TITLE

A person-centred approach to improving uptake of Fracture Prevention drug Treatments (iFraP): a randomised controlled trial of the iFraP intervention in Fracture Liaison Services

SHORT STUDY TITLE

The iFraP Study

ACRONYM

Improving uptake of **Fra**cture **P**revention drug Treatments (**iFraP**)

PATIENT-FACING NAME

Being informed and involved: Improving appointments about your bone health

PROTOCOL VERSION NUMBER AND DATE

Version 1.1, 05-Oct-2022

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1 SIGNATURE PAGE

For Keele University sponsored studies, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required. The sponsor must be notified of all amendments to the protocol, both substantial and non-substantial. Review of amendments by the sponsor will act as the confirmation that the sponsor confirms approval of the amended protocol.

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the research in compliance with the approved protocol, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: 

Date: 22-Jul-2022

Name (please print): Dr Zoe Paskins

Sponsor statement:

Where Keele University takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.

VERSION CONTROL

Version	Issue date	Reasons for amendments; additional changes
1.0	20-Jul-2022	N/A
1.1	05-Oct-2022	Response to ethics provisional opinion

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3 LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Associate Investigator
AWS	Amazons Web Server
CDST	Computerised Decision Support Tool
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DA	Decision Aid
DCAP	Data Custodian and Academic Proposals
DCS	Decisional Conflict Scale
DST	Decision Support Tool
DXA	Dual X-ray Absorptiometry
FLS	Fracture Liaison Service
FRAX	Fracture Risk Assessment Tool
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
HROC	Health Research Oversight Committee
HSCR SOPs	Health and Social Care Quality Management System's Standard Operating Procedures
ICF	Informed Consent Form
iFraP	Improving uptake of Fracture Prevention drug Treatments
IMD	Index of Multiple Deprivation
IP	Intellectual Property
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trials
MDC	Minimum Data Collection
MRR	Medical Record Review
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NPT	Normalisation Process Theory
PAG	Patient Advisory Group
PI	Principal Investigator
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement Group
PPIQ	Patient Practitioner Interaction Questionnaire
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
ROS	Royal Osteoporosis Society
RUG	Research User Group
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TDF	Theoretical Domains Framework
TFA	Theoretical Framework of Acceptability
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VOI	Value of Information

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TRIAL SUMMARY

Trial Title	A person-centred approach to improving uptake of Fracture Prevention drug Treatments (iFraP): a randomised controlled trial of the iFraP intervention in Fracture Liaison Services with parallel process evaluation and value of information analysis
Internal Ref. Number (or short title)	The iFraP trial
Trial Design	Individual randomised controlled trial with parallel mixed methods processes evaluation and health economic evaluation
Trial Intervention	Delivery of the iFraP consultation intervention, comprising a computerised decision support tool (CDST), training package, and information resources led by Fracture Liaison Service clinicians to improve ease in decision making about osteoporosis medicines, increasing the uptake of osteoporosis drug treatments
Trial Participants	Adults aged ≥50 years referred to the Fracture Liaison Service
Planned Sample Size	N = 328 <u>Process evaluation</u> A sample of iFraP and FLS usual care consultations (approximately n=40-60 in total) will be audio/ video recorded, if both the patient and clinician consents. Semi-structured interviews with a sample of patient participants in the iFraP intervention arm (iFraP-i) (n=20); all FLS clinicians delivering the iFraP intervention (n=5-10); and GPs or primary care clinicians who have consulted with patients who have received the iFraP intervention (iFraP-i) (n=5-10)

<table>
<tr><td>Treatment duration</td><td colspan="2">Fracture Liaison Service consultation will last around 30 minutes</td></tr>
<tr><td>Follow up duration</td><td colspan="2">3 months</td></tr>
<tr><td>Planned Trial Period</td><td colspan="2">01-Sep-2022 – 30-Sept 2024</td></tr>
<tr><td rowspan="2">Primary</td><td>Objectives</td><td>Outcome Measures</td></tr>
<tr><td>Patient ease in decision making about osteoporosis medicines</td><td>Decisional conflict scale (DCS) [1]</td></tr>
<tr><td>Secondary</td><td colspan="2"><u>Patient-level secondary outcomes</u>
1. Satisfaction with information [2] and experience
2. Self-perceived fracture risk [3]
3. Worry about further falls and fractures [4]
4. Health related QOL [5]
5. Recall of consultation
6. Physical activity
7. Self-reported weight, smoking and alcohol
8. Patient-Professional Interaction Questionnaire (PPIQ) [6]
9. Modified brief illness perceptions questionnaire [7]

If medicines were discussed in the consultation:
10. Medicine perceptions (specific) [8]
11. Satisfaction with Information about Medicines Scale (SIMS) [9]
12. Osteoporosis specific values
13. Medicine adherence [10] (including self-reported initiation, persistence, discontinuation) and initiation and discontinuation from hospital medical record
14. Medicine side effects</td></tr>
</table>

4 TRIAL FLOW CHARTS

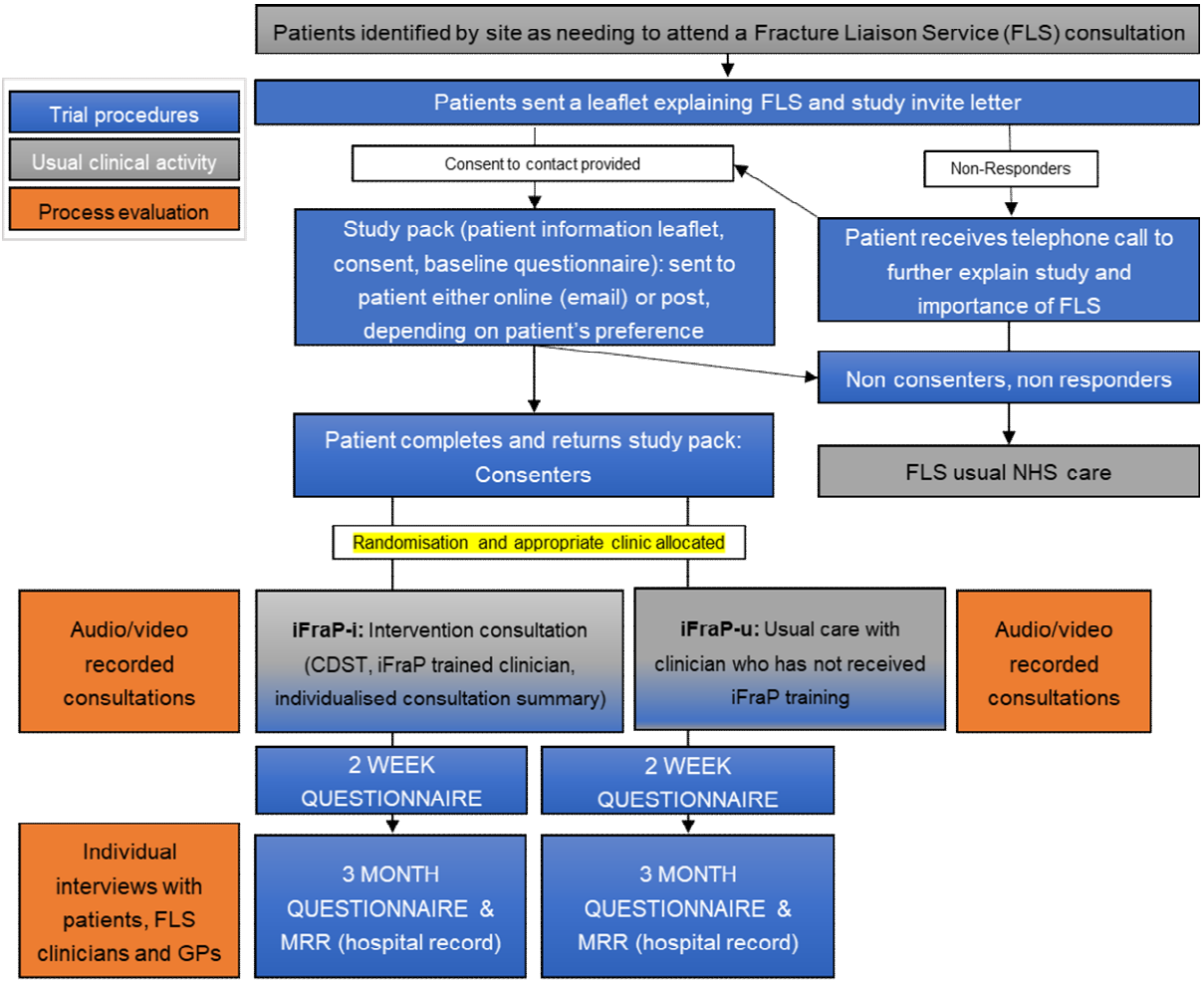

Figure 1. *Overview of trial processes*

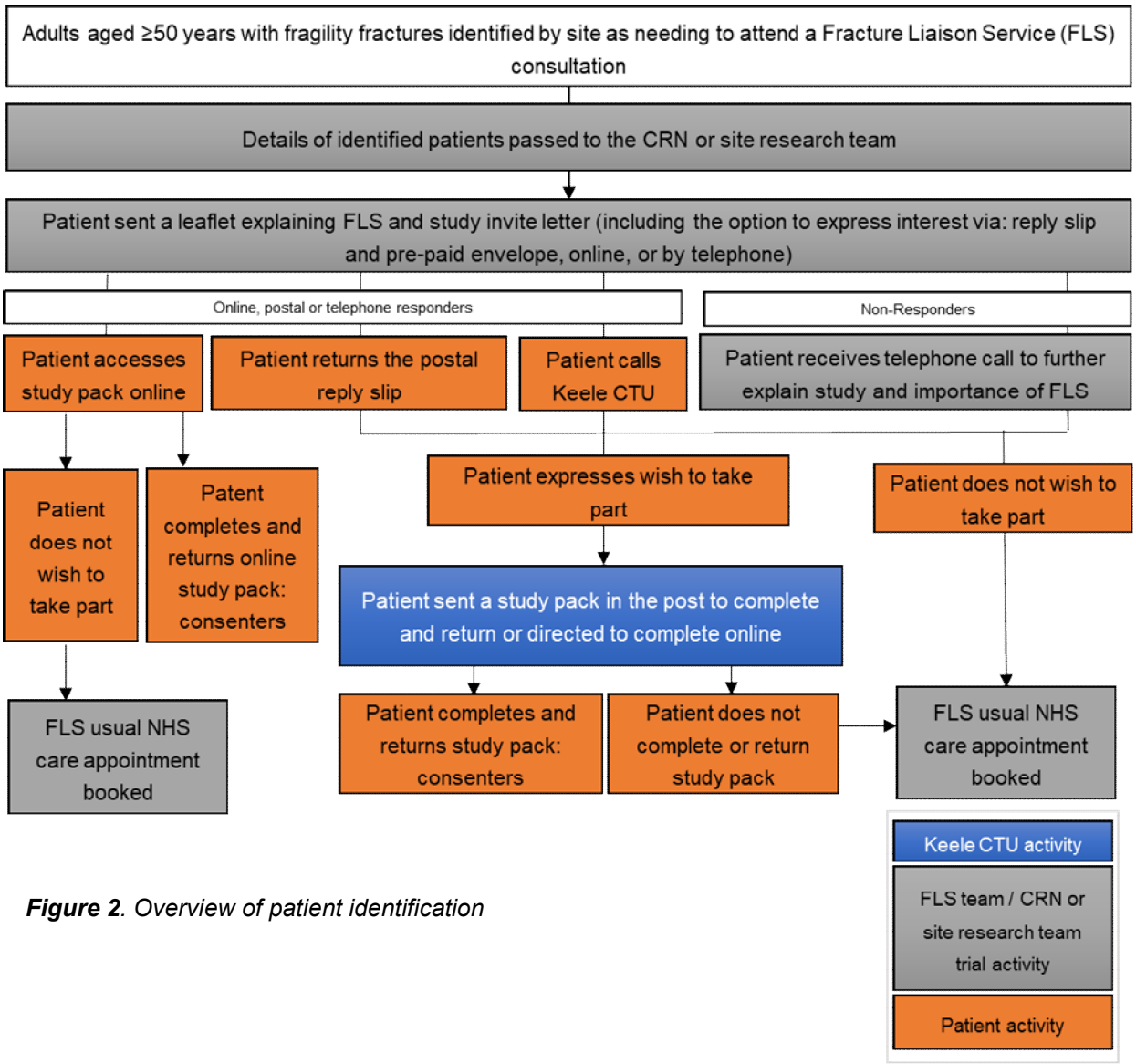

***Figure 2**. Overview of patient identification*

5 BACKGROUND

Person-centred care is a philosophy that sees patients as equal partners in care to ensure it is most appropriate for their needs.[11] To be person-centred, delivered care needs to be responsive to the patient's individual abilities, preferences, lifestyles, and goals. In recent years, person-centred care has gained importance in the UK and internationally, with the Department of Health,[12] King's Fund,[13, 14] Health Foundation [15] and Healthwatch England [16] each emphasising that high quality care means placing patients and their families at the heart of all decisions. Evidence shows that person-centred care can help to improve outcomes, such as patient satisfaction, self-management, and increased adherence to medicines.[11, 17]

A core component of person-centred care is shared decision making.[18] NICE describes shared decision making as a joint process that involves the patient and healthcare professional working together to make decisions based on evidence and on the person's individual preferences, beliefs and values, and ensures that, by sharing information, the patient understands the risks, benefits, and possible options.[19] Within the consultation, both patients and clinicians need the skills to understand relevant clinical evidence and articulate their values and preferences.[20] When successful, effective use of information within a consultation increases patient satisfaction, facilitates participation in the consultation and promotes trust.[20]

NICE's shared decision making guidelines recommend that, where available, clinicians should use decision aids (DAs) or decision support tools (DSTs) to support shared decision making.[19] DAs are designed to help people to be involved in decision making about healthcare options; supporting people to make informed, values-based decisions.[21, 22] A recent Cochrane review reported, when used across a range of conditions, DAs increased patient informed decision making and involvement by increasing patient certainty about decisions (decreased decisional conflict), increasing patient knowledge, and improving the accuracy of risk perception.[21] Evidence also suggests that shared decision making is an important mechanism to improve patient uptake of medicines.[23] Evidence from pooled analyses of studies where there was no equipoise (meaning that DAs were used to give information about recommended drug treatments, rather than to choose between treatment options with perceived equal benefits), has indicated that DAs improve treatment initiation rates.[21]

6 RATIONALE

In the UK, three million people are estimated to have osteoporosis,[24] contributing to over 500,000 fragility fractures (fractures resulting from low trauma) per year, costing an estimated £4.4 billion per annum.[25] Fragility fractures can be devastating, sometimes resulting in loss of independence and mortality.[26] Hip fractures alone account for 85,000 unplanned hospital admissions and 1.8 million bed-days in the UK per year.[27] Evidence-based treatments, such as bisphosphonates, are recommended by the National Institute for Health and Care Excellence (NICE) for patients with osteoporosis and/or a high fracture risk. They are inexpensive, cost-effective, readily available and reduce fracture risk by 20-70% (depending on fracture site).[28] Despite this, a treatment gap exists. Up to 80% of patients who experience a fragility fracture do not receive medication in the year following fracture,[29] 25% of people who are offered medication decline it (non-initiation),[30] and among those who do start bisphosphonates, few persist for long enough for it to be effective, with adherence estimated at 16-60% at one year.[31] Closing this treatment gap may prevent at least 20,000 hip fractures annually in the UK.[27]

Patient reasons for non-initiation and non-persistence of oral bisphosphonates (the mainstay of osteoporosis treatment) are complex and include: perceptions that drugs are not effective, not necessary and/or not safe; limited understanding of the consequences of non-treatment; and, concerns about perceived or experienced side effects.[32, 33] Despite national osteoporosis guidance recommending the provision of information as a core component of management,[34] patients report great dissatisfaction with the information they receive and that osteoporosis information provided in consultations is often not easily understandable[35]. The recent shift to base treatment recommendations on fracture risk rather than bone density readings,[36] is not without challenge: patients struggle to understand fracture risk assessments [37] and frequently underestimate their risk of fracture.[38] A UK population survey of 1188 people with osteoporosis and fragility fractures identified ‘improving access to information from health professionals’ as the number one patient priority for research.[39] Insufficient or inaccessible patient information that does not address health literacy needs limits patient involvement in the consultation and treatment decisions.[40–42]

Patients ultimately decide whether to start and continue taking medication, but this decision making is influenced by the clinician-patient interaction. In order to decide to start and persist with medication, patients need to believe that recommended drug treatment is necessary, relevant, safe, and practicable. Effective communication that enables patients to understand complex medical terms and concepts in lay terms and facilitates participation in the consultation may increase patients’ commitment to

medication.[43] This highlights potential role for an osteoporosis DA to promote and support effective communication between clinician and patients, and suggests that improving communication of the harms and benefits of osteoporosis medications using a DA may be beneficial in reducing the treatment gap.

Despite evidence of DA effectiveness, as described previously, existing osteoporosis DAs fail to comprehensively meet international quality standards and patient needs [44] and are not used in UK clinical practice. Furthermore, national guidelines recommend DAs are used as one part of a 'toolkit' alongside other clinician skills,[19] including evidence-based risk communication and health literacy techniques (e.g. chunk and check and Teach Back [45]). This recommendation aligns with recent evidence that multicomponent interventions to support patient involvement and shared decision making are needed to improve osteoporosis medication uptake.[23] With this in mind, our team developed a package of resources including a new theoretically-informed, computerised (C)DST and clinician training programme, in line with guidelines for developing and evaluating complex interventions.[46, 47] We hypothesised that the iFraP intervention would facilitate shared decision making, improving patient ease in decision making about osteoporosis medicines (by increasing the extent that the patient was informed and involved in the consultation), increasing informed treatment initiation and reduce treatment discontinuation (see appendix 2 – Logic Model).

7 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The overall aim is to examine the experience of care, effectiveness, within-trial cost-effectiveness, and value of information of the iFraP intervention compared with usual FLS practice.

7.1 Primary objectives

1. To determine the effect of the iFraP intervention on patient reported ease in decision making about osteoporosis medicines.
2. To determine the cost-effectiveness of iFraP intervention compared to usual Fracture Liaison Services; and the value of acquiring additional information (i.e. value of information (VoI)) on iFraP's cost-effectiveness.

7.2 Secondary objectives

1. To determine the effect of the iFraP intervention on a range of patient reported outcomes and experience measures including provision of person-centred care, satisfaction with information, and illness and treatment beliefs.
2. To determine the clinical effectiveness of the iFraP intervention on adherence including treatment initiation and discontinuation rates.
3. To determine the acceptability of iFraP for patients and clinicians, and explore the mechanisms and processes underlying observed effects.
4. To determine clinician adherence to iFraP and clinical guidelines, including the fidelity of the delivered iFraP intervention, and to explore the mechanisms and processes underlying observed effects.
5. To determine barriers and enablers to implementation of iFraP.

7.3 Outcome measures/endpoints

Quantitative data collection

1. Self-reported patient participant questionnaires will be collected:

   Pre-consultation (baseline) including demographic characteristics (e.g. socioeconomic status (Index of Multiple Deprivation; IMD); health literacy) and other self-reported outcomes, as listed in

   Table ***1***.

   2 weeks post consultation, including measures that facilitate investigation of patient-assessed decisional difficulty and patient perception of being involved and informed in the consultation, self-reported initiation, and other outcome measures, as listed in

   Table ***1***.

   3 months – including measures of self-reported adherence and other outcome measures, as listed in

   Table ***1***.

2. Electronic case report forms (CRFs) – to include clinician self-reported fidelity checklists, record of whether the consultation was face-to-face or telephone, clinician decision making outcomes and brief clinical details (e.g. bone density, glucocorticoid use)
3. Tool tracking data – aggregated data summarising CDST use, including session length, treatment recommendation selected, patient decision regarding the recommended treatment, printing and/or saving of the bone health record.

4. Medical record review – appointments/visits related to bone health and prescription (and discontinuation) of osteoporosis drug treatment will be collected from hospital medical records at 3 months.
5. Resource use data on key elements associated with iFraP (e.g. printed materials, staff time required to deliver training sessions, duration of iFraP consultations).
6. Checklist assessment of recorded consultations – fidelity and shared decision making (OPTION 5 scores [48, 49])

Qualitative data collection

See section 11.11

7.4 Primary endpoint/outcome

1. Decisional difficulty using the decisional conflict scale [1] at 2 weeks

7.5 Secondary endpoints/outcomes

Patient-level self-reported secondary outcomes

1. Perceptions of fracture risk [3] assessed at baseline and 2 weeks
2. Satisfaction with amount of verbal information [2] and experience assessed at 2 weeks
3. Satisfaction with the amount of written information [2] at 3 months
4. Generic health-related quality of life assessed using the EQ-5D-5L [5], at baseline, 2 weeks, and 3 months
5. Worry about further falls and fracture [50] assessed at 2 weeks
6. Modified brief illness perceptions [7] assessed at baseline, 2 weeks, and 3 months
7. Patient-Professional Interaction Questionnaire (PPIQ) [6] at 2 weeks
8. Self-reported weight, smoking and alcohol assessed at baseline and 3 months and self-reported change in physical activity assessed at 3 months
9. Recall of consultation content

If osteoporosis drug treatments were discussed in the consultation:

1. Osteoporosis specific values: the relative perceived importance of osteoporosis drug treatment benefits and possible side effects and adverse events at 2 weeks

2. Satisfaction with Information about Medicines Scale [9] at 2 weeks
3. Medicine perceptions (BMQ specific) [8] assessed at 2 weeks and 3 months
4. Self-reported initiation or intention to initiate (2 weeks) and self-reported adherence [10], initiation, persistence, discontinuation, and side effects with osteoporosis drug treatments (3 months)
5. Medicine initiation (prescription) and discontinuation from hospital electronic prescribing records at 3 months

Process measures

1. Self-reported clinician fidelity checklist (captured using CRF)
2. Observed fidelity checklist
3. Consultation length
4. Patient recollection of whether specific aspects were covered in the consultation at 2 weeks and receipt of written patient information at 3 months
5. Aggregate data on proportion of clinician drug recommendation in line with clinical guidelines captured via CDST analytics

Observed secondary outcome

1. Engagement in the decision-making process (observer measured OPTION 5 scale [48, 49])

8 TRIAL DESIGN

This study is an individual randomised controlled trial with parallel process evaluation and health economic evaluation.

We considered randomisation at site, clinician, and patient level [51].

An individual patient level randomised controlled trial was chosen to (a) minimise disruption of clinician turn over (b) minimise complexity of using multiple sites in a cluster design (c) minimise risk of unbalanced recruitment.

Contamination between intervention arms was previously hypothesized as a concern. However, contamination is thought to be minimal as only clinicians delivering iFraP will have access to the Clinical Decision Support Tool (CDST) and receive the iFraP clinician training programme. We will attempt to minimise contamination by excluding patients who have a friend or relative in the study, as outlined in the Patient Information Sheet and consent form. Evidence of contamination will be explored in the process evaluation, for example by comparing

the fidelity of audio/ video recorded intervention and usual care arms in the process evaluation, using a contamination checklist.

8.1 Interventions/Treatments Recommendations

Fracture Liaison Services

The intervention (iFraP-i) and comparator (iFraP-u) will both be situated in existing Fracture Liaison Services (FLSs). In both the intervention and comparator, the identification of patients will remain in line with usual care, by systematically identifying adults aged ≥ 50 years with fragility fractures. Services are usually nurse-led and address secondary fracture prevention by assessing the patient's bone health, risk of falls and future fracture and providing treatment recommendations to the patient and primary care at a consultation typically 2 months after the fracture.

Service provision varies across FLSs, with services ranging from operating a 'one-stop shop' model of care, meaning that, if appropriate, patients have a bone density scan (DXA), nurse assessment, drug treatment recommendation, and blood tests as part of one consultation. Other FLS models may not complete all components for all patients (for example, not all patients receive a DXA scan), or may split these components across multiple appointments, supported by different communication modalities (remote, face-to-face, letter).

Our baseline is taken as the FLS consultation where treatment recommendations are given.

iFraP-i: iFraP intervention

iFraP is a consultation intervention delivered by FLS clinicians to eligible adults aged ≥ 50 years systematically identified as having a fragility fracture(s), with the aim of facilitating shared decision making about osteoporosis drug treatment. We hypothesize this will increase the likelihood of informed treatment initiation and reduce treatment discontinuation.

The iFraP intervention consists of:

- A CDST to communicate individual fracture risk. This will include clinician decision-support and a patient-facing decision aid (DA). It will be dynamic, interactive, and tailored to risks and needs of the patient. It will incorporate fracture risk (calculated in external systems (e.g. FRAX)), an indicator for clinicians of whether treatment is recommended, a pictorial presentation of individualised fracture risk, fracture risk with medication (to show benefits of

treatment), and possible treatment harms. The CDST will be used by trained clinicians in a model (face-to-face or remote) consultation with patients.

- Clinician training in delivering the consultation intervention. This will encompass a prioritised list of key tasks for the clinician (both information giving and eliciting) to undertake. The training will include face-to-face sessions and an e-learning package to introduce the intervention, coach clinicians in listening skills, shared decision-making skills and universal precautions for health literacy and provide opportunities to practice using the CDST.
- Information resources (paper and online) for the patient and GP to refer to after the initial or follow-up consultation, including an individualised printout ('personal bone health record') from the CDST.

iFraP is delivered in one consultation when treatments are recommended to the patient by the FLS (and baseline for this study) which may be conducted face-to-face or remotely by video or telephone, depending on a variety of local factors including service commissioning, staffing, and the impact of COVID-19, and takes approximately 30 minutes.

The clinician enters key patient characteristics into the first part of the CDST to receive evidence-based treatment recommendations in line with clinical guidelines. Medicines and Healthcare products Regulatory Agency (MHRA) have advised that the tool is not a notifiable medical device because the tool '*presents a treatment recommendation informed by national clinical guidelines; that it is a guide only and the clinician ultimately chooses treatment using pre-defined parameters to make a treatment recommendation and is not calculating any new parameters*'.

The second part of the CDST is used by the patient and clinician together to navigate discussion about: why bone health is important; the patient's bone health; and ways to improve bone health, including lifestyle and drug treatment recommendations. Together, the patient and clinician will complete the iFraP CDST personal bone health record which will form an information sheet provided to the patient and their GP.

The clinician will also have the opportunity to provide the patient with other information resources, including a dentist card that the patient can show their dentist to support conversations around bisphosphonate treatment and online videos which explain the Bone Health Record in more detail.

iFraP has been developed in line with guidance on development and evaluation of complex interventions.[52] Extensive intervention development work included [52]: a Delphi e-survey underpinned by an evidence synthesis of clinical guidelines and a

review of patient information sources [53, 54]; qualitative data collection with patients recently attending FLS, FLS clinicians and GPs; a usual care survey of FLSs; and in-practice testing of prototype iFraP consultations at one FLS site. Throughout the development programme of work, we had extensive involvement from relevant stakeholders and our dedicated osteoporosis Research User Group.[52]

iFraP-u: Comparator Usual FLS NHS care

In usual FLS care, patients will be invited to attend an FLS appointment conducted face-to-face or remotely by video or telephone, depending on a variety of local factors including service commissioning, staffing and the impact of COVID-19, including any ongoing social distancing measures. At present, usual FLS care does not use CDSTs to support patient-clinician discussion, nor do FLS clinicians have access to the clinician skills training or information resources that would be provided as part of the iFraP intervention. FLS clinicians delivering iFraP-u will be offered the opportunity to partake in the training at the end of the trial.

8.2 iFraP Intervention Training

The iFraP training package for FLS clinicians will cover communication skills such as health literacy techniques and strategies to support informed decision-making, communication about osteoporosis and of risk and benefit in personalised discussions about osteoporosis drug treatments, and guides on how to use the CDST in the context of a model FLS consultation.

Training will be provided by experts in osteoporosis, clinician communication skills and shared decision making. A comprehensive, interactive e-learning course including expert video presentations and example videos of ‘model’ consultations will be supplemented by facilitated remote or face-to-face group training sessions. Group training sessions offer supported discussion and feedback regarding role play in simulated consultations. FLS clinicians will be given the opportunity to use the CDST in-practice. To decrease the risk of contamination by the sharing of information regarding the intervention between clinicians, we will emphasize to participating clinicians the importance of not sharing information about the intervention with their colleagues during the study.

FLS clinicians and other team members (e.g. FLS administrators) will also be provided with study-specific training including training on completion of study documentation, good clinical practice as applicable to research and the maintenance of the study site file and study records. Reporting of serious adverse events and adverse events will also be covered.

9 STUDY SETTING

The iFraP study will be delivered from participating FLSs across England, with support of the National Institute for Health and Care Research (NIHR) Clinical Research Networks (CRN).

10 ELIGIBILITY CRITERIA

Fracture Liaison Services

- FLSs which decide, recommend, and communicate osteoporosis drug recommendations to patients in face-to-face and/or remote consultations.
- FLSs in England, with minimum of 2 clinicians.

Individual patient participants

The eligibility criteria for individuals to take part in the iFraP study reflects the eligibility criteria for FLS.

10.1 Inclusion criteria

1) Adult patients aged ≥50 years eligible for FLS consultation based on having a previous fragility fracture(s)
2) Adult patients able to participate in an FLS appointment (face-to-face or remote consultation) with a participating NHS hospital or associated FLS

10.2 Exclusion criteria

1) Patients who are unable to give full informed consent or unable to comply with study procedures
2) Patients with a friend or relative in the study (identified through self-report)

11 TRIAL PROCEDURES

11.1 Identification, recruitment, and consent of FLSs and clinicians

The research team will work with the ROS, existing clinical networks and the NIHR CRN to identify eligible FLSs for the iFraP study as outlined in section 6.

The study team will meet with identified FLSs (face-to-face or remotely) to fully explain the study and describe the study requirements. Informed consent for FLSs to participate will be provided by the research lead/authorised person in each service, acting as ‘guardian’ for patients in their care, following agreement with the team clarifying willingness to undertake the iFraP intervention. FLS consent to participate in the iFraP study will be formalised through a Sponsor-site agreement. The number of FLSs approached, declining, or considered not eligible will be recorded.

11.2 Patient identification (Figure 2)

As part of FLS usual care, adults aged ≥50 years with fragility fractures are systematically identified (primary inclusion criteria). Details of identified patients that require a face-to-face or remote consultation will be passed to the NHS site staff who will post the initial mail-out including a flyer explaining that the patient needs a bone health check in FLS as part of usual NHS care (developed as part of iFraP or service own flyer) and a letter introducing the study.

Participating NHS site will send an Excel file to the study team on a regular basis (approximately weekly), via secure transfer. Sites will also have the option to upload this file directly onto the study REDCap database. This file will contain the Organisational Code, NHS number, age, sex and date of invite for each patient sent an invitation to take part in the study. Age, sex will be collected to compare the characteristics of non-responders with responders. NHS numbers are collected as an identifier in order that the NHS site staff know which patients have not responded, to call about their FLS appointment (see Figure 2).

This file will be imported into the secure Amazons Web Server (AWS), within the REDCap database, by an authorised study administrator/ site staff member. When reply slips are received into the CTU (online or paper) or entered directly onto the database by an authorised CTU administrator or NHS site staff, the information from the patient's consent to take part in the study will be matched to the information from the import file, this will also ensure that the correct patient is taking part in the study.

Patients interested in hearing more about the study can either access a website, phone, or post back a reply slip to Keele CTU giving consent to contact for more information. Patients that enter further details into the website consent form or give verbal (via phone) or postal consent to contact will be entered onto the Keele study database and allocated a unique participant study ID. Patients who do not respond to the initial mail-out within a defined time window will be telephoned by NHS site staff to explain the purpose of the FLS, explain and gauge interest in the study, and encourage those who do not wish to participate in the study to continue to engage with their usual NHS care FLS appointment. In line with the definition outlined in Article 4(11) of the GDPR guidance, Keele CTU will only have “any freely given, specific, informed and unambiguous indication of the data subject’s wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her” (European Union, 2016). If the identified patient does not respond within the agreed time window or declines participation (by contacting the NHS site staff or Keele CTU admin, or verbally declining consent to contact when called by the NHS site staff), this will be

communicated to site allowing a FLS appointment to be booked as per usual NHS care.

At a mid-point in patient recruitment, the Data Monitoring Committee (DMC) will examine the characteristics of the patients recruited to the trial to determine if the sample is representative of the general population. This insight will allow the NHS site staff to adapt their approach to the introduction telephone calls to focus on underserved groups, who may not be adequately represented.

Patients that provide consent to contact will be asked their preferences for receiving study documents (by post or online/email). If the patient prefers the study pack to be emailed, they will be asked to provide their email address and a link will be sent that provides access to the study pack on a secure database. The study pack will include the PIS, baseline questionnaire, consent form, and prepaid return envelope (if posted). The study pack will also include contact details (or opportunity to request contact details) for the Keele CTU to discuss consent or provide support with data collection. If, when returned by post, or direct to the clinical team, the reply slip, baseline questionnaire, and/or consent form contains missing, ambiguous, or illegible data, the patient may be contacted by Keele CTU admin by telephone, email or post. No more than 3 attempts will be made to contact the participant.

If the patient does not return the study recruitment pack within an agreed time window or declines participation (by informing the NHS site staff or Keele CTU admin), this will be communicated to site and a FLS appointment will be booked, as per usual NHS care. Non-responders who attend face-to-face appointments and subsequently express a wish to participate will only be able to do so if completion of baseline data collection, randomisation and allocation is possible on the day of attendance.

Non-identifiable sample demographic data of those invited (including age and sex) will be provided to the research team by the FLS clinical team. NHS number on its own is not identifiable, as described by NHS Digital,[55] although when joined with other NHS data could be linked to an individual. The research team at Keele has no access or permissions to NHS systems to make the number identifiable. In this instance, the NHS number is being used for administrative processing only and does not provide any identifiable information to the research team. The NHS numbers of those that do not respond to the study invitation will be deleted.

11.3 Consent

FLS clinician consent

FLS clinician agreement to take part in the trial will be captured as part of the written agreement completed by the research lead/authorised person in each service, as described in section 11.1. Consent will be sought from individual FLS clinicians for optional data collection for the process evaluation. Optional consent is provided by return of the consent form included within the study pack prior to patient recruitment commencing (sent by post or email, depending on FLS clinician preference). Consent is requested for:

- Audio/video recording of consultations (for FLS clinicians in both trial arms)
- Semi-structured interviews (for FLS clinicians delivering the iFraP intervention only)

If the FLS clinician does not to provide consent to the above optional data collection, this will not affect their participation in the trial.

Patient consent

Patient consent to participate in the iFraP trial is provided by return of the consent form included within the study pack (sent by post or email, depending on patient preference). Consent is requested for;

- Taking part in the iFraP study (read and understood the iFraP PIS, voluntary participation, completion of baseline and follow up questionnaires).
- Access to electronic medical records.

Consent (optional) is also requested for

- Audio/video recording of their FLS consultation
- Contact about future related research studies, including nested process evaluation (e.g. participation in a semi-structured interview) and methodology development.

The remote consent process is proportionate for this research that will be supporting the implementation of existing NICE guidance. This means that, in accordance with HRA guidance, the intervention involves 'relatively low risks and levels of burden which are no higher than that of usual medical care' and therefore the methods used for seeking consent 'can be adapted in a proportionate manner so that they comply with the law but do not unduly burden either the patient or the care professional/researcher seeking consent.' [56] Remote consent is also appropriate as patients may be identified virtually and have their consultation by telephone, rendering face-to-face written consent inappropriate. As consent is taken remotely,

the clinician will affirm consent at the start of their appointment, and ensure the patient has capacity and remains eligible.

In order not to deter potential participants with visual impairment, low literacy, or other barriers to communication from participating, participants will be offered the option to discuss the PIS and have data collection via phone or with support of a carer. The study pack will include contact details (or opportunity to request contact details) for the Keele CTU to discuss consent or provide support with data collection, including the opportunity to access translation services.

Upon receipt of patient consent, a letter will be sent to the patient's GPs informing them that the patient is taking part in the iFraP trial and the possibility that the GP or other primary care clinicians would be invited for interview.

11.4 The randomisation scheme

Following informed consent and baseline data collection, the randomisation CRF will be completed, and participants will be randomised in a 1:1 ratio, using blocked randomisation stratified by FLS to iFraP-i or iFraP-u. Randomisation will be conducted by an authorised administrator (at site or CTU, depending on service preference) via REDCap. This is a secure web-based data collection system that uses a randomisation module; the randomisation sequence will be computer-generated. Emergency telephone backup will also be available.

The following information will be required for randomisation:

- Participant details, including initials, sex, date of birth, and FLS site
- Participant study ID number (as found on the completed Consent Form)
- Name of person undertaking randomisation
- Confirmation Baseline Questionnaire completed and checked for completeness
- Confirmation of eligibility
- Confirmation of returned informed consent and date

On completion of the web-based randomisation service, the authorised staff member will be notified of the participant's treatment allocation. The site will then book the appropriate clinic appointment. Concealment of the allocation process is ensured through the remote computer-generation of the randomisation sequence and web-based interface including entry of participant details prior to a unique participant identification number being generated and disclosure of treatment allocation.

11.5 Blinding

Participants and clinicians will not be blind to allocation to iFraP or usual care. However, any member of the research study team undertaking minimum data collection (MDC) will remain blind to treatment allocation. The statistician will also be blind to arm allocation. The qualitative researcher will not be blinded to trial arm allocation.

11.6 Baseline data

The baseline questionnaire will collect information on participant characteristics (for example, date of birth, sex, fracture site, fracture risk factors, experience of osteoporosis treatment, ethnicity, health literacy, digital access, socioeconomic status), self-perceived fracture risk and medicines, and worry about falls and fractures.

Table 1 (below) summarises all outcome measures and their respective time points of data collection.

11.7 Follow up assessments

To collect outcome data, participants will be sent a postal or online questionnaire (depending on participant preference) at 2 weeks and 3 months after the FLS consultation (baseline). If posted, participants will be asked to return the questionnaire to Keele CTU in a pre-paid addressed envelope that will be provided. The 2-week questionnaire will include the primary outcome along with a range of secondary outcome measures. The 3-month questionnaire will include selection of secondary outcome measures. Outcome measures at baseline, 2 weeks and 3 months are detailed in

Table *1*.

Standard Keele CTU procedures will be followed to maximise follow up. Non-responders to 2-week questionnaires will receive a reminder by post or email, as per participant's preference, after approximately 10 days. Non-responders to the reminder will be telephoned (by a blinded trial administrator) after approximately 10 days for MDC. A brief questionnaire for MDC will be sent by post or email to those who cannot be contacted after 3 telephone attempts, as per participant's preference. Non-responders to 3-month questionnaires will receive a reminder by post or email, as per participant's preference, after approximately 10 days. Non-responders to the reminder will be telephoned (by a blinded trial administrator) after a further approximately 10 days for MDC. A brief questionnaire for MDC will be sent by post or email to those who cannot be contacted after 3 telephone attempts, as per participant's preference. The MDC questionnaires are a shorter version of the outcome questionnaire and will be used to collect the primary outcome (if

appropriate), EQ5D and self-reported medicine use, along with date of birth and sex to ensure the data are provided by the intended participant.

Respondents who return the 2-week and 3-month questionnaires, however, do not complete or provide ambiguous/illegible responses to the MDC set may be contacted by telephone, email or post (by a blinded trial administrator). No more than 3 attempts will be made to contact the participant.

11.8 Trial assessments

Patient self-reported questionnaires will contain the outcomes listed below and shown in Table 1.

Table 1: Patient participant questionnaire content

Trial assessments	**Baseline**	**2-week**	**3-month**
Demographics (date of birth, sex at birth)	✓	✓*	✓*
Employment status	✓		
Marital status	✓		
Fracture occurrence including site and date	✓		✓
Fracture risk factors: • self-reported height • rheumatoid arthritis • family history • secondary causes see FRAX https://www.sheffield.ac.uk/FRAX/)	✓ ✓ ✓ ✓		
Ethnicity	✓		
Health literacy [57]	✓		
Barriers to communication (hearing, vision) and first language	✓		
Digital access	✓		
Experience of osteoporosis medicine	✓		

Socioeconomic status (IMD)	✓		
Beliefs about medicines (BMQ-general) [8]	✓		
Primary outcome			
Decisional conflict [1]		✓	

Trial assessments **Secondary outcome measures for all**	**Baseline**	**2-week**	**3-month**
Patient-Professional Interaction Questionnaire (PPIQ) [6]		✓	
Satisfaction with verbal information [2] and experience		✓	
Recall of, and satisfaction with written information [2]			✓
Recall of consultation – including key elements included in the training, being shown the computer, receiving diagnosis, receiving drug recommendation		✓	
Modified Brief Illness Perceptions Questionnaire [7]	✓	✓	✓
Self-reported change in physical activity			✓
Worry about further falls and fractures [50]	✓	✓	
Self-perceived fracture risk [3]	✓	✓	
Self-reported weight	✓		✓
Alcohol	✓		✓
Smoking	✓		✓
Secondary outcomes: Recommended medication only			
Beliefs about medicines (BMQ-specific) [8]			✓
Satisfaction with medicines information (SIMS) [9]		✓	
Osteoporosis specific values		✓	
Self-reported medicine initiation or intention to initiate		✓	✓

Self-reported adherence [10] and, persistence or discontinuation with medicine			✓
Medicine self-reported side effects	✓		✓
Health Economic Outcomes			
Health status - EQ5D-5L [5]	✓	✓	✓
Health care utilisation	✓		✓

*date of birth and sex at birth collected to verify identify at 2 weeks and 3 months

Patient centred care will be assessed using the Patient-Professional Interaction Questionnaire (PPIQ).[6] The scale includes 16 statements covering 4 subscales: effective communication; interest in the patient's agenda; empathy; and patient involvement in care. Patient responses to each statement range on a 5-point scale from 1 "not at all" to 5 "very much" to determine a global score ranging from 16 – 80, with higher scores indicating higher perceptions of person-centred care. The PPIQ has been validated in a sample of 1139 patients reflecting on care received from a variety of healthcare professionals, including nurses.[6] We will make slight changes to i) improve readability ii) ensure relevance for non-face-to-face consultations iii) remove the need for binary (he/she) gender pronouns.

Worry about further falls and fractures will each be measured using an adapted single item measure [50] asking patients to rate their 'worry over further falls in the next two months' and 'worry over future fractures in the next two months' using a 6-response scale from 'not at all worried' to 'very worried' at baseline and 2 weeks.

Beliefs about Medicines questionnaire (BMQ) [8] is linked to the Necessity-Concerns Framework (NCF); a theoretical framework that underpinned the iFraP intervention development to explain how medication beliefs might influence patients' decisions about using prescribed medication.[58] The BMQ includes two domains, the BMQ-general (to assess views about medicines in general) and BMQ-specific (views about a specific prescribed medicine). At baseline, the BMQ-general subscale will be administered, consisting of 8-items across two subscales (general-harm and general-overuse) rated using 5 response categories from strongly agree to strongly disagree). The BMQ has been validated for use in patients with chronic illnesses [59] and has been shown to predict adherence to treatment.[60]

Patient satisfaction will include two concepts: satisfaction with consultation experience and satisfaction with information.

Patient satisfaction with the consultation will be assessed with a single-item statement: "Overall, I had a good experience of care from the Fracture Liaison Service" using 6 response categories from "strongly agree" to "strongly disagree" at 2 weeks.

Patient satisfaction with verbal and written information will be measured using an adapted version of the Satisfaction with Cancer Information Profile [2] which was derived from the Satisfaction with Information about Medicines (SIMS) questionnaire, with the intention of understanding satisfaction about information given about conditions (rather than medicine).[9] This study will uses items adapted from the 7-item form and timing of information subscale including 5 response categories from 'very satisfied' to 'very dissatisfied'. Satisfaction with verbal information will be

assessed at 2 weeks, with satisfaction with written information assessed at 3 months to allow sufficient time for the patient to receive the bone health record.

Perceptions of fracture risk [3] will assessed at baseline and 2 weeks by asking patients to rate their perceived risk of fracture compared with a person of the same age using a five-point scale ranging from “much lower” to “much higher”. This measure has been previously used in an international, observational cohort study of osteoporosis.[61]

Illness perceptions will be assessed at baseline, 2 weeks and 3 months using a modified version of the Brief Illness Perception Questionnaire (B-IPQ).[7] This measure includes 9 items to cover relevant domains in the B-IPQ and revised-IPR (R-IPQ) (timeline; consequences; personal control; treatment control; emotional representations; understanding; illness coherence; concern; and causal/identity) on a scale of 0 to 10. Items have been modified with PPIE members to focus on ‘broken bones’ and ‘bone health’ rather than ‘illness’.

Self-reported change in physical activity will be measured at 3 months using a single bespoke statement: “Since your Fracture Liaison Service appointment, have you increased the amount of physical activity or exercise you do?” (yes/no/unsure). If the participant responds yes, they will be asked to tick the motivation for the behaviour change.

EQ-5D-5L is a generic measure of health-related quality of life that provides a single index value for health status.[5] Patients will rate their degree of impairment in five health domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on a 5-point scale. Participants will also be asked to rate, using a visual analogue scale from 0 (the worst health you can imagine) to 100 ‘how good or bad your health is TODAY’ (the worst health you can imagine). The EQ-5D-5L will be administered at baseline, 2 weeks, and 3 months.

Recollection of whether specific aspects were covered, including key elements of the training in the FLS consultation, will be examined by asking patients at 2 weeks what aspects of the consultation they could recall with response options including ‘Not at all’ to ‘very much’ or ‘yes’, ‘no’ or ‘unsure’. In addition, participants will be asked if they received a diagnosis of osteoporosis or a drug treatment recommendation. At 3 months, recall about the receipt of written information (and whether this was personalised) will also be examined.

Healthcare resource use questionnaire, developed for iFraP, will collect relevant patient reported healthcare resource use data at baseline and 3 months, including details of osteoporosis drug treatment (e.g. bisphosphonates) use, relevant prescribed supplement use, and healthcare professional contact post-consultation.

If medicines were discussed in the consultation:

Decisional Conflict Scale (DCS) measures personal perceptions of: (a) uncertainty in choosing options; (b) modifiable factors contributing to uncertainty such as feeling uninformed, unclear about personal values and unsupported in decision making; and (c) effective decision making such as feeling the choice is informed, values-based, likely to be implemented and expressing satisfaction with the choice.[1] Decisional conflict will be evaluated at 2 weeks, including 16 statements and 5 response categories: “strongly agree”, “agree”, “neither agree nor disagree”, “disagree” and “strongly disagree”. The DCS is recognised as the most commonly used outcome measure in decision aid trials.[62]

Satisfaction with Information about Medicines Scale (SIMS) aims to assess patients’ satisfaction with the amount of medication information provided during their consultation with a clinician.[9] Patient satisfaction with medicine information will be evaluated at 2 weeks using 17-items and 5 response categories: “too much”, “about right”, “too little” “non received”, and “none needed”. The SIMS has been widely validated in patients with a variety of diagnostic categories in inpatient and outpatient settings.[9]

Beliefs about Medicines (BMQ) comprises two domains, the BMQ-general (to assess views about medicines in general) and BMQ-specific (views about a specific prescribed medicine). At 3 months, the BMQ-specific will be administered by asking patients for their views about medicines prescribed for their bone health. The BMQ-specific includes 11-items to assess positive and negative beliefs about specific prescribed medication and provides a numerical assessment of the way in which perceived benefit (necessity) is rated against perceived risk (concerns). All items are scored using 5 response categories from “strongly disagree” to “strongly agree”. The BMQ has been validated for use in patients with chronic illnesses [59] and has been shown to predict adherence to treatment.[60]

Specific osteoporosis values will be assessed using a bespoke questionnaire (also included at the end of the CDST, completed with the clinician) about the relative perceived importance of osteoporosis drug treatments benefits (“how important are these treatment benefits to you… maintaining independence”) and possible side effects and adverse events (“How likely is it, that you would be put off taking this treatment, because of concerns about… common side-effects with medicines such as indigestion and reflux”) using 5-response categories, from “not at all” to “extremely".

Self-reported medicine initiation or intention to initiate: Patients will self-report if they have started to take or intend to start taking the recommended medication at 2 weeks and 3 months.

Self-reported adherence, including initiation and persistence or discontinuation will be assessed at 3 months by asking patients if they have been using the recommended medication since their Fracture Liaison Service appointment and if they are still using the medicine, including the opportunity to record the date they decided to stop using the medicine, giving insight into medicine discontinuation. Patients will also be asked to complete the Medication Adherence Report Scale (MARS) [10] consisting of 5 statements about different ways in which the patients might take their medication ('I forget to take my medicines') scored on a 5-point Likert-type scale (1=never to 5=always). The questionnaire has been validated,[63] with statements introduced in a non-threatening manner to minimise social pressure to under-report nonadherence.

Side effects will be assessed at baseline and 3 months by asking patients if they have experienced any of a list of symptoms in the past 3 months and whether they think that the symptoms can be attributed to their osteoporosis/osteoporosis drug treatment/neither or don't know.

11.9 Case Report Forms

Case report forms (CRFs) will be completed electronically using REDCap.

11.10 Medical record review

Medication adherence including initiation and persistence (discontinuation):

- Hospital medical record review of appointments/visits related to bone health and prescription data completed at 3 months to identify the number of participants prescribed osteoporosis drug treatment in the 3-month time-period after FLS consult
    - Number initiated (prescribed osteoporosis drug treatment since FLS date yes/no)
    - Number discontinued (last date of prescription ≥ 6 weeks prior to MRR = yes), expressed as % of those initiated

11.11 Nested studies

Process Evaluation

A mixed methods process evaluation, in line with the Medical Research Council (MRC) guidance [64] to address what components of iFraP were delivered and how (fidelity), whether iFraP results in a change in osteoporosis drug treatment initiation rates and how, and how context affects implementation of iFraP and outcomes

(secondary objectives 2, 3, 4, and 5). Below, the data collected to inform the process evaluation will be discussed in turn, with information provided about identification and recruitment, if appropriate.

(1) iFraP template: CRFs will be used in all iFraP intervention consultations and will capture intervention fidelity (was the intervention delivered as intended) and dose (how much was delivered).

(2) iFraP consultation recordings: FLS clinicians taking part in either trial arm (iFraP-i or iFraP-u) will have the opportunity to provide optional consent to audio/video recording of consultations as part of additional trial data collection. FLS clinicians that provide optional consent will audio/video record all FLS consultations with consenting patients in a specified time window.

Patient consent to the trial will include optional recording of the consultation using audio/ video recording equipment. FLS clinicians will affirm consent prior to the start of the consultation. If patients agree to this, consultations will be audio/ video recorded using a digital audio/ video recorder, which will be switched on by the FLS clinician or researcher prior to the start of the consultation (approximately n=40-60). For remote consultations, the FLS clinician will use the speaker function of their phone and ensure the recorder is placed close to the speaker to pick up conversations. This was successful in the iFraP in-practice testing development study. Following the consultation, the FLS clinician will securely upload the recording to Keele CTU for analysis.

Recordings of iFraP intervention consultations allows fidelity of intervention delivery to be assessed (for example, was the content of the training evident in FLS clinician behaviour, were there gaps in implementation of the intervention?) using a pre-defined fidelity checklist. Recording of FLS usual care consultations will examine how risk was discussed and extent of any contamination, using a contamination checklist. In addition, shared decision making (as measured using the OPTION 5 scale) will be evaluated in both arms.[48, 49]

(3) CDST event tracking data: Aggregate data summarising clinician use of the CDST (e.g. length of session, clinician adherence to treatment recommendations, patient decision to take medicines, printing/saving of the bone health record) in intervention consultations will capture intervention fidelity and dose.

(4) Semi-structured interviews with all FLS clinicians delivering the iFraP intervention (n=5-10); a sample of patient participants in the iFraP intervention arm (n=20); and GPs or primary care clinicians (n=5-10) who consult with a patient following an iFraP intervention consultation. The identification and recruitment processes of interview

participants are detailed below for each participant group in turn and presented as flowcharts in Appendix 3.

FLS clinicians delivering the iFraP intervention (iFraP-i), who have provided optional consent to take part in an interview, will be invited to take part. Consent procedures for all interview participants are described below. FLS clinicians will be contacted by a researcher to schedule a mutually convenient appointment. The interviews may be conducted face-to-face, by telephone or video software. Face-to-face interviews will be arranged at a location convenient for the interviewee, likely to be their FLS site. An interview confirmation letter will be sent to the clinician specifying the date, time, and location (or telephone number) of the interview. FLS sites will be recompensated for lost time.

Patients receiving the iFraP intervention (iFraP-i) will be invited for interview. A sample of patients will be identified from responders to the 2 week follow up questionnaire who indicated consent to contact about interview in their initial consent, meaning that all patient interviews will take place after the 2-week questionnaires have been completed and returned to Keele CTU. A purposive sample of patients will be derived according to age, sex, FLS site, and decision to take medicine (yes/no/unsure). Patient participants identified as consenting to be contacted for interview can be contacted by email or telephone. Consent procedures for all interview participants are described below. The researcher and patient will arrange a mutually convenient time and location for this. Face-to-face interviews are likely to take place in the participants' own home. When interviews take place in a person's home, they will be conducted in accordance with Keele University's lone working guidelines. The qualitative researcher(s) and a nominated contact will follow standard procedures regarding contact before and after the interview. An interview confirmation letter will be sent specifying the date, time, and location (or telephone number). All patient participants who are interviewed will be offered a £20 voucher to thank them for their time. Once the target sample size of 15-20 participants has been reached, all subsequent participants who expressed interest in taking part when contacted by the researcher will be sent a letter thanking them for their interest and informing them that we will not be inviting them to take part on this occasion.

GPs and other primary care clinicians will be invited to take part in an interview, identified from patient questionnaires who received the iFraP intervention or from any primary care clinician contacting the study team directly, where patients have indicated they have visited their general practice post-consultation. GPs will be aware about the possibility of being contacted for interview in the letter sent to notify them of their patient participation in the trial. GPs or other primary care clinician that consult with participating patients about their FLS appointment since attending their iFraP FLS appointment (as identified by patient self-report) will be contacted by the

research team. Details regarding consent procedures outlined below. The interviews may be conducted face-to-face, or by telephone or video conferencing software. Face-to-face interviews will be arranged at a location convenient for the interviewee, likely to be their GP practice. An interview confirmation letter will be sent, specifying the date, time, and location (or telephone number) of the interview. Primary care participants will be offered remuneration for their time.

All participants will be given opportunity to read the PIS and provide informed consent prior to participating in an interview. Interviews may be conducted face-to-face, by telephone or video software. Interviewees will provide informed consent in one of three ways before the interview commences: face-to-face, online, or by post. If the interview is conducted face-to-face, informed consent will be completed in-person prior to interview. For interviews completed remotely, the participant will receive the study pack, including PIS, and asked to complete and return an online or postal consent form, depending on their preference. Following receipt of a completed consent form, the researcher will arrange a mutually convenient time for the interview. If consent is completed remotely, the researcher will read through the consent form with the participant over the phone / by video before commencing with the interview to affirm informed consent.

Topic guides will include questions informed by theory on behaviour change (TDF), acceptability of interventions (TFA), and on social processes and work required to implement iFraP (NPT). Topic guides will be iteratively updated to include insights not anticipated. Interview recordings will be transcribed verbatim and analysed using a framework approach.[65, 66] Following data familiarisation, a thematic framework will be developed, considering the functions of implementation, mechanisms of action, and context,[67] supplemented with TDF,[68] TFA [69] and NPT constructs to facilitate data interpretation.[70]

Triangulation protocol

A Triangulation Protocol will be used to integrate the quantitative and qualitative findings[71] to generate novel insights about the intervention under evaluation.[72] Key finding statements will be developed from each dataset and compared side-by-side using a convergence coding matrix.[73] Multiple independent analysts, stakeholders, and PPIE members will facilitate interpretation of the convergence coding matrix, thereby enhancing rigour and credibility.[74]

11.12 Withdrawal criteria

In line with usual clinical care, cessation, or alteration of the intervention at any time will be at the discretion of the treating clinician or the participants themselves. All participants withdrawn from trial intervention, will still receive follow-up questionnaires, in accordance with the trial schedule, unless unwilling to do so, and CRFs and questionnaires will continue to be completed and returned to Keele CTU.

Participants are free to withdraw from the study at any time. Keele CTU will make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the study are defined and documented using the Withdrawal CRF in order that the correct processes are followed following the withdrawal of consent.

Participants will remain free to withdraw from the process evaluation study at any time without giving reasons. Participants will be informed if they withdraw 2 weeks after the date of their interview(s) it will not be possible to delete their anonymous comments as we will have already begun to use the information, in line with their consent. Keele University's Standard Operating procedures for Health and Social Care Research will be used for all phases of research.

11.13 End of trial

The end of the study is defined as the point at which data collection is complete and the study database is locked. All CRFs, audio/ video files and transcripts will have been received by the data management team at Keele CTU and any data queries will have been resolved. The CI will notify the REC of the end of the study within 90 days of study completion.

12 STATISTICS AND DATA ANALYSIS

12.1 Sample size calculation

This study is powered to detect a between group effect size of at least 0.4 in the primary outcome at 2-week follow-up, with 2-tailed 5% significance and 80% power. With an estimated standard deviation of 15,[75, 76] this translates to minimum clinically important difference (MCID) of 6 points on the DCS (scale range 0 – 100) – a difference considered by the study team to be meaningful and one that produces an effect size in the range of meaningful effect sizes recommended by the authors of the tool.[1] To achieve an effect size of 0.4 between the study arms, we plan to randomise 328 patients. This recruitment target assumes that approximately 32% of patients will not receive a treatment recommendation (hence for whom the primary outcome is not relevant) and for 10% loss to follow-up in the primary outcome at 2-weeks; our target at 2-week follow-up is therefore 200 i.e. 100 per arm.

The figure of 68% of patients receiving a treatment recommendation is derived from estimates that 40% of patients at Stoke will receive a drug recommendation and 90% at Oxford and Portsmouth[1] and that Stoke will contribute to 43% of recruitment.

12.2 Planned recruitment rate and feasibility

We estimate that an average FLS identifies approximately 120 patients per month for FLS appointments, 90% will meet the eligibility criteria (N = 108) and that 20% will consent to the study (N=21 per month). Enrolling two FLSs to the trial, who each recruit for 5-months and a further site which recruits for 8 months yield a potential sample size of (N= 378), which would be sufficient pool of patients to achieve our randomised sample size of 327 participants. Additional sites will be enrolled if needed.

12.3 Statistical analysis plan

The full statistical analysis plan will be written and agreed with the Trial Steering Committee prior to analysis, hence only an outline of the analysis is described below.

12.3.1 Summary of baseline data and flow of patients

A CONSORT flow diagram will be produced to describe the number of participants included in the study at the multiple stages of recruitment and follow-up. Any reported serious adverse events and protocol deviations will be reported throughout the study. Descriptive statistics (means, standard deviations, medians, inter-quartile ranges and numbers and percentages as appropriate) will be used to describe the baseline characteristics of participants at each stage of recruitment and follow-up, and by blinded treatment arm, to assess if there is any evidence of selection bias and to evaluate the success of the randomisation procedure.

12.3.2 Primary outcome analysis

The primary outcome analysis will be conducted blind to treatment arm, on an intention-to-treat basis. Analysis of covariance (ANCOVA) will be used to analyse the primary outcome (the total DCS score) at the 2-week primary endpoint, by comparing the mean outcome in each treatment arm, after adjustment for any pre-specified baseline covariates. The results of the primary analysis will be presented as means and 95% confidence intervals.

[1] These are different because of different service models. Oxford and Portsmouth assess all patients before consultations so in theory, all patients seen in consultation should be offered drug recommendation and be able to complete primary outcome. We have estimated there may be a small number of consultations in which a drug recommendation is not given for unforeseen reasons (10%). In Stoke, patients are assessed in the appointment meaning low risk patients are not offered treatment. Source of 40% figure - FLS-DB National Audit – most conservative from range 40-55%

12.3.3 Secondary outcome analysis

Treatment effects for secondary outcomes measured at a single follow-up time-point will be explored using similar methods to the primary outcome analysis, but with ANCOVA, logistic and ordinal regression used as appropriate for continuous, binary, and ordinal outcomes. For outcome measures collected at more than one time-point, linear mixed models will be used to model change in the outcome over time. Results will be presented either as mean or percentage differences/odds ratios alongside their associated 95% confidence intervals.

Descriptive statistics (numbers and percentages) will be used to describe patients experience of their FLS appointment and exploratory analysis conducted to explore whether patients' perception of their fracture risk changes following the intervention, and whether their post intervention perception of risk is more in line with their predicted fracture risk (as calculated by their FRAX score). In addition, we will also explore whether patients' level of worry about falls and fractures changes following their FLS consultation and whether such changes are similar in both trial arms.

12.3.4 Adjusted analysis

Covariates included in an adjusted analysis will be specified a priori in the analysis plan, but are likely to include the baseline in the outcome of interest (if this is measured for the outcome of interest) and the stratification variable used in the randomisation process, along with other key baseline variables of interest e.g. age, health literacy and socio-economic status. The adjusted model will be the primary model used in the study.

12.3.5 Subgroup analyses

Any subgroup analyses completed in the trial will be exploratory and will be stated in the analysis plan *a priori* before the main trial analysis is undertaken.

12.3.6 Sensitivity analyses

A sensitivity analysis of the primary outcome model will be conducted to explore whether study conclusions change when outcome variation between FLS clinicians is accounted for in the model. This will be achieved by adapting the ANCOVA model in section 12.3.2 into a mixed model framework and incorporating a random effect term to represent the clinician who treated the patient. The magnitude of the treatment effect from this model will then be compared to that from the primary analysis in the study.

12.3.7 Interim analysis and criteria for the premature termination of the study

No interim analysis is planned to be undertaken during the study to assess effectiveness.

12.4 Subject population

We will analyse all participants who have been randomised to the study on an intention-to-treat basis, except for those outcome measures collected only for participants who receive a drug recommendation. These latter outcomes will be evaluated on an intention to treat basis but only for patients who have received a drug recommendation from the treating clinician.

12.5 Procedure(s) to account for missing or spurious data

We will consider using multiple imputation to impute the patient-level missing data if the missing data rate is greater than 5% for at least one patient-level outcome or predictor of interest [77]. If multiple imputation is used, this will be regarded as the primary analysis over a complete-case analysis.

12.6 Other statistical considerations

Logistic regression will be used to develop a predication model to predict treatment initiation at 3-month follow-up in those participants who were given a drug recommendation. Candidate predictors will be listed *a priori* in the analysis plan, but are likely to include: age, sex, fracture risk, self-reported receipt of osteoporosis diagnosis, consultation length, consultation modality (face-to-face vs telephone), receipt of a DXA scan, level of health literacy and socioeconomic status. In addition, we will use linear regression to explore whether factors (such as age, sex, health literacy and socioeconomic status) are associated with the primary outcome of interest (the DCS).

12.7 Economic evaluation

The economic evaluation will comprise a within-trial cost-effectiveness and value of information (VoI) analysis to determine whether the iFraP intervention is cost-effective compared with usual care. A detailed record of all the resources (i.e. financial, staff, equipment, training, etc.) required to set-up and deliver the iFraP intervention will be made. Resource use information will be obtained from patient self-reports (see sections 7.3.4 and 11.10) and the medical record review.

We will conduct a trial-based Bayesian value of information analysis to identify the main sources of uncertainty regarding the value for money of iFraP when compared with usual care.

13 DATA HANDLING

13.1 Data collection tools and source document identification

Online/postal self-report questionnaires, clinical data collected on study specific CRFs, audio/video-recordings (of consultations and interviews) and prescribing data from linked medical records will form the basis of the data collection. A dedicated study database will be developed using REDCap which is housed on a secure Amazons Web Server (AWS) and managed by a Senior Data Manager and will be the final repository for the data collection.

Patients that enter further details into the website consent form or give verbal (via phone) or postal consent to contact will be entered onto the REDCap study database and allocated a unique participant study ID so that only anonymised data are used for analysis. The unique study numbers will be generated from the study database and allocated to each patient before sending recruitment packs. The number will be made up of site ID followed by a sequence of unique numbers. The study number will be for use on CRFs, other study documents and the electronic database. The documents will also use participants' initials (of first and last names separated by a hyphen) and date of birth (DD/MMM/YYYY).

Questionnaires will include the participant's Study ID plus date of birth and sex to confirm the correct participant's study ID has been provided. Study data, including relevant information from participating patient medical records, will be recorded on CRFs by clinicians or local research staff who are taking part in the study and will be trained in accordance with the protocol on completing CRFs. Data extracted from medical records will be linked to the participant's Study ID and to other study data attributed to each participant. The study site is responsible for redacting all other personal identifiable data prior to CRFs and any other reports being sent to Keele CTU, where appropriate. Following receipt, Keele CTU will contact the site to resolve any missing or discrepant data queries relating to clinical data in accordance with Keele CTU procedures.

Consultations from consenting participants will be audio/ video recorded using a video camera or Dictaphone provided by Keele University. Interviews will be electronically audio recorded using a Dictaphone provided by Keele University. Audio/ video files will be securely transferred from study sites to Keele University immediately after the consultation. Once received these will be stored in Keele's Secure Network. We will be using audio/ video devices commonly used for research purposes. Although the devices are not password protected, the device will not be left unattended at any point until the data is transferred to Keele University's password protected secure network.

13.2 Data handling and record keeping

Data management will be carried out in accordance with a Data Management Plan, in accordance with Keele University Health and Social Care Research (HSCR) Standard Operating Procedures (SOPs). The study data will be stored on Keele University storage services and protected by industry standard security tools. All confidentiality arrangements adhere to relevant data protection regulations and guidelines (General Data Protection Regulation (GDPR), Data Protection Act 2018, Caldicott, General Medical Council (GMC), Medical Research Council (MRC) UK Policy) and the Data Custodian has responsibility for the use, security and management of all data generated by the study.

Completed postal self-report questionnaires will be returned to Keele CTU in pre-paid envelopes provided to participants. Questionnaires will be date stamped on receipt at Keele CTU.

CRFs will be sent to the Keele CTU either electronically or in pre-paid envelopes provided to each centre. The CTU data administrator will enter postal questionnaire and CRF data on to the study database around the time that they are received.

Following receipt of associated consent forms, audio/ video files will be securely transferred from study sites into Keele CTU's Secure Network and then audio files will be securely transferred from Keele CTU to a professional transcription company, who are contracted under strict terms of confidentiality, via a secure portal. Transcripts will be password encrypted when being returned by the transcription company via email to Keele CTU and will then be securely uploaded back onto Keele's Secure Network and the email version deleted. At this point, all transcripts will be anonymised. Anonymised transcripts may be shared with other team members, for example, using Microsoft Teams to facilitate analysis.

All data collected during the study will be kept strictly confidential and will be handled and stored in line with the local NHS and Keele CTU Data Security procedures and Keele University's Health and Social Care Quality Management System's Standard Operating Procedures (HSCR SOPs), which are in accordance with the relevant Data Protection regulations and good practice guidelines.

Audit of data entry is undertaken for questionnaires and CRFs by Keele CTU following HSCR SOPs and the verification checks supported by the research team.

13.3 Access to Data

Direct access to study-specific data only will be given to authorised representatives of the Sponsor to permit study monitoring and audit.

13.4 Data Sharing Agreements

Pseudoanonymised data sets, on patients invited, requested by the research team will be shared by NHS sites subject to a Data Sharing Agreement. The data generated from this study will remain the responsibility of the Sponsor.

Audio files containing qualitative data will be securely shared with a professional UK based transcription company under the terms of a confidentiality and data sharing agreement.

Release of data will be subject to a data use agreement between the Sponsor and the third party requesting the data. Individual participant data will be encrypted on transfer. All data shared will be anonymised before transfer, with the exception of video files, where ensuring anonymity will not be possible due to the nature of the data.

The full statement on data sharing can be found at https://www.keele.ac.uk/informationgovernance/fortheuniversity/dataprotection/datasharing.

13.5 Archiving

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 10 years after end of study declaration and until the sponsor authorises destruction. Archiving will be carried out in accordance with Keele University SOPs.

14 MONITORING & AUDIT

14.1 Trial Management

14.1.1 Sponsor

Keele University as the sponsor is responsible for initiation, operationalisation, and financial management of the study. These functions are devolved to Keele CTU as will be detailed in the Delegation of Sponsorship Functions agreement, as follows:

14.1.2 Chief Investigator (CI)

The CI (ZP) has overall responsibility for the scientific quality and delivery of the study. The CI will also be responsible for safety reporting and escalation of reportable adverse events.

14.1.3 Associate Investigator (LB)

The Associate Investigator (LB) will support the CI in the day-to-day conduct, co-ordination, and management of the study, ensuring the study is delivered in line with this protocol.

14.1.4 Keele CTU

The Study Sponsor, Keele University, delegates the management of the study to Keele CTU. Keele CTU will provide set-up and monitoring of study conduct to Keele University HSCR SOPs, and GCP, database and web application development and maintenance, protocol development, CRF design, study design, monitoring schedule and statistical analysis for the study. In addition, Keele CTU will support obtaining research ethics and governance approvals and site set-up, ongoing management including training, monitoring reports and promotion of the study. In association with the CI and AI, Keele CTU will be responsible for the day-to-day running of the study including study management and administration, database administrative functions, data management, safety reporting and all statistical analyses. Regular monitoring of study recruitment will be performed and intervention eCRFs will be monitored, against the study protocol for compliance.

14.1.5 NIHR Clinical Research Networks

NIHR CRNs will co-ordinate CRN support across the sites and will provide funding or staff resource to secure the additional clinical time associated with service support to embed the study into the sites to allow identification of potentially eligible participants.

14.1.6 Trial Management Group (TMG)

The TMG, convened by the CI, will comprise members of the research team and Keele CTU and will have overall responsibility for the clinical set-up, promotion, ongoing management and monitoring of the study, and for analysis and interpretation of results. The CI (ZP) or delegate (AI) will chair the TMG to oversee; obtaining regulatory approvals from the HRA and general practices; monitoring and managing funding; CRF development; protocol delivery; monitoring of recruitment, intervention delivery and follow-up procedures; data collection and database development; completion of regulatory reporting requirements; reporting of unexpected events to the REC, Trial Steering Committee (TSC) and Sponsor; and completing funder reporting requirements. The TMG will meet on a regular basis throughout the study.

14.1.7 Trial Steering Committee (TSC)

This study forms part of a 5-year research programme. An independent TSC has been appointed according to the funder's (NIHR) requirements. The TSC will provide overall supervision of the research programme according to agreed timelines. The TSC includes an Independent Chair (Consultant & Honorary Professor of Endocrinology) and four additional independent members including a statistician, a health services researcher with expertise in complex intervention, and two patients and the public representatives, see Key Trial Contacts. The TSC will meet at agreed time points, at least annually, for the duration of the 5-year programme. The CI and AI will attend the TSC meetings to report on progress, together with other members of the research team, including the Lead Statistician, as appropriate.

14.1.8 Data Monitoring Committee (DMC)

The DMC, see Key Trial Contacts, are an independent team with relevant knowledge and expertise in the conduct and methodological aspects of clinical trials, and who are responsible for ensuring the integrity and appropriate running of the trial. The DMC may request to review overall unblinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

14.2 Monitoring arrangements

Monitoring will be conducted according to a Study Monitoring Plan developed by the TMG based on the study risk assessment and in accordance with Keele CTU and Sponsor SOPs. Monitoring will also be undertaken by the approving Research Ethics Committee (REC) in the format of annual progress reports, and the funder in the format of progress reports as required by the NIHR Clinician Scientist funding stream.

14.3 Safety Reporting

14.3.1 Adverse events

The potential harms of this study are minimal. The clinical management recommendations given to participating FLS clinicians in participating practices are evidence-based best practice, following national guidelines and in line with normal NHS care.

A Serious Adverse Event (SAE) is defined by the Health Research Authority (HRA) as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator.

A SAE occurring to a research participant must be reported to the REC where in the opinion of the treating clinician & CI the event was: “Related” that is, it resulted from administration of any of the research procedures, including the use of the CDST, and “Unexpected” that is, the type of event that is not an expected occurrence as a result of the intervention provided.

All SAEs either confirmed or suspected to be related to the trial procedures will be reviewed by the Data Monitoring Committee and reported to the Trial Steering Committee.

14.3.2 Safety Reporting Exceptions

Expected adverse events (AEs) related to medicine use will not be reported, because medicine administration is not a research procedure, and this is not a CTIMP.

14.3.3 Safety Reporting Process

In addition to participant self-report, iFraP FLS clinicians will be asked to report related and/or unexpected adverse events and SAEs if they become aware of them during the study. Reporting procedures will be made clear during the protocol study training and will be contained in site files for all clinicians involved in the study.

Clinicians in participating services will be asked to record events or concerns about the safety of subjects that arise as a result of the study, even if these events or concerns do not meet the definition of a serious adverse event requiring notification to the regulatory authorities.

All SAEs occurring from the point at which participants consent to participation in the iFraP study must be notified to Keele CTU:

- via telephone within 1 working day of the study clinicians becoming aware of the event AND
- via email

The Study CI or AI will be asked to assess SAE causality.

Any follow-up information should be sent to the Sponsor via the Study Team as it is available, and where appropriate. Events will be followed up until the event has been resolved or the participant reaches the end of follow up.

Once a SAE is identified and reported, this information is to be passed to the Study Manager who will ensure that the necessary paperwork is completed and will inform the CI. In line with Keele University's HSCR SOPs the treating clinician will assess causality/ relatedness and the CI will assess expectedness, according to the process laid out in Keele University's HSCR SOPs.

Any SAE considered to be related and unexpected will be reported to the REC and the TSC Chair by the CI within 15 calendar days of becoming aware of the event. All related or unexpected SAEs will also be reported to the study sponsor.

14.3.4 Responsibilities for safety reporting

Chief Investigator (CI,) delegate or independent reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.

- Review of all SAEs as detailed in the study monitoring plan.

Sponsor:

- Expedited reporting of Related Unexpected SAEs to the main REC.

- Reporting of confirmed related and unexpected SAEs to the Health Research Oversight Committee (HROC) in accordance with their requirements.

14.4 Trial timeline

See Appendix 1 - Study timelin

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee (REC) review & reports

The study will be submitted to and approved by the HRA (which includes REC) to gain the appropriate NHS Permissions prior to recruiting participants into the study. Keele CTU will provide the final protocol, PISs, consent forms and all other relevant study documentation as part of the ethical approval process.

Following initial approval from the REC, they will continually be informed of all substantial changes to the management of the study. Routine reporting will take place in line with REC requirements.

All correspondence with the REC will be retained in the Trial Master File (TMF). Study Site Files including details of the original REC approval will be updated with any REC approval letters acknowledging a substantial change.

The CI will be responsible for producing the annual reports as required and will:

- Notify the REC of the end of the study;
- Notify the REC if the study is ended prematurely, including the reasons for the premature termination and;
- Submit a final report with the results, including any publications/abstracts, to the REC within one year after the end of the study.

15.2 Peer review

This study is part of a programme of research that has obtained independent peer review, prior to award of funding, by NIHR Research Design Service (West Midlands) and through the NIHR Clinician Scientist funding application process. Further review has been undertaken within Keele CTU to ensure additional quality checks and compliance with standard operating procedures.

15.3 Public and Patient Involvement

A group of patients with osteoporosis and their carers was convened from Keele's Research Users' Group (RUG), to support the development of the iFraP research programme and the NIHR funding application. The group met prior to funding, helping to define the research questions, and influencing research design. Members of this group have subsequently been invited to form a Patient Advisory Group (PAG) to support delivery of the iFraP research programme, including this study. The PAG have and will continue to meet face-to-face or remotely at specified times over the course of the trial.

During the intervention development work that preceded this study, the PAG advised on:

- Wording of the patient-facing documents, including PISs and invitation letters
- Design of the Delphi exercise for patients including the clinical vignettes, how best to recruit and explain the Delphi to patients. PAG members also supported the development of decision rules that supported Delphi survey analysis.

- Analysis and interpretation of the focus group findings
- Design of the CDST and how it would be implemented in remote consultations
- The conduct of in-practice testing with FLS clinicians and patients
- Interpretation of findings from the in-practice testing and changes needed to the iFraP intervention

PAG members also contributed to the development of videos used in the prototype iFraP clinician training programme, including a patient testimonial and a mock consultation using the iFraP CDST. In addition, patients were members of the stakeholder group (also including representatives from the ROS, FLS clinicians, and consultant rheumatologists) that, over 4 stakeholder workshops, influenced the design the iFraP intervention.

Meetings with the PAG have facilitated the design of the trial outlined in this protocol by:

- Developing an appropriate and understandable patient-facing trial name
- Deciding the most appropriate outcomes, including the person-centric primary outcome
- Discussing patient recruitment approaches, including patient-facing recruitment materials (wording of patient invites and PISs)

PAG meetings will continue throughout the course of the iFraP trial by:

- Planning of the process evaluation, including input to topic guide
- Interpretation of trial results, implications for any further iFraP modification and dissemination (and implementation) planning

The patient perspective will be embedded within study management and oversight. There have been two independent lay members of the Trial Steering Committee during the 2-year development who will continue as members of the TSC representing the interests of patients and the public.

Keele University has a national and international reputation for good practice in PPIE and has strong PPIE infrastructure. The NIHR INVOLVE "jargon buster" will be used for participant information. Patients will be supported by a dedicated PPIE coordinator and user support worker. Patients have an induction, receive a plain English glossary of research terms, and have access to training resources (e.g. contributing assertively to meetings). Feedback is provided after meetings on how discussions impact on the research. Payment will be offered according to INVOLVE guidelines.

15.4 Regulatory Compliance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in research studies, the UK Policy Framework for Health and Social Care Research. Keele University as the Sponsor has a quality management system in place containing standard operating procedures which will be adhered to in the conduct of the study. Studies run by Keele CTU may be subject to an audit by Keele University as the Sponsor for quality assurance.

15.5 Protocol compliance

The Trial Management Group will monitor protocol compliance of recruitment, treatment, and follow-up procedures during conduct of this study, and this will be discussed at monthly TMG meetings.

Technical deviations from protocol that do not result in harm to the study participants, do not compromise data integrity or significantly affect the scientific value of the reported results of the study will be documented and appropriate corrective and preventative actions will be taken by the research team with the CI being responsible for these with agreement from the TMG. Deviations which are found to frequently recur are not acceptable and will require consideration from the CI, sponsor, and agreement from the trial management as to whether they are to be classified as a serious breach.

15.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research.

Keele CTU has systems in place to ensure serious breaches of GCP of the study protocol are identified and reported.

In the event of doubt, or for further information or guidance, the investigator should contact the Study Manager or CI at Keele CTU. All protocol deviations and breaches of GCP will be recorded and reported to the Sponsor, REC and TSC according to the applicable HSCR SOP.

The Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor will notify the REC in writing of any serious breach of

a. the conditions and principles of GCP in connection with that study; or

b. the protocol relating to that study, within 7 days of becoming aware of that breach.

15.7 Data protection and patient confidentiality

The standard data protection procedures operating in Keele CTU will be employed to protect confidentiality and anonymity. Each participant is allocated a unique study identification (ID) number, so that only anonymised data are used for analysis. At the end of the study, database anonymisation and locking will be carried out in accordance with HSCR SOPs. Transcriptions from interviews and consultations will be checked for accuracy against the audio/ video recording. Transcripts will be fully anonymised (names of people or places removed, labelled with unique study ID numbers).

Keele CTU has robust data security systems and procedures in place, which are regularly reviewed, and which achieve the legal obligations set by the Data Protection Act (2018) and the General Data Protection Regulation (GDPR) and follow GMC Caldicott Guardian and British Computer Society standards and guidelines. Information about Keele University's Privacy Notice will be included in the Patient Information Leaflet.

All participant data will be housed in the CTU Infrastructure, which is a secure virtual network requiring two factor authentication (2FA) to access the data stored within. Permissions are applied to users within the network to restrict access to study data as required. Only authorised members of staff will have access to the study data.

The CTU Secure Infrastructure has been independently audited and achieved level one of the Government backed Cyber Essentials Scheme. All hard copy information will be stored securely in locked cabinets in accordance with HSCR SOPs. Data used for analysis will be kept separate from consent forms containing participant identifiable information.

All confidentiality arrangements adhere to relevant regulations and guidelines and the CI, study team and study statisticians (Data Custodian) have responsibility to ensure the integrity of the data and that all confidentiality procedures are followed.

15.8 Financial and other competing interests for the CI, and committee members for the overall trial/ management

The CI, AI, TMG members and independent TSC members have no financial or other competing interests to declare.

15.9 Indemnity

The study is sponsored by Keele University. The University carries Professional Liability and Medical Malpractice insurance to indemnify it, subject to the terms and conditions of the policy, for its legal liability for claims or damages arising out of any bodily injury, mental injury, illness, disease, or death of any patient caused by negligent act, error or omission committed by the University during its business.

The NHS has a duty of care to patients whether they are taking part in research or not. The NHS organisations remain liable for clinical negligence and other negligent harm to patients under their duty of care.

15.10 Amendments

The detailed protocol will be updated in response to approved amendments, as required.

15.11 Post-trial care

All participants in the study will continue to receive usual care from their treating clinician(s).

15.12 Access to the final trial dataset

At the end of the study, archiving of essential study documents at Keele University will be authorised by the sponsor following submission of end of study reports which will be for a minimum of 10 years after the end of the study. Destruction of essential documents requires authorisation from the Sponsor.

A record of consent will be held in the local investigator site file. All other data will be held by Keele CTU and will be archived in the designated Keele CTU archive facility. Following authorisation from the Sponsor, arrangements for the destruction of all confidential data will be made.

Any subsequent requests for access to the data from anyone outside of Keele CTU (e.g. collaboration, joint publication, data sharing requests from publishers) will follow Keele University's standard operating procedure.

The anonymised datasets generated during and/or analysed during the current study will be available upon request from medicine.datasharing@keele.ac.uk. A data request form is required to be completed and must outline the type of data to be obtained, the reason for obtaining this data (research question / objective), the timing for when the data is required to be available (start date/end date). Checks will be performed by a Data Custodian and Academic Proposals (DCAP) committee at

Keele to ensure that the data set requested is appropriately suited to answer the research question/objective and that the request fits with the original ethical approval and participant consent and adheres to funder and legal restrictions. Only anonymous data will be available for request in aggregated format or at the level of the individual participant.

16 DISSEMINIATION POLICY

16.1 Dissemination policy

All foreground intellectual property (IP) arising from this trial will be managed by Keele University. A consortium agreement between North Staffordshire Clinical Commissioning Group and Keele assigns all foreground IP to Keele and provides the legal framework for identification, management, protection, and exploitation of IP. The copyright of all materials will belong to Keele University.

On completion of the study the data will be analysed, and a final study report prepared. This report will be included in the annual report submitted to NIHR in accordance with the conditions of the grant award. All publications, presentations, correspondence, and advertisements arising or related to the grant must acknowledge NIHR as the study's funding source. When acknowledging NIHR UK support, the grant reference number must be quoted.

The results of this study will be made widely and freely available to all stakeholders in ways that are easy to access at no cost. Our Patient Advisory Group will advise on how to translate these into easily understandable messages and on how best to disseminate the results to the wider public. We will feedback/publish a summary of the results on the iFraP study webpage (www.ifrap.co.uk) and Royal Osteoporosis Society website. In addition to publications in open-access peer-reviewed journals, we will use our website, NHS networks and links to professional bodies to support dissemination of the findings to all stakeholders and will use social media to promote the findings via our dedicated Twitter and Facebook feeds.

16.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship for the final report of this study will be the iFraP study team, protocol contributors and individuals involved in study management. Authorship on any publication resulting from the work described in this protocol will follow the criteria of The International Committee of Medical Journal Editors which has defined authorship criteria for manuscripts submitted for publication.

17 REFERENCES

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18 APPENDICIES

Appendix 1 - Study timeline

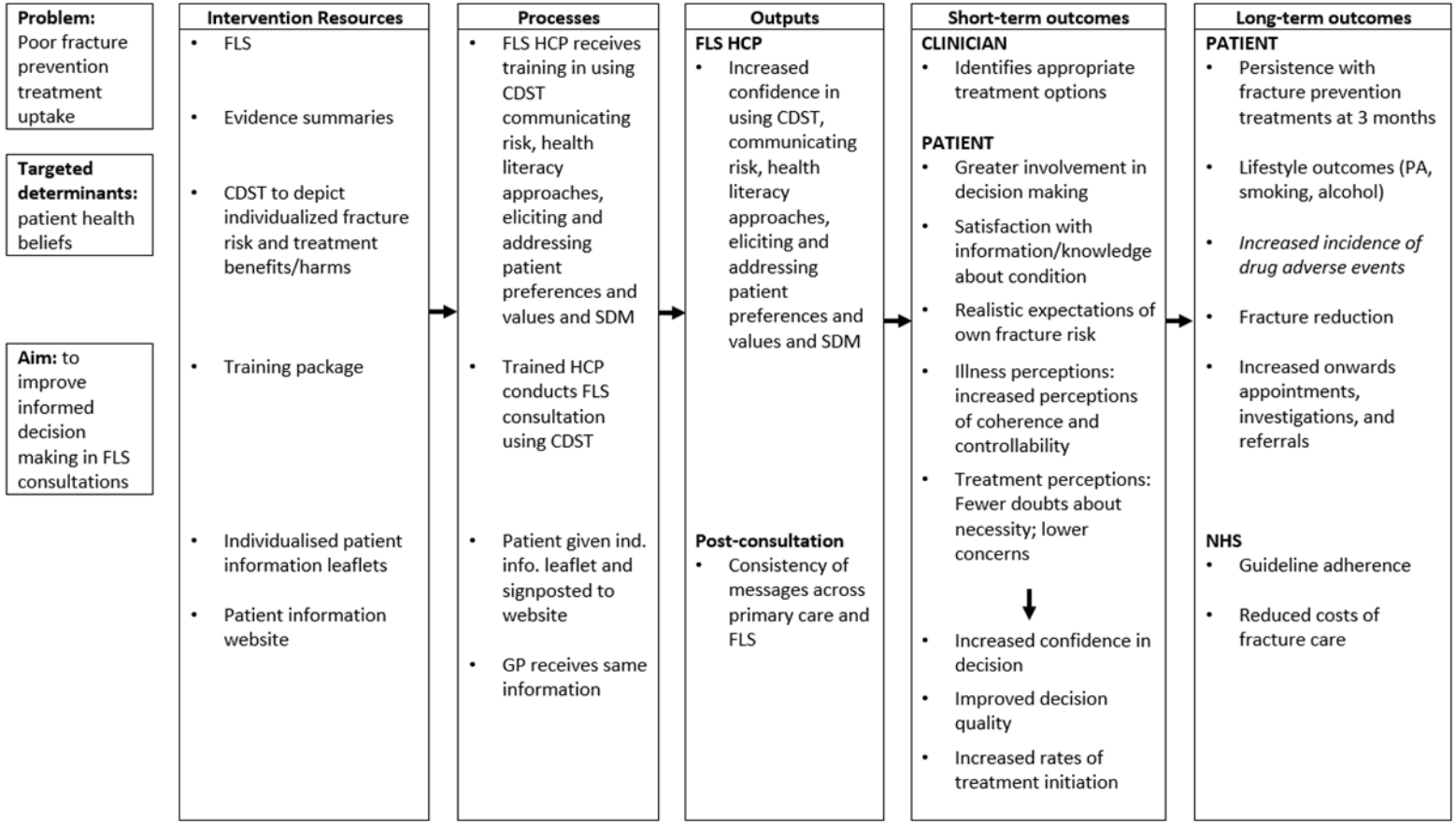
Appendix 2 – Logic model

Appendix 3 - Flowcharts of interview participant identification

Appendix 1 - Study timeline

	3	Year 4												Year 5												7 month extension							
	2022													2023												2024							
	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S
Request trial changes NIHR: approval March 22																																	
Complete trial protocol and trial documents																																	
Ethics and HRA approval: Submit May 22																																	
Site set up and study training									site 1	site 1		site 2/3	site 2/3																				
iFraP training										site 1			site 2/3																				
Recruitment of participants (phased: first site followed by others)																																	
Randomisation																																	
FLS consultation																																	
Data Collection follow up 2/52																																	
Data Collection follow up 12/52																																	
Interviews (after 2/52 follow up)																																	
Consultation recordings																																	
Qualitative analysis																																	
Data cleaning																																	
Quantitative Analysis																																	
Health Economics																																	
Integration of qualitative and quantitative findings																																	
Dissemination																																	
Project Management and Advisory Groups																																	
PPIE group																																	
CoP																																	
Trial Management Group																																	
Trial Steering Group																																	

Appendix 2 – Logic Model



*CDST computerised decision support tool, FLS Fracture Liaison Service, HCP healthcare professional, PA physical activity, GP general practitioner, SDM shared decision-making

Appendix 3 - Flowcharts of interview participant identification

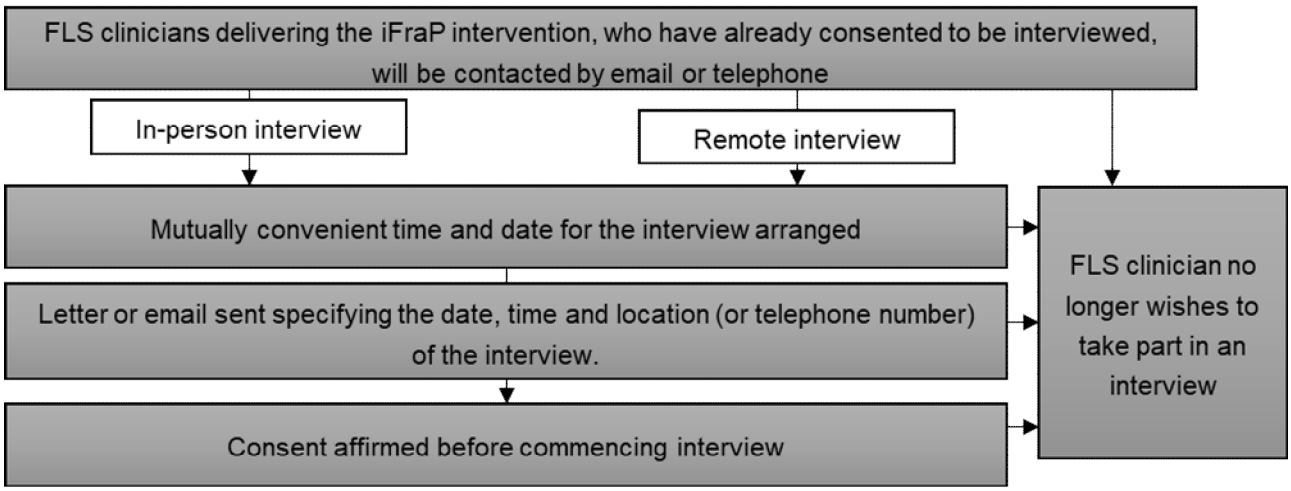


Figure 3. *FLS clinician interview identification*

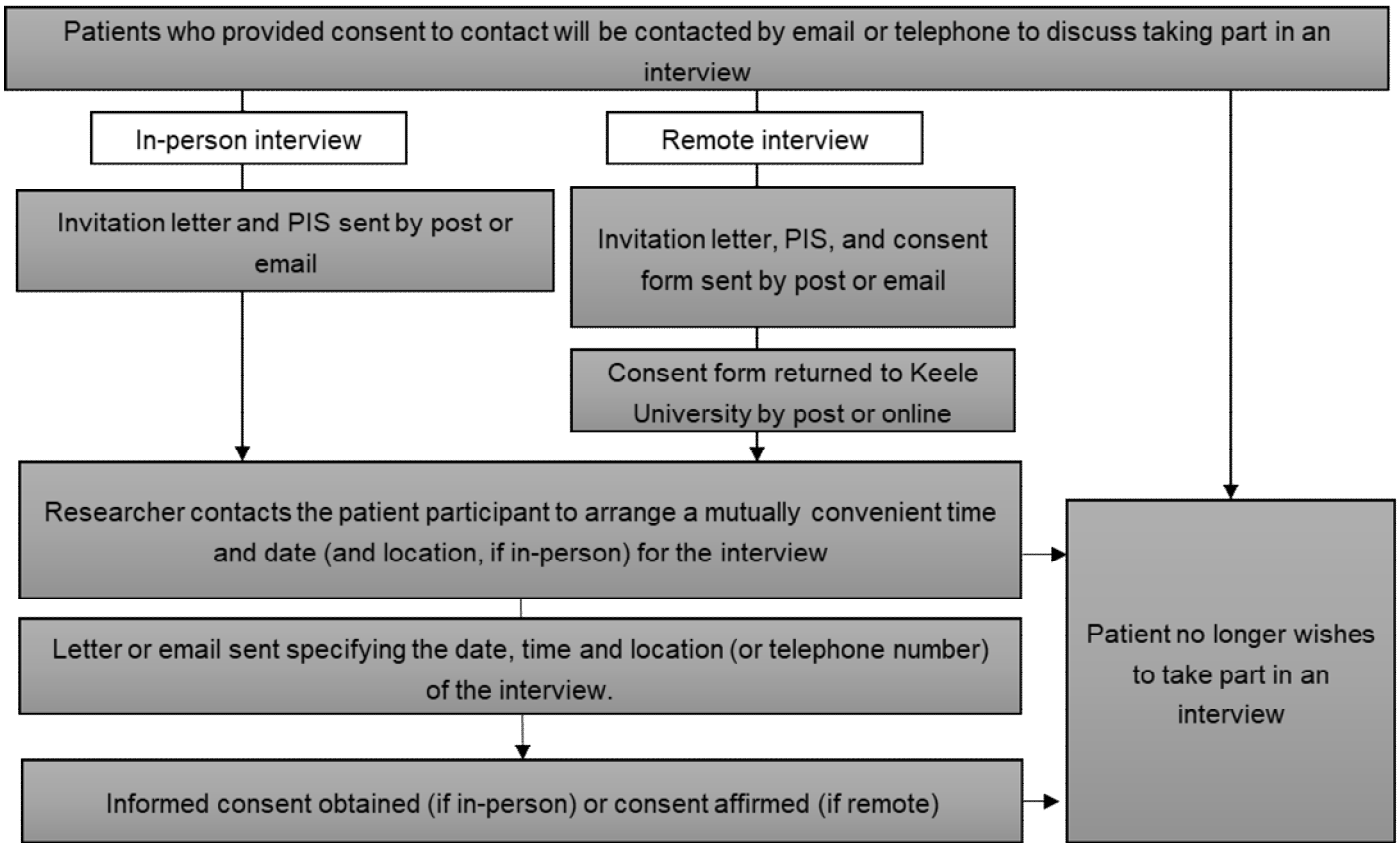


Figure 4. *Patient interview identification*

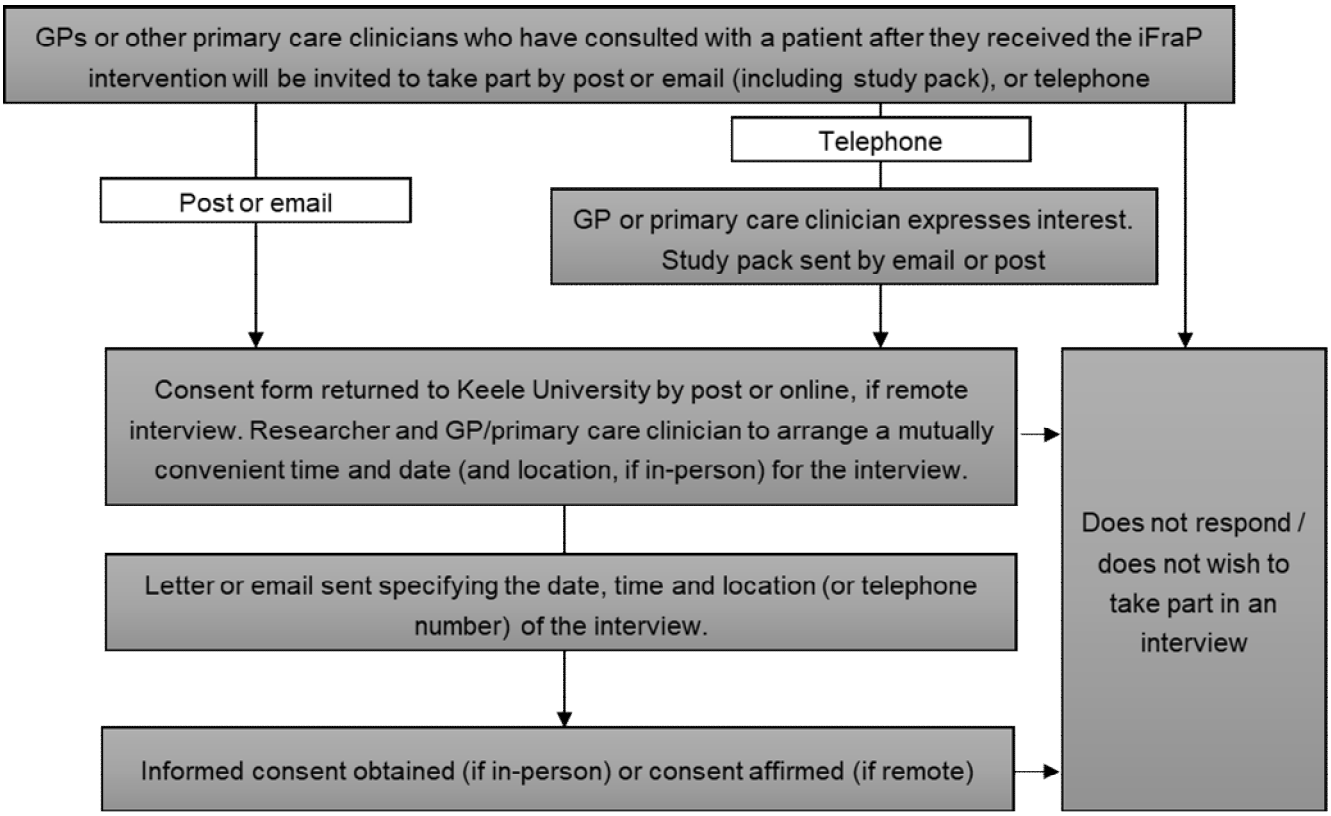


Figure 5. *GP and primary care clinician interview identification*