Study Title: A qualitative research study to explore patient and surgeon considerations for revision knee replacement for unexplained chronic pain

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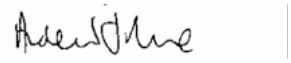
Chief Investigator:	Prof Andrew Price, Professor of Orthopaedics, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)
Investigators:	Mr Shiraz Sabah, Doctoral Research Fellow, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) Dr Francine Toye, Qualitative Research Lead, Physiotherapy Research Unit, Oxford University Hospitals NHS Foundation Trust Nuffield Orthopaedic Centre, Oxford Dr Loretta Davies, SITU Trials Portfolio Manager, Surgical Interventions Trials Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) Prof David Beard, Professor of Musculoskeletal and Surgical Science, Surgical Interventions Trials Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS)
Sponsor:	University of Oxford Joint Research Office, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB ctrg@admin.ox.ac.uk 01865 616480
Funder:	National Institute for Health Research (NIHR)
Chief Investigator Signature:	

No potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, HRA (where required) unless authorised to do so.

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1. KEY STUDY CONTACTS

Chief Investigator	Prof Andrew Price Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Botnar Research Centre, Oxford OX3 7LD andrew.price@ndorms.ox.ac.uk 01865 223421
Sponsor	University of Oxford RGEA, Joint Research Office, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB ctrg@admin.ox.ac.uk 01865 616480
Funder(s)	National Institute for Health Research (NIHR)
DPhil student	Mr Shiraz Sabah, Doctoral Research Fellow, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), shiraz.sabah@ndorms.ox.ac.uk
Additional Supervisor(s)	Dr Francine Toye, Qualitative Research Lead, Physiotherapy Research Unit, Oxford University Hospitals NHS Foundation Trust Nuffield Orthopaedic Centre, Oxford, Francine.Toye@ouh.nhs.uk Dr Loretta Davies, SITU Trials Portfolio Manager, Surgical Interventions Trials Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), loretta.davies@ndorms.ox.ac.uk Prof David Beard, Professor of Musculoskeletal and Surgical Science, Surgical Interventions Trials Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), david.beard@ndorms.ox.ac.uk

2. LAY SUMMARY

Around one-in-every-five patients reports chronic pain following knee replacement surgery. Many of these patients seek medical help, which prompts the search for a diagnosis to explain their symptoms. However, for a large proportion of patients, no cause is ever found and the pain is said to be 'unexplained'. In this situation, current guidelines recommend initial supportive treatment (for example, with physiotherapy or pain management). Recent evidence suggests around two-thirds of patients will improve with this treatment. However, the remaining one-third of patients remain the same or are worse off. For these patients, the best treatment option is not known, and some patients request a surgical solution. However, surgery to revise a knee replacement for chronic pain is controversial. The surgery itself may be complex and carry a high risk of complications, whilst the odds of an improvement in symptoms are only about 50/50. Our understanding of the important considerations when deciding whether or not to operate for chronic pain are very limited. The aim of this study is to gain a deeper understanding of these considerations from the perspectives of both patients and surgeons. This study will involve interviews with patients and surgeons, which will take place either over the telephone, via videoconference [using Microsoft Teams] or in-person. These interviews will be recorded and analysed using qualitative research methods. This study will benefit patients and surgeons in the future by providing information on the considerations that should be borne in mind when faced with the clinical dilemma of whether to offer revision surgery to treat chronic pain after knee replacement.

3. SYNOPSIS

Study Title	A qualitative research study to explore patient and surgeon considerations for revision knee replacement for unexplained chronic pain
Internal ref. no. / short title	Qual rTKR
Sponsor	University of Oxford RGEA, Joint Research Office, , Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB ctrg@admin.ox.ac.uk 01865 616480
Funder	National Institute for Health Research (NIHR)
Study Design, including methodology	Qualitative interview study
Study Participants, including sampling strategy	(i) Patients with unexplained chronic pain after knee replacement (ii) Surgeons treating patients with unexplained chronic pain after knee replacement
Sample Size	We will sample patients and surgeons until theoretical saturation has been reached. We are expecting to recruit between 10-15 patients and between 10-15 surgeons.
Planned Study Period	01/03/2022 to 28/02/2023
Planned Recruitment period	01/03/2022 to 28/02/2023
Aim:	To gain a deeper understanding of the important considerations surrounding the decision to operate for unexplained chronic pain after knee replacement and the outcomes most important to patients and surgeons.

4. ABBREVIATIONS

BASK	British Association for Surgery of the Knee
CI	Chief Investigator
CRF	Case Report Form
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance Ethics and Assurance Team
rTKR	Revision Total Knee Replacement
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

One-in-every-five patients report chronic pain following knee replacement surgery (Wylde et al., 2018a). Many of these patients, though not all (Moore and Gooberman-Hill, 2020), seek medical help, which prompts the search for a diagnosis to explain their symptoms. However, for some patients, no cause is ever found and the pain is said to be 'unexplained'. In this situation, current guidelines recommend initial supportive treatment (for example, with physiotherapy or pain management) (BOA, 2020). Recent evidence suggests that around two-thirds of patients will improve with this treatment (Wylde et al., 2018b). The remaining one-third of patients remain the same or are worse off. For these patients, the best treatment option is not known and some request a surgical solution. However, surgery to revise a knee replacement for unexplained chronic pain is controversial. The surgery itself may be complex and carry a high risk of complications, whilst the odds of an improvement in symptoms are only about 50/50 (Baker et al., 2012). Our understanding of the important considerations when deciding whether or not to operate for unexplained chronic pain are very limited. The aim of this study is to gain a deeper understanding of these considerations from the perspectives of both patients and surgeons. We will conduct qualitative interviews with patients who have chronic pain after knee replacement or who have received revision surgery for this problem, and with surgeons who manage these patients. The interviews will be recorded so that they can be analysed, and will take place either face-to-face, via videoconference [using Microsoft Teams] or over the telephone – according to the preference of the participant. This study will benefit patients and surgeons in the future by increasing understanding of the considerations that should be borne in mind when faced with the clinical dilemma of whether to offer revision surgery to treat unexplained chronic pain after knee replacement. The risks from this research are anticipated to be low. However, we recognise that discussions around chronic pain may generate an emotional response. The research team will be sensitive to participants' feelings (for example, by monitoring for signs of fatigue or distress and offering to suspend or stop data collection accordingly). Participants will have the opportunity to decline to answer any of the questions they are posed. Our aim is to ensure that participants leave the research process no more distressed than when they began. We will debrief with participants at the end of each interview and direct to appropriate support (such as their General Practitioner, or a support group) where necessary. The interview transcripts will be stored securely, separate from the medical notes. We will use some direct quotations in research publications. These will be anonymised to maintain confidentiality and we will remove any information that might allow others to identify a participant (for example names and geographic locations). However, with this type of research, it is not possible to guarantee that nobody will recognise an account.

6. AIM / RESEARCH QUESTIONS / OBJECTIVES

Aim:	To gain a deeper understanding of the important considerations surrounding the decision to operate for unexplained chronic pain after knee replacement and the outcomes most important to patients and surgeons.
Objectives:	1. To explore patients' perspectives of the important considerations that underpin the decision to choose surgery or non-operative management for unexplained chronic pain after knee replacement. 2. To explore surgeons' perspectives of the important considerations that underpin the decision to offer surgery or non-operative management for unexplained chronic pain after knee replacement. 3. To explore the outcomes following surgery that are most important to patients and surgeons.

7. STUDY DESIGN

7.1 Methodology

This is a qualitative research study, which will take an interpretivist perspective. The chosen approach is a thematic analysis, which was chosen as a flexible analytic method, not dependent on a pre-existing theoretical framework. The study will involve qualitative interviews with patients and surgeons. This methodology is appropriate to gain deeper insights on the important considerations that underpin the decision to choose surgery or non-operative management for unexplained chronic pain after knee replacement.

7.2 Sampling Strategy

Patients will be recruited using purposive sampling from painful knee replacement clinics at the Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Foundation Trust. Around half of patients seen in these clinics are referred from other centres in England for a tertiary opinion. We are interested to capture the perspectives of patients from different backgrounds (for example, age, socio-economic status, ethnicity), which we expect to encounter within these clinics. The sample of revision knee replacement surgeons will be recruited from centres around the United Kingdom. We will contact surgeons directly if they are already known to us and will send invitations to the British Association for Surgery of the Knee mailing list. We expect to encounter surgeons from a variety backgrounds (for example, age, ethnicity, clinical experience). Sampling for each group will continue until theoretical saturation (which will be defined as the point where we fully understand the ideas that are emerging). We are expecting to recruit between 10-15 patients and between 10-15 surgeons.

7.3 Methods of Data Collection

Patients will complete an initial data collection form, which will include questions on background (age, gender, ethnicity, marital status, employment status, dependents, living arrangements, other health conditions). This will provide information that can be drawn from during the qualitative interview. There is no initial data collection form for surgeons. Semi-structured interviews will be conducted with patients and surgeons. A topic guide has been developed, which includes initial open-ended questions followed by prompts and supplementary questions. Sample questions are provided below.

Patients:
"Can you talk me through your experience so far with your knee replacement?"
"Can you talk me through any treatments you've had for problems with your knee replacement?"
"Can you talk to me about what the treatment plan is for you knee?"

Surgeons:
"Tell me your experience of treating patients with unexplained pain after knee replacement"
"Tell me your thoughts on offering further surgery to some patients with unexplained pain".

Patients and surgeons will be asked about their preferences for interview, with in-person (at the Nuffield Orthopaedic Centre), telephone and video-conference options made available. Interviews will be audio recorded with consent using Open Broadcaster Software (OBS).

7.4 Methods of Data Analysis

Our chosen approach is thematic analysis, as described by Braun and Clarke. This is a flexible analytic method, not dependent on a pre-existing theoretical framework, where we will code qualitative interviews to develop themes, which are our ultimate analytic purpose.

7.5 Study Sequence and Duration

Participants will undergo one interview, which is expected to last around one hour. Participants will provide informed consent at the beginning of the interview. Patient participants only will complete a data collection form.

8. PARTICIPANT IDENTIFICATION

8.1 Study Participants

(i) 10-15 patients aged 18 years and over who have been diagnosed with unexplained pain following total knee replacement.
(ii) 10-15 surgeons who treat patients with unexplained pain after total knee replacement.

Sampling will continue until theoretical saturation (defined as the point where no new ideas are emerging).

8.2 Inclusion Criteria for patients and surgeons

- Participant is willing and able to give informed consent for participation in the study (including audio recording of interview).
- Male or Female, aged 18 years or above.
- Diagnosed with unexplained pain at least 1 year after total knee replacement (Patients only).
- Currently treats patients with painful knee replacements (Surgeons only).

8.3 Exclusion Criteria for patients and surgeons

The participant may not enter the study if ANY of the following apply:

- Non-fluent English speaker (because translation is a form of interpretation).

9. STUDY ACTIVITIES

- Patient participants will be identified by members of their routine care team at outpatient appointments and provided with a patient information sheet. Their clinician will ask for verbal consent to pass their contact details on to Mr Shiraz Sabah (DPhil student).
- Surgeon participants will be able to register their interest in the study by responding to either an email from the study team or an advert sent by the British Association for Surgery of the Knee.
- For both patients and surgeons, informed consent will be taken by Mr Shiraz Sabah (DPhil student) who is a senior surgical trainee experienced in this task. Informed consent will be obtained prior to a qualitative interview lasting around one hour (either face-to-face at the Nuffield Orthopaedic Centre or Botnar Research Centre, over the telephone or via videoconference [using Microsoft Teams]).
- Interviews will be audio recorded using Open Broadcaster Software, which we have previously used for this type of research. Audio files will be stored on encrypted hard drives at the Botnar Research Centre.
- Interviews will be professionally transcribed using a secure service approved by the University of Oxford.
- Transcripts will be password protected and stored on encrypted hard drives at the Botnar Research Centre. Each transcript will be assigned a unique study identifier and we will remove names, addresses and other potentially identifying information.
- We will ask patients if they would like to receive a short summary of their interview transcript (or their full transcript). Patients will be given the option to change, add to or develop upon these documents, or not, as they see fit.

- We will ask surgeons if they would like to receive their full interview transcript, with a similar request to provide any feedback or clarifications at their discretion.
- All transcripts and summaries will be sent to participants via email as a password protected .zip file. The password will be sent separately via text message.
- We have chosen to send patients a summary of their interview as our default position as we felt this would be less burdensome than the full transcript.
- After we have uploaded the anonymised transcripts to NVivo we will delete the corresponding audio files. Each transcript will then be coded and we will develop themes.
- A draft of our research report will be sent to all participants before publication.

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9.1 Recruitment

Patients will be recruited from painful knee clinics at the Nuffield Orthopaedic Centre. Clinicians running these clinics will be provided with information on the study and trained to identify eligible participants. Clinicians will ask participants for verbal consent before forwarding contact details to the research team. Mr Shiraz Sabah (DPhil student) will then contact patients to obtain informed consent. Surgeon participants will be able to register their interest in the study by responding to either an email from the study team or an advert sent by the British Association for Surgery of the Knee.

9.2 Informed Consent

Mr Shiraz Sabah (DPhil student) will take informed consent. Participants (patients and surgeons) will be provided with a written Participant Information Sheet and Informed Consent document detailing: the nature of the study; what it will involve for the participant; and any risks involved in taking part. The participant will be allowed as much time as they need to consider the information, and given the opportunity to question the Investigator, their GP (if relevant) or other independent parties to decide whether they will participate in the study. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care (if relevant), without affecting their legal rights, and with no obligation to give the reason for withdrawal. For face-to-face interviews, the participant must personally sign and date the latest approved version of the Informed Consent form before the qualitative interview. A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site. For remote interviews, verbal consent will be taken and recorded by the researcher. A remote consent form has been developed for this task. The participant will be sent a copy of the consent form via email [as a password protected file, with the password sent via text message] (or confidential post if preferred). We will not recruit patients from vulnerable groups.

9.3 Screening and Eligibility Assessment

Screening has been described above within 8.2 and 8.3. There will be no exceptions made regarding eligibility (i.e., each participant must satisfy all the approved inclusion and exclusion criteria of the protocol).

9.4 Subsequent Visits

There is only one study visit for the qualitative interview.

9.5 Discontinuation/Withdrawal of Participants from Study

During the course of the study a participant may choose to withdraw early at any time. This may happen for several reasons, including but not limited to:

- The occurrence of significant distress during study interviews

- Inability to comply with study procedures
- Participant decision

1) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

2) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis. This option is available to participants only up to the point of anonymisation of their transcript.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- The occurrence of significant distress during study interviews

Withdrawn participants will be replaced if necessary. The reason(s) for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

9.6 Definition of End of Study

The end of study is the point at which all the study data has been transcribed and clarification or feedback on transcriptions has been received from participants. .

10. ANALYSIS

10.1 Description of Analytical Methods

The chosen approach is a thematic analysis as described by Braun and Clarke, which was chosen as a flexible analytic method, not dependent on a pre-existing theoretical framework. Semi-structured interviews will be performed with patients and surgeons. An interview schedule has been drafted by the study team and will be sent to the SORE Knee Patient and Public Involvement group and revision knee surgeons outside the study team for feedback. Interviews will be transcribed word-for-word and transcripts will be sent to participants for checking as described above. Anonymised transcripts will be uploaded to NVivo software. An inductive ('bottom up') approach will be used to identify themes. The credibility of the findings will be checked by circulating the first draft of the study report to participants for comment. We will establish confirmability by setting up an audit trail in NVivo which sets out each step in the analysis of data and provides a rationale for the decisions made, thus providing evidence that the study's findings accurately portray participants' responses.

11. DATA MANAGEMENT

11.1 Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2 Data Recording and Record Keeping

All study data will be entered into NVivo software for qualitative data analysis. The participants will be identified by a unique study specific number and/or code in any database. The name and any other identifiers will NOT be included in any study data electronic file. Participant audio recordings will be captured using Open Broadcaster Software, which we have previously used for this type of research. Audio recordings will be stored on an encrypted hard drive in the Botnar Research Centre and kept until the interview transcript has been returned, checked and coded and will then be deleted. An external, University of Oxford approved, transcription service will be used. Participant confidentiality will be protected through a contract with the transcriber where they are required to delete all data on its return to the researcher. Participants will not be approached for future research.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

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

13.2 Approvals

Following Sponsor approval, the protocol, informed consent form, and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) and Health Research Authority (HRA).

The Investigator will submit and, where necessary, obtain approval for all substantial amendments to the original approved documents.

13.3 Other Ethical Considerations

Participants who are unable to consent for themselves will not be recruited. Participation will be voluntary and without pressure, with patients and surgeons free to choose whether or not to participate. We recognise that discussions around chronic pain may generate an emotional response. The research team will be sensitive to participants' feelings (for example, by monitoring for signs of fatigue or distress and offering to suspend or stop data collection accordingly). Participants will have the opportunity to decline to answer any of the questions they are posed. Our aim is to ensure that participants leave the

research process no more distressed than when they began. We will debrief with participants at the end of each interview and direct to appropriate support (such as their General Practitioner, or a support group) where necessary. The interview transcripts will be stored securely, separate from the medical notes. We will use some direct quotations in research publications. These will be anonymised to maintain confidentiality and we will remove any information that might allow others to identify a participant (for example names and geographic locations).

13.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5 Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

13.6 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. A contribution of £30, in the form of a gift voucher, will be made to thank participants for their time.

14. FINANCE AND INSURANCE

14.1 Funding

This study is funded by the National Institute for Health Research (NIHR) as part of a Doctoral Research Fellowship Award (Ref: NIHR301771).

14.2 Insurance

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

14.3 Contractual arrangements

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

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research (NIHR). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

16. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

17. ARCHIVING

The study database will be retained for 3 years after study completion to be able to answer any queries that arise post-publication.

18. REFERENCES

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APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	14/04/2022	Shiraz Sabah	Response to REC conditions

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, and HRA (where required).