STUDY PROTOCOL

FULL TITLE:

Implementing improved fracture risk assessment in primary care: Enhancing capture and quality of self-reported risk factors in electronic health records in primary care: The SELF-FRAX study

SHORT TITLE:

SELF-FRAX study

PROTOCOL VERSION NUMBER:

V1.0 FINAL

DATE:

25 September 2023

RESEARCH REFERENCE NUMBERS:

IRAS Number:	334004
Sponsor Number:	173851
Funder:	The Royal Osteoporosis Society (ROS)
Funder Number:	476

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ABBREVIATIONS

Abbreviation	Definition
CI	Chief Investigator
CRN	Clinical Research Network
EHR	Electronic Health Record
FRAX	Fracture Risk Assessment tool
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
MSK	Musculoskeletal
MTA	Material Transfer Agreement
n	Number
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIHR	National Institute of Health and Care Research
PCN	Primary Care Network
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
R&D	Research and Development
REC	Research Ethics Committee
RDM	Research Data Management
ROS	Royal Osteoporosis Society
ROSE	Danish Risk-stratified Osteoporosis Strategy Evaluation study
SCOOP	Screening for Osteoporosis in Older Women for the Prevention of Fracture study
SMC	Study Management Committee
SMS	Short Message Service
SOS	SALT Osteoporosis Study
URL	Uniform Resource Locator

LAY SUMMARY

Background

Good news! – we can identify patients at increased risk of broken bones (fractures) using simple questionnaire-based tools. Significant advances in osteoporosis treatment and care have occurred over the last two decades. We now have access to a range of relatively inexpensive and safe treatments to reduce the risk of fracture. These treatments work well.

Bad news! - 3 out of 4 people at increased risk of fracture don't receive treatment, largely because this risk goes unidentified. Sadly, a gap persists between fracture risk identification and the receiving of osteoporosis treatment. This could be due to high workloads and limited awareness in GP practices. There may also be a lack of information on some risk factors within GP electronic health records.

A strategy that can raise awareness of increased fracture risk would lead to an improvement in the prescribing of osteoporosis treatments. This study (the SELF-FRAX study) will start to develop such a strategy. We believe that patient-centred, interactive approaches, devised with the involvement of patients and the public, can improve the quality of fracture risk information in GP electronic health records.

What is the aim of our study?

This is an era of increasing digital communications (e.g. emails, texting) and interaction with our own health records (e.g. mobile health apps). We will explore opportunities provided by technology to enable patients to voluntarily complete a fracture risk factor assessment questionnaire. We will determine the most effective way(s) of doing this so that, in the future, patients could update their health records directly.

What will the study involve?

Through their GP, we will invite men and women ages 50 years and older to tell us about their fracture risk factors using a simple online questionnaire. We will also ask them if we can link their questionnaire answers with the information held in their GP electronic health records. This will help us to see how well the information from the questionnaires agrees with their electronic health records. We want to approach around 30,000 men and women aged 50 years and older from across England.

Who will we work with?

During this study we will work with patients, GPs, nurses, and other community-based health professionals from primary care. These interactions will help us to identify opportunities and address barriers to delivering a step change in osteoporosis care.

We will work with the Royal Osteoporosis Society (ROS), UK (the funders of the SELF-FRAX study) and the Lay Advisory Panel for Musculoskeletal Research, University of Sheffield. The Lay Advisory Panel for Musculoskeletal Research and the Lead Volunteer Patient Advocate (ROS) have already helped us with the design of the study and wording of the approaches to be made to potential participants. We will approach the ROS and the panel for advice on how best to share the findings of our study with participants, the public, and other groups. This will increase the chance that the SELF-FRAX study will make a real difference to patients.

How will our study benefit patients?

We will share our findings with participating GP practices and community musculoskeletal services. To publicise our findings more widely, we will write press releases, briefings and articles and arrange interviews for radio and newspapers. We will also give presentations at high-profile scientific and health policy conferences including NHS Evidence, Society for Academic Primary Care and Public Health England. We will write scientific articles for journals, and local NHS and research newsletters.

Ultimately, our work will result in an increase in awareness of fracture risk factors and improvements in osteoporosis care. This will lead to a reduction in the number of patients suffering fractures and an improvement in their quality of life.

1. BACKGROUND AND RATIONALE

Public Health England's 5-year strategy for musculoskeletal (MSK) health (2019-2024) includes a commitment to "high quality, accessible data and intelligence tools to support surveillance and reduce unwarranted variation of MSK conditions across the population pathway."[1]

The current study – an observational cohort study of women and men (age ≥ 50 years) providing information to enhance fracture risk assessments in general practice and ultimately improve treatment access – can be seen as one component of this programme. It seeks to better integrate data from different clinical settings within the MSK clinical pathway in order to inform system-wide changes that can reduce the burden of common MSK conditions. To date, meaningful data collected from population level surveys and primary care electronic health records (EHRs) have not been co-ordinated and compared to inform potential developments in public health and primary care policy making.

In order to see how we might best link this information, we plan to compare data collected from two sources:

(1) *Patient questionnaires*

To capture self-reported presence or absence of fracture risk factors used in the FRAX risk assessment tool (the tool was largely built on self-reported data).

(2) *Electronic health record (EHR) data*

For recorded fracture risk factors (e.g. previous fractures, smoking, alcohol, glucocorticoid use).

By comparing these sources of data, we will better understand the variations in risk factor capture and develop solutions to harmonising these data. Our project outcomes will impact on discussions and decisions about the need for treatment to reduce fracture risk in individuals within routine care.

2. STUDY AIM

The overall aim of this cohort study is to investigate the prevalence of fracture risk factors in the primary care population ages ≥ 50 years, and the concordance between self-reported risk factors and those captured within the EHR in general practice.

The study comprises two main components:

(1) *Patient-reported risk factors for fracture*

Collection via predominantly online (URL or app-based) questionnaires of patient-reported risk factors and, with the individuals' consent, linkage to primary care EHR data.

(2) *EHR-risk factors for fracture*

Extraction and analysis of pseudonymised data from the primary care EHR on recorded variables containing information of relevance to the FRAX fracture risk factors. By separate descriptive analysis of variable-level data on the total underlying target population (men and women age ≥ 50 years), we will be able to evaluate self-selection bias in the patient self-reported cohort.

3. OBJECTIVES

3.1 Primary objectives

(1) To compare the prevalence of FRAX fracture risk factors and FRAX fracture probabilities derived from self-reported risk factor data and related data from within the EHR.

(2) To estimate the concordance/discordance between self-reported fracture risk factors and those derived from the EHR.

3.2 Secondary objectives

(1) To examine the associations between risk factor prevalence and response rates and other factors including, for example, deprivation index.

(2) To compare risk factor prevalence with those in published literature.

(3) To evaluate patterns of non-response and non-participation and their implications for bias in the estimates.

4. STUDY DESIGN

This is a cross-sectional observational cohort study.

5. SETTING

We will use the SystmOne GP software system (TPP, Leeds, UK) during our study and include

General Practitioner (GP) surgeries throughout England.

6. ELIGIBILITY CRITERIA

6.1 For GP practices

Inclusion criteria	Exclusion criteria
– Uses compatible IT system (SystmOne) – Uses a compatible SMS messaging service (e.g. MJog, AccuRx, Airmid)	– None

6.2 For participants

Inclusion criteria	Exclusion criteria
– Patients aged ≥ 50 years	– Has indicated in the EHR that they do not consent to be approached about research studies
– Registered with a participating GP practice during the study period	– Bereavement
– Able to read/understand English with or without assistance	– Mental health issues
– Able to provide informed consent	– Receiving palliative care
	– Diagnosed with dementia
	– Unable to provide informed consent

7. STUDY PROCEDURES

7.1 Overview

Potential participants will be those men and women ages ≥ 50 years registered with a participating GP practice. Eligible patients with an active mobile phone number will be invited via SMS text message, sent from the GP surgery computer system, to complete a web-based questionnaire based on a secure server at the University of Sheffield. Patients without an active mobile telephone number at the GP practice will be posted a questionnaire for pen-and-paper completion via Docmail, a secure remote document

compilation, print and mailing solution. Reminders (SMS or postal) will be sent after 4 weeks if no response is received from the first invitation.

All patients, identified as being eligible for participation in the SELF-FRAX study, will be asked to provide informed consent to (i) extract pseudonymised information from their primary care EHRs and (ii) link their questionnaire responses to their primary care EHR data. This will be analysed and presented at the level of the GP practice and primary care network (PCN) to add a wider view of between-surgery and between-PCN variation in risk factor prevalence.

7.2 Strategies to improve inclusion and reduce bias

Participation rates in cohort studies have been declining over several years raising concerns over inefficiency and the potential for selection bias. The use of web-based data collection is increasingly pursued as a low-cost solution to the former problem but may have lower response rates [2] and is still susceptible to selective participation. Internet access in UK households continues to increase year-on-year (96% in 2020 [3]) but people most likely to be 'digitally excluded' are (i) older people, (ii) people in lower income groups, (iii) people without a job, (iv) people in social housing, (v) people with disabilities, (vi) people with fewer educational qualifications, (vii) people living in rural areas, (viii) homeless people and (ix) people whose first language is not English [4]. These groups may be 'disadvantaged' or 'under-served' [5] and have more complex health needs and poorer outcomes.

We will employ the following strategies to improve inclusion and reduce bias:

(1) Explicit reassurance will be given that relatives, friends and carers can assist (but not participate) in questionnaire completion for the intended respondent.

(2) Keeping questionnaire length to a minimum [2,6]. We will (i) present questions in a logical order, (ii) minimise the cognitive burden of the questions, and (iii) explain, where possible, the purpose of questions.

(3) Raising awareness of the survey among the GP practices and registered patient population prior to going live. We will use reminders to encourage questionnaire completion [2,6].

(4) Collection of brief information in the questionnaire on important social characteristics (e.g. age, gender, ethnicity, care home resident status) to help understand participation, care, and outcomes in under-served groups [6].

(5) Using pseudo-anonymised extracts from the GP clinical system to describe the

characteristics of those invited to participate (e.g. GP surgery code, age, gender, deprivation index (from postcode), ethnicity), as well as the characteristics of the total eligible population to enable evaluation and possible modelling of selective participation.

7.3 Study workflow

7.3.1 GP practice identification, invitation and recruitment

A list of GP practices in England, currently using the SystmOne GP software system (TPP, Leeds, UK), will be generated. In the first instance, each practice will be approached via a short email message inviting them to participate in the SELF-FRAX study. A link to a GP invitation letter, GP practice information sheet and the study webpage will be provided within the initial email message. A medically qualified representative from the GP practice will follow the links which provide detailed information regarding the (i) study purpose and aims and (ii) what the study team will ask the practice to do if they agree to participate.

There are four possible outcomes following this initial invitation:

(1) *The GP practice agrees to participate:*

- A link is provided in the GP practice information sheet. This will direct the practice to an electronic consent form. This should be completed by a medically qualified representative from the practice. The consent format cannot be altered by the GP practice and will be dated automatically by the web-based system for online completion. Responses will be collated on the University of Sheffield secure server (see Section 7.3.4 – Data Collection). The study team will monitor this to identify those GP practices returning a positive response. The study team will then provide instructions, to each consenting GP practice, on how to extract the NHS numbers of potential study participants with an active mobile phone number which can receive SMS messages. Once this has been completed, the GP practice will send the list of NHS numbers to the study team. A cohort of potential participants will be randomly selected and age- and gender-stratified by the study team. This list of NHS numbers will be returned to the GP practice. The practice will send out invitations to these potential participants using their in-house SMS messaging service. The study team may re-approach the GP practice to ask them to participate in one more round of

invitations. This will be dependent on the uptake at the practice. The GP practice will then be thanked for participating in the SELF-FRAX study.

(2) *The GP practice declines to participate:*

- If GP practices decline to participate, they will receive an on-screen notification thanking them for considering participation in the SELF-FRAX study and explaining that they will not be contacted further by the study team.

(3) *The GP practice is unsure whether to participate:*

- The practice should contact the study team for more information.

(4) *The GP practice does not respond:*

- A reminder will be sent out to the practice after 4 weeks.

7.3.2 Participant invitation and recruitment

In the first instance, each patient will receive a SMS message from their GP practice inviting them to participate in the SELF-FRAX study (see Section 7.3.1 – GP practice identification, invitation and recruitment). A link to a patient invitation letter, participant information sheet and the study webpage will be provided within the initial message. The patient will follow the links which provide detailed information regarding the (i) study purpose and aims and (ii) what the study team will ask the patient to do if they agree to participate. The participant is thanked for taking part in the SELF-FRAX study.

There are four possible outcomes following this initial invitation:

(1) *The patient agrees to participate:*

- A link is provided in the participant information sheet. This will direct the patient to an electronic consent form. This should be completed by the patient. A relative, friend or carer may help the patient to complete this. The consent format cannot be altered by the patient and will be dated automatically by the web-based system for online completion. Patients completing the online consent will be given the option to obtain a copy of the consent form by emailing the study team.

  The participant will then be directed to an online fracture risk assessment questionnaire and asked to complete this. A relative, friend or carer can assist the

participant with the filling in of the questionnaire but they should not answer for the participant. As part of the questionnaire, a minimal set of participant identifiable data will be collected in order to ensure that each individual can be correctly identified. Responses will be collated on the University of Sheffield secure server (see Section 7.4 – Risk Mitigation).

(2) *The patient declines to participate:*

- If potential participants decline to participate, they will receive an on-screen notification thanking them for considering participation and explaining that they will not be contacted further by the study team.

(3) *The patient is unsure whether to participate:*

- The patient should contact the study team for more information.

(4) *The patient does not respond:*

- A reminder SMS message will be sent out to the patient after 4 weeks.

7.3.4 Data collection

Data will be collected in accordance with the University of Sheffield's research ethics and integrity policies, guidance and information (Research Ethics Policy | Research Services | The University of Sheffield). Table 1 lists the patient-reported risk factors and other information to be collected by the patient questionnaires.

The content of the questionnaire was informed by experience with the FRAX questionnaire, in the online tool https://frax.shef.ac.uk/FRAX/cemark.aspx, and other population-based studies including the (i) Screening for Osteoporosis in Older Women for the Prevention of Fracture (SCOOP) study [7], (ii) Danish Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study [8], and (iii) SALT Osteoporosis Study (SOS) [9].

7.3.4 Data linkage and extraction

Information on comorbidities and health variables, including those needed to address the primary objective, will be collected from the primary care EHR. This will include relevant prescription medications.

7.3.5 Withdrawal criteria

Patients and GP practices can withdraw from the study at any time by contacting and informing the study team by telephone, email or letter. Withdrawal will mean that any information provided up to that point will be anonymised and retained unless the request is made for data to be destroyed.

Table 1). Patient-reported data to be collected from the questionnaire.

Fracture Risk Factors	
Prior fracture	✔
Parental hip fracture	✔
Glucocorticoid use	✔
Rheumatoid arthritis	✔
Alcohol intake	✔
Current smoking	✔
Secondary osteoporosis	✔
BMD scan	✔
Current osteoporosis treatment[a]	✔
Recent falls (last year)	✔
General health	
Height and weight	✔
Demographic/socioeconomic	
Age (date of birth)	✔
Sex	✔
Ethnicity	✔
Administrative	
NHS number	✔
GP surgery	✔

[a] Other than calcium and/or vitamin D (cholecalciferol)

7.4 Risk Mitigation

The NHS number will be used as the key link variable ensuring that consenting participants completing the patient-reported questionnaire are appropriately linked to the EHR data. GP surgery and date of birth will also be collected and used as further validation items.

7.5 End of study

The end of the study will be reached when all relevant EHR and questionnaire data have been collected, linked and analysed.

8. STATISTICS AND DATA ANALYSIS

8.1 Sample size calculation

8.1.1 Patient self-reported questionnaire (primary and secondary objectives)

The sample will be stratified by age (in line with the National Institute for Health and Clinical Excellence (NICE) guidance) and gender (Table 2):

- Stratum 1: patients aged 50-65 years
- Stratum 2: patients >65 years

Table 2). Potential participants from each GP practice will be age- and gender- stratified as follows:

Stratum	Age (years)	Gender	Participants (n)
1	50 to 65	Male	150
	50 to 65	Female	150
2	Over 65	Male	150
	Over 65	Female	150

A total of 7,500 men and 7,500 women will be approached within each age stratum resulting in a total study population of 30,000. The median registered GP surgery population size in England is 9538. Assuming that 38% of the patients registered with each GP practice are aged ≥ 50 years, 3625 patients could be approached per practice. We propose to limit the patient sample to 500 patients per practice by using the age and gender stratified approach (above). Assuming a 25% response rate, a total of 240 GP surgeries would have to be approached to ensure that 60 surgeries were recruited to the study. This would enable us to achieve our total target population of 30,000 patients.

8.2 Planned recruitment rate

Given the electronic nature of the study, we expect to recruit and initiate the study within a total, staggered period of 4-6 months.

8.3 Statistical analysis plan

8.3.1 Summary of data

We will determine the percentage of eligible patients who respond and descriptively compare responders to all eligible patients consulted during the recruitment time period using age, gender, GP practice and PCN.

We will report summary statistics (overall and stratified by age and gender) including mean and standard deviation, median and interquartile range or frequencies and percentages, as appropriate. We will also weight responses by age, gender and GP surgery to assess the potential impact of non-response on our estimates.

We will use:

(1) Chi-square testing to compare the prevalence of FRAX fracture risk factors and FRAX fracture probabilities derived from self-reported risk factor data and related data from within the EHR.

(2) Cohen's Kappa scores [10] and Bland and Altman plots [11] to assess the concordance/discordance between self-reported fracture risk factors and those derived from the EHR.

(3) Regression analysis to examine associations between risk factor prevalence and response rates and other factors including, e.g. deprivation index.

9. DATA MANAGEMENT

9.3 Data collection tools and source document identification

Data will be managed in accordance with the University of Sheffield's data management policies and procedures (Research data management (RDM) | Library | The University of Sheffield. A Data Management Plan (DMP) will be written by the study team (using DMPonline Sheffield) and reviewed by the University of Sheffield.

Patient-reported data will be captured through a secure online platform, hosted by the University of Sheffield, to ensure that all regulatory requirements are met (Data Protection Act 2018, UK General Data Protection Regulation (UK GDPR), NHS Information Governance framework, and Good Clinical Practice (ICH-GCP)). Data will also be collected via paper questionnaires (on request by the participant). These data will be entered manually into the on-line platform by the study team. Docmail will be used when patients wish to complete paper-based documentation. Docmail is a standards-compliant hybrid mail service providing document management and ISO 27001 secure mailings (Hybrid Mail -

Print & Post Customer Communications | Docmail).

Eligible patients with an active mobile telephone number registered at the GP surgery will be sent a SMS text message containing a URL link/QR code to an online questionnaire. Patients who do not have an active mobile telephone number at the GP surgery will be sent, on request, an invitation pack including an invitation letter, a PIS, a paper questionnaire, and a pre-paid return envelope. All patients who have not responded will be sent a reminder message approximately 4 weeks after the initial invitation was sent. Those sent a paper questionnaire will be sent a reminder 4 weeks after the package was sent. If patients do not respond after receiving this reminder, the study team will make no further contact.

9.4 Data handling and record keeping

Data will be managed in accordance with the University of Sheffield's data management policies and procedures (Research data management (RDM) | Library | The University of Sheffield). Data will be handled in accordance with the SELF-FRAX study DMP (Section 9.1). Questionnaire data acquired from the participants will be stored on the University of Sheffield secure server and password protected. Data extracted from EHRs will be stored on the University of Sheffield secure server, password protected and linked for the purposes of analysis. All confidentiality arrangements adhere to relevant data protection regulations and guidelines including (i) Data Protection Act 2018, (ii) UK General Data Protection Regulation (UK GDPR), (iii) Caldicott Principles, (iv) General Medical Council (GMC) and Medical Research Council (MRC) UK Policy and (v) the Confidentiality NHS Code of Practice. The Chief Investigator (CI) and Study Statistician (Data Custodian) have responsibility to ensure the integrity of the data and that all confidentiality procedures are followed.

Paper-based study related documents will be stored in the secure facilities (locked filing cabinets in offices with key-code access) managed by the Academic Unit of Bone Metabolism, The University of Sheffield.

All information will be held securely and in strict confidence. Each person who consents to take part in this study will be given a study ID so that data stored from the study will contain only essential identifiable information, such as NHS number and date of birth. On this basis, these anonymised data will be kept electronically and may be used in other research studies. Files will be password protected.

9.5 Access to Data

The University of Sheffield has a longstanding commitment to sharing data from our studies to improve research reproducibility and to maximise benefits for patients, the wider public, and the health and care system. De-identified individual participant data that underlie the results from this study will be securely stored on the University of Sheffield servers and made available to bona-fide researchers upon reasonable request via our controlled access procedures. Unless there are exceptional circumstances, data will be available upon publication of the main study findings or within 18 months of study completion (whichever is later) and with no end date. We encourage collaboration with those who collected the data, to recognise and credit their contributions.

Any requests for access to the data from anyone outside of the study team (e.g. collaboration, joint publication, data sharing requests from publishers) will follow the University of Sheffield data sharing policies (Sharing research data | Library | The University of Sheffield).

9.6 Data Sharing Agreements

The data generated from this study will remain the responsibility of the Sponsor (the University of Sheffield). Release of data will be subject to a material transfer agreement (MTA) between the Sponsor and the third party requesting the data (Contracts | Research Services | Staff hub (sheffield.ac.uk)). De-identified individual participant data will be encrypted on transfer.

9.7 Archiving

At the end of the study, data will be securely archived in line with the University of Sheffield's policies and procedures for a minimum of 10 years after the end of study declaration and until the Sponsor authorises destruction. Archiving of paper-based documentation will be carried out in accordance with the University of Sheffield policies and procedures (Preserving data | Library | The University of Sheffield). Paper-based study related documents will be stored in the secure facilities (secure document archiving room) managed by the Academic Unit of Bone Metabolism, The University of Sheffield at the Metabolic Bone Centre, Northern General Hospital, Sheffield. This facility has restricted access and key-coded entry.

10. MONITORING & AUDIT

10.3 Study Management

The study CI is responsible for the conduct of the study and will convene a Study Management Committee (SMC) comprising members of the research team including Patient and Public Involvement and Engagement (PPIE) representatives. Regular meetings of the SMC will take place throughout the study.

The SMC will oversee the writing of the protocol (and study-related documents), obtaining regulatory approval and site set-up. It will be responsible for the delivery of the study, data collection and the ongoing management. The SMC will monitor recruitment procedures, review recruitment against timelines and complete regulatory reporting requirements. In addition, it will also oversee the analyses and the interpretation of the results. The SMC will ensure there is sufficient staffing support available for the study.

Our experience demonstrates that the combination of detailed plans and regular SMC meetings ensures successful delivery. Good communication across the study will be facilitated by shared study specific areas on the University of Sheffield's secure server.

Study monitoring will be carried out in accordance with the University of Sheffield's Study Monitoring and Data Management policies which lay out the procedures for monitoring data collection, protocol compliance and data management (Research data management (RDM) | Library | The University of Sheffield).

10.4 Study timeline

	Activity	Projected Timeline
□	Discussions on project logistics held with study team	January-July 2023
□	Study documentation finalised	September 2023
□	Submit to HRA/Ethics review	End September 2023
□	Approvals anticipated	December2023
□	Docmail process set-up	December 2023
□	Online application and database sign-off	January 2024
□	Site recruitment and set-up	January 2024
□	Eligibility search at first GP surgery	February 2024
□	Patients recruited	March - August 2024
□	Extracting GP data can commence	March-August 2024
□	Data cleaning process can commence	September 2024
□	Data linkage and statistical analysis	September 2024
□	End of Study	December 2024

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.3 Research Ethics Committee (REC) review

This study will be submitted for approval by an appropriate NHS Research Ethics Committee (REC). It will also be submitted for inclusion within the National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN) Portfolio.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed by NHS Research and Development (R&D) departments before they can be implemented in practice at the study sites).

All correspondence with the REC will be retained in the Sponsor Study Master File/local Investigator Site File.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

It is the responsibility of the CI to produce the annual reports as required.

The CI will notify the REC of the end of the study.

If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

11.4 Health Research Authority (HRA) approvals

Health Research Authority (HRA) UK approvals will be applied for and obtained before study commencement. HRA approval brings together the assessment of governance and legal compliance with the independent REC opinion.

11.5 Peer review

This study protocol has been subject to internal peer review and external peer review by the ROS.

11.6 Public and Patient Involvement and Engagement

The Mellanby Centre for Musculoskeletal Research has recruited a Lay Advisory Panel for Musculoskeletal Research. An outline of this project has been presented, reviewed and approved by the panel. They are pleased to support our project and feel that it is worthwhile research. The panel will be informed of our progress, be consulted on the dissemination of results and asked to review a lay summary of the outcomes of this project. The SMC comprises members of the study team and includes PPIE representatives from the ROS. Regular meetings of the SMC will take place throughout the study. PPIE representatives on the SMC have reviewed all study documentation and have been actively involved in providing advice on necessary revisions.

PPIE representatives have/will:

(1) Contribute to discussions on how to maximise inclusion and diversity in this research study
(2) Contribute to and review participant facing study documents and materials used in the study
(3) Provide the patient perspective on the design of the online fracture risk factor questionnaire
(4) Review the study recruitment figures and methods and providing advice on promoting and advertising the study to patients
(5) Contribute to study oversight
(6) Contribute to the interpretation and dissemination of the SELF-FRAX study findings

11.7 Regulatory Compliance

Data within the FRAX fracture risk factor questionnaire is to be captured through secure online forms that meet the University of Sheffield's and NHS's information governance requirements. Participant data will be acquired, anonymised, transferred and stored according to the (i) Data Protection Act 2018, (ii) UK General Data Protection Regulation (UK GDPR) (Regulation (EU) 2016/679), (iii) Confidentiality NHS Code of Practice and (iv) Caldicott Principles.

11.8 Protocol compliance

The study will be conducted in compliance with this protocol and ICH-GCP guidelines. In the unlikely event of a protocol deviation occurring, the study team will document the deviation and take appropriate corrective and preventative actions in accordance with the

University of Sheffield's policies and procedures. It will be the responsibility of the CI to report any such deviations to the University of Sheffield (Research governance: Monitoring and reporting | Research Services | Student hub (sheffield.ac.uk) via the Faculty of Health, Division of Clinical Medicine, School of Medicine & Population Health and Research Services.

11.9 Notification of Serious Breaches to ICH-GCP and/or the protocol

In the unlikely event of a serious breach occurring, its severity will be assessed by the CI (or their delegate). All serious breaches will be documented, and appropriate corrective and preventative actions will be taken by The University of Sheffield with responsibility being taken by the CI (Research governance: Monitoring and reporting | Research Services | Student hub (sheffield.ac.uk). Any serious breaches will be reported via the Faculty of Health, Division of Clinical Medicine, School of Medicine & Population Health and Research Services should they occur.

11.10 Data protection and patient confidentiality

For details of how data is protected and patient confidentiality maintained throughout this study see section 9 - Data Handling.

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper and managed electronically through the University of Sheffield (Research data management (RDM) | Library | The University of Sheffield) whilst complying with all the following data protection procedures:

(1) Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
(2) Consent from participants for access to their EHRs by responsible individuals from the study team or from regulatory authorities, where it is relevant to study participation.
(3) Consent from participants for the data collected for the study to be used to evaluate safety and develop new research.
(4) All data collection forms that are transferred to and from the University of Sheffield will be coded with a study number.
(5) All research staff involved in this study adhere to robust data security procedures and have explicit duties of confidentiality. These practices are written into their employment contracts and are equivalent to the duty placed on NHS staff.

11.11 Indemnity

The University of Sheffield has in place Clinical Trials Indemnity which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of a study. This indemnity may, and at the University's discretion, provide cover for non-negligent harm to participants.

Agreements between the sponsor (University of Sheffield) and participating NHS organisations, detailing study conduct and the responsibilities to be honoured by each party, will be fully executed before the study can start within the NHS setting.

11.12 Amendments

The need for any potential protocol amendment will be raised with the CI and will be discussed with both the SMC and Sponsor prior to being agreed. Updated versions of the protocol will not be circulated for use until the appropriate regulatory parties have approved the amendment, at which point every effort will be made to implement this updated protocol as soon as is practicably possible, superseding the previous version and documenting the date at which the new protocol was implemented.

12. DISSEMINATION OF STUDY FINDINGS

12.3 Dissemination plan

The University of Sheffield has a dedicated infrastructure, linked to strong regional, national and international health care and academic networks, which facilitate dissemination of our research findings to key policy, commissioning clinical, health education and patient stakeholders. The research team will be able to access our dedicated infrastructure to identify and promote research outputs that lend themselves to translation by health providers.

Expected main outcomes from this study include:

(1) New data, information and intelligence on inequalities and variations in MSK health outcomes, experiences and care.

(2) New insights into the feasibility, validity and persuasiveness of new MSK health indicators and data visualisations.

The key audiences for our research outputs are:

(1) Patients with MSK conditions and the wider public.

(2) Healthcare professionals, with particular emphasis on GPs and first contact practitioners.

(3) Local health policymakers, including clinical commissioners and PCN leads.

(4) External statutory bodies (e.g. NHS England, Public Health England), patient groups and charities (e.g. ROS).

(5) Anticipated study outputs:

- Written aggregate-level reports and data visualisations to participating GP surgeries and PCNs.
- Press releases, briefings, articles, and interviews for local radio and newspapers
- Written and oral presentation to local policy/planning meetings.
- Use of electronic media including a study website, institutional websites, social media including Twitter, YouTube video.
- Links with key local, national and international organisations including the Royal Osteoporosis Society, Public Health England, NICE.
- Publications including a full report, an executive summary and a plain English summary, peer-reviewed journals, and local NHS and research newsletters.
- Presentations at high-profile scientific and health policy conferences (e.g. NHS Evidence, Society for Academic Primary Care, Public Health England)

12.4 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be available to those who fulfil the International Committee of Medical Journal Editors (ICMJE) criteria. No-one who fulfils the ICMJE criteria should be excluded from authorship credit and, of equal importance, no-one who fails to fulfil the four criteria should receive authorship credit. This includes academic staff and students as well as administrative, informatics, IT and nursing staff, and patient/public representatives where they fulfil all four criteria above. However, individuals have the right to choose not to be an author on a particular paper.

Staff heavily involved in the practicalities of study operationalisation and delivery, including dedicated study co-ordinators, will be considered for co-authorship of papers on the condition they can contribute to critical revision of drafts, approve the final version, and be accountable for the content.

There is no intention to use professional writers.

13. REFERENCES

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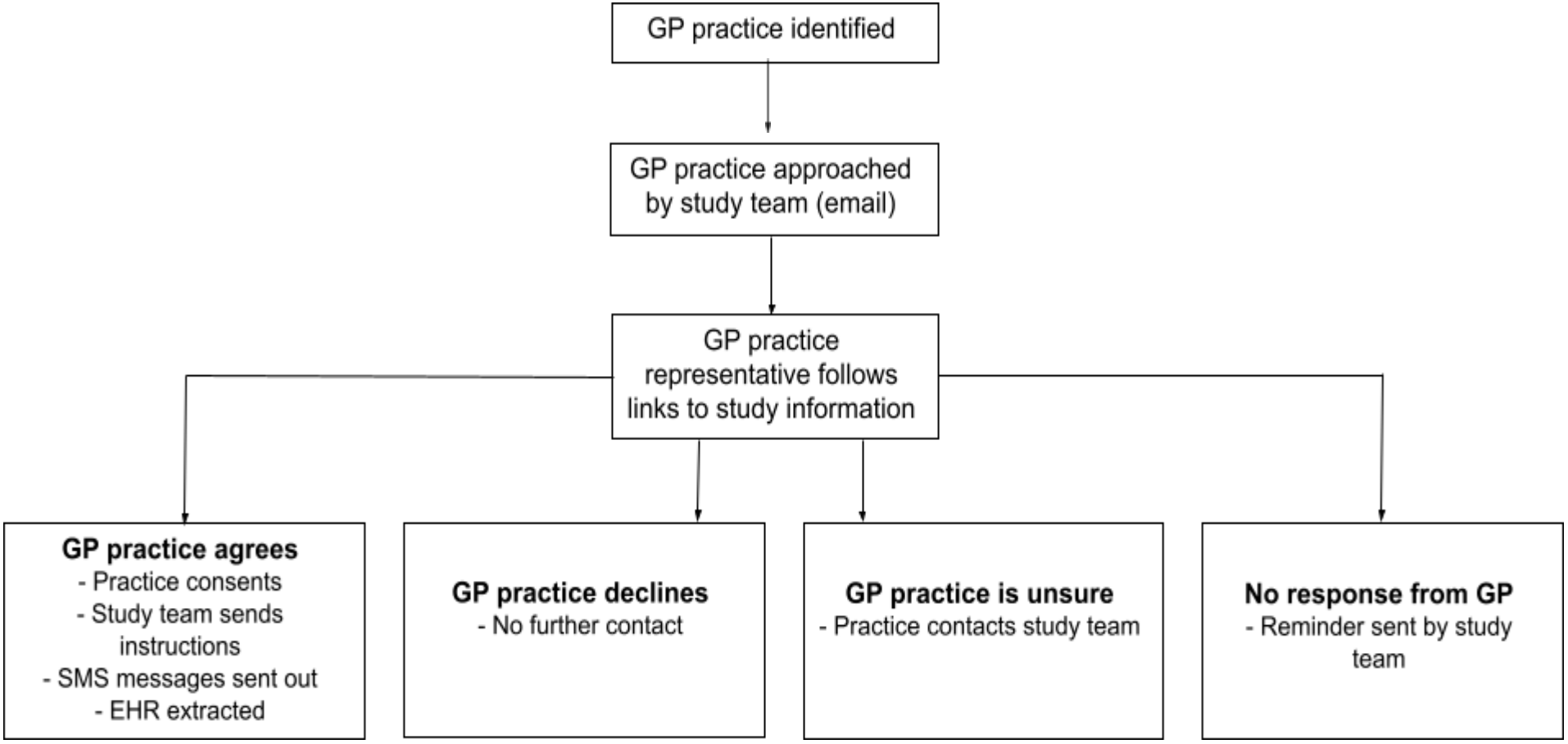
14. APPENDICES

14.3 Figure 1). Study workflow – GP practice identification, invitation and recruitment



14.4 Figure 2). Study workflow – Participant identification, invitation and recruitment