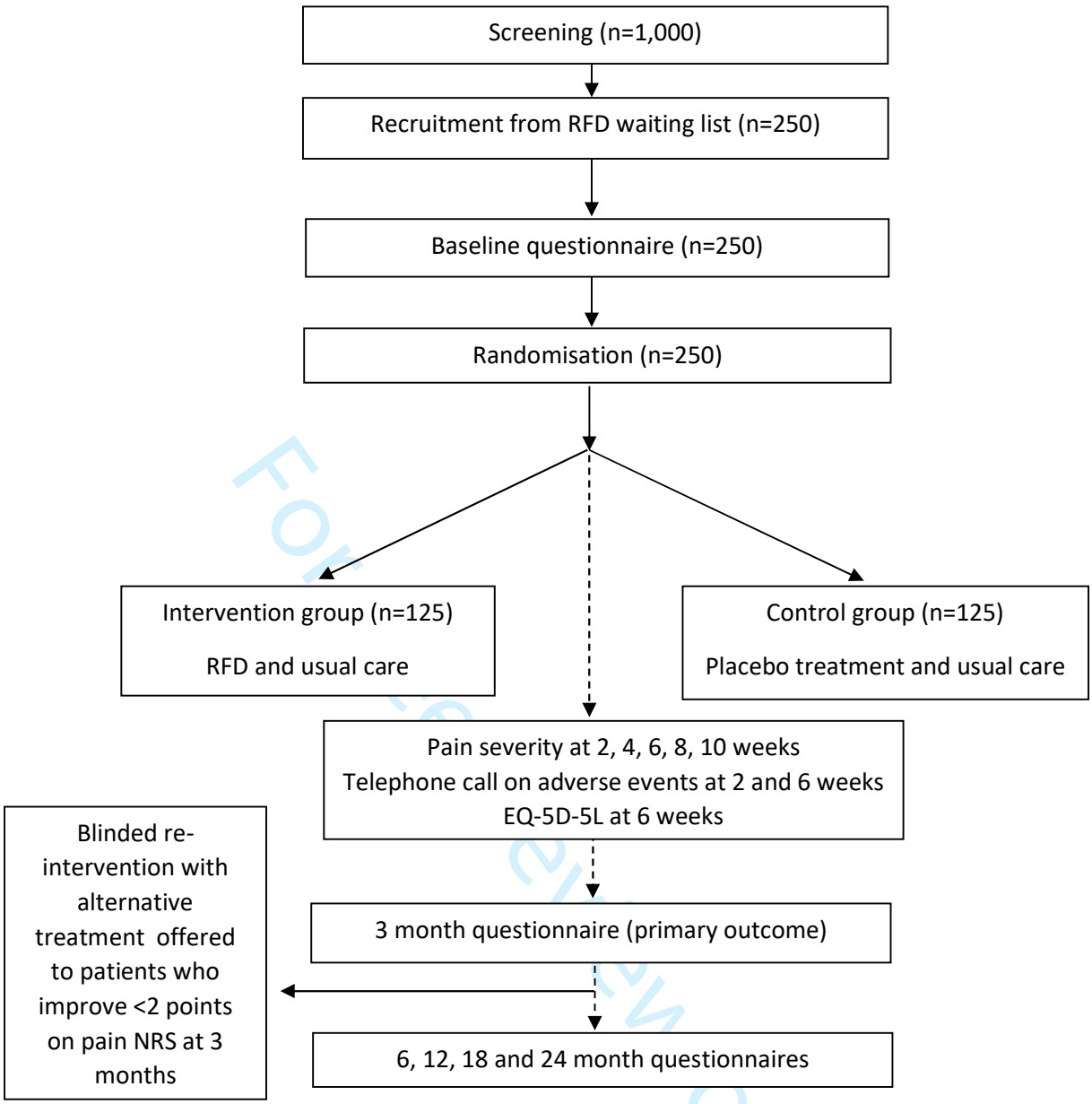

Table 1 Schedule of data collection

	Baseline	Randomisation & intervention	Post-randomisation									
			2	4	6	8	10	3	6	12	18	24
			weeks					months				
Sociodemographic details	X											
HADS	X											
Medical history including pain location	X											
STarT Back tool	X											
NRS pain score	X		X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	X				X			X	X	X	X	X
SF-12	X							X	X	X	X	X
ODI	X							X	X	X	X	X
WPAI	X							X	X	X	X	X
Procedural data		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

Supplementary Information

Mandatory and recommended components of the RFD procedure

Mandatory components include that the numbers and laterality of medial branches to be lesioned should be based on response to the MNBB; lesions to be carried out at 80° Celsius for 90 seconds with two lesions per medial branch, unless a multipronged needle is used (only one lesion required in this case); the position of the RF cannula tip should be adjusted for the second lesion (if required); and x-rays from at least three views should be saved so that needle placement can be evaluated (as required).

Recommended, but not mandatory, components include: a maximum of eight medial branches at a maximum of four vertebral levels lesioned in a single sitting, and participants with unilateral pain to receive unilateral treatment; Chlorhexidine applied for skin preparation, unless the patient is allergic; full aseptic technique used; Lignocaine (local anaesthetic) used for skin infiltration; a curved 18 G RF cannula with a 10mm active tip used for targeting the medial branch (multi-pronged versions permitted); position of RF cannula confirmed with inferior, superior and oblique views; once the needle position is confirmed, optional routine motor testing can be carried out; and local anaesthetic (Lignocaine 20mg/mL in 0.5mL boluses recommended) is infiltrated before the lesion in order to minimise discomfort.

Baseline demographic and medical history

- Sex
- Age
- Body mass index
- Index of multiple deprivation
- Ethnicity
- Employment status
- Smoking status
- E-cigarette user
- Myocardial infarction
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular accident
- Transient ischaemic attack
- Dementia

- Chronic obstructive pulmonary disease
- Connective tissue disease
- Peptic ulcer disease
- Hemiplegia
- Liver disease
- Diabetes mellitus
- Moderate to severe chronic kidney disease
- Solid tumour
- Leukaemia
- Lymphoma
- AIDS
- Previous back surgery

TSC and DMSC details

The TSC is made up of representatives from the RADICAL study team and independent members approved by the funder. The DMSC consists of an independent medical statistician and medical experts in this field approved by the funder. The TSC and DMSC meet as frequently as they feel is necessary, usually at least once a year.

Examples of methods used with different Radiofrequency (RF) machines to ensure blinding

Make of the RF machine	Method
Diros	A custom switching box has been developed which allows the unblinded randomiser to switch between 'RFD' and 'placebo' mode, whilst maintaining blinding of the rest of team and the patient in theatre.
Stryker	The beeping noise that is made when a lesion is performed (for RFD) is the same as the beeping noise that is made when sensory mode is on, even at 0.0v. This means that sensory mode at 0.0v can be selected by the randomiser for patients that are allocated to the 'placebo' treatment, and as far as the rest of the team and the patient in theatre are concerned it would sound the same as 'RFD', therefore maintaining blinding.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 20-21
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7

	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Figure 1
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealmen t mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementat ion	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request: radical-study@bristol.ac.uk
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for chronic and moderate to severe low back pain: study protocol for the RADICAL randomised controlled trial

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Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for chronic and moderate to severe low back pain: study protocol for the RADICAL randomised controlled trial

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Abstract

Introduction

Low back pain (LBP) is the leading global cause of disability. Patients with moderate to severe LBP who respond positively to a diagnostic medial nerve branch block can be offered radiofrequency denervation (RFD). However, high-quality evidence on the effectiveness of RFD is lacking.

Methods and analysis

RADICAL is a double-blind, parallel group, superiority randomised controlled trial. A total of 250 adults listed for RFD will be recruited from approximately 20 National Health Service (NHS) pain and spinal clinics. Recruitment processes will be optimised through qualitative research during a 12-month internal pilot phase. Participants will be randomised in theatre using a 1:1 allocation ratio to RFD or placebo. RFD technique will follow best practice guidelines developed for the trial. Placebo RFD 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 the alternative intervention to the one provided at the outset without disclosing the original allocation. The primary clinical outcome will be pain severity, measured using a pain Numeric Rating Scale, at 3 months after randomisation. Secondary outcomes will be assessed up to 2 years after randomisation and include disability, health-related quality of life, psychological distress, time to pain recovery, satisfaction, adverse events, work outcomes and healthcare utilisation. The primary statistical analyses will be by intention-to-treat and will follow a pre-specified analysis plan. 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 over the 2-year follow up period.

Ethics and dissemination

Ethics approval was obtained from the London - Fulham Research Ethics Committee (21/LO/0471). Results will be disseminated in open access publications and plain language summaries.

Registration: ISRCTN registration number: ISRCTN16473239

Article summary

Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- Guidelines for RFD technique were developed during a national workshop with pain clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and reflect best practice recommendations
- A training video has been developed to support clinicians in performing the RFD technique to be used in the trial
- Offering participants who do not experience an improvement in pain after 3 months the alternative intervention to which they were randomised may increase trial acceptability while maintaining blinding
- There is a time lag between consent (waiting list for RFD) and randomisation (in theatre), which may impact on participant engagement

INTRODUCTION

Low back pain (LBP) is the leading global cause of healthy life years lost due to disability(1), and between 58% and 84% of people in the UK will experience back pain in their lifetime(2). LBP is associated with high personal, societal and economic burden(3). It can impact on many aspects of patients' lives, and in some cases cause life-changing psychological and social consequences including disengagement from meaningful activities, changed identity, psychological problems, damaged relationships and inability to work(4, 5). LBP is the most common musculoskeletal reason for General Practitioner (GP) appointments, accounting for 417 consultations per year per 10,000 patients registered(6); approximately a third of the direct health care costs associated with LBP are incurred in the hospital sector(7).

Non-surgical interventions recommended by the National Institute for Health and Care Excellence (NICE) for conservative management of LBP are: self-management, exercise, psychological therapy, combined physical and psychological programmes, and non-steroidal anti-inflammatory drugs(8). NICE guidelines also recommend that patients with moderate to severe LBP, clinical features suggesting that a facet joint is the main source of pain and insufficient improvement in symptoms with conservative management, can be offered radiofrequency denervation (RFD) of the medial nerve to a facet joint, providing that they have a positive response to a diagnostic, local anaesthetic medial nerve branch block (MNBB). RFD is a minimally invasive outpatient procedure, where a needle is placed into the back and heated up to damage the nerve, thereby interrupting the pain signal. Approximately 13,000 RFDs of the lumbar facet joints are performed annually in the NHS, with a cost to the NHS of around £22 million per year(9).

Systematic and narrative reviews of the effectiveness of RFD have been published with conflicting conclusions(10-16). A Cochrane review, published in 2015, concluded that there was no high-quality evidence that RFD provides pain relief for patients with chronic LBP(15). In 2017, the MINT trial (published after the systematic reviews), concluded that RFD combined with an exercise programme was not superior to an exercise programme alone(17). However, this trial received criticism on a number of methodological grounds, including, variation in RFD operator protocols, and high numbers of patients in the control

group receiving RFD(18-22). Hence, the effectiveness of RFD is uncertain due to a lack of high-quality evidence(15), and NICE recommends that further research is needed(8).

The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference between groups in pain severity 3 months after RFD; (ii) differences between groups in 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; and (iii) the cost-effectiveness of RFD compared to placebo.

METHODS AND ANALYSIS

Trial design

RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled, superiority randomised controlled trial. Patients will be recruited from approximately 20 multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure 1).

Eligibility criteria

Patients will be eligible for the study if all the following apply:

1. ≥18 years of age
2. LBP is the primary source of pain
3. Positive response to a single diagnostic MNBB with no steroids administered. Based on the outcome of a meeting of RADICAL clinicians(23), 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 on a 0-10 numerical rating scale (NRS) after MNBB.

4. Chronic LBP (>3 months duration), assumed due to the fact the patient was listed for MNBB
5. Moderate to severe LBP (NRS score ≥5)
6. Listed for RFD

Patients will be excluded if any of the following apply:

1. Known pregnancy
2. Severe depression (Hospital Anxiety and Depression Scale (HADS)(24) depression score ≥15) (assessed following consent)
3. Known previous RFD
4. Known previous back surgery where metal-work has been used in the lumbar spine
5. Pacemaker or implantable cardioverter defibrillator
6. Clinical suspicion that an alternative diagnosis is the reason for LBP (as defined by NICE(8), including, but not limited to: metastatic spinal cord compression, spinal injury, spondyloarthritis, or cancer)
7. Prisoners
8. Lacks capacity to consent
9. Existing co-enrolment in another clinical study if: i) the intervention in the other study is expected to influence the primary outcome; ii) it is considered too burdensome for the patient; or iii) it is not permitted by the other study

No restrictions will be placed on usual care, and all co-interventions are permitted to reflect usual NHS practice. Data on co-interventions will not be collected.

Patient recruitment

Potential patients will be identified from RFD waiting lists and those potentially eligible will receive a patient information leaflet (PIL). The PIL will contain a web address where patients can access an information video to supplement the PIL. The local research team will then contact the patient to discuss the study further and answer any questions they may have. If a patient meets the initial eligibility criteria and decides to participate, the research team will request written informed consent. A copy of the Informed Consent Form can be

requested by contacting the RADICAL study team at radical-study@bristol.ac.uk. Eligibility for randomisation will depend on further (post-consent) eligibility checks.

Details of all patients approached and reasons for non-participation will be documented. Participants will also be given the option for their data to be stored for potential use in future research and/or training. Participants can withdraw at any time and will be treated according to standard hospital procedures. Data collected up until the point of withdrawal will be included in the analysis.

Randomisation and blinding

Randomisation of eligible participants will be performed using a secure internet-based randomisation system, ensuring allocation concealment. Participants will be allocated in a 1:1 ratio to either RFD or placebo. A computer-generated allocation sequence will be prepared by an independent statistician, using random permuted blocks of varying size and stratified by operator to ensure that any operator effect is distributed equally across groups.

Participants, their clinical care team and the local research team will not be informed of the allocation. Radiofrequency machines to be used in the trial will have to meet key criteria, including having an appropriate method for maintaining blinding of the clinical team and the participant. The trained randomiser will randomise the participant and then control the electrode temperature. The machine display (showing the temperature) will not be visible to the rest of the team in theatre. This person will have no other role in the trial. Treatment allocation will only be unblinded on participant request or if clinically indicated; for example, in the event of a serious adverse event requiring knowledge of the allocation for treatment. The success of blinding will be assessed using the Bang Blinding Index(25).

Intervention

The intervention is RFD of the lumbar medial branches of the dorsal rami performed under local anaesthetic, with sedation if needed. Although there are international consensus practice guidelines for performing RFD(26), there is considerable variation in RFD technique across clinicians and centres in the UK(27). To refine the RFD technique for the trial, a national consensus meeting was held with clinicians, patients and academics(23).

Components of the RFD procedure were classified as mandatory or recommended (see Supplementary file), based on existing best practice recommendations.

Placebo

A placebo control will be used to minimise bias, which is important as the primary outcome is patient-reported. The placebo treatment will follow the same RFD protocol as the intervention group, but the temperature of the electrode tip will not be raised.

Clinical training

Clinicians who are unfamiliar with the RFD technique used within the trial will complete training prior to delivering the trial intervention. This will include an online video (https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver workshops.

Quality assurance measures

X-rays from at least three views for each lesion, from each clinician's first case, will be shared with a clinical expert on the Trial Management Group (TMG), so that needle placement can be checked. Placement quality will be recorded, and feedback given. If needle placement is poor, the study clinical experts will agree on a way forward, discuss with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least three views for each lesion, for every participant procedure, will be saved locally, for potential future monitoring.

Adverse Events

Adverse events that are expected due to RFD will be recorded between randomisation and two weeks post-randomisation. Serious adverse events will be recorded between randomisation and the two-year follow up. Between randomisation and 6 months post-randomisation, all unexpected or fatal serious adverse events will be reported to the Sponsor.

Outcomes

The primary outcome is LBP severity (average intensity of LBP over the past week, assessed using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected up to 2 years after randomisation and include:

1. Functional disability measured using the Oswestry Disability Index (ODI)(28) version 2.1b
2. HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D-5L)(29)
3. General health measured using the 12-Item Short Form Survey (SF-12) Physical Component Score(30)
4. Mental health measured using the SF-12 Mental Component Score
5. Time to pain recovery: time from randomisation until the participant first reports a pain reduction of ≥60% that remains at ≥60% lower than baseline at their next assessment.
6. Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3 months.
7. Satisfaction with treatment outcome using a Likert scale
8. Adverse health events
9. Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire(31)
10. Resource use assessed via a patient-reported resource use questionnaire

Data collection

Screening data will be collected before consent to establish patient eligibility. Some demographic data (see Supplementary file), information about pain severity and duration of current LBP episode will also be collected from participants and non-participants, as far as possible, at the time of screening, to characterise the population and to interpret the applicability of the trial findings to the reference population. The schedule of data collection outlined in Supplementary Table 1 will take place after consent has been received. Data will

either be collected on paper data collection forms and entered onto the study database, or entered directly onto the database. Data for the primary outcome and most secondary outcomes will be collected via patient-completed questionnaires. Participants will be followed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and adverse health events at 2 and 6 weeks. After this, participants will complete postal/online questionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end after they have completed follow-up at 24 months post-randomisation. The end of the study as a whole will be after all participants have completed follow-up, all data queries have been resolved, the database locked and the analysis completed.

Sample size

A sample size of 250 participants (125 per group) is sufficient to detect a difference of at least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90% power and 5% 2-tailed significance, assuming:

a) The standard deviation for the pain NRS is 2.0(17).
b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the MINT trials provided by collaborator Professor Raymond Ostelo)
c) Allowing for up to 10% attrition at 3 months.

The trial will therefore have sufficient power to detect the target difference used by NICE (1-point difference) and reflects a moderate effect size(32).

Statistical analyses

The data will be analysed on an intention-to-treat basis and will follow a pre-specified Statistical Analysis Plan.

The primary outcome (NRS) will be analysed using linear mixed effect models, including all available repeated pain measurements up to 3 months, adjusted for timepoint and the

treatment*timepoint interaction as fixed effects, and operator and participant as random effects. Treatment effects at 3 months will be reported with 95% confidence intervals. Protocol deviations will be documented, and a per-protocol secondary analysis will be considered if there are a substantial number of protocol deviators. A secondary responder analysis of the primary outcome will be performed, exploring the between-group difference in the proportion of participants achieving ≥30% improvement in pain from baseline as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)(33, 34), and the number needed to treat will be calculated based on this analysis(35-37).

Continuous and binary secondary outcomes will also be compared using mixed models; and if the treatment*timepoint interaction is significant at the 10% level, treatment effects at 3, 6, 9, 12, 18 and 24 months will be reported. Time to pain recovery will be analysed using survival methods. Frequencies of adverse events will be described. Missing data on patient questionnaires will be dealt with according to the scoring manuals. Imputation methods e.g. multiple imputation, will be considered if the proportion of missing data is >5%, otherwise complete case analysis will be undertaken.

Sub-group analyses for the primary outcome will be analysed by adding a treatment by subgroup interaction to the model. Sub-groups include: younger vs older age (split at median); sex; lower vs higher (split at median) index of multiple deprivation; isolated vs widespread pain; >=80% reduction in NRS vs >=60-79% reduction in NRS in response to the MNBB; low/medium vs high risk of persistent disabling pain based on the STarT Back tool(38).

Exploratory analyses will assess the effect of re-intervention with the alternative treatment using methods developed to appropriately adjust for treatment switching(39). Exploratory analyses 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. Screening data will be compared descriptively between randomised and non-randomised patients, to ascertain generalisability of results. No formal interim analysis is planned.

Cost-effectiveness analyses

The analysis will follow a pre-specified Health Economic Analysis Plan. We will use NHS reference costs to estimate the cost to NHS purchasers 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 WPAI administered to participants throughout follow up. We will seek consent for data linkage to access Hospital Episode Statistics (HES) inpatient, day case, outpatient and emergency department datasets. Hospital, primary and community care will be costed using national unit costs(40, 41). Quality of life will be assessed using EQ-5D-5L(42) to calculate quality-adjusted life years (QALYs). An index score will 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.

The economic analysis will take an intention to treat approach with imputation of missing data (e.g. using multiple imputations). In the primary economic analysis we will estimate the cost per QALY gained of RFD at 2 years from the perspective of NHS and social services. Based on the current NICE willingness to pay thresholds for a QALY of £20,000-£30,000 we will 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 a cost-effective use of NHS funds. Uncertainty will be explored using cost effectiveness acceptability curves. In additional analyses we will also estimate the cost per QALY gained and cost per additional responder (>=30% improvement in pain) at 3 months and expand the perspective of the analysis to include informal care and productivity costs.

Internal pilot phase

RADICAL includes a 12-month internal pilot phase with embedded qualitative research. Progression from the pilot to the main study will be contingent on demonstrating that after

12 months of recruitment, enough patients are eligible for the trial and can be randomised. Progression criteria are:

1. 13 sites are open to recruitment
2. 79 patients consented
3. 25 patients randomised (this accounts for a 3-month time lag between consent and randomisation)
4. Consent rate of 1.5 patients/site/month

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. Up to 20 recruitment consultations will be audio-recorded, and telephone interviews with up to 20 participants will elicit patient understanding of trial procedures and interventions, equipoise, acceptability of recruitment pathways, and quality of patient information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow understanding of trial personnel's equipoise and perspectives on the protocol, usual care, and recruitment pathways. Data will be subjected to rapid thematic framework analysis(43, 44) to ensure findings are reported and implemented in a timely fashion.

Data handling, storage and sharing

Most data will be stored in a bespoke database hosted on the NHS network. Some data items will be held on a separate database, hosted on the University of Bristol server, comprising the randomisation system, information about the intervention delivered and the quality of needle placement. Access to both databases will be via secure password-protected web-interfaces.

All study documentation will be retained in a secure location during the conduct of the study and for five years afterwards, when all participant 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 afterwards, 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 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.

Patient and public involvement (PPI)

RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of Bristol. A PPI group involving patients with experience of RFD has also been convened specifically for this study. This group has played an integral part in designing the research, including development of accessible participant documents. They will continue to co-work with the research team on all aspects of the study, including interpretation of results and development of public dissemination strategies and material. The Trial Steering Committee (TSC) also includes two patient members.

Ethics and dissemination

The study received Research Ethics Committee (REC) approval from London - Fulham REC in July 2021 and Health Research Authority (HRA) approval in September 2021. The study is sponsored by North Bristol NHS Trust (https://www.nbt.nhs.uk/research-innovation) who are responsible for the oversight of the study and ensuring it is managed appropriately. The study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data Monitoring and Safety Committee (DMSC) (see Supplementary file).

Changes to the protocol since REC/HRA approval

Following REC and HRA approval the following changes have been made to the study protocol: i) two amendments to the time frame for assessing response to the MNBB; ii) increase in number of x-ray images to be saved for quality assurance purposes; iii) clarification regarding the mandatory and recommended components of the RFD procedure protocol, to match usual variability in standard practice, whilst still adhering to the same technique, and to reflect advances in equipment; iv) muting the sound of the radiofrequency machine (the original proposed method to maintain blinding) was found not to be an option due to safety factors, therefore it was mandated that sites must have an alternative appropriate solution in place (further details are provided in the Supplementary file); v) telephone calls instead of two-way text messages for assessment of pain severity over the first 10 weeks after randomisation ; vi) recruitment pathway shortened so that patients are recruited once listed for RFD rather than after listing for MNBB; vii) added flexibility regarding protocol for MNBB. Protocol version 5.0 (dated 6th April 2023) is currently in use. All relevant parties are informed of protocol amendments.

Dissemination of findings

Findings will be presented at conferences and published open access in peer-review journals. Impact on clinical practice will be through engagement with relevant organisation such as NICE, British Pain Society, Clinical Reference Group for Spinal Services, and UK Spine Societies Board. We will work with our PPI group and relevant charities on public dissemination.

Discussion

Findings from the RADICAL trial will contribute to shaping clinical guidelines and service provision for patients living with chronic LBP. Study training resources, developed in line with the consensus-based best practice guidelines for RFD produced by the RADICAL

team(23), have been positively received and taken up by clinicians across the country, demonstrating that the trial is already impacting on RFD provision by improving standards. The study opened to recruitment on 27th May 2022 and is currently recruiting across 17 centres. As of the 8th February 2024 , 83 patients have been recruited and 47 randomised. The original study end date was 31st December 2024. An extension until 31st July 2026 is currently being requested to complete the study.

During the internal pilot phase, RADICAL experienced three substantial challenges to delivery: delays in site opening, complex screening processes limiting sites capacity to recruit patients and long NHS waiting times for RFD. Opening sites has been an ongoing issue due to the continuing impact of the COVID-19 pandemic on research infrastructure; we have experienced delays of up to two years from feasibility assessment to site opening due to research and development departments' limited capacity to process local approvals. However, we have recently seen an improvement in site opening timelines, with a recent site opening in 4 months. Identification of sites with the necessary clinical expertise and engagement, alongside the research infrastructure to deliver the trial, has been key, and we have achieved this through a combination of national calls for sites through the National Institute for Health Research (NIHR) Clinical Research Network and one-to-one discussions with clinicians.

During our internal pilot phase, we identified that recruitment was slower than anticipated. To understand site-level barriers to recruitment, we held three recruitment training meetings with 17 staff members from seven sites. Feedback from local delivery teams was that patients were willing to participate but our screening processes were complex, and that the workload associated with our recruitment processes was limiting their capacity to recruit patients. Our original recruitment process was to screen patients listed for a MNBB and then recruit patients prior to their MNBB. Patients who had ≥60% pain relief from the MNBB (approximately 40% of patients(45)) were then eligible to proceed in the trial and were listed for RFD and randomised in theatre. This process meant there was a significant time lag (often 18 months or more since the pandemic) between recruitment and randomisation due to NHS waiting lists for MNBB and RFD. Our original pathway also meant that 625 patients needed to be consented into the trial for us to randomise 250. We

designed the trial this way to optimise acceptability to patients, as we were concerned that once they are on an established pathway to RFD, they would find randomisation (including the possibility of receiving a placebo) unacceptable. However, the feedback from sites was that patients are willing to participate and are motivated by the desire to help future patients. In particular, they are reassured by a feature we included in the design to promote recruitment, namely the offer of blinded reintervention with the alternative treatment if they do not experience a clinically important improvement in pain after 3 months. In light of this feedback from sites, we simplified our screening and recruitment processes by recruiting patients after they are listed for RFD. This approach substantially reduces the screening and recruitment workload to sites, reduces the time lag between consent and randomisation, and means that we no longer need to consent many more patients than will be randomised.

In summary, our internal pilot phase identified some challenges to trial delivery. We have been proactive in understanding how best to address these challenges and adapting our trial design to optimise delivery.

Author contributions

KA is involved in conducting the trial, assembled the manuscript from the trial protocol and is the guarantor. VW is the chief investigator, identified the funding opportunity and co-designed the trial. CPr is the clinical pain lead for the trial. BR and CR, respectively, lead on methodology and statistics for the trial. RE drafted the statistical analysis plan. AM and CPa carry out qualitative research within the trial. LF has assisted with set up and delivery of the trial. WH is the health economics lead and NJ the health economist working on the trial. LC provides senior trial management oversight and advice. NF, NO and AB provide clinical advice as part of the Trial Management Group. CJ coordinates the PPI involvement in the trial. VW, CPr, AB, BR, LC, CR, NF, NO, WH and AM all co-designed the trial and obtained funding. All authors have been involved in preparation of the study protocol and have read and approved the final manuscript.

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Competing interests statement

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No other conflicts were reported.

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The authors thank all of the research and clinical team members at participating site; members of the Trial Steering Committee and independent Data Monitoring and Safety Committee; members of the patient and public involvement group, and additional collaborators Professor Raymond Ostelo and Professor Steven Cohen, who will be involved in the management of the trial and will contribute key expertise on aspects of trial design as needed.

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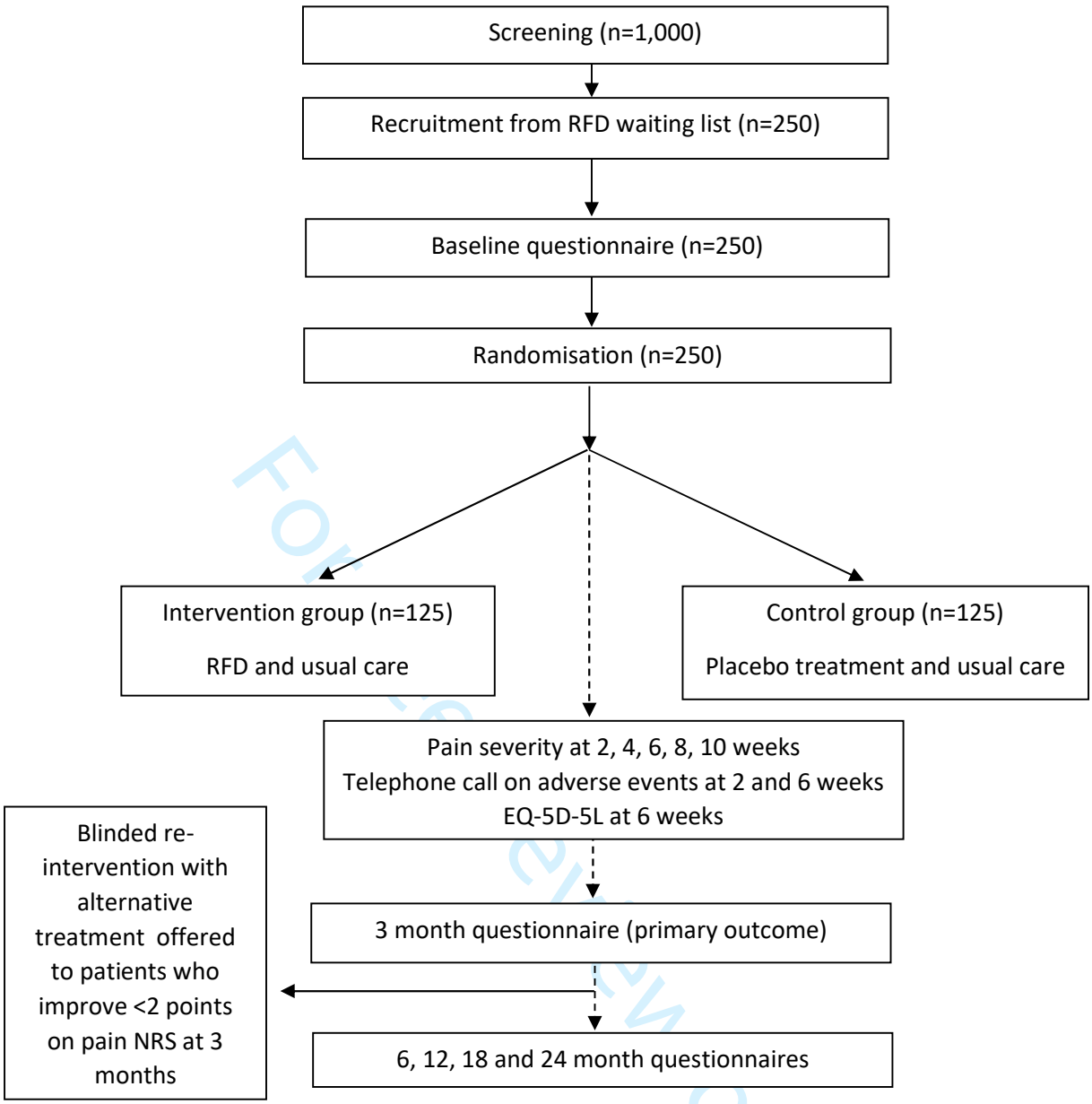
Figure Legend:

Figure 1 – Trial schema



Supplementary Table 1 Schedule of data collection

	Baseline	Randomisation & intervention	Post-randomisation									
			2	4	6	8	10	3	6	12	18	24
			weeks					months				
Sociodemographic details	X											
HADS	X											
Medical history including pain location	X											
STarT Back tool	X											
NRS pain score	X		X	X	X	X	X	X	X	X	X	X
EQ-5D-5L	X				X			X	X	X	X	X
SF-12	X							X	X	X	X	X
ODI	X							X	X	X	X	X
WPAI	X							X	X	X	X	X
Procedural data		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

Supplementary Information

Mandatory and recommended components of the RFD procedure

Mandatory components include that the numbers and laterality of medial branches to be lesioned should be based on response to the MNBB; lesions to be carried out at 80° Celsius for 90 seconds with two lesions per medial branch, unless a multipronged needle is used (only one lesion required in this case); the position of the RF cannula tip should be adjusted for the second lesion (if required); and x-rays from at least three views should be saved so that needle placement can be evaluated (as required).

Recommended, but not mandatory, components include: a maximum of eight medial branches at a maximum of four vertebral levels lesioned in a single sitting, and participants with unilateral pain to receive unilateral treatment; Chlorhexidine applied for skin preparation, unless the patient is allergic; full aseptic technique used; Lignocaine (local anaesthetic) used for skin infiltration; a curved 18 G RF cannula with a 10mm active tip used for targeting the medial branch (multi-pronged versions permitted); position of RF cannula confirmed with inferior, superior and oblique views; once the needle position is confirmed, optional routine motor testing can be carried out; and local anaesthetic (Lignocaine 20mg/mL in 0.5mL boluses recommended) is infiltrated before the lesion in order to minimise discomfort.

Baseline demographic and medical history

- Sex
- Age
- Body mass index
- Index of multiple deprivation
- Ethnicity
- Employment status
- Smoking status
- E-cigarette user
- Myocardial infarction
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular accident
- Transient ischaemic attack
- Dementia

- Chronic obstructive pulmonary disease
- Connective tissue disease
- Peptic ulcer disease
- Hemiplegia
- Liver disease
- Diabetes mellitus
- Moderate to severe chronic kidney disease
- Solid tumour
- Leukaemia
- Lymphoma
- AIDS
- Previous back surgery

TSC and DMSC details

The TSC is made up of representatives from the RADICAL study team and independent members approved by the funder. The DMSC consists of an independent medical statistician and medical experts in this field approved by the funder. The TSC and DMSC meet as frequently as they feel is necessary, usually at least once a year.

Examples of methods used with different Radiofrequency (RF) machines to ensure blinding

Make of the RF machine	Method
Diros	A custom switching box has been developed which allows the unblinded randomiser to switch between 'RFD' and 'placebo' mode, whilst maintaining blinding of the rest of team and the patient in theatre.
Stryker	The beeping noise that is made when a lesion is performed (for RFD) is the same as the beeping noise that is made when sensory mode is on, even at 0.0v. This means that sensory mode at 0.0v can be selected by the randomiser for patients that are allocated to the 'placebo' treatment, and as far as the rest of the team and the patient in theatre are concerned it would sound the same as 'RFD', therefore maintaining blinding.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 20-21
	5b	Name and contact information for the trial sponsor	16
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7

	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Figure 1
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealmen t mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementat ion	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request: radical-study@bristol.ac.uk
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.