

Clinical and cost-effectiveness of the STAR care pathway compared to usual care for patients with chronic pain after total knee replacement: study protocol for a UK randomised controlled trial

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ABSTRACT (max of 350 words, currently 336)

Background

Approximately 20% of patients experience chronic pain after total knee replacement. There is little evidence for effective interventions for the management of this pain, and current healthcare provision is patchy and inconsistent. Given the complexity of this condition, multimodal and individualised interventions matched to pain characteristics are needed. We have undertaken a comprehensive programme of work to develop a care pathway for patients with chronic pain after total knee replacement. This protocol describes the design of a randomised controlled trial to evaluate the clinical and cost-effectiveness of a complex intervention care pathway compared with usual care.

Methods

This is a pragmatic two-armed, open, multi-centred randomised controlled trial conducted within secondary care in the UK. Patients will be screened at 2 months after total knee replacement and 381 patients with chronic pain at three months post-operative will be recruited. Recruitment processes will be optimised through qualitative research during a six-month internal pilot phase. Patients are randomised using a 2:1 intervention:control allocation ratio. All participants receive usual care as provided by their hospital. The intervention comprises an assessment clinic appointment at 3 months post-operative with a physiotherapy Extended Scope Practitioner and up to six telephone follow-up calls over 12 months. In the assessment clinic, a standardised protocol is followed to identify potential underlying causes for the chronic pain and enable appropriate onward referrals to existing services for targeted and individualised treatment. Outcomes are assessed by questionnaires at six months and 12 months after randomisation. The co-primary outcomes are pain severity and pain interference assessed using the Brief Pain Inventory at 12 months after randomisation. Secondary outcomes relate to resource use, function, neuropathic pain, mental well-being, use of pain medications, satisfaction with pain relief, pain frequency, capability, health-related quality of life, and bodily pain. After trial completion, up to 30 patients in the intervention group will be interviewed about their experiences of the care pathway.

Discussion

If shown to be clinically and cost-effective, this care pathway intervention could improve the management of chronic pain after total knee replacement.

Trial registration: ISRCTN registry (ISRCTN92545361), prospectively registered on 30/08/2016

Key words (3-10): Total knee replacement, chronic post-surgical pain, care pathway, randomised controlled trial

BACKGROUND

Treatment of osteoarthritis with total knee replacement aims to reduce pain, functional limitations and associated disability. Over 100,000 primary total knee replacements were performed in the United Kingdom (UK) in 2015 [1, 2]. Despite good outcomes for many, a systematic review found that approximately 20% of patients report chronic pain after total knee replacement [3]. Chronic post-surgical pain is defined as pain that occurs or increases in intensity at three months or longer after surgery [4]. Patients with bothersome pain at three months after surgery are often disappointed with their outcome [5, 6], feel abandoned by healthcare [7] and struggle to make sense of ongoing pain [8]. Chronic pain after knee replacement is an under-investigated area, but the wider literature shows the impact of chronic pain on all areas of life. Chronic pain is associated with poor general health, interference with daily activities, disability and depression [9-11]. Compared with the general population, patients with chronic musculoskeletal pain report lower satisfaction with life [12-14]. Older people with pain are likely to become socially isolated, which is a risk factor for other problems [15], limiting their capacity to bring about change or to seek help for their pain.

Healthcare provision for patients with chronic pain after total knee replacement has been shown to be patchy and inconsistent in the UK: only some orthopaedic centres have standardised protocols to guide the assessment and management of patients with this condition [16]. A systematic review identified that only one trial has evaluated an intervention for the management of chronic pain after knee replacement – namely, an injection with antinociceptive and anticholinergic activity [17]. There is also insufficient evidence on the effectiveness of interventions for the management of chronic pain after any surgery type [18]. Therefore, there is a need for robust evidence to guide the early screening, identification and management of patients with chronic pain after total knee replacement.

Treatment of chronic pain is challenging, and evaluation of treatments in combination or matched to patient characteristics is advocated [19], yet no such trials have been evaluated in the context of chronic post-surgical pain [18]. It has been argued that rather than new interventions for pain, improvements are required to access existing treatments with combination treatments matched to pain characteristics [19]. Chronic pain after total knee replacement may be caused by biological and mechanical factors. Biological causes include

the sensitising impact of chronic pain from osteoarthritis [20-22], development of Complex Regional Pain Syndrome [23-25], persistent post-operative inflammation, infection and/or localised nerve injury [26]. Mechanical causes include altered gait, prosthesis loosening, and weakening effects on ligaments [27, 28]. Psychological factors may also influence post-operative outcomes [29].

To improve the management of chronic pain after total knee replacement, we have developed the STAR (Support and Treatment After joint Replacement) care pathway. This consists of early post-operative screening to identify patients with pain and an assessment clinic at 3 months post-operative with a physiotherapy Extended Scope Practitioner and telephone follow-up as required. The intervention aims to enable appropriate onwards referral to existing services to ensure that underlying reasons for chronic pain are considered early in the post-operative pathway and that treatment is targeted at these to improve pain management and to reduce the impact of pain. In line with UK Medical Research Council (MRC) guidance on complex interventions, comprehensive development work has been undertaken to design and refine this intervention. The design of the intervention is underpinned by a systematic review [17], survey of current practice [30], focus groups with health professionals [31], expert deliberation and patient involvement activities [32]. Further development and refinement work included consensus work with health professionals to refine intervention content, testing intervention delivery and acceptability to patients, and evaluation of views about implementation of the intervention within the context of a randomised controlled trial [33]. The aim of this multi-centre randomised controlled trial is to evaluate the clinical and cost-effectiveness of the care pathway for patients with chronic pain after total knee replacement.

METHODS/DESIGN

This protocol follows guidance from SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [34, 35]. A SPIRIT figure for the schedule of enrolment, interventions and assessment is provided in Table 1 and a SPIRIT checklist is provided in Appendix 1.

Aim

The primary aim of this trial is to evaluate the clinical effectiveness of a new care pathway ('the STAR pathway') when compared with usual care for people with chronic pain after knee replacement. Secondary objectives of embedded aspects of the trial include:

1. Pilot phase with qualitative work to optimise recruitment and refine trial processes;
2. Economic analysis to evaluate the cost-effectiveness of the care pathway;
3. Qualitative study with patients who received the intervention to explore their experiences of the care pathway.

Design

This is a pragmatic, parallel, 2-arm, superiority, multi-centred randomised controlled trial using 2:1 intervention:control randomisation, with an internal pilot phase and embedded economic evaluation and qualitative studies. The trial is currently taking place at four high-volume National Health Services (NHS) centres for total knee replacement, and will be expanded to include 8-10 trial sites.

Regulatory approvals

Ethics approval was obtained from South West – Central Bristol Research Ethics Committee in July 2016 (REC reference 16/SW/0154) and HRA approval in August 2016. Any protocol amendments will be submitted to the HRA for approval prior to implementation and updated on the ISRCTN registry.

Trial status

The first participant was recruited into the trial in October 2016. Recruitment is scheduled to be completed by March 2019, and follow-up and data collection are scheduled to be completed by March 2020.

Patient involvement in trial design

Patients were involved in trial design through the University of Bristol's Musculoskeletal Research Unit's 'Patient Experience Partnership in Research' (PEP-R) patient involvement groups [32]. PEP-R Musculoskeletal comprises nine patients with musculoskeletal conditions, most of whom have had joint replacement. PEP-R STAR is a specialised group established for this programme of work, comprising five patients with experience of chronic pain after knee replacement. Both of these groups inputted into trial design, acceptability of

randomisation, design of data collection and primary outcomes, questionnaires, patient information leaflets, recruitment consultations and qualitative topic guides.

Patient recruitment

A diagram of participant flow in the trial is provided in Figure 1.

Eligibility criteria

Inclusion criteria include:

- Adults aged ≥ 18 years who have received a primary total knee replacement because of osteoarthritis at a participating NHS Trust.
- Adults who report pain in their operated knee at 2-3 months after surgery. This is assessed using the 7-item pain subscale of the Oxford Knee Score (OKS) [36]. Each item on the OKS is scored 0-4, with a total pain score of 0-28 (severe pain to no pain). Based on previous cluster analysis [37], patients with pain are defined as those with a score of 0-14 on the OKS pain subscale.

Exclusion criteria include:

- A lack of capacity to provide informed consent to participate
- Previous participation in the STAR trial for the contralateral knee
- Participation in another research study that interferes unacceptably with the STAR trial

Screening process to identify patients with chronic pain after knee replacement

Patients who are two months after a primary total knee replacement because of osteoarthritis will be identified from hospital computer systems by an NHS employee and posted a pre-screening notification card followed by a screening study pack 2-4 days later. Anonymised data on age and gender of all patients sent a screening pack will be recorded. The screening pack includes a cover letter, patient information leaflet, screening questionnaire, a freepost enveloped and a complimentary teabag. One reminder screening pack will be sent if no response is received within 1-2 weeks. Patients are asked to complete and return the screening questionnaire and consent form. On receipt of a completed screening questionnaire, the research team scores the OKS to identify patients with pain in their replaced knee (score of 0-14 on the OKS pain subscale).

Recruitment process

Patients who score 0-14 on the screening OKS pain subscale and consent to further contact from the research team will be posted a trial information pack and then telephoned by a researcher 3-5 days later. If they are interested in participating, they will then complete a second OKS via telephone with the researcher to ensure they still meet the inclusion criteria for the trial. A face-to-face recruitment consultation at the participant's home or local hospital is then arranged. Some of the final detailed aspects of this recruitment consultation will be informed by work during the pilot phase of the trial and follows a model consultation process [38]. If a patient would like to participate in the trial, they will be asked to provide informed, written consent. All patients will be provided with a sheet of contact details for relevant charities or organisations, such as Arthritis Care, Pain Concern and Mind. Participants are then given a baseline questionnaire to complete and return to the research team. All researchers involved in recruitment have Good Clinical Practice (GCP) and trial-specific training.

Randomisation

After patients have provided written, informed consent and have returned a completed baseline questionnaire, they will be randomly allocated to the STAR pathway or usual care. Patients will be informed of their allocation by a member of the research team.

Randomisation occurs as soon as possible after the baseline questionnaire is received.

Randomisation with allocation concealment is conducted remotely via the Bristol Randomised Trials Collaboration using a web-based randomisation system. Randomisation takes place on a 2:1 basis to ensure that the intervention service is running at sufficient capacity to enable a pragmatic assessment of its clinical and cost-effectiveness. Moreover, if the intervention is operating to a sufficient degree of capacity then per-protocol and Complier Average Causal Effect (CACE) analyses will be more reliable and have higher power. To ensure reasonable balance between the two treatment groups, allocation is minimised by pain severity and pain interference scores for the replaced knee (assessed with the Brief Pain Inventory Severity and Interference Scales and categorised into tertiles based on data from a previous study [39]), and stratified by trial centre.

Blinding of participants and trial personnel to treatment allocation is not possible due to the nature of the intervention. After patients have been randomised, the research team will send the patient and their General Practitioner (GP) a letter to inform them of treatment allocation.

Usual care

All patients in the trial receive usual care as provided by their hospital. The trial sites all provide a routine six week post-operative follow-up, and one centre provides an additional three-month appointment. All centres provide additional follow-up with a surgeon if requested but do not include routine follow-up by practitioners specialising in pain.

Intervention

Participants randomised to the intervention group will receive usual care and the STAR intervention, which consists of one hour-long assessment clinic appointment with a trained physiotherapy Extended Scope Practitioner (a registered physiotherapist with specialist training in orthopaedics) and up to six telephone follow-up calls over 12 months (Figure 2). Adherence to the intervention is defined as attendance at the assessment clinic appointment. Patients will be offered an assessment clinic appointment as soon as possible after randomisation, ideally within one week. Booking an appointment is arranged over the telephone and confirmed by letter.

The clinic appointment is booked for one hour and involves the Extended Scope Practitioner taking a clinical history, reviewing patient-reported outcome measures, conducting a knee examination, and reviewing radiographs and blood test results. Patient-reported outcome measures include the Brief Pain Inventory (BPI) [40], Hospital Anxiety and Depression Scale [41], PainDETECT [42] and Douleur Neuropathique 4 [43]. The knee examination involves evaluating the sites and nature of knee tenderness, surgical wound healing, range of motion, alignment, stability, patellofemoral joint function, signs of infection and signs and symptoms of Complex Regional Pain Syndrome as per the Budapest criteria [44]. A blood sample is taken to test for markers of infection. Patients have anteroposterior long leg alignment, lateral and patella skyline knee radiographs taken if these have not already been performed as part of their usual care to evaluate alignment and assess for evidence of fracture or concerns with sizing, fixation or position of the implants. The appointment may last longer than one hour if additional time is required for radiographs.

Findings from the assessment clinic appointment are recorded on a standardised proforma and entered into the research database. On the basis of the STAR assessment, patients are referred to appropriate existing services for further treatment, which may include one or more

of the following: a surgeon when pain is attributable to surgical factors; physiotherapy for exercise and mobility advice and support; a GP for treatment of depression or anxiety; and/or pain specialists for neuropathic pain or complex regional pain syndrome (via GPs).

Monitoring is also available if this is appropriate. The STAR care pathway is individualised and flexible, and other referrals can be made depending on the needs of the patient. Copies of all referral letters are sent to the patient, their treating orthopaedic surgeon and their GP.

Patients receive telephone follow-up from the Extended Scope Practitioner based on clinical need, up to a maximum of six times over 12 months. These telephone calls are to follow-up on the care that patients are receiving and to ensure that any referrals are being undertaken. Additionally, further referrals can be made on the basis of these telephone follow-up consultations. Details of these telephone calls and any additional referrals made after the follow-up telephone call are documented on a standardised proforma.

All Extended Scope Practitioners delivering the intervention attend a one-day training session and are provided with a comprehensive intervention training manual that includes standard operating procedures for the assessment. Further details of the development and content of the intervention, in line with the template for intervention description and replication (TIDieR) [45], will be published separately.

Co-treatments

Participants can seek treatment for related or unrelated medical conditions as needed during the trial. Use of health services are recorded in follow-up questionnaires and will be used in the health economics analysis.

Assessment of intervention fidelity

Intervention fidelity evaluates the degree to which an intervention is delivered as intended [46]. In this trial, assessment clinics and telephone follow-up calls will be observed to evaluate if the intervention is being delivered as intended in the intervention training manual. A minimum of one assessment clinic for each Extended Scope Practitioner involved in intervention delivery will be observed annually. Observations are recorded on a standardised proforma and any additional training needs are highlighted and actioned.

Outcome measurement

All participants are assessed at baseline prior to randomisation (3 months after surgery), 6 months after randomisation (9 months after surgery) and 12 months after randomisation (15 months after surgery). All outcome measurement will be undertaken via self-report questionnaires and participants are provided with a complimentary teabag with each questionnaire. Participants are offered the option of completing study questionnaires on paper or online through REDCap (<http://project-redcap.org/>). If completed questionnaires are not received within two weeks, a reminder questionnaire will be sent. If no response is received to the reminder, a researcher will telephone the participant to offer support in completing the questionnaire on the telephone. Telephone calls to patients who do not return a follow-up questionnaire will be performed by a researcher from a different trial centre to ensure that the researcher is blinded to treatment allocation.

The primary and major secondary outcomes map directly onto the eight domains of the core outcome set for the assessment of chronic pain after knee replacement [47]. The co-primary outcomes are pain severity and pain interference assessed using the BPI [40] at 12 months after randomisation. Participants will be asked to complete the BPI in relation to their operated knee. Secondary outcomes include physical function, neuropathic pain, psychological factors, use of pain medications, improvement and satisfaction with pain relief, pain frequency, capability, health-related quality of life and pain elsewhere. The final questionnaire includes free-text questions that ask participants to explain what has and has not helped with their knee pain over the duration of the trial. Further details of the assessment of these outcomes are provided in Figure 1.

Resource use

Resources used in relation to the intervention (including initial face-to face assessment and telephone contacts) will be recorded on a standardised proforma. Use of health services including primary, secondary and tertiary care, use of personal social services and additional costs (private healthcare, travel, lost income, home modifications) will be collected in the follow-up questionnaires at 6 and 12 months after randomisation. Participants are provided with resource diaries and prescribed medication folders to prospectively record and document any health resources they have used, to assist them in the completion of the questionnaires [48]. Resource use data including inpatient stays and outpatient visits for all patients at the treating hospitals will be obtained from hospital electronic systems or extracted from hospital records and recorded on standardised proformas.

Internal pilot phase

The six-month internal pilot phase at four trial sites will evaluate patient identification and eligibility, recruitment rates, withdrawal rates and reasons for withdrawal, questionnaire completion rates, adverse reactions and protocol compliance. Embedded qualitative research, involving audio-recording of recruitment consultations and telephone interviews with participants, will be undertaken to optimise recruitment and trial processes. Anonymised transcripts from the recruitment consultations and interviews will be imported into the qualitative data management software QSR NVivo™. Data will be analysed thematically, involving inductive and deductive coding and categorisation [49]. Data from the pilot phase will be used to inform refinements to recruitment and trial processes. Patients recruited into the pilot phase will continue with the follow-up schedule and be retained in the full trial analysis.

Safety

Data on adverse events reactions (adverse events directly attributable to the intervention) are collected and closely monitored to ensure the ongoing safety of participants. All serious adverse events will be notified to the study sponsor and reviewed by the Trial Steering Committee.

Withdrawals

Participants are free to withdraw from the trial at any point. All withdrawals will be recorded on a standardised form. Patients who withdraw from the trial will be asked if they would be willing to discuss their reasons for withdrawal to allow the identification of any barriers to participation and highlight whether measures to facilitate participation in the trial need to be implemented.

Qualitative study

After the 12-month follow-up, a purposive sample of up to 30 patients from the intervention group will be interviewed about the STAR care pathway. This sample size should be sufficient to achieve data saturation in keeping with standards of qualitative research [50, 51]. Interviews will address participants' experiences of the pathway and their experience of surgery, pain, and resource use. With participants' consent interviews will be audio-recorded and anonymised transcripts imported into QSR NVivo™ and analysed using a thematic

approach [49]. Findings will be used to further inform the interpretation of the trial's findings as well as implementation into clinical practice.

Thank you cards and newsletters

Cards will be sent to participants at three and nine months after randomisation to thank them for their continuing involvement in the STAR trial and to remind them when they can expect to receive the next STAR questionnaire. Newsletters will be sent to all participants every 6-12 months to keep them updated on trial progress.

Sample size

For a 2:1 intervention:control randomisation ratio, a sample size of 285 patients would have a power of 80% to 90% to detect standardised differences of between 0.35 to 0.40 standard deviations (SDs) using a 2-sided 5% significance level. From previous studies [52, 53], the SD for each of the BPI Interference and Pain Severity scales for patients with chronic post-surgical pain have been observed to be approximately 2, in which case the target effect size translates to a difference between intervention and control groups of between 0.7 and 0.8 scale points for both scales. Such a difference is worthwhile detecting clinically, since the current consensus statement indicates that differences of approximately one scale point can be deemed the minimally important difference for both of these scales [53, 54]. To allow for a conservative 25% loss to follow-up in the STAR trial, 381 participants will be recruited.

Data management

Participants' personal data will be regarded as strictly confidential and will be entered onto a secure administrative Microsoft Access™ database stored on a University of Bristol server. Only STAR team members with appropriate contracts/letters of access with NHS trusts will have access to participants' personal data. Anonymised trial data will be stored using REDCap, an online secure web application. REDCap will also be used to administer online questionnaires to trial participants. Double data entry of the primary outcome measure for all participants completing paper questionnaires and full Case Report Forms (CRFs) for a random sample of participants will be undertaken to ensure data quality.

Data monitoring

The trial will be overseen by an independent Trial Steering Committee (TSC), composed of four clinical or non-clinical academics and one member of the public. The TSC will meet at

regular intervals to review trial progress, protocol adherence and patient safety. The TSC decided that a Data Monitoring Committee was not necessary for this trial and that safety data and data quality will be reviewed by the TSC. No formal interim analysis will be conducted; however, data from the pilot phase were analysed to evaluate the feasibility of proceeding to the main trial. The trial will be stopped prematurely if mandated by the NHS Ethics Committee, recommended by the TSC, funding for the trial ceases or for any other relevant major clinical or therapeutic reason.

Auditing

The coordinating centre will regularly monitor trial sites to ensure data quality and completeness. The trial sponsor (North Bristol NHS Trust) will monitor the trial, potentially including reviewing the Site Files and participants' medical records.

Statistical analysis

The full statistical analysis plan for the STAR trial can be accessed at the University of Bristol publications repository [55]. Data analysis will be conducted in accordance with CONSORT guidelines, commencing with descriptive analyses to compare groups at baseline. The primary comparative analysis will apply the intention-to-treat principle including all participants as randomized and with primary outcome data available at 12 months after randomisation. The usual care and intervention groups will be compared using linear regression models adjusted for baseline values of the minimisation/stratification variables, presenting both 95% confidence intervals and p-values. Sensitivity analyses will use standard imputation techniques to impute missing primary outcome data. The secondary outcomes will be analysed using regression models in a similar manner to the primary analysis. Subgroup analyses will investigate variation in the treatment effect between orthopaedic centres and by pain severity, using interaction terms added to the regression models. Explanatory analyses such as CACE methodology will be used to estimate the effect in those patients able to comply with their allocated intervention. Compliance in the intervention group is defined as attendance at the STAR assessment clinic.

Cost-effectiveness analysis

The primary cost-effectiveness analysis will take an NHS and Personal Social Services perspective. A secondary analysis will take a broader perspective to include patients' costs. Only resources used in relation to the treatment of chronic pain will be measured from

randomisation to 12 months follow-up. All resources will be valued using routine data sources and information from hospital finance departments. All analyses will be on an intention-to-treat basis and there will be no discounting of costs or effects given the one year duration of the study. The primary outcome for the economic evaluation will be the Quality Adjusted Life Year (QALY). The difference in costs and QALYs between the arms will be assessed using the Net Benefit framework using appropriate regression models adjusted for baseline values of the minimisation/stratification variables. Additionally, the difference in costs and the differences in the primary outcomes will be examined. If no arm is dominant then incremental cost-effectiveness ratios will be calculated using, if appropriate, Seemingly Unrelated Regressions (SUR) to account for the potential correlation between costs and the primary outcomes. Given the number of important secondary outcomes, a cost consequence analysis will also be conducted in relation to these outcomes. Uncertainty will be addressed using cost-effectiveness acceptability curves and sensitivity analyses.

Dissemination policy

Publications will include a final report, presentations at scientific meetings and open-access articles in peer-review journals. Avenues for disseminating findings to patients and the public will be identified and developed in collaboration with the PEP-R patient involvement groups and relevant charity organisations, such as Arthritis Care. In addition, all participants who indicate that they wish to receive study results will be sent a plain English summary of the final results.

DISCUSSION

To our knowledge, this is the first randomised controlled trial to evaluate the clinical and cost-effectiveness of a care pathway when compared with usual care for patients screened as having early indications of chronic pain after total knee replacement. The care pathway aims to identify the potential causes of pain to enable early appropriate onwards referral to existing services for targeted and individualised treatment to improve pain management and to reduce the impact of pain. The design and development of this complex intervention has been informed by multiple stages of work, in line with MRC guidance on the development of complex interventions.

There are practical and operational issues pertinent to this trial, particularly regarding screening and randomisation of patients. Approximately 1 in 5 patients experience chronic pain after total knee replacement and therefore this trial involves a stage of screening to identify this subgroup of patients early in the post-operative period. An issue is that patients with poorer outcomes after joint replacement are less likely to respond to postal questionnaires [56]. A Cochrane review identified a number of strategies to improve response rates to questionnaires [57], and we have implemented some of these including pre-notification screening cards and non-monetary incentive in the form of a teabag to indicate that the study team appreciate that completion of trial questionnaires requires time and effort from the participant.

In this trial we are randomising patients on a 2:1 intervention:control allocation ratio. Justification for the use of unequal randomisation allocation is often poorly reported [58]. There are numerous reasons given for the use of unequal randomisation ratios, including to reduce cost, improve recruitment, increase the amount of information on the new treatment including safety data, and to account for differential loss to follow-up and cross-over [58-60]. In this trial, randomisation will take place on a 2:1 basis to ensure that the intervention service is running at sufficient capacity to enable a pragmatic assessment of its effectiveness and, particularly, cost-effectiveness. Providing potential participants with an explanation for the reasons behind 2:1 randomisation is important to ensure that equipoise is conveyed adequately. To address this concern, we are undertaking patient involvement activities and qualitative research within the internal pilot phase with the aim of improving the verbal and written information we provide to potential participants about randomisation.

The findings of this trial will provide evidence to guide decisions by clinicians, policymakers and patients and inform commissioning of services. If shown to be clinically and cost-effective, this intervention could improve the early identification and management of chronic pain after total knee replacement. It is also possible that this model of care delivery could be adapted for evaluation for the management of chronic post-surgical pain in other surgical contexts.

List of abbreviations

STAR: Support for treatment after joint replacement

MRC: Medical Research Council

SPIRT: Standard Protocol Items: Recommendations for Interventional Trials

NHS: National Health Service

ISRCTN: International Standard Randomised Controlled Trial Number

PEP-R: Patient Experience Partnership in Research

OKS: Oxford Knee Score

GCP: Good Clinical Practice

CACE: Complier Average Causal Effect

GP: General Practitioner

TIDieR: Template for intervention description and replication

BPI: Brief Pain Inventory

SDs: Standard deviations

TSC: Trial Steering Committee

QUALY: Quality Adjusted Life Year

SUR: Seemingly Unrelated Regressions

Declarations

The authors have no conflicts of interest to declare.

Ethics approval and consent to participate

Ethics approval for this study was provided by the South West – Central Bristol Research Ethics Committee on the 7th July 2016 (reference 16/SW/0154). Health Research Authority (HRA) approval was given on the 4th August 2016. All participants will provide informed, written consent.

Consent for publication

Not applicable

Availability of data and material

After the trial is complete, anonymised data will be stored on the University of Bristol Research Data Storage Facility and will be shared via the University of Bristol Research Data Repository. Access to the data will be restricted to ensure that data is made available to

bona fide researchers only, after they have signed a data sharing agreement.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the design of the trial. VW drafted the manuscript and all authors revised it critically for important intellectual content.

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The research team would like to thank members of the Trial Steering Committee for providing oversight of the trial. This publication is based on work undertaken as part of the STAR Programme and as such it benefits from involvement of the whole STAR team.

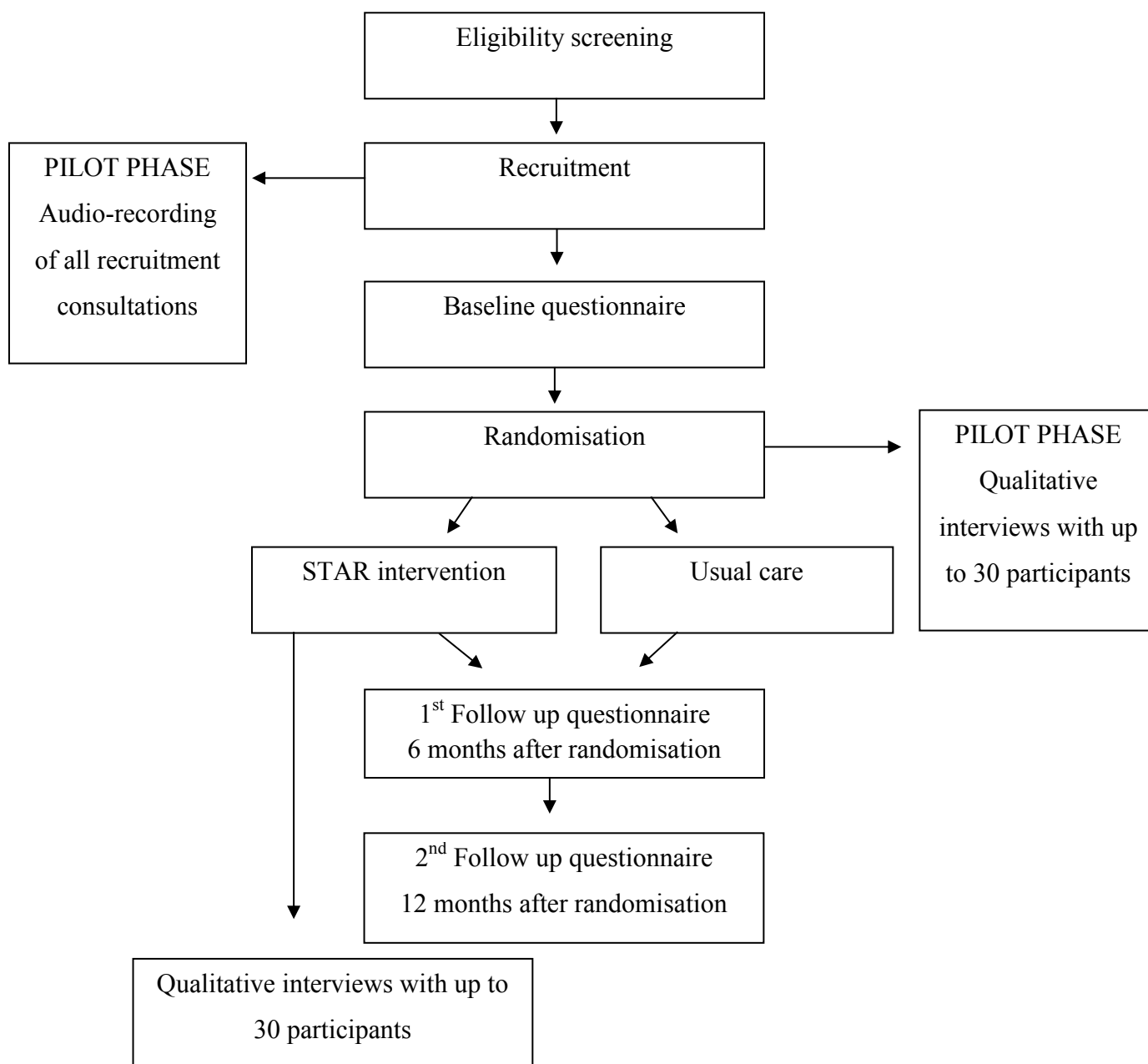


Figure 1: Participant flow through the trial

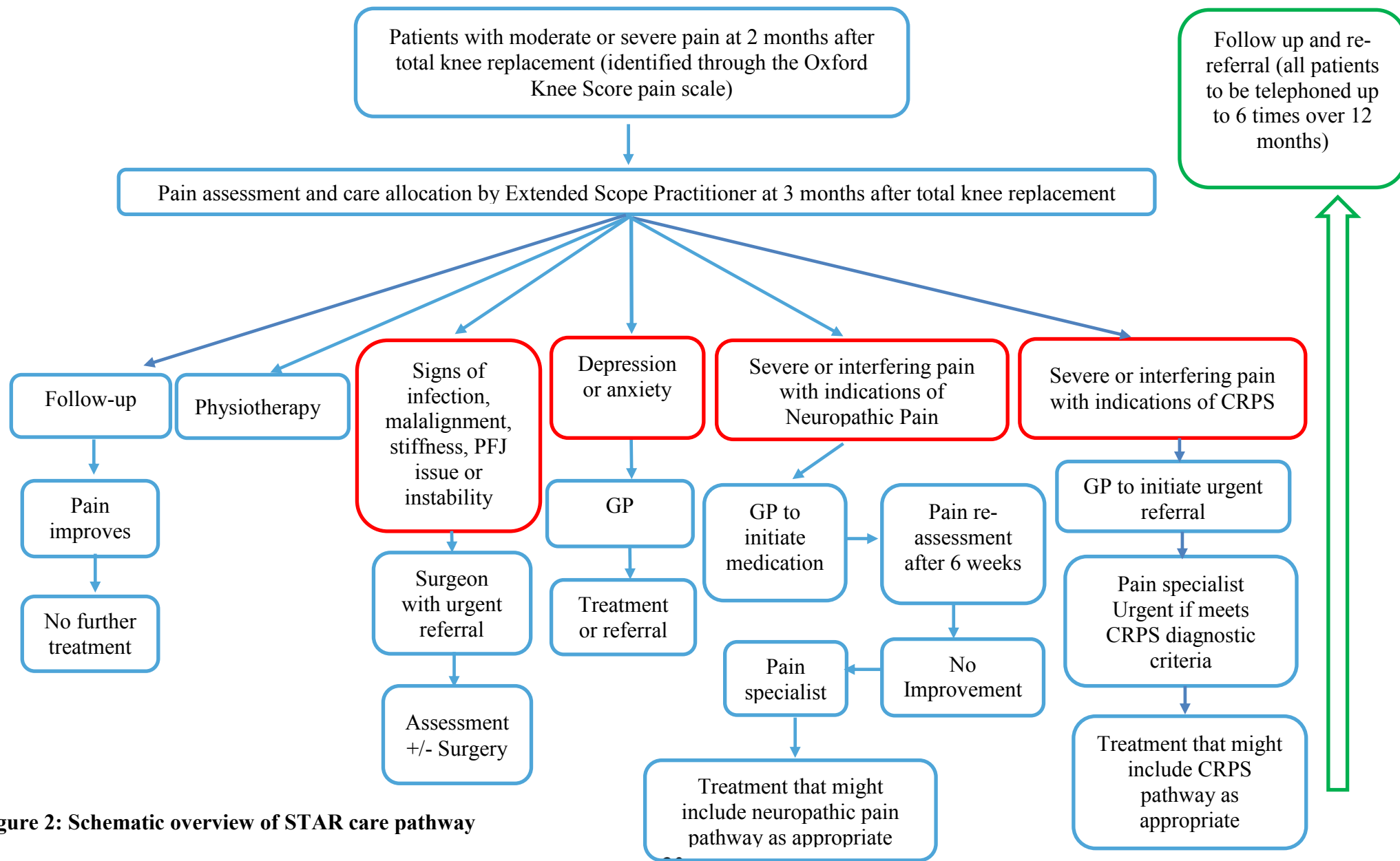


Figure 2: Schematic overview of STAR care pathway

Table 1: SPIRIT Figure for the schedule of enrolment, interventions, and assessments

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	
	$-t_1$	0	t_1	t_2
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
STAR care pathway and usual care			←————→	
Usual care			←————→	
ASSESSMENTS:				
Socioeconomic details	X			
Brief Pain Inventory	X		X	X
Oxford Knee Score [36]	X		X	X
PainDETECT [42]	X		X	X
Douleur Neuropathique 4 [43]	X		X	X
Hospital Anxiety and Depression Scale [41]	X		X	X
Pain Catastrophizing Scale [61]	X		X	X
Possible Solutions to Pain Questionnaire [62]	X		X	X
Self-Administered Patient Satisfaction Scale [63]	X		X	X
Comparison to pre-operative pain	X		X	X
Pain frequency questions	X		X	X
ICECAP-A [64]	X		X	X
EQ-5D-5L [65]	X		X	X
SF-12 [66]	X		X	X
Body pain diagram [67]	X		X	X
Resource and medication use	X		X	X
Free-text question				X

0=baseline, t_1 =6 months after randomisation, t_2 =12 months after randomisation

Appendix 1: SPIRIT 2013 checklist To complete just prior to submission

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____
	5b	Name and contact information for the trial sponsor	_____
	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	_____

	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)	_____
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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	_____
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	6b	Explanation for choice of comparators	_____
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Objectives	7	Specific objectives or hypotheses	_____
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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)	_____
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____
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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)	_____
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____
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	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)	_____
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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
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	_____
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)	_____
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	_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____
	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	_____
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	_____
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	_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	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)	_____

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____
	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	_____
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	_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____
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)	_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
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	_____

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
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	_____
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	_____
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	_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
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	_____

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

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