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Research Protocol

Full title	**Rec**U**r**rent **I**ntra-articular **C**orticosteroid injections in **O**steoarthritis: The RUbICOn qualitative study
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Study Co-ordinating Centre	Musculoskeletal Research Unit Bristol Medical School University of Bristol Level 2, Learning and Research Southmead Hospital Bristol, BS10 5NB
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Signatures Chief Investigator	Dr Andrew J Moore

BACKGROUND AND RATIONALE

Osteoarthritis is the most common musculoskeletal condition worldwide[1] and it is a global public health burden.[2] It is an irreversible and progressive disease, which leads to joint pain, inflammation and stiffness, functional decline, morbidity and loss in quality of life. Osteoarthritis is one of the

leading causes of global disability[3] and is associated with substantial healthcare system and societal costs.[4]

The National Institute for Health and Care Excellence (NICE) Clinical Guideline for Osteoarthritis: care and management recommends that the core treatments for osteoarthritis include information, self-management, exercise, weight loss, and pharmacological treatments (medicines). The use of intra-articular corticosteroid injections is recommended as an adjunct to these core treatments for the relief of moderate-to-severe, uncontrolled pain in people with osteoarthritis.[5] Evidence for this recommendation was based on limited data which indicated a short-term benefit of repeated intra-articular corticosteroids for pain relief in osteoarthritis of the knee.[6-9]

Since the publication of the NICE guidance, further reports on the benefits of intra-articular corticosteroid injections for osteoarthritis management have been published or presented.[10-14] The overall evidence from these further findings suggest a short-term benefit of intra-articular corticosteroids on pain relief and mild or no evidence of adverse effects with intra-articular corticosteroid therapy. Given that the prevalence of osteoarthritis is expected to rise over the coming years and concerns that intra-articular corticosteroid injections will be used more frequently in patients, robust evidence on the long-term benefits and risks associated with recurrent use of intra-articular corticosteroid injections for osteoarthritis is urgently warranted. Evidence on the practice and patterns of use of intra-articular injections is needed, as this is important to help guide switching, augmentation, or dosing of treatment in relation to clinical outcomes. In response to this lack of contemporary evidence the National Institute for Health Research Health Technology Assessment has commissioned a large mixed methods study entitled "RecUrrent Intra-articular Corticosteroid injections in Osteoarthritis - the RUbICOn study". The data generated in this study will provide comprehensive information on the patterns of use of intra-articular injections of joints for osteoarthritis in primary care. The safety of use and the treatment effect will be assessed as well as the effect of receiving the intervention on the timing of subsequent surgical interventions. Where the subsequent intervention is joint replacement (arthroplasty), the influence of intra-articular injection on the risk of adverse events following arthroplasty and patient reported pain and function will be assessed. This protocol focuses on the qualitative work package which is part of RUbICOn study and aims to explore the experiences and views of patients and general practitioners who have received/administered intra-articular corticosteroid injections for osteoarthritis and the views and motivations of those who have not.

AIMS

The aims of the RUbICOn Qualitative study are:

- to understand patients' and health care practitioners' experience, perspectives and beliefs about the use of intra-articular corticosteroids for osteoarthritis.
- To establish what factors affect decision-making on use of intra-articular corticosteroid injections including complications, comorbidities, and perceived risks of repeated use, and clinicians' awareness of and views on current guidelines and recommendations for the use of intra-articular injections of corticosteroid

OBJECTIVES

The specific objectives of the study are:

1. To explore patients' experiences of and beliefs about receiving intra-articular corticosteroid injections (IACIs) for osteoarthritis, the benefits and disadvantages of treatment, including impact on daily activities.

2. To understand patients' knowledge about intra-articular corticosteroid injections for osteoarthritis, perceived risks, information needs and their motivations for accessing treatment or not.
3. To explore healthcare practitioners' views and experiences of prescribing/administering (IACIs), including their beliefs about the efficacy of IACIs, and their motivations for using them or not.
4. Interviews will also explore factors affecting decision-making on use of intra-articular corticosteroid injections including complications, comorbidities, and perceived risks of repeated use, and clinicians' awareness of and views on current guidelines and recommendations for the use of intra-articular injections of corticosteroid.
5. To develop a narrative report and explanatory model to explain patient and clinician use of intra-articular corticosteroid injections in the current management of osteoarthritis.
6. Findings from the study will be used to inform the development of a Delphi study which aims to gain expert consensus on key questions and feasibility considerations in future research.

STUDY DESIGN

Qualitative methods are the best way to understand people's experiences, perceptions and their personal contexts and can lead to improvements in healthcare guidance.[15] The study will use in-depth interviews to investigate patients' and health care practitioners' experiences of and perspectives on the use of intra-articular corticosteroid injections for osteoarthritis. Up to 40 patients and 30 clinicians from across a range of primary care practices in the South West region will be interviewed. Interviews will be conducted via telephone or video-calling (e.g. Skype) to increase opportunities for participation.

STUDY SETTING

The study will include adults in the South West of England who have or have not received intra-articular corticosteroid injections (IACIs) for osteoarthritis, within a primary care setting, within the last 3 years, and clinicians serving diverse populations from across the South West of England who have or have not administered intra-articular injections of corticosteroid for osteoarthritis. Participants will be identified through the NIHR West of England Clinical Research Network (CRN), facilitated by the Bristol North Somerset & South Gloucestershire (BNSSG) CCG Research & Evidence Team (BNSSG R&ET).

SAMPLING AND RECRUITMENT

Purposive maximum variation sampling [18, 19] will be used to identify adults who have received intra-articular injections of corticosteroid for the treatment of osteoarthritis within a primary care setting, within the last 3 years, including those who have received surgical intervention will be identified through the NIHR West of England Clinical Research Network (CRN) using GP Read Codes. Using a similar sampling strategy, patients who have the same conditions but have not received injections and those who have received recurrent injections will be identified. We will stratify patients by age, practice locale, affected joint and clinical setting.

Clinicians serving diverse populations from across the South West of England will be identified through the CRN West of England. Those who have administered intra-articular injections of corticosteroid for osteoarthritis and those who have not (or only a small number of occasions) will be purposively sampled.

Sample size

Up to 40 patients and 30 clinicians from across a range of primary care practices in the South West of England region will be interviewed. The sample size of 40 patients is an approximation expected to achieve data saturation, so that no new data is emerging by the time that data collection is complete, but final sample size will depend on the achievement of this.[20] There is substantial variation in population, rural/urban setting, sociodemographics and healthcare provision across the SW of England. As such, we believe that with the figures we have suggested we can achieve a representative cross section sample for the wider NHS from this geographical area.

Inclusion criteria - patients

- Patients above 45 years old who have received one or more intra-articular corticosteroid injections for osteoarthritis within the last 3 years.
- Patients above 45 years old who have never received intra-articular corticosteroid injections for osteoarthritis.
- Patients who have or have not received surgical intervention (e.g. joint replacement, replacement, fusion, osteotomy, debridement) for their osteoarthritis.

Inclusion criteria - Clinicians

- Primary care clinicians in the South West who have administered intra-articular injections of corticosteroid for osteoarthritis within the last 3 years.
- Primary care clinicians in the South West with no experience (or only on a small number of occasions) of administering intra-articular injections of corticosteroid for osteoarthritis.

Exclusion criteria – Patients and Clinicians

- Any individual who lacks capacity to provide informed consent (including dementia & learning difficulties).
- Any individuals who cannot converse fluently in English language.

Sample identification

The NIHR Clinical Research Network West of England will be responsible for engaging research active primary care practices in the study and will pass on details of the study via a Research Information Sheet for Practices (RISP) seeking expressions of interest for the study (EOIs). Primary care practices interested in taking part will then contact the research team. Clinicians interested in taking part in an interview will contact the research team by telephone, text, or email.

Primary care practices will screen patient information and GP Read Codes to identify eligible patients with capacity to consent and will post out information packs about the study. Patients interested in taking part will then contact the research team for more information by email, text, or telephone, and to discuss arranging an interview.

Patients' confidentiality will be maintained as patients who are eligible for the study will be identified and sent an information pack about the study by a member of their own care team - usually a GP research lead, or research nurse at or working with the primary care practice. Patients and GPs interested in participating in the study will then be able to contact the research team directly if they wish to discuss participation.

Consent processes

The information sheet will describe the purpose and aims of the study stating that if patients or clinicians are interested in taking part in the study they should either contact the research team

directly by email, text or telephone to discuss the study. During the telephone call, a member of the research team will describe the study and answer any questions that the potential participant has about the study. If the potential participant wishes to proceed then the member of the research team will continue the email or telephone conversation to arrange a date and time for interview.

Prior to the interview, participants will be asked to provide verbal consent which will be audio-recorded, or to complete an electronic eConsent form.

Given the topics are not expected to provoke distress, and to remove as much as possible any technical barriers or administrative workload that are likely to discourage patients and clinicians from participating, we are offering verbal consent in keeping with the proportionate approach recommended by the HRA for non-CTIMP and low-risk non-interventional studies. Following government advice on shielding and physical distancing during the COVID-19 pandemic, participants may also be unwilling to venture out to post copies of consent forms or reply slips, especially if shielding. Our Patient Advisory Group also suggested verbal consent as the main option, as e-consent would 'put them and their friends off'. Verbal consent will be audio-recorded at the beginning of the interview and therefore transcribed, and a signed copy of a verbal consent form will be sent to the participant following the interview for their records.

For the electronic eConsent form, potential participants will receive the consent form as a Word Document by email, check the boxes by each statement by clicking on them and then sign the form by typing their name and date at the bottom, and return this by email to the researcher prior to the interview. This is in keeping with the joint HRA and MHRA statement on seeking consent by electronic method (https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seekingconsent/)

Logging of recruitment details

Recruitment will be logged on a secure database kept on a University of Bristol secure server. Details of the number of individuals invited to the study by each practice will be recorded. A unique study ID will be allocated to each individual that participates in the study for use in all subsequent documents (interview transcripts etc.). Contact details of all participants in the study will be logged on a password protected database on a secure University of Bristol server. While the research team will only have details of those who agreed to participate in the study, they will then be able to ascertain response rates from the number of individuals contacted by GP practices.

DATA COLLECTION

Potential participants will be invited to take part in an in-depth interview. Interviews will be conducted by an experienced qualitative research fellow and will take place via telephone or video-calling (e.g. Skype). Interviewees will be asked to provide informed consent prior to the interview commencing, including consent to be audio-recorded and for anonymised quotes to be used in the final report and any peer-reviewed literature. The interviews will be audio-recorded, fully transcribed and anonymised.

During the interviews, the researcher will use a topic guide developed in collaboration with the research programme's PPI group and research team. Topics will include questions on patients' and health care practitioners' experience, perspectives and beliefs about the use of intra-articular corticosteroids for osteoarthritis, including factors that affect decision-making about the use of intra-articular corticosteroid injections including complications, comorbidities, and perceived risks of

repeated use, and clinicians' awareness of and views on current guidelines and recommendations for the use of intra-articular corticosteroid injections for osteoarthritis. Each topic guide (patient and clinician) will be piloted in the first 2 interviews and refined as data collection progresses. The order and phrasing of questions will be revised as necessary over the course of the study to reflect findings as they emerge and to facilitate discussion.

DATA ANALYSIS

To analyse the data from interviews, the audio-recorded interviews will first be transcribed by a University of Bristol approved transcription company before being anonymised by the researcher. Transcripts will be imported into software package QSR NVivo and analysed using a thematic approach. Transcripts will be coded, and the codes will be grouped, using inductive methods, into categories.[16] A portion of the transcripts will be independently coded by other members of the research team and following discussion the coding framework will be revised accordingly and reapplied across the data set to ensure that all salient themes and patterns are identified. The analysis will focus on participant views and experiences of using intra-articular injections of corticosteroid for osteoarthritis and will be underpinned by health behaviour theories applicable to both patients and practitioners such as the Health Belief Model.[17]

STUDY DATES

Work package start date: 1st March 2020
Work package end date: 31st August 2022

PATIENT AND PUBLIC INVOLVEMENT

To refine the design of the RUbICOn Qualitative study we have collaborated with our established, dedicated patient public involvement group (The Patient Experience Partnership in Research Musculoskeletal: PEP-R MSK) which comprises members with musculoskeletal conditions and experience of joint injections and joint replacement. The group felt that it would be appropriate for this group to meet regularly during the course of the study to discuss progress and provide input into dissemination strategies. The group will be supported by the Research Unit's experienced Patient and Public Involvement co-ordinator (Amanda Burston). PPI Co-applicant, Edith Anderson, has experience of osteoarthritis and joint injections, and is a core member of the Project Management Committee and overall research team, and will attend our monthly PMC meetings with the support of our PPI group coordinator.

During meetings that occurred in November 2017 with 8 members of the PEP-R group, members felt it was important to establish where injections fitted into treatment pathways and said that they may have reconsidered having joint injections if they had been told this may delay a joint replacement. Questions related to this have been incorporated into the patient and clinician topic guides.

A minority recalled being told of possible adverse effects of injections and they felt that further good quality evidence was required in this area so that they could make fully informed choices. Members of the group were very supportive of the proposed design and were pleased to hear that we intended to incorporate qualitative interviews with patients to gather evidence on their views and experiences of injections and felt this was a vital component of the research. PEP-R MSK members offered very useful feedback on the plain English summary of the research. They felt it reflected the proposal well and used appropriate language. They particularly requested that the term "pain killers" was avoided as such medications alter pain but do not "kill" it.

Following a meeting in May 2020, members also recommended that consent was taken verbally over the telephone to reduce burden, and also to reduce risks associated with postal consent during the COVID 19 pandemic. Two members suggested e-consent would not be attractive to patients, but we have kept this in as an extra option.

The lived experience offered by the PPI co-applicant and PEP-R group members will be central to guiding the presentation and development of our research outputs as well as informing the focus and acceptability of future research studies in this area. The PEP-R MSK group as a whole meet five times a year and project updates will be provided to the group on five occasions throughout the period of research, allowing us to gain the insight and feedback of the wider group throughout the programme of work and incorporate this into the research and outputs.

EXTERNAL REVIEW OF RESEARCH

This project is funded by a grant from the National Institute for Health Research Health Technology Assessment (NIHR HTA) in response to a commissioned funding call. Throughout the design and development of the project the Bristol, North Somerset & South Gloucestershire NHS Clinical Commissioning Group, and the NHS South West Clinical Research Network have also reviewed the study. As such, the scientific and statistical validity have been externally peer-reviewed by representatives from the NIHR where the proposal was scrutinised and found to be of scientific merit to justify funding.

ASSESSEMENT & MANAGEMENT OF RISK

Possibility of participant distress

Although it is unlikely that participants will become distressed given the nature of the topic, it is always a risk. The interviewer has extensive experience of conducting interviews with patients with long-term and painful musculoskeletal conditions and also has training and experience in person-centered counselling. He will be well-supported in eliciting sensitive and potentially distressing information. While there is limited literature on developing distress protocols for research on sensitive topics[21] the interviewer (Dr Andrew Moore) and methodological expert for the study (Prof. Rachael Gooberman-Hill) have developed a distress protocol based on their own extensive experience of interviewing participants on a range of sensitive topics including orthopaedic surgery, terminal illness, and life-limiting conditions in children. The protocol has been based on the principle of non-maleficence and will be used if participants should become upset. The protocol includes guidance about cessation of interview if needed, resuming if appropriate, and signposting patients to sources of further help and support.

Indemnity

This study will be sponsored by the University of Bristol. The University has Public Liability Insurance to cover the liability of the University to research participants. In the event that something goes wrong and a participant is harmed during the research study there are no special compensation arrangements. If a participant is harmed and this is due to someone's negligence then they may have grounds for a legal action for compensation against Bristol University or the NHS Trust or one of the other parties to the research, but they may have to pay their own legal costs.

Researcher safety

We will conduct a risk assessment before conducting interviews. However, as the interviews will be conducted remotely by telephone or video-calling any risk posed by travelling off site to conduct

interviews or by contact with participants and possible exposure (for participants and researcher) to COVID-19 will be minimal.

Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)
All AEs will be recorded in the study file with a note that will identify when the event occurred, the details of the AE, any potential study relation, action taken and resolution / closure of the AE. An assessment of seriousness will be made by the researcher and serious adverse events (SAEs) will be reported in line with legislation and university guidance.

The University has a Service Level Agreement with UH Bristol to ensure that all SAE reporting is managed by UH Bristol on behalf of the University. For that reason, all SAEs must be recorded and reported to UH Bristol, in accordance with UH Bristol Research Safety Reporting Standard Operating Procedure. UH Bristol will regularly inform the University about SAEs. Expedited reporting takes place where necessary to agree corrective / preventative actions. In addition, all SAEs should be reported to the NHS Research Ethics Committee in the Annual Progress Report.

CONFIDENTALITY AND DATA STORAGE
All participants will be assured of the confidentiality of the data collected but will be asked during the consent process for their permission to publish anonymised quotations from the study.
All interviews will be conducted by an experienced qualitative researcher and audio-recorded using an encrypted audio-recorder, transcribed by a University of Bristol approved transcription company (a company with a confidentiality agreement in place with University of Bristol), and anonymised by the qualitative researcher, removing any personally identifiable data, such as personal names, place names, dates etc. Participants will be assigned a pseudonym and study ID. Any quotations used in publications will be anonymised and attributed to a pseudonym. All data (electronic copies of consent forms, transcripts, audiofiles) held on the computing network will be protected by using a combination of passwords and file permissions.

Arrangements for storage of research data after the study has ended
Personal data (e.g. participant contact details) will be stored for 12 months after the study has ended. In line with NIHR guidance which encourages the sharing of anonymised data sets we will be seeking consent from participants for their anonymised data to be shared with other researchers. Anonymised electronic research data (anonymised electronic transcripts of the audio-recordings) will be stored indefinitely in keeping with the University of Bristol Research Data Repository policy, which has processes in place for providing access to bone fide researchers. All data procedures will be in keeping with MRC guidelines, the GDPR and Data Protection Act 2018 [http://www.highlights.rsc.mrc.ac.uk/GDPR/keep.html].

Data sharing
Data will be stored under controlled access and made available only to bona fide researchers who meet the criteria for access to confidential data, and after the University of Bristol Data Access Committee has approved their request.

DISSEMINATION
On completion of data collection and analysis, a final study report will be prepared for the funder. We will also prepare summaries of research to send to all participants. We will submit the research findings for consideration by appropriate peer reviewed journals.

Findings from the research will be presented at a variety of relevant conferences. These may include the Royal College of General Practitioners Annual Conference, the Royal Society of Medicine minor surgery and joint injection courses, the British Society of Rheumatology, the European League against Rheumatism Conference, the British Orthopaedic Association, the British Association for Surgery of the Knee and the British Hip Society. BNSSG CCG Research & Evidence Team will lead our dissemination of results to local and national CCGs. We will work with the 'Patient Experience Partnership in Research' (PEP-R) group to develop accessible information for dissemination through other appropriate outlets, e.g. press releases, web-based resources.

FUNDING

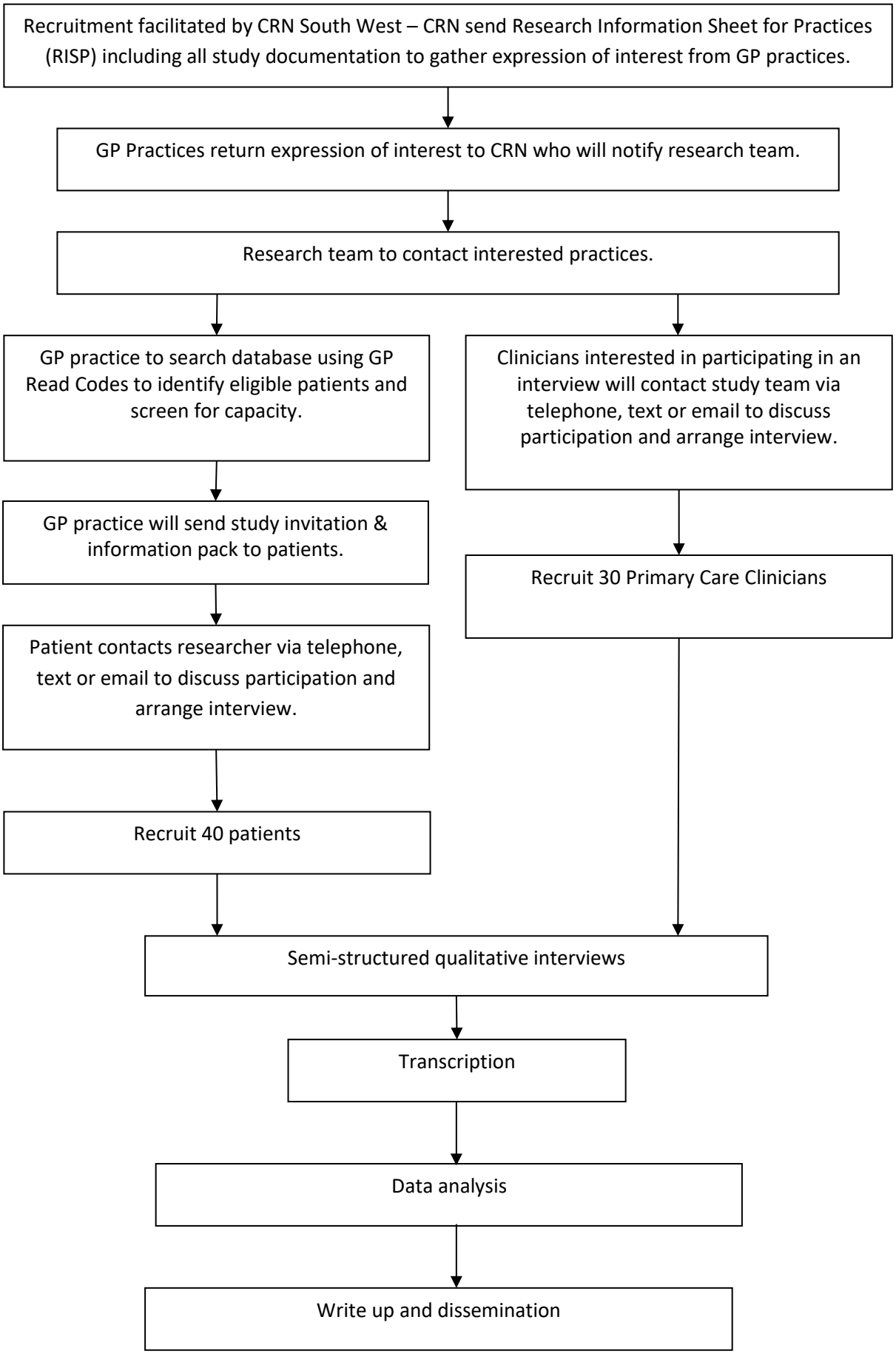
This project is funded as one work package within an NIHR Health and Technology Assessment Grant (NIHR reference number: NIHR 129011). Total costs for the grant are £520,447.90. This grant provides funding for transcription of interviews, travel costs for interviews, patient and public involvement, dissemination and administration. Salary costs for the research team are also funded within this grant.

RESEARCH GOVERNANCE

Sponsorship and insurance for this study will be provided by the University of Bristol (sponsorship reference 2019 – 3337; insurance reference NHE 05 CA 06 0013).

Ethical approval for the study has been provided by East Midlands - Leicester Central Research Ethics Committee Research Ethics Committee (REC ref. 20/EM/0185).

FLOW DIAGRAM



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