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

29 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.

34 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.

52 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.

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59 Article summary

60 Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- 62 Guidelines for RFD technique were developed during a national workshop with pain
- 63 clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and
- 64 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
- 70 There is a time lag between consent (waiting list for RFD) and randomisation (in theatre),
- 71 which may impact on participant engagement

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Low back pain (LBP) is the leading global cause of healthy life years lost due to disability¹, and between 58% and 84% of people in the UK will experience back pain in their lifetime². LBP is associated with high personal, societal and economic burden³. 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 work⁴⁵. LBP is the most common musculoskeletal reason for General Practitioner (GP) appointments, accounting for 417 consultations per year per 10,000 patients registered⁶; approximately a third of the direct health care costs associated with LBP are incurred in the hospital sector⁷.

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 drugs⁸. 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 year⁹.

Systematic reviews of the effectiveness of RFD have been published with conflicting conclusions¹⁰⁻¹⁵. A Cochrane review, published in 2015, concluded that there was no high-quality evidence that RFD provides pain relief for patients with chronic LBP¹⁵. 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 alone¹⁶. 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 RFD¹⁷⁻²¹.

2 3		
4	103	Hence, the effectiveness of RFD is uncertain due to a lack of high-quality evidence ¹⁵ , and
5 6	104	NICE recommends that further research is needed ⁸ .
7 8	105	The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this
9 10	106	evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for
11 12	107	chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference
13 14	108	between groups in pain severity 3 months after RFD; (ii) differences between groups in
15 16	109	back-specific disability, health-related quality of life (HRQoL), psychological distress, time to
17	110	pain recovery, satisfaction with treatment outcome, frequency of uptake of offer of repeat
18 19	111	RFD, adverse events, work outcomes and further healthcare use; and (iii) the cost-
20 21	112	effectiveness of RFD compared to placebo.
22 23	110	
24 25	113	
26 27	114	METHODS AND ANALYSIS
28		
29 30 21	115	Trial design
32 33	116	RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled,
33 34 35	117	superiority randomised controlled trial. Patients will be recruited from approximately 20
35 36	118	multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure
37 38	119	1).
39 40		
41 42	120	Eligibility criteria
43	101	Detionts will be clicible for the study if all the following apply
44 45	121	Patients will be engible for the study if an the following apply.
46 47	122	1. ≥18 years of age
48 49	123	2. LBP is the primary source of pain
50 51	124	3. Positive response to a single diagnostic MNBB with no steroids administered. Based
52 52	125	on the outcome of a meeting of RADICAL clinicians ²² , a positive response is defined
55 54	126	as ≥60% pain relief in the first 24 hours, based on patient-reported assessment. Final
55 56	127	eligibility will be met if a patient's pain returns to ≥5 on a 0-10 numerical rating scale
57 58	128	(NRS) after MNBB.
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3 4	129	4.	Chronic LBP (>3 months duration), assumed due to the fact the patient was listed for			
5 6	130		MNBB			
7	131	5.	Moderate to severe LBP (NRS score ≥5)			
o 9	132	6.	Listed for RFD			
10 11						
12 13	133	Patien	ts will be excluded if any of the following apply:			
14 15	134	1.	Known pregnancy			
16 17	135	2.	Severe depression (Hospital Anxiety and Depression Scale (HADS) ²³ depression score			
18 10	136		≥15) (assessed following consent)			
20 21	137	3.	Known previous RFD			
21 22 23	138	4.	Known previous back surgery where metal-work has been used in the lumbar spine			
23 24	139	5.	Pacemaker or implantable cardioverter defibrillator			
25 26	140	6.	Clinical suspicion that an alternative diagnosis is the reason for LBP (as defined by			
27 28	141		NICE ⁸ , including, but not limited to: metastatic spinal cord compression, spinal injury,			
29 30	142		spondyloarthritis, or cancer)			
31 32	143	7.	Prisoners			
33 34 35 36 37 38 39	144	8.	Lacks capacity to consent			
	145	9.	Existing co-enrolment in another clinical study if: i) the intervention in the other			
	146		study is expected to influence the primary outcome; ii) it is considered too			
	147		burdensome for the patient; or iii) it is not permitted by the other study			
40 41						
42 43	148					
44 45	149	Patien	t recruitment			
45 46 47 48 49 50 51 52						
	150	Potent	ial patients will be identified from RFD waiting lists and those potentially eligible will			
	151	receive a patient information leaflet (PIL). The PIL will contain a web address where patients				
	152	can ac	cess an information video to supplement the PIL. The local research team will then			
53 54	153	contac	t the patient to discuss the study further and answer any questions they may have. If			
55 56	154	a patie	ent meets the initial eligibility criteria and decides to participate, the research team			
57 57	155	will rea	quest informed consent. Eligibility for randomisation will depend on further (post-			
58 59	156	conser	nt) eligibility checks.			
60						

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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.

162 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 Index²⁴.

177 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 centres²⁵, a national consensus meeting with clinicians, patients and academics was held to refine the RFD technique for the trial²². Components of the RFD procedure were classified as mandatory or recommended (see Supplementary file), based on existing best practice recommendations.

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2 3	185	Placebo
4 5 6 7 8 9	186	The control is placebo treatment in which participants will receive the same RFD protocol as
	187	the intervention group, but the temperature of the electrode tip will not be raised.
	188	
10 11	189	Clinical training
12 13	190	Clinicians who are unfamiliar with the RFD technique used within the trial will complete
14 15	191	training prior to delivering the trial intervention. This will include an online video
16 17	192	(https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver
18	193	workshops.
20 21	194	
21 22	195	Quality assurance measures
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	196	X-rays from at least three views for each lesion, from each clinician's first case, will be
	197	shared with a clinical expert on the Trial Management Group (TMG), so that needle
	198	placement can be checked. Placement quality will be recorded, and feedback given. If
	199	needle placement is poor, the study clinical experts will agree on a way forward, discuss
	200	with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least
	201	three views for each lesion, for every participant procedure, will be saved locally, for
	202	potential future monitoring.
	203	
	204	Adverse Events
	205	Adverse events that are expected due to RFD will be recorded between randomisation and
	206	two weeks post-randomisation. Serious adverse events will be recorded between
	207	randomisation and the two-year follow up. Between randomisation and 6 months post-
46	208	randomisation, all unexpected or fatal serious adverse events will be reported to the
47 48 49 50 51 52 53 54 55 56	209	Sponsor.
	210	Outcomes
	211	The primary outcome is LBP severity (average intensity of LBP over the past week, assessed
	212	using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected
57 58 59 60	213	up to 2 years after randomisation and include:

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2			
3 4	214	1.	Functional disability measured using the Oswestry Disability Index (ODI) ²⁶ version 2.1b
5 6 7	215	2.	HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D-5L) ²⁷
	216	3.	General health measured using the 12-Item Short Form Survey (SF-12) Physical
8 9	217		Component Score ²⁸
10 11 12 13 14 15 16	218	4.	Mental health measured using the SF-12 Mental Component Score
	219	5.	Time to pain recovery: time from randomisation until the participant first reports a pain
	220		reduction of \geq 60% that remains at \geq 60% lower than baseline at their next assessment.
	221	6.	Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3
17	222		months.
19 20	223	7.	Satisfaction with treatment outcome using a Likert scale
21 22	224	8.	Adverse health events
23 24	225	9.	Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI)
24 25 26 27	226		questionnaire ²⁹
	227	10.	Resource use assessed via a patient-reported resource use questionnaire
28 29			
30 31	228		
32 33	229	Dat	a collection
34 35	223	Dut	
36 27	230	Scre	eening data will be collected before consent to establish patient eligibility. Some
37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	231	den	nographic data (i.e. age, sex and deprivation index), information about pain severity and
	232	dur	ation of current LBP episode will also be collected from participants and non-
	233	par	ticipants, as far as possible, at the time of screening, to characterise the population and
	234	to ii	nterpret the applicability of the trial findings to the reference population. The schedule
	235	of d	ata collection outlined in Table 1 will take place after consent has been received. Data
	236	will	either be collected on paper data collection forms and entered onto the study database,
	237	or e	entered directly onto the database. Data for the primary outcome and most secondary
	238	out	comes will be collected via patient-completed questionnaires. Participants will be
	239	follo	owed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and
	240	adv	erse health events at 2 and 6 weeks. After this, participants will complete postal/online
56 57	241	que	stionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end
57 58 59 60	242	afte	er they have completed follow-up at 24 months post-randomisation. The end of the study

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243	as a whole will be after all participants have completed follow-up, all data queries have			
244	been resolved, the database locked and the analysis completed.			
245				
246	Sample size			
247	A sample size of 250 participants (125 per group) is sufficient to detect a difference of at			
248	least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90%			
249	power and 5% 2-tailed significance, assuming:			
250	a) The standard deviation for the pain NRS is 2.0^{16} .			
251	b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the			
252	MINT trials provided by collaborator Professor Raymond Ostelo)			
253	c) Allowing for up to 10% attrition at 3 months.			
254				
255	Statistical analyses			
256	The data will be analysed on an intention-to-treat basis and will follow a pre-specified			
257	Statistical Analysis Plan.			
258	The primary outcome (NRS) will be analysed using linear mixed effect models, including all			
259	available repeated pain measurements up to 3 months, adjusted for timepoint and the			
260	treatment*timepoint interaction as fixed effects, and operator and participant as random			
261	effects. Treatment effects at 3 months will be reported with 95% confidence intervals.			
262	Protocol deviations will be documented, and a per-protocol secondary analysis will be			
263	considered if there are a substantial number of protocol deviators. A secondary responder			
264	analysis of the primary outcome will be performed, exploring the between-group difference			
265	in the proportion of participants achieving ≥30% improvement in pain from baseline as			
266	recommended by IMMPACT 3031 , and the number needed to treat will be calculated based			
267	on this analysis ³²⁻³⁴ .			
	243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 256 257 258 259 260 261 262 261 262 263 264 265 264 265			

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 tool³⁵. Exploratory analyses will assess the effect of re-intervention with the alternative treatment using methods developed to appropriately adjust for treatment switching³⁶. 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-5L³⁹ 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

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3 4	295	analysis. QALYs will be estimated adjusting for baseline differences in utility scores and any			
5 6 7	296	mortality observed during follow up.			
, 8 9	297	The economic analysis will take an intention to treat approach with imputation of missing			
9 10	298	data. In the primary economic analysis we will estimate the cost per QALY gained of RFD at 2			
12	299	years from the perspective of NHS and social services. Based on the current NICE willingness			
13 14	300	to pay thresholds for a QALY of £20,000-£30,000 we will use net benefit regressions,			
15 16	301	adjusting for baseline EQ-5D-5L scores and baseline characteristics to estimate the			
17 18	302	incremental net benefit (and 95% confidence intervals) and determine whether RFD is a			
19 20 21 22 23 24 25 26	303	cost-effective use of NHS funds. Uncertainty will be explored using cost effectiveness			
	304	acceptability curves. In additional analyses we will also estimate the cost per QALY gained			
	305	and cost per additional responder (>=30% improvement in pain) at 3 months and expand			
	306	the perspective of the analysis to include informal care and productivity costs.			
27 28 29	307				
30 31 32	308	Internal pilot phase			
33 34	309	RADICAL includes a 12-month internal pilot phase with embedded qualitative research.			
35 36 37 38 39 40	310	Progression from the pilot to the main study will be contingent on demonstrating that after			
	311	12 months of recruitment, enough patients are eligible for the trial and can be randomised.			
	312	Progression criteria are:			
41	242				
42	313	1. 13 sites are open to recruitment			
44 45	314	2. 79 patients consented			
46 47	315	3. 25 patients randomised (this accounts for a 3-month time lag between consent and			
48 49 50	316	randomisation)			
	317	4. Consent rate of 1.5 patients/site/month			
52	318	Qualitative research will be conducted in the internal pilot to evaluate trial acceptability and			
55 54	319	equipoise and facilitate improvements in communication about the trial to optimise			
55 56	320	recruitment. Up to 20 recruitment consultations will be audio-recorded, and telephone			
57 58	321	interviews with up to 20 participants will elicit patient understanding of trial procedures and			
59 60	322	interventions, equipoise, acceptability of recruitment pathways, and quality of patient			

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3 4	323	information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow
5 6	324	understanding of trial personnel's equipoise and perspectives on the protocol, usual care,
7	325	and recruitment pathways. Data will be subjected to rapid thematic framework analysis ^{40 41}
o 9 10	326	to ensure findings are reported and implemented in a timely fashion.
11 12 13	327	
14 15 16	328	Data handling, storage and sharing
17 18	329	Most data will be stored in a bespoke database hosted on the NHS network. Some data
19 20	330	items will be held on a separate database, hosted on the University of Bristol server,
21 22	331	comprising the randomisation system, information about the intervention delivered and the
23 24	332	quality of needle placement. Access to both databases will be via secure password-
25 26 27	333	protected web-interfaces.
28	334	All study documentation will be retained in a secure location during the conduct of the
29 30	335	study and for five years afterwards, when all participant identifiable paper records will be
31 32	336	destroyed by confidential means. All audio-recording files will be retained in a secure
33 34	337	location during the conduct of the study and for 12 months afterwards, when these files will
35 36	338	be deleted. Where trial related information is documented in the medical records, these
37 38	339	records will be identified by a label bearing the name and duration of the trial. In
39 40	340	compliance with the Medical Research Council Policy on Data Sharing, and with participant
40	341	agreement, relevant 'meta'-data about the trial and the full dataset, but without any
42 43	342	participant identifiers other than the unique study identifier, will be held indefinitely. These
44 45	343	will be retained because of the potential for the raw data to be used subsequently for
46 47 48	344	secondary research and/or training.
49 50 51	345	
52 53 54	346	Patient and public involvement (PPI)
55 56	347	RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of
57 58	348	Bristol. A PPI group involving patients with experience of RFD has also been convened
59 60	349	specifically for this study. This group has played an integral part in designing the research,

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2		
3 4	350	including development of accessible participant documents. They will continue to co-work
5 6	351	with the research team on all aspects of the study, including interpretation of results and
7 8	352	development of public dissemination strategies and material. The Trial Steering Committee
9	353	(TSC) also includes two patient members.
10 11		
12 13	354	
14 15	355	Ethics and dissemination
10	256	The study received Research Ethics Committee (REC) approval from London - Fulbam REC in
18 19	250	The study received Research Ethics Committee (REC) approval from London - Furnam REC in
20 21	357	July 2021 and Health Research Authority (HRA) approval in September 2021. The study is
22	358	sponsored by North Bristol NHS Trust (<u>https://www.nbt.nhs.uk/research-innovation</u>) who
23 24	359	are responsible for the oversight of the study and ensuring it is managed appropriately. The
25 26	360	study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration
27 28	361	registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data
29	362	Monitoring and Safety Committee (DMSC) (see Supplementary file).
30 31		
32 33	363	
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33 34 35 36	364	Changes to the protocol since REC/HRA approval
33 34 35 36 37 38	364 365	Changes to the protocol since REC/HRA approval Following REC and HRA approval the following changes have been made to the study
33 34 35 36 37 38 39 40	364 365 366	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)
33 34 35 36 37 38 39 40 41 42	364 365 366 367	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
 33 34 35 36 37 38 39 40 41 42 43 44 	364 365 366 367 368	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 	364 365 366 367 368 369	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 40 	364 365 366 367 368 369 370	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 	364 365 366 367 368 369 370 371	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 	364 365 366 367 368 369 370 371 372	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)
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 	364 365 366 367 368 369 370 371 372 373	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 	364 365 366 367 368 369 370 371 372 373 374	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 	364 365 366 367 368 369 370 371 372 373 374 375	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
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 	364 365 366 367 368 369 370 371 372 373 374 375 376	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 6 th April 2023) is currently in use.

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3	378									
5 6	379	Dissemination of findings								
7 8	010									
9 10	380	Findings will be presented at conferences and published open access in peer-review								
11 12	381	journals. Impact on clinical practice will be through engagement with relevant organisation								
13	382	such as NICE, British Pain Society, Clinical Reference Group for Spinal Services, and UK Spine								
14 15	383	Societies Board. We will work with our PPI group and relevant charities on public								
16 17 18	384	dissemination.								
19 20 21	385									
22 23 24	386	Discussion								
25 26	387	Findings from the RADICAL trial will contribute to shaping clinical guidelines and service								
27 28	388	provision for patients living with chronic LBP. Study training resources, developed in line								
29 30	389	with the consensus-based best practice guidelines for RFD produced by the RADICAL team ²² ,								
31 22	390	have been positively received and taken up by clinicians across the country, demonstrating								
32 33	391	that the trial is already impacting on RFD provision by improving standards. The study								
34 35	392	opened to recruitment on 27 th May 2022 and is currently recruiting across 13 centres. To								
36 37 38	393	date, 46 patients have been recruited and 14 randomised.								
39 40	394	During the internal pilot phase (ongoing at the time of manuscript submission), RADICAL has								
41 42	395	experienced three substantial challenges to delivery: delays in site opening, complex								
43 44	396	screening processes limiting sites capacity to recruit patients and long NHS waiting times for								
45 46	397	RFD. Opening sites has been an ongoing issue due to the continuing impact of the COVID-19								
47	398	pandemic on research infrastructure; we have experienced delays of up to two years from								
48 49	399	feasibility assessment to site opening due to research and development departments'								
50 51	400	limited capacity to process local approvals. However, we have recently seen an								
52 53	401	improvement in site opening timelines, with a recent site opening in 4 months.								
54 55	402	Identification of sites with the necessary clinical expertise and engagement, alongside the								
56 57	403	research infrastructure to deliver the trial, has been key, and we have achieved this through								
58 50	404	a combination of national calls for sites through the National Institute for Health Research								
60	405	(NIHR) Clinical Research Network and one-to-one discussions with clinicians.								

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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.

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

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SF-12	Х							Х	Х	Х	Х	X ,		
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3 4	477	is the health economics lead and NJ the health economist working on the trial. LC provides
5	478	senior trial management oversight and advice. NF, NO and AB provide clinical advice as part
7	479	of the Trial Management Group. CJ coordinates the PPI involvement in the trial. VW, CPr,
8 9	480	AB, BR, LC, CR, NF, NO, WH and AM all co-designed the trial and obtained funding. All
10 11	481	authors have been involved in preparation of the study protocol and have read and
12 13	482	approved the final manuscript.
14 15 16 17	483	
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21 22	485	This study is funded by the NIHR Health Technology Assessment Programme (project
23 24	486	reference NIHR127457). The views expressed are those of the authors and not necessarily
25 26 27	487	those of the NIHR or the Department of Health and Social Care.
28 29 30	488	
31 32 22	489	Competing interests statement
33 34	490	All authors received support from the National Institute for Health and Care Research for
35 36 37	491	the project associated with this manuscript, which was paid to their employing institution.
38 39 40	492	No other conflicts were reported.
41 42 43	493	Acknowledgements
44 45	494	The authors thank all of the research and clinical team members at participating site;
46 47	495	members of the Trial Steering Committee and independent Data Monitoring and Safety
48 49	496	Committee; members of the patient and public involvement group, and additional
50 51	497	collaborators Professor Raymond Ostelo and Professor Steven Cohen, who will be involved
52 53	498	in the management of the trial and will contribute key expertise on aspects of trial design as
54 55 56	499	needed.
57 58 59 60	500	Full references

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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.

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

Section/item	ltem No	Description	Page number
Administrative	informa	ation	
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	5a	Names, affiliations, and roles of protocol contributors	1 & 20-21
responsibilities	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

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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: Part	icipants,	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: Assig	gnment	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	collecti	on, 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

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	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: Mor	nitoring		
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

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@bristo I.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.

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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Keywords:	Chronic Pain, Pain management < ANAESTHETICS, Clinical Trial, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Quality of Life
	SCHOLARONE"
	Manuscripts
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3 4	1	Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for
5 6	2	chronic and moderate to severe low back pain: study protocol for the RADICAL
7 8	3	randomised controlled trial
9 10 11	4	Ashton KE ^{1*} , Price C ² , Fleming L ¹ , Blom AW ³ , Culliford L ¹ , Evans RN ¹ , Foster NE ⁴ ,
12	5	Hollingworth W ⁵ , Jameson C ^{5,6} , Jeynes N ⁵ , Moore A ⁵ , Orpen N ⁷ , Palmer C ⁵ , Reeves BC ¹ ,
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3 4	24	
5 6 7	25	Keywords: Low back pain; radiofrequency denervation; chronic pain; pain management;
7 8 9	26	pain clinic; clinical trial; health-related quality of life
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 55 56 57 58 59 60	26	pan cinic; cinical tria; health-related quality of ine

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28 Abstract

29 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.

34 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 guality 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.

52 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.

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59 Article summary

60 Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- 62 Guidelines for RFD technique were developed during a national workshop with pain
- 63 clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and
- 64 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
- 70 There is a time lag between consent (waiting list for RFD) and randomisation (in theatre),
- 71 which may impact on participant engagement

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74 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).

99 In 2017, the MINT trial (published after the systematic reviews), concluded that RFD

- 100 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,
- 102 including, variation in RFD operator protocols, and high numbers of patients in the control

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3 4	103	group receiving RFD(18-22). Hence, the effectiveness of RFD is uncertain due to a lack of
5 6	104	high-quality evidence(15), and NICE recommends that further research is needed(8).
7 8	105	The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this
9 10	106	evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for
11 12	107	chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference
13	108	between groups in pain severity 3 months after RFD; (ii) differences between groups in
15	109	back-specific disability, health-related quality of life (HRQoL), psychological distress, time to
16 17	110	pain recovery, satisfaction with treatment outcome, frequency of uptake of offer of repeat
18 19	111	RFD, adverse events, work outcomes and further healthcare use; and (iii) the cost-
20 21	112	effectiveness of RFD compared to placebo.
22		
23	113	
25 26	11/	
27 28	114	
29 30 31	115	Trial design
32 33	116	RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled,
34 35	117	superiority randomised controlled trial. Patients will be recruited from approximately 20
36 27	118	multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure
38	119	1).
39 40		
41 42	120	Eligibility criteria
43 44	121	Patients will be eligible for the study if all the following apply:
45		
40 47	122	1. ≥18 years of age
48 49	123	2. LBP is the primary source of pain
50 51	124	3. Positive response to a single diagnostic MNBB with no steroids administered. Based
52 53	125	on the outcome of a meeting of RADICAL clinicians(23), a positive response is
54 55	126	defined as ≥60% pain relief in the first 24 hours, based on patient-reported
56	127	assessment. Final eligibility will be met if a patient's pain returns to ≥5 on a 0-10
57 58	128	numerical rating scale (NRS) after MNBB.
59 60		

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2 3			
5 4 5 6	129	4. Chronic LBP (>3 months duration), assumed due to the fact the patie	nt was listed for
	130	MNBB	
7 8	131	Moderate to severe LBP (NRS score ≥5)	
9 10	132	6. Listed for RFD	
10 11 12 13 14 15 16 17	133	ratients will be excluded if any of the following apply:	
	134	1. Known pregnancy	
	135	2. Severe depression (Hospital Anxiety and Depression Scale (HADS) (24)	depression
18 19	136	score ≥15) (assessed following consent)	
20	137	3. Known previous RFD	
21 22	138	4. Known previous back surgery where metal-work has been used in the	e lumbar spine
23 24	139	5. Pacemaker or implantable cardioverter defibrillator	
25 26	140	6. Clinical suspicion that an alternative diagnosis is the reason for LBP (a	as defined by
27 28	141	NICE(8), including, but not limited to: metastatic spinal cord compres	sion, spinal
29 30	142	injury, spondyloarthritis, or cancer)	
31 22	143	7. Prisoners	
32 33 34 35 36 37	144	8. Lacks capacity to consent	
	145	9. Existing co-enrolment in another clinical study if: i) the intervention in	n the other
	146	study is expected to influence the primary outcome; ii) it is considere	d too
38 39	147	burdensome for the patient; or iii) it is not permitted by the other stu	ıdy
40 41			
42 43 44 45 46 47 48	148	Io restrictions will be placed on usual care, and all co-interventions are perr	nitted to reflect
	149	sual NHS practice.	
	150	Patient recruitment	
49 50	151	otential patients will be identified from RFD waiting lists and those potentia	ally eligible will
50 51	152	eceive a patient information leaflet (PIL). The PIL will contain a web address	where patients
53	153	an access an information video to supplement the PIL. The local research te	am will then
54 55	154	ontact the patient to discuss the study further and answer any questions th	ey may have. If
56 57	155	patient meets the initial eligibility criteria and decides to participate, the re	esearch team
58 59 60			

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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.

163 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).

178 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).

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3 4 5 6 7	184	Components of the RFD procedure were classified as mandatory or recommended (see
	185	Supplementary file), based on existing best practice recommendations.
	186	
8 9	187	Placebo
10 11	188	A placebo control will be used to minimise bias, which is important as the primary outcome
12 13	189	is patient-reported. The placebo treatment will follow the same RFD protocol as the
14 15	190	intervention group, but the temperature of the electrode tip will not be raised.
16 17	191	
18	192	Clinical training
20	193	Clinicians who are unfamiliar with the RFD technique used within the trial will complete
21 22	194	training prior to delivering the trial intervention. This will include an online video
23 24	195	(https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver
25 26	196	workshops.
27 28 29 30 31 32 33 34 35 36	197	
	198	Quality assurance measures
	199	X-rays from at least three views for each lesion, from each clinician's first case, will be
	200	shared with a clinical expert on the Trial Management Group (TMG), so that needle
	201	placement can be checked. Placement quality will be recorded, and feedback given. If
30 37	202	needle placement is poor, the study clinical experts will agree on a way forward, discuss
38 39	203	with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least
40 41	204	three views for each lesion, for every participant procedure, will be saved locally, for
42 43	205	potential future monitoring.
44 45	206	
46 47	207	Adverse Events
48	208	Adverse events that are expected due to RFD will be recorded between randomisation and
49 50	209	two weeks post-randomisation. Serious adverse events will be recorded between
51 52	210	randomisation and the two-year follow up. Between randomisation and 6 months post-
53 54	211	randomisation, all unexpected or fatal serious adverse events will be reported to the
55 56 57 58	212	Sponsor.
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213	Outcomes
214	The primary outcome is LBP severity (average intensity of LBP over the past week, assessed
215	using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected
216	up to 2 years after randomisation and include:
217	1. Functional disability measured using the Oswestry Disability Index (ODI)(28) version
218	2.1b
219 220	 HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D- 51)(29)
221	 General health measured using the 12-Item Short Form Survey (SF-12) Physical
222	Component Score(30)
223	4. Mental health measured using the SF-12 Mental Component Score
224	5. Time to pain recovery: time from randomisation until the participant first reports a pain
225	reduction of \geq 60% that remains at \geq 60% lower than baseline at their next assessment.
226	6. Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3
227	months.
228	7. Satisfaction with treatment outcome using a Likert scale
229	8. Adverse health events
230	9. Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI)
231	questionnaire(31)
232	10. Resource use assessed via a patient-reported resource use questionnaire
233	
234	Data collection
235	Screening data will be collected before consent to establish patient eligibility. Some
236	demographic data (see Supplementary file), information about pain severity and duration of
237	current LBP episode will also be collected from participants and non-participants, as far as
238	possible, at the time of screening, to characterise the population and to interpret the
239	applicability of the trial findings to the reference population. The schedule of data collection

240 outlined in Supplementary Table 1 will take place after consent has been received. Data will

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3 4	241	either be collected on paper data collection forms and entered onto the study database, or
5 6	242	entered directly onto the database. Data for the primary outcome and most secondary
7	243	outcomes will be collected via patient-completed questionnaires. Participants will be
8 9	244	followed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and
10 11	245	adverse health events at 2 and 6 weeks. After this, participants will complete postal/online
12 13	246	questionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end
14 15	247	after they have completed follow-up at 24 months post-randomisation. The end of the study
16 17	248	as a whole will be after all participants have completed follow-up, all data queries have
18	249	been resolved, the database locked and the analysis completed.
20 21 22	250	
23 24 25	251	Sample size
20 27	252	A sample size of 250 participants (125 per group) is sufficient to detect a difference of at
28 29	253	least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90%
30 31 32	254	power and 5% 2-tailed significance, assuming:
33 34	255	a) The standard deviation for the pain NRS is 2.0(17).
35 36	256	b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the
37 38	257	MINT trials provided by collaborator Professor Raymond Ostelo)
39 40	258	c) Allowing for up to 10% attrition at 3 months.
40		
42 43	259	The trial will therefore have sufficient power to detect the target difference used by NICE (1-
44 45 46	260	point difference) and reflects a moderate effect size.
47 48 49	261	
50 51 52	262	Statistical analyses
53	263	The data will be analysed on an intention-to-treat basis and will follow a pre-specified
54 55 56	264	Statistical Analysis Plan.
57 58	265	The primary outcome (NRS) will be analysed using linear mixed effect models, including all
59 60	266	available repeated pain measurements up to 3 months, adjusted for timepoint and the

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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 \geq 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.

1		
2 3 4 5	296	
6 7 8	297	Cost-effectiveness analyses
8 9 10	298	The analysis will follow a pre-specified Health Economic Analysis Plan. We will use NHS
11 12	299	reference costs to estimate the cost to NHS purchasers of RFD. NHS (secondary, primary
13	300	care, prescriptions), social service, informal care, and absenteeism due to LBP will be
14	301	collected using resource use questionnaires and the WPAI administered to participants
16 17	302	throughout follow up. We will seek consent for data linkage to access Hospital Episode
18 19	303	Statistics (HES) inpatient, day case, outpatient and emergency department datasets.
20 21	304	Hospital, primary and community care will be costed using national unit costs(39, 40).
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38	305	Quality of life will be assessed using EQ-5D-5L(41) to calculate quality-adjusted life years
	306	(QALYs). An index score will be derived using the UK value set recommended by NICE at the
	307	time of analysis. QALYs will be estimated adjusting for baseline differences in utility scores
	308	and any mortality observed during follow up.
	309	The economic analysis will take an intention to treat approach with imputation of missing
	310	data (e.g. using multiple imputations). In the primary economic analysis we will estimate the
	311	cost per QALY gained of RFD at 2 years from the perspective of NHS and social services.
	312	Based on the current NICE willingness to pay thresholds for a QALY of £20,000-£30,000 we
	313	will use net benefit regressions, adjusting for baseline EQ-5D-5L scores and baseline
39 40	314	characteristics to estimate the incremental net benefit (and 95% confidence intervals) and
41 42	315	determine whether RFD is a cost-effective use of NHS funds. Uncertainty will be explored
43 44	316	using cost effectiveness acceptability curves. In additional analyses we will also estimate the
45 46	317	cost per QALY gained and cost per additional responder (>=30% improvement in pain) at 3
47	318	months and expand the perspective of the analysis to include informal care and productivity
48 49	319	costs.
50 51 52 53	320	
54 55 56	321	Internal pilot phase
57 58	322	RADICAL includes a 12-month internal pilot phase with embedded qualitative research.
59 60	323	Progression from the pilot to the main study will be contingent on demonstrating that after

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3 4	324	12 months of recruitment, enough patients are eligible for the trial and can be randomised.
5 6 7	325	Progression criteria are:
8	326	1. 13 sites are open to recruitment
10	327	2. 79 patients consented
11 12	328	3. 25 patients randomised (this accounts for a 3-month time lag between consent and
13 14	329	randomisation)
15 16 17	330	4. Consent rate of 1.5 patients/site/month
18 19	331	Qualitative research will be conducted in the internal pilot to evaluate trial acceptability and
20 21 22 23	332	equipoise and facilitate improvements in communication about the trial to optimise
	333	recruitment. Up to 20 recruitment consultations will be audio-recorded, and telephone
24	334	interviews with up to 20 participants will elicit patient understanding of trial procedures and
25	335	interventions, equipoise, acceptability of recruitment pathways, and quality of patient
27 28	336	information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow
29 30	337	understanding of trial personnel's equipoise and perspectives on the protocol, usual care,
31 32	338	and recruitment pathways. Data will be subjected to rapid thematic framework analysis(42,
33 34	339	43) to ensure findings are reported and implemented in a timely fashion.
35 36 37	340	
38 39 40 41	341	Data handling, storage and sharing
41 42 43	342	Most data will be stored in a bespoke database hosted on the NHS network. Some data
43	343	items will be held on a separate database, hosted on the University of Bristol server,
45 46 47 48 49 50 51	344	comprising the randomisation system, information about the intervention delivered and the
	345	quality of needle placement. Access to both databases will be via secure password-
	346	protected web-interfaces.
52 53 54	347	All study documentation will be retained in a secure location during the conduct of the
	348	study and for five years afterwards, when all participant identifiable paper records will be
55 56	349	destroyed by confidential means. All audio-recording files will be retained in a secure
57 58	350	location during the conduct of the study and for 12 months afterwards, when these files will
59 60	351	be deleted. Where trial related information is documented in the medical records, these

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352	records will be identified by a label bearing the name and duration of the trial. In
353	compliance with the Medical Research Council Policy on Data Sharing, and with participant
354	agreement, relevant 'meta'-data about the trial and the full dataset, but without any
355	participant identifiers other than the unique study identifier, will be held indefinitely. These
356	will be retained because of the potential for the raw data to be used subsequently for
357	secondary research and/or training.
358	
359	Patient and public involvement (PPI)
360	RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of
361	Bristol. A PPI group involving patients with experience of RFD has also been convened
362	specifically for this study. This group has played an integral part in designing the research,
363	including development of accessible participant documents. They will continue to co-work
364	with the research team on all aspects of the study, including interpretation of results and
365	development of public dissemination strategies and material. The Trial Steering Committee
366	(TSC) also includes two patient members.
367	
368	Ethics and dissemination
369	The study received Research Ethics Committee (REC) approval from London - Fulham REC in
370	July 2021 and Health Research Authority (HRA) approval in September 2021. The study is
371	sponsored by North Bristol NHS Trust (<u>https://www.nbt.nhs.uk/research-innovation</u>) who
372	are responsible for the oversight of the study and ensuring it is managed appropriately. The
373	study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration
374	registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data
375	Monitoring and Safety Committee (DMSC) (see Supplementary file).
376	
	 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376

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377 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.

393 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.

400 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

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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

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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 gualitative 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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21 22 23	469	the project associated with this manuscript, which was paid to their employing institution.
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37 38	476	in the management of the trial and will contribute key expertise on aspects of trial design as
39 40 41	477	needed.
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Table 1 Schedule of data collection

Sociodemographic details

Medical history including

HADS

pain location

STarT Back tool

NRS pain score

Procedural data

Blinded re-intervention

Uptake of blinded re-

EQ-5D-5L

SF-12

ODI

WPAI

offered

intervention

Satisfaction with

Adverse events

treatment outcome

Resource and health

service use questionnaire

Baseline

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Post-randomisation

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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.

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

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- 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.

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

Section/item	ltem No	Description	Page number
Administrative	informa	ation	
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	5a	Names, affiliations, and roles of protocol contributors	s 1 & 20-21
responsibilities	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

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	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: Part	ticipants	, 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: Assi	gnment	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	collecti	ion, 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

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	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: Mon	itoring		
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
Data monitoring	21a 21b	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 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	16 13
Data monitoring Harms	21a 21b 22	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 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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16 13 10
Data monitoring Harms Auditing	21a 21b 22 23	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 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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16 13 10 N/A

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			

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Informe consent material	d : Is	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request: radical- study@bristo I.ac.uk
Biologic specime	al ens	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.

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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Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Evidence based practice

Keywords:	Chronic Pain, Pain management < ANAESTHETICS, Clinical Trial, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Quality of Life
	SCHOLARONE"
	Manuscripts

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3 4	1	Effectiveness and cost-effectiveness of radiofrequency denervation versus placebo for
5	2	chronic and moderate to severe low back pain: study protocol for the RADICAL
7 8	3	randomised controlled trial
9 10	4	Ashton KE ^{1*} , Price C ² , Fleming L ¹ , Blom AW ³ , Culliford L ¹ , Evans RN ¹ , Foster NE ⁴ ,
12	5	Hollingworth W ⁵ , Jameson C ^{5,6} , Jeynes N ⁵ , Moore A ⁵ , Orpen N ⁷ , Palmer C ⁵ , Reeves BC ¹ ,
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25 26	10	⁴ STARS Education and Research Alliance, Surgical Treatment and Rehabilitation Service
27 28 29	11	(STARS), The University of Queensland and Metro North Health, Australia
30 31 32	12	⁵ Musculoskeletal Research Unit, Bristol Medical School, University of Bristol, UK
33 34	13	⁶ NIHR Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS
35 36 37	14	Foundation Trust and University of Bristol, UK
38 39 40	15	⁷ BMI Healthcare, The Ridgeway Hospital, UK
41 42	16	
43 44	17	*Corresponding author: Kate Ashton, Bristol Trials Centre, University of Bristol, Bristol UK
45 46 47	18	Email: kate.ashton@bristol.ac.uk
48 49 50	19	
51 52	20	Word Count: 4138/4000 (excluding title page, abstract, figures and tables,
53 54 55	21	acknowledgements, contributions and references)
56 57 58	22	Number of figures: 1
59 60	23	Number of tables: 1

RADICAL Protocol Paper v6.0 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
1 2		
3 4	24	
5 6 7	25	Keywords: Low back pain; radiofrequency denervation; chronic pain; pain management;
7 8 9	26	pain clinic; clinical trial; health-related quality of life
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 55 56 57 58 59 60	26	pan cinic; cinical tria; health-related quality of ine

28 Abstract

29 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.

34 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 guality 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.

52 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.

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2 3 4	56	Registration: ISRCTN registration number: ISRCTN16473239
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59 Article summary

60 Strengths and limitations of this study

- The trial has a pragmatic design integrated into standard care pathways
- 62 Guidelines for RFD technique were developed during a national workshop with pain
- 63 clinicians, ensuring that the techniques used in the trial are acceptable to clinicians and
- 64 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),
- 71 which may impact on participant engagement

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74 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

¹³ Systematic and narrative reviews of the effectiveness of the brectiveness of the brectiveness of the brave been published with
 ¹³ conflicting conclusions(10-16). A Cochrane review, published in 2015, concluded that there
 ¹⁴ was no high-quality evidence that RFD provides pain relief for patients with chronic LBP(15).
 ¹⁵ In 2017, the MINT trial (published after the systematic reviews), concluded that RFD
 ¹⁶ combined with an exercise programme was not superior to an exercise programme
 ¹⁶ alone(17). However, this trial received criticism on a number of methodological grounds,
 ¹⁶ including, variation in RFD operator protocols, and high numbers of patients in the control

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3 4	103	group receiving RFD(18-22). Hence, the effectiveness of RFD is uncertain due to a lack of
5 6	104	high-quality evidence(15), and NICE recommends that further research is needed(8).
7 8	105	The RADICAL (RADIofrequenCy denervAtion for Low back pain) trial aims to provide this
9 10	106	evidence by comparing the effectiveness and cost-effectiveness of RFD versus placebo for
11 12	107	chronic moderate to severe localised LBP. Specific objectives are to estimate: (i) difference
13 14	108	between groups in pain severity 3 months after RFD; (ii) differences between groups in
15	109	back-specific disability, health-related quality of life (HRQoL), psychological distress, time to
16 17	110	pain recovery, satisfaction with treatment outcome, frequency of uptake of offer of repeat
18 19	111	RFD, adverse events, work outcomes and further healthcare use; and (iii) the cost-
20 21	112	effectiveness of RFD compared to placebo.
22 23		
23 24 25	113	
25 26	114	METHODS AND ANALYSIS
27 28		
29 30	115	Trial design
31 32		
33	116	RADICAL is a multicentre, pragmatic, double-blind, parallel group, placebo controlled,
34 35	117	superiority randomised controlled trial. Patients will be recruited from approximately 20
36 37	118	multidisciplinary pain and spinal clinics providing RFD in secondary care NHS centres (Figure
38 30	119	1).
40	420	
41 42	120	Eligibility criteria
43 44	121	Patients will be eligible for the study if all the following apply:
45		
40 47	122	1. ≥18 years of age
48 49	123	2. LBP is the primary source of pain
50 51	124	3. Positive response to a single diagnostic MNBB with no steroids administered. Based
52 53	125	on the outcome of a meeting of RADICAL clinicians(23), a positive response is
54 55	126	defined as ≥60% pain relief in the first 24 hours, based on patient-reported
56	127	assessment. Final eligibility will be met if a patient's pain returns to ≥5 on a 0-10
57 58	128	numerical rating scale (NRS) after MNBB.
59 60		

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3 4	129	4. Chronic LBP (>3 months duration), assumed due to the fact the patient was listed for
5 6 7	130	MNBB
	131	Moderate to severe LBP (NRS score ≥5)
8 9	132	6. Listed for RFD
10 11		
12 13	133	Patients will be excluded if any of the following apply:
14 15	134	1. Known pregnancy
16 17	135	2. Severe depression (Hospital Anxiety and Depression Scale (HADS)(24) depression
18 19	136	score ≥15) (assessed following consent)
20 21	137	3. Known previous RFD
22	138	4. Known previous back surgery where metal-work has been used in the lumbar spine
23 24	139	5. Pacemaker or implantable cardioverter defibrillator
25 26	140	6. Clinical suspicion that an alternative diagnosis is the reason for LBP (as defined by
27 28	141	NICE(8), including, but not limited to: metastatic spinal cord compression, spinal
29 30	142	injury, spondyloarthritis, or cancer)
31 32	143	7. Prisoners
33	144	8. Lacks capacity to consent
35	145	9. Existing co-enrolment in another clinical study if: i) the intervention in the other
30 37	146	study is expected to influence the primary outcome; ii) it is considered too
38 39 40 41 42 43 44 45 46 47	147	burdensome for the patient; or iii) it is not permitted by the other study
	140	
	148	No restrictions will be placed on usual care, and all co-interventions are permitted to reflect
	149	usual NHS practice. Data on co-interventions will not be collected.
	150	Patient recruitment
48		
49 50	151	Potential patients will be identified from RFD waiting lists and those potentially eligible will
51 52	152	receive a patient information leaflet (PIL). The PIL will contain a web address where patients
53 54 55	153	can access an information video to supplement the PIL. The local research team will then
	154	contact the patient to discuss the study further and answer any questions they may have. If
57	155	a patient meets the initial eligibility criteria and decides to participate, the research team
58 59 60	156	will request written informed consent. A copy of the Informed Consent Form can be

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requested by contacting the RADICAL study team at <u>radical-study@bristol.ac.uk</u>. 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.

164 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).

179 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).

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3 4	185	Components of the RFD procedure were classified as mandatory or recommended (see
5 6 7 8 9	186	Supplementary file), based on existing best practice recommendations.
	187	
	188	Placebo
10 11	189	A placebo control will be used to minimise bias, which is important as the primary outcome
12 13	190	is patient-reported. The placebo treatment will follow the same RFD protocol as the
14 15 16 17	191	intervention group, but the temperature of the electrode tip will not be raised.
	192	
18	193	Clinical training
19 20	194	Clinicians who are unfamiliar with the RFD technique used within the trial will complete
21 22	195	training prior to delivering the trial intervention. This will include an online video
23 24	196	(https://www.youtube.com/watch?v=j4nzkdgMWgI) and/or attendance at cadaver
25 26	197	workshops.
27 28	198	
20 29 20	199	Quality assurance measures
31	200	X-rays from at least three views for each lesion, from each clinician's first case, will be
32 33	201	shared with a clinical expert on the Trial Management Group (TMG), so that needle
34 35	202	placement can be checked. Placement quality will be recorded, and feedback given. If
36 37	203	needle placement is poor, the study clinical experts will agree on a way forward, discuss
38 39	204	with the TMG, and feedback to the clinician on a case-by-case basis. X-rays from at least
40 41	205	three views for each lesion, for every participant procedure, will be saved locally, for
42 43	206	potential future monitoring.
44	207	
45 46	208	Adverse Events
47 48	209	Adverse events that are expected due to RFD will be recorded between randomisation and
49 50	210	two weeks post-randomisation. Serious adverse events will be recorded between
51 52	211	randomisation and the two-year follow up. Between randomisation and 6 months post-
53 54 55 56 57 58 59 60	212	randomisation, all unexpected or fatal serious adverse events will be reported to the
	213	Sponsor.

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214	Outcomes
215	The primary outcome is LBP severity (average intensity of LBP over the past week, assessed
216	using the 0-10 NRS) at 3 months post-randomisation. Secondary outcomes will be collected
217	up to 2 years after randomisation and include:
218	1. Functional disability measured using the Oswestry Disability Index (ODI)(28) version
219	2.1b
220 221	 HRQoL measured using the EuroQol 5-dimension five level questionnaire (EQ-5D- 5L)(29)
222	3. General health measured using the 12-Item Short Form Survey (SF-12) Physical
223	Component Score(30)
224	4. Mental health measured using the SF-12 Mental Component Score
225	5. Time to pain recovery: time from randomisation until the participant first reports a pain
226	reduction of \geq 60% that remains at \geq 60% lower than baseline at their next assessment.
227	6. Uptake of offer of alternative treatment (i.e. blinded crossover to RFD/placebo) after 3
228	months.
229	7. Satisfaction with treatment outcome using a Likert scale
230	8. Adverse health events
231	9. Work outcomes assessed using the Work Productivity and Activity Impairment (WPAI)
232	questionnaire(31)
233	10. Resource use assessed via a patient-reported resource use questionnaire
234	
235	Data collection
236	Screening data will be collected before consent to establish patient eligibility. Some
237	demographic data (see Supplementary file), information about pain severity and duration of
238	current LBP episode will also be collected from participants and non-participants, as far as
239	possible, at the time of screening, to characterise the population and to interpret the
240	applicability of the trial findings to the reference population. The schedule of data collection
241	outlined in Supplementary Table 1 will take place after consent has been received. Data will

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3 4	242	either be collected on paper data collection forms and entered onto the study database, or
5	243	entered directly onto the database. Data for the primary outcome and most secondary
7	244	outcomes will be collected via patient-completed questionnaires. Participants will be
8 9	245	followed up at 2, 4, 6, 8 and 10 weeks for pain severity, as well as HRQoL at 6 weeks and
10 11	246	adverse health events at 2 and 6 weeks. After this, participants will complete postal/online
12 13	247	questionnaires at 3, 6, 12, 18 and 24 months. The participant's time on the study will end
14 15	248	after they have completed follow-up at 24 months post-randomisation. The end of the study
16 17	249	as a whole will be after all participants have completed follow-up, all data queries have
17 18 19	250	been resolved, the database locked and the analysis completed.
20 21 22	251	
23 24 25	252	Sample size
26 27 28	253	A sample size of 250 participants (125 per group) is sufficient to detect a difference of at
29	254	least 0.84 in the pain severity NRS (scored 0-10) between randomised groups with 90%
30 31 32	255	power and 5% 2-tailed significance, assuming:
33 34	256	a) The standard deviation for the pain NRS is 2.0(17).
35 36	257	b) Correlation between NRS at baseline and 3 months is 0.3 (based on data from the
37 38	258	MINT trials provided by collaborator Professor Raymond Ostelo)
39 40 41	259	c) Allowing for up to 10% attrition at 3 months.
42	260	The trial will therefore have sufficient power to detect the target difference used by NICE (1-
43 44 45	261	point difference) and reflects a moderate effect size(32).
46 47 48	262	
49 50 51	263	Statistical analyses
52 53	264	The data will be analysed on an intention-to-treat basis and will follow a pre-specified
54 55 56	265	Statistical Analysis Plan.
57 58	266	The primary outcome (NRS) will be analysed using linear mixed effect models, including all
59 60	267	available repeated pain measurements up to 3 months, adjusted for timepoint and the

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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 \geq 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.

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3 4	325	12 months of recruitment, enough patients are eligible for the trial and can be randomised.
5 6 7 8 9 10	326	Progression criteria are:
	327	1. 13 sites are open to recruitment
	328	2. 79 patients consented
11 12	329	3. 25 patients randomised (this accounts for a 3-month time lag between consent and
13 14 15 16 17	330	randomisation)
	331	4. Consent rate of 1.5 patients/site/month
18 19 20 21	332	Qualitative research will be conducted in the internal pilot to evaluate trial acceptability and
	333	equipoise and facilitate improvements in communication about the trial to optimise
22 23	334	recruitment. Up to 20 recruitment consultations will be audio-recorded, and telephone
24	335	interviews with up to 20 participants will elicit patient understanding of trial procedures and
25	336	interventions, equipoise, acceptability of recruitment pathways, and quality of patient
27 28	337	information. Telephone interviews with up to 15 clinicians and 10 recruiters will allow
29 30	338	understanding of trial personnel's equipoise and perspectives on the protocol, usual care,
31 32	339	and recruitment pathways. Data will be subjected to rapid thematic framework analysis(43,
33 34	340	44) to ensure findings are reported and implemented in a timely fashion.
35 36 37 38 39 40 41 42	341	
	342	Data handling, storage and sharing
	343	Most data will be stored in a bespoke database hosted on the NHS network. Some data
45 44	344	items will be held on a separate database, hosted on the University of Bristol server,
45 46 47 48 49 50 51 52 53 54 55 56 57 58	345	comprising the randomisation system, information about the intervention delivered and the
	346	quality of needle placement. Access to both databases will be via secure password-
	347	protected web-interfaces.
	348	All study documentation will be retained in a secure location during the conduct of the
	349	study and for five years afterwards, when all participant identifiable paper records will be
	350	destroyed by confidential means. All audio-recording files will be retained in a secure
	351	location during the conduct of the study and for 12 months afterwards, when these files will
59 60	352	be deleted. Where trial related information is documented in the medical records, these

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3 4	353	records will be identified by a label bearing the name and duration of the trial. In
5 6	354	compliance with the Medical Research Council Policy on Data Sharing, and with participant
7 8 9	355	agreement, relevant 'meta'-data about the trial and the full dataset, but without any
	356	participant identifiers other than the unique study identifier, will be held indefinitely. These
10 11	357	will be retained because of the potential for the raw data to be used subsequently for
12 13 14 15 16 17 18 19 20	358	secondary research and/or training.
	359	
	360	Patient and public involvement (PPI)
21 22	361	RADICAL was designed in collaboration with a musculoskeletal PPI group at the University of
23 24	362	Bristol. A PPI group involving patients with experience of RFD has also been convened
25 26	363	specifically for this study. This group has played an integral part in designing the research,
20	364	including development of accessible participant documents. They will continue to co-work
28 29	365	with the research team on all aspects of the study, including interpretation of results and
30 31 32 33 34	366	development of public dissemination strategies and material. The Trial Steering Committee
	367	(TSC) also includes two patient members.
35 36 37	368	
38 39 40	369	Ethics and dissemination
41 42	370	The study received Research Ethics Committee (REC) approval from London - Fulham REC in
43 44 45 46 47 48 49 50 51 52 53 54	371	July 2021 and Health Research Authority (HRA) approval in September 2021. The study is
	372	sponsored by North Bristol NHS Trust (<u>https://www.nbt.nhs.uk/research-innovation</u>) who
	373	are responsible for the oversight of the study and ensuring it is managed appropriately. The
	374	study is coordinated by the Bristol Trials Centre (BTC), a UK Clinical Research Collaboration
	375	registered Clinical Trials Unit (UKCRC Reg. No 70), and overseen by the TSC and a Data
	376	Monitoring and Safety Committee (DMSC) (see Supplementary file).
55 56 57 58 59 60	377	

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378 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.

394 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.

401 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

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

During the internal pilot phase, RADICAL experienced three substantial challenges to 411 412 delivery: delays in site opening, complex screening processes limiting sites capacity to 413 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; 414 we have experienced delays of up to two years from feasibility assessment to site opening 415 due to research and development departments' limited capacity to process local approvals. 416 417 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 418 419 engagement, alongside the research infrastructure to deliver the trial, has been key, and we 420 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 421 with clinicians. 422

During our internal pilot phase, we identified that recruitment was slower than anticipated. 423 To understand site-level barriers to recruitment, we held three recruitment training 424 425 meetings with 17 staff members from seven sites. Feedback from local delivery teams was 426 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 427 recruit patients. Our original recruitment process was to screen patients listed for a MNBB 428 and then recruit patients prior to their MNBB. Patients who had ≥60% pain relief from the 429 MNBB (approximately 40% of patients(45)) were then eligible to proceed in the trial and 430 431 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 432 433 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 434

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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18 19	169	Competing interests statement
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21	470	All such any user in all success the Matienal Institute for Uselth and Care Descende for
22 23	470	All authors received support from the National Institute for Health and Care Research for
24	471	the project associated with this manuscript, which was paid to their employing institution.
25		
20 27	472	No other conflicts were reported.
28		
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32	171	The suthers thank all of the research and clinical team members at participating site.
33 34	4/4	The authors thank an of the research and clinical team members at participating site;
35	475	members of the Trial Steering Committee and independent Data Monitoring and Safety
36 37	476	Committee; members of the patient and public involvement group, and additional
38 39	477	collaborators Professor Raymond Ostelo and Professor Steven Cohen, who will be involved
40 41	478	in the management of the trial and will contribute key expertise on aspects of trial design as
42	479	needed.
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							Post-ra	andomisation				
	Baseline	Randomisation & intervention	2	4	6	8	10	3	6	12	18	24
					wee	ks				month	s	
Sociodemographic details	Х		ĺ									
HADS	Х											
Medical history including pain location	X	K										
STarT Back tool	Х		C									
NRS pain score	Х		Х	X	X	X	Х	Х	Х	Х	Х	X
EQ-5D-5L	Х				Х			Х	Х	Х	Х	Х
SF-12	х						21	Х	Х	Х	Х	X
ODI	Х							X	Х	Х	Х	X
WPAI	Х							Х	X	Х	Х	Х
Procedural data		Х										
Blinded re-intervention offered								х				
Uptake of blinded re- intervention								х	X	X	x	x
Satisfaction with treatment outcome								X	X	X	X	X
Adverse events			Х		Х			Х	X	Х	X	Х
Resource and health service use questionnaire								х	х	Х	х	Х

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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.

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

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- 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.

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

Section/item	ltem No	Description	Page number
Administrative	informa	ation	
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	5a	Names, affiliations, and roles of protocol contributors	s 1 & 20-21
responsibilities	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

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	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: Part	ticipants	, 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: Assi	gnment	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	collecti	ion, 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

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	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: Mon	itoring		
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
Data monitoring	21a 21b	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 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	16 13
Data monitoring Harms	21a 21b 22	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 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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16 13 10
Data monitoring Harms Auditing	21a 21b 22 23	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 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 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16 13 10 N/A

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			

Informe consent material	d : Is	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request: radical- study@bristo I.ac.uk
Biologic specime	al ens	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.