Study Title: Vertebral fracture clinical decision tool for older women with back pain (Vfrac) – a feasibility study

Short title: Vfrac feasibility

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There are no potential conflicts of interest.

Confidentiality Statement

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

TABLE OF CONTENTS

1. SYNOPSIS

Study Title	Vertebral fracture clinical decision tool for older women with back pain (Vfrac) – a feasibility study	
Internal ref. no. / short title	Vfrac feasibility	
Study Design	Feasibility study with nested evaluations	
Study Participants	General practices to be recruited. Vfrac to be used for older women (>65) who present with back pain	
Planned Sample Size	Work Package (WP) 1: 6 general practices WP2: 16-24 women; 16-24 healthcare professionals WP3: 60 women	
Planned Study Period	1st April 2022 to 30th August 2023	
	Objectives	**Output**
1	Feasibility study of Vfrac implementation within primary care	1A Contribution to finalisation of future study design: 1A-1 training requirements for healthcare staff; 1A-2 IT requirements and options for ideal integration within IT systems; 1A-3 options for ideal integration within clinical pathways; 1A-4 required length of follow-up for future study (one of the Stop/Go criteria) 1B Contribution to Manual for Vfrac Implementation 1C Manual for optimisation of future data collection 1D Contribution to understanding of 'usual care'
2	Nested qualitative assessment of acceptability	2A Assess if the Vfrac decision tool is acceptable to healthcare professionals and patients (one of the Stop/Go criteria) 2B Identification of barriers and facilitators to delivery

		2C Recommendations for future implementation and delivery 2D Contribution to manual for Vfrac implementation
3	Nested assessment of agreement between use of Vfrac within general practices and self-completion at home	3A Decision as to whether Vfrac can be used remotely i.e. as self-completion by patients at home Decision based on (1) size of agreement between self-completion and F2F assessment; and (2) patient satisfaction and ease of use of the self-completion questionnaire and written instructions. If Cohen's kappa is <0.6 (substantial agreement) remote use (self-completion) will not be incorporated into any future trial. If Cohen's kappa is ≥0.6, data from the satisfaction questionnaire will be used to make modifications, if necessary, to facilitate remote use (self-completion) of Vfrac in the future RCT. 3B Contribution to finalisation of future study design
4	Decision as to whether a future definitive evaluation is warranted, based on the Stop/Go criteria	Stop/Go criterial for future trial: 1. Accuracy of Vfrac tool – already completed and results are favourable (not part of this ethics application) 2. Modelled cost-effectiveness - already completed and results are favourable (not part of this ethics application)

		3. Realistic proportion of older women with back pain identified with vertebral fractures by Vfrac - already completed and results are favourable (not part of this ethics application) 4. Realistic required sample size based on analyses of national data (not part of this ethics application) 5. Realistic required length of follow-up for the future trial based on results of Objective 1A plus additional analyses of national data (not part of this ethics application) 6. Evidence that the Vfrac tool is acceptable to healthcare professionals and patients based on results of Objective 2 above

2. ABBREVIATIONS

ABQ	Algorithm-Based Qualitative
GP	General Practitioner
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
OVF	Osteoporotic vertebral fracture
PI	Principal Investigator
REC	Research Ethics Committee
VF	Vertebral Fracture

3. BACKGROUND AND RATIONALE

3.1 Brief background to the study, including scientific justification for the research

Having an osteoporotic vertebral fracture (OVF) considerably increases the chances of having another osteoporotic fracture (including hip fracture) for both men and women and is considered a marker of osteoporosis[1]. However, only 25% of OVFs result from falls, with the majority caused by daily activities such as bending forwards, climbing stairs or lifting objects[2]. Health-related quality of life in patients with OVFs is reduced significantly: they experience more pain, reduced physical function (even in the absence of pain[3]) and are more likely to be socially isolated[4].

Therefore, identifying OVFs provides the opportunity to intervene with bone protection therapies that can reduce the risk of further fractures by 30–50% [5,6] but an estimated two-thirds of OVFs are undiagnosed[7]. Potential reasons for this include a high prevalence of all-cause back pain in older people[8] and lack of understanding about which clinical features should be used to trigger referral for a diagnostic spinal radiograph[9].

To address this, we have developed the Vfrac clinical tool using the MRC framework for development and evaluation of complex interventions[10], funded by Versus Arthritis[11,12]. The intention of Vfrac is to help healthcare practitioners in primary care decide if an older woman with back pain is at high risk of an OVF and therefore requires a spinal radiograph to confirm the diagnosis. It contains 15 simple components based on self-reported data and a physical examination, and takes approximately 5 minutes to perform. 12 of the items are questions about pain and past medical history. The other three items are height, weight and wall-to-tragus distance.

Vfrac produces a binary output of "Low risk - spinal X-ray is not recommended" or “High risk - spinal X-ray is recommended as may have a vertebral fracture". Statistical modelling suggests it is valid (AUC of 0.802, 95%CI 0.764-0.840). Of those recommended for radiographs by Vfrac, approximately one-third will have a vertebral fracture. Vfrac identifies 93% of those with more than one fracture and two-thirds of those with one. Statistical modelling shows no evidence of over/underfitting; optimism in the estimate of the AUC was 0.019 estimated using 500 bootstrapped samples; and multiple imputation to account for the missing data produced results that were similar to our final model.

Pre-trial economic evaluation estimated the incremental cost-effectiveness ratio (ICER) for Vfrac compared to standard care was £17,000 per QALY and there was a 49.4% probability that the ICER is under £20,000. Therefore, although Vfrac has the potential to be cost-effective based on the data and assumptions within the pre-trial economic evaluation, there is currently uncertainty around the cost-effectiveness of using the Vfrac tool. Value of information (VoI) analysis suggests that the value of obtaining perfect information on the cost-effectiveness of Vfrac is £526 per woman presenting with back pain, which equates to £229 to £458 million per annum (expected consultation rates for older women with back pain ranging from 800 (local pilot data) to 1600[13] per 100,000 registered). Therefore, the value of reducing this uncertainty through future research is likely to comfortably outweigh the cost of any large scale randomized controlled trial.

The current plan for the future definitive (late) evaluation is a parallel cluster-randomised trial, with randomisation at the level of GP practices or Primary Care Networks (PCNs) to reduce contamination.

The primary co-outcomes of this trial will be the clinical and cost-effectiveness of Vfrac from the NHS perspective, compared to standard care of older women with back pain. These outcomes will be based on treatment of OVFs and osteoporosis identified as a result of Vfrac, and are the same as the original trial of the prototype[14].

Uncertainties that require clarification before design of the future definitive evaluation of Vfrac

Before we plan the future trial, we need more information to clarify uncertainties around trial parameters. From our previous work where we have utilised 38 general practices[14,15], we can quantify the response rate for recruitment, along with retention, and understand procedures to optimise this. However, data are required to inform length of follow-up required for the future trial: during the final development of Vfrac[12] we collected data to estimate resource usage for the pre-trial economic modelling, but it became clear that 3- months was not long enough for completion of the pathway from assessment to final management. Information is required on our ability to accurately and comprehensively collect data on resource use in both the intervention and control clusters to inform the future RCT.

Information is also needed to understand how acceptable Vfrac is to healthcare professionals (providers) and patients (recipients) and identify factors that impact on implementation, including barriers and facilitators to delivery. The implementation of interventions in real-world clinical settings is challenging[16]. 'Acceptability' is a key consideration in designing and implementing interventions since it impacts how likely participants are to engage with it[17]. Successful implementation is also influenced by additional factors, including the contextual factors that characterise healthcare systems such as time available[18,19]. Understanding these issues will enable us to develop a series of recommendations to modify the Vfrac tool and its delivery. This will help to ensure that healthcare professionals and patients engage with Vfrac and enable us to optimise delivery during the full study trial.

No testing of Vfrac has been undertaken within a real-world clinical setting. Discussions with primary care colleagues have highlighted how much the model of consultation/service delivery has changed in the pandemic, and it is highly unlikely that there will be a full-scale return to face-to-face (F2F) consultations with GPs as the primary mode of clinical assessment. It is envisaged that the Vfrac tool may be used in a variety of ways, most likely incorporating virtual (telephone or video) consultations with a clinician (doctor, nurse or first contact physio) for completion of the self-reported questions, and F2F consultations with practice nurses to measure height, weight and wall-to-tragus distance; or fully F2F with practice nurses only. The Vfrac tool was originally planned to be used by practice nurses (all research data were collected by research nurses trained to the level of a practice nurse), and hybrid use of the tool as described above, is appropriate if needed. There is also a question about whether Vfrac could be used fully remotely, with patients completing all questions and carrying out a self-assessment of physical characteristics over the telephone or through video-conferencing. IT requirements to incorporate Vfrac within the various IT systems in use in primary care needs to be established. The acceptability of Vfrac and identification of factors that impact on implementation, including barriers and facilitators to delivery are also unknown. Recommendations are needed to help modify Vfrac and improve its delivery. Clarification of these uncertainties form part of this study, particularly in the context of different primary care IT systems across the UK (for example EMIS Web or SystmOne), Covid-19, and the change in primary care workforce with increased use of allied healthcare professionals such as First Contact Physiotherapists.

Finally, 'usual care' is undefined, with no clear understanding of what this entails, nor the national variation in current management of older women consulting in primary care with back pain. We have a current study looking at the lived experiences of patients and healthcare professionals (NIHR201523) during the process of diagnosing an osteoporotic vertebral fracture, aiming to clearly define pathways to diagnosis. Further information is required to define usual care for older women with back pain but without vertebral fractures. This will help with study design for the future definitive evaluation to ensure all necessary data is collected.

This study will fill this demonstrable evidence gap and allow design of a high quality future definitive trial. The aims of this study are

1. To optimise use of the Vfrac decision tool within a real-world clinical situation in primary care by (a) assessing the acceptability of Vfrac to healthcare professionals (providers) and patients (recipients), and (b) identifying factors that impact on its implementation, including barriers and facilitators to delivery. Findings will be used to develop a series of recommendations to modify Vfrac and improve delivery in the future RCT.
2. To quantify required trial parameters including (a) final design of the intervention i.e. does it need to be delivered F2F, (b) a clear description of usual care, and (c) length of time needed for trial follow up by assessment of UK-wide variability in length of time between initial consultation for back pain and eventual management implementation.
3. To identify processes required to collect accurate and comprehensive data on resource use as a result of Vfrac utilisation through a pilot study.
4. To contribute to the final decision as to whether a future definitive evaluation of Vfrac is warranted.

3.3 Study design

There are four work packages (WP):

WP1: Vfrac implementation within primary care

Six general practices will be recruited purposively to include large/small practices, practices within different PCNs/clusters and practices that use different IT systems (EMISWeb/SystmOne for example). General practices will be identified and approached by the Bristol Primary Care CRN. Baseline data will be collected from all recruited practices. A clinical update on osteoporosis will be offered to all. Three practices will then be assigned to the implementation arm and three to the control. Those in the implementation arm will be trained in the use of Vfrac and will have it made accessible from their IT systems (through provision of a URL via pop-ups on typing relevant words such as back pain). Use of the Vfrac tool will be encouraged within their clinical pathways for management of older women who consult with back pain. Use of the tool in a manner that fits each practices service delivery model will be facilitated by the research team in discussion with the clinical team. The control practices will use standard clinical processes for older women consulting with back pain. Regular data will then be collected on consultations by older women with back pain from all 6 general practices every 3 months for 12 months. Data collection will be by download from electronic systems and will include use of the Vfrac tool, subsequent investigations, onward referrals and new medication prescriptions.

Outputs of this work package will include
WP1.1 *contribution to final study design* such as training requirements for healthcare staff; IT requirements and options for ideal integration within IT systems; options for ideal integration within clinical pathways; required length of follow-up for future study; and better understanding of usual care for comparison purposes.
WP1.2 *Contribution to the Manual for Vfrac Implementation* including recommendations for ideal integration from the IT and research teams perspective (along with WP2.2)
WP1.3 *The Manual for Optimisation of Future Data Collection* including lists of codes, ideal steps within data download and other strategies, and data needed from control and intervention practices.

WP2: Nested qualitative assessment of acceptability
Overview: This WP will use eight focus groups: four with patients who were assessed using the Vfrac tool and four with healthcare professionals. Focus groups aim to assess views on the acceptability of Vfrac and identify factors that impact on implementation, including barriers and facilitators to delivery. Findings will be used to develop a taxonomy of barriers and facilitators to implement that will form the basis of recommendations for future implementation and delivery.

Plan: Patients who were assessed using the Vfrac tool during a consultation for back pain in intervention practices (WP1) will be identified by healthcare professionals working within the practice. They will be identified by the unique code generated and embedded within their GP records at the time the result of Vfrac was recorded. They will be approached by the direct clinical care team in their general practice with an Information Pack about the study. The information pack will contain an Introductory Letter, a Participant Information Booklet, a Consent Form and a pre-paid envelope for return to the research team. Those who reply by returning the completed Consent Form will be recruited. Purposive sampling will be used to take into account age, comorbidities and other relevant sociodemographic chanracteristics[20]. An estimated 4-6 patients will be included in each focus group, totalling 16-24 patients. Final sample size will be determined by data saturation[21].

Healthcare professionals from intervention practices (WP1) will be approached via their Research Lead. Research Leads will send an invitation email to potential participants with information about the study and asking them to contact the research team if they are interested in taking part. Participants will include a range of healthcare professionals involved in the identification of OVFs in primary care including GPs and first contact physiotherapists. Purposive sampling will be used to account for professional roles, years of experience, intervention practice and other relevant characteristics[20]. Written informed consent will be sought prior to data collection. An estimated 4-6 participants will be included in each focus group, totalling 16-24 healthcare professionals. Final sample size will be determined by data saturation, as above[21].

A total of eight focus groups will be conducted: four with patients and four with healthcare professionals. Focus groups will aim to understand and assess the perceived acceptability of Vfrac and identify factors that impact on implementation. Factors that impact implementation may include patient-related factors and provider-related factor such as working practices, or service constraints such as time and resources. 'Topic guides' for patients and healthcare professionals will be used to guide discussions, with flexibility to pursue emerging ideas[22]. These will be informed by the Theoretical Framework of Acceptability[23], a framework that has been developed to guide the assessment of

acceptability for providers and recipients; and implementation science theory[24], theories developed to explore the implementation of complex interventions. Similarities and differences between participants views will be explored. Initial focus groups will inform topic guide refinement. If refinements are minor, these will contribute to the main analysis.

Focus groups with patients will be conducted either in person on University of Bristol premises (travel expenses will be reimbursed) or remotely using video conferencing software. Focus groups with healthcare professionals will be carried out remotely using video conferencing software. If F2F focus groups with patients are not feasible due to Covid restrictions, or participants do not feel they have the necessary IT skills to participate in online group discussions, they will also be given the option of taking part in one-to-one interviews. Similarly, focus groups with healthcare professionals may not be possible given their time constraints and provisions will be put in place for individual interviews. Individual interviews will either be conducted F2F, by telephone or using videoconferencing software, using the Topic Guides as above. This will ensure maximum diversity and inclusion.

Outputs of this work package will include
WP2.1 *Assessment of acceptability of the Vfrac decision tool* by healthcare professionals and patients using the 'Theoretical Framework of Acceptability' to inform findings
WP2.2 *Contribution to the Manual for Vfrac Implementation* through identification of barriers and facilitators to delivery using implementation science theory, and development of recommendations for future implementation and delivery (along with WP1.2)

<u>WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home</u>
Older women who consulted with back pain and had Vfrac used during their clinical consultation within one of the three intervention practices will be recruited to take part in this work package. They will be identified by the unique code generated and embedded within their GP records at the time the result of Vfrac was recorded. They will be approached by the direct clinical care team in their general practice with an Information Pack about the study. The information pack for this nested assessment will be sent after the information pack sent about WP2. It will contain an Introductory Letter, a Participant Information Booklet, a Consent Form, a paper version of the Vfrac tool they can self-complete at home, plus a pre-paid envelope for return to the research team. Those who reply by returning the completed Consent Form and completed paper version of Vfrac will be recruited. Satisfaction and ease of use of remote Vfrac (self-completion) compared to F2F assessment will be investigated using a questionnaire. Outputs of the remote self-completion Vfrac (high risk vs low risk) will be compared to the F2F Vfrac (high risk vs low risk) completed at the general practice during WP1, and agreement assessed using Cohen's kappa. Outputs of the satisfaction and ease of use questionnaire will be used to modify the tool if necessary.

<u>WP4: Decision as to whether a future definitive evaluation is warranted, based on the Stop/Go criteria</u>
Data from WP1-3 and other data including that from an analysis of CPRD and a national survey will be used to make a decision based on the following criteria:
4.1 Accuracy of Vfrac tool – already completed and results are favourable (not part of this ethics application)

4.2 Modelled cost-effectiveness - already completed and results are favourable (not part of this ethics application)
4.3 Realistic proportion of older women with back pain identified with vertebral fractures by Vfrac - already completed and results are favourable (not part of this ethics application)
4.4 Realistic required sample size based on analyses of national data (not part of this ethics application)
4.5 Realistic required length of follow-up for the future trial based on results of WP1 plus additional analyses of national data (not part of this ethics application)
4.6 Evidence that the Vfrac tool is acceptable to healthcare professionals and patients based on results of WP2 above

3.4 Summary of the known and potential risks and benefits, if any, to human participants.

This study is low risk.

The main ethical issue relates to the clustering of the intervention. The Vfrac clinical decision tool will be incorporated into the clinical pathways of the three intervention general practices (clusters) and cannot be avoided by individual patients, as they will be the recipient if they consult with back pain. Given the use of this Vfrac clinical tool poses only minimal/no risk, the use of a waiver of consent for this cluster-level intervention is being sought (as discussed in Nix HP et al, Informed consent in cluster randomised trials. BMJ Open 2021;11:e054213. doi:10.1136/bmjopen-2021-054213).

The main risk relates to the coronavirus pandemic. Prior to any face-to-face data collection for WP2, a risk assessment will be undertaken to minimise risk of exposure to Covid-19 by both the participant and researcher, based on current governmental guidelines.

There be no direct benefits for the participants taking part in the nested evaluations.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Objective 1 Feasibility study of Vfrac implementation within primary care	<u>Intervention and control practices</u> 1.1 descriptives of each practice -number of registered patients -number of women ≥50 and ≥65 -computer system -name of PCN/cluster -other demographic characteristics 1.2 type of healthcare professional carrying out initial consultation for back pain 1.3 number and date of consultations by older women with back pain 1.4 resource use after initial consultation for back pain including -consultations in primary and secondary care -referrals inc rheumatology, osteoporosis clinics, geriatrics, physiotherapy, pain clinic -investigations inc DXA, radiology -new medication prescriptions 1.5 new diagnoses since initial consultation for back pain <u>Intervention practices only</u> 1.6 proportion of consultations for back pain where Vfrac was used 1.7 other consultations where Vfrac was used 1.8 results of the Vfrac tool completed in primary care	1.1 baseline – from Practice Manager 1.2 and 1.3 initial consultation – data collected by electronic download from GP records every 3 months for 12 months 1.4 and 1.5 data collected by electronic download from GP records every 3 months for 12 months 1.6, 1.7 and 1.8 data collected by electronic download from GP records every 3 months for 12 months. Identified from unique code generated and embedded within GP records at the time the result of Vfrac was recorded

Objective 2 Nested qualitative assessment of acceptability	2.1 Understanding of acceptability to healthcare professionals and patients, based on the Theoretical Framework of Acceptability[17]. 2.2 Identification of factors that impact on implementation, including barriers and facilitators to delivery, informed by implementation science theory[24].	2.1 and 2.2 one off assessment during single data-collection exercise after recruitment to this nested evaluation
Objective 3 Nested assessment of agreement between use of Vfrac within general practices and self-completion at home	3.1 Outputs of self-completion Vfrac 3.2 Satisfaction and ease of use of self-completion questionnaire based on the framework on Quality in Healthcare developed by Huycke et al[25] to cover process, interpersonal and technical attributes, plus relevant questions from the validated question on remote consultations by Mekhjian et al[26] 3.3 participants views of whether they preferred F2F assessment in primary care, or self-completion at home 3.4 decision as to whether Vfrac can be carried out as a self-completion assessment, or whether it needs to be delivered F2F based on (1) size of agreement: If Cohen's kappa is <0.6 (substantial agreement) remote use (self-completion) will not be incorporated into any future trial, and (2) patient satisfaction and ease of use of the self-completion questionnaire and written instructions.	3.1, 3.2 and 3.3 one-off self-completion data collection after recruitment to this nested evaluation 3.4 N/A
Objective 4 Decision as to whether a future definitive evaluation is warranted, based on the Stop/Go criteria	Stop/Go criterial for future trial: 4.7 Accuracy of Vfrac tool – already completed and results are favourable (not part of this ethics application)	N/A

	4.8 Modelled cost-effectiveness - already completed and results are favourable (not part of this ethics application) 4.9 Realistic proportion of older women with back pain identified with vertebral fractures by Vfrac - already completed and results are favourable (not part of this ethics application) 4.10 Realistic required sample size based on analyses of national data (not part of this ethics application) 4.11 Realistic required length of follow-up for the future trial based on results of Objective 1A plus additional analyses of national data (not part of this ethics application) 4.12 Evidence that the Vfrac tool is acceptable to healthcare professionals and patients based on results of Objective 2 above	

5. STUDY DESIGN

Feasibility study with nested evaluations

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

WP1: Vfrac implementation within primary care

For this work package only general practices will be recruited and then assigned to either intervention or control.

WP2: Nested qualitative assessment of acceptability

Patients: Within the three intervention practices, older women who consulted with back pain and had Vfrac used during that consultation will be recruited.

Healthcare professionals: Healthcare professionals who used Vfrac, or were involved in the implementation of Vfrac within IT systems or clinical pathways will be recruited from within the three intervention practices.

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Within the three intervention practices, older women who consulted with back pain and had Vfrac used during that consultation will be recruited.

6.2. Inclusion Criteria

WP1: Vfrac implementation within primary care

- General practices willing to take part in research
- Within the Bristol area

WP2: Nested qualitative assessment of acceptability

Patients

- Female aged ≥65
- Had Vfrac used during a consultation for back pain
- Patient is willing and able to give informed consent for participation in this nested evaluation

Healthcare professionals

- Used Vfrac during a consultation for back pain OR were involved in the implementation of Vfrac within IT systems or clinical pathways within one of the three intervention practices
- Healthcare professional is willing and able to give informed consent for participation in this nested evaluation

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

- Female aged ≥65
- Had Vfrac used during a consultation for back pain
- Patient is willing and able to give informed consent for participation in this nested evaluation

6.3. Exclusion Criteria

WP1: Vfrac implementation within primary care

- None

WP2: Nested qualitative assessment of acceptability

Patients

- Aged <65
- Has not had Vfrac used during a consultation for back pain
- Patients who do not have the capacity to provide informed consent. Capacity to consent will be assessed by the researcher, in consultation with a clinical members of the study team (EC). This is in accordance with the Mental Capacity Act 2005 (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/).
- Participants who are unwilling to provide informed consent.

Healthcare professionals

- Participants who are unwilling to provide informed consent.

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

- Aged <65
- Has not had Vfrac used during a consultation for back pain
- Patients who do not have the capacity to provide informed consent. Capacity to consent will be assessed by the researcher, in consultation with a clinical members of the study team (EC). This is in accordance with the Mental Capacity Act 2005 (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/mental-capacity-act/).
- Participants who are unwilling to provide informed consent.

7. STUDY PROCEDURES

7.1. Recruitment

WP1: Vfrac implementation within primary care

Recruitment of general practices will be facilitated by the West-of-England Primary Care CRN with whom we have an excellent working relationship (they helped recruit the practices used in development of Vfrac). Purposive recruitment will be via approach to relevant practices from the list of Research Ready practices. Discussions with primary care have identified three potential operational characteristics that may impact on uptake, ease of use and acceptability of Vfrac: these are IT system (EMIS Web and SystmOne), size (small versus large), and within different PCNs/clusters. More generalised advertising will include use of WeReach. Strategies to motivate practices include registration of this study on the national portfolio so patients included count towards practices recruitment numbers (intervention practices only); and offering a clinical update on osteoporosis by the PI, relevant to primary care (intervention and control).

WP2: Nested qualitative assessment of acceptability

Patients: Patients who were assessed using the Vfrac tool during a consultation for back pain in intervention practices (WP1) will be identified by the unique code generated and embedded within their electronic records when Vfrac was used. Healthcare professionals working within the practice will provide potential participants a study information pack including an invitation letter, information booklet and consent form to return to the study team. Purposive sampling will be used, taking into account age, comorbidities and other relevant sociodemographic characteristics. If replies are low (less than the required number of 16-24) a reminder letter will be sent 4-6 weeks after the original invitation. This recruitment of patients will take place before the recruitment for the nested assessment of agreement between remote and hybrid/F2F use.

Healthcare professionals: Healthcare professionals from intervention practices (WP1) will be approached via their Research Lead. Research Leads will send an invitation email to potential participants with information about the study (Healthcare Professional Information Leaflet) and ask them to complete the consent form, contact preferences and availability calendar by clicking on a link within the email to an online Microsoft Form. After giving consent they will also be asked to provide basic demographics (age, gender, ethnicity, professional grouping) and to indicate how they have been involved in setting up or using Vfrac. Participants will include a range of healthcare professionals involved in the identification of OVFs in primary care including GPs and first contact physiotherapists. Purposive sampling will be used to account for professional roles, years of experience, intervention practice and other relevant characteristics. If less than the required number of staff have replied (16-24) a reminder email will be sent 4-6 weeks after the original.

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Patients who were assessed using the Vfrac tool during a consultation for back pain in intervention practiced (WP1) will be identified by the unique code generated and embedded within their electronic records when Vfrac is used. Potential participants will then be sent a study information pack including an invitation letter, information booklet, consent form, and a paper version of the Vfrac tool. If no reply, a reminder letter will be sent 4-6 weeks after the original. To recruit 60 participants, 150 participants will be invited (50 per practice) assuming a 40% recruitment rate based on our previous studies. Pilot data shows that in an average general practice there were 65 consultations for back pain in 2019 by women ≥65, so recruiting 20 per practice to this nested evaluation is realistic. This recruitment of patients will take place after the recruitment for the nested qualitative assessment of acceptability.

7.2. Screening and Eligibility Assessment

WP1: Vfrac implementation within primary care

For this work package only potentially eligible general practices will be invited

WP2: Nested qualitative assessment of acceptability

Patients: Only patients who had Vfrac performed during their clinical consultation for back pain in WP1 will be approached. Only those who send back a completed consent form are eligible to take part.

Healthcare professionals: Only healthcare professionals who used Vfrac, or were involved in the implementation of Vfrac within IT systems or clinical pathways will be approached.

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Only patients who had Vfrac performed during their clinical consultation for back pain in WP1 will be approached. Only those who complete their consent form and send back a completed Vfrac questionnaire are eligible to take part.

7.3. Informed Consent

WP1: Vfrac implementation within primary care

Given that the Vfrac clinical decision tool will be incorporated into the clinical pathways of the three intervention practices (clusters), it cannot be avoided by individual patients consulting with back pain. As use of Vfrac poses only minimal/no risk, the use of a waiver of consent by individual patients for this cluster-level intervention is appropriate.

WP2: Nested qualitative assessment of acceptability

Patients: Informed consent will be by self-completion of the Consent Form, after they have had time to read the Patient Information Leaflet and asked any questions. Patients will be invited to contact the study team if they have any questions. The Consent Form will be included in the study information pack, meaning patients will be able to complete and return them in their own time. This is the same methodology used for the previous studies. The consent form will be checked, initialled and dated by a Vfrac study team member. The information will be logged onto the study database. The hardcopy will be scanned and then stored in a locked filing cabinet.
Healthcare professionals: Informed consent will be by self-completion of a Consent Form that can be accessed by clicking on a link within the recruitment email to an online Microsoft Form, after they have had time to read the Healthcare Professional Information Leaflet. Healthcare professionals will be invited to contact the study team if they have any questions, as above. Informed consent will ensure participants understand that their participation is voluntary, and they are willing to let the research team include anonymous quotations from them in the write up of the study.
WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home
Informed consent will be by self-completion of the Consent Form, after they have had time to read the Patient Information Leaflet and asked any questions. As the forms and questionnaire will be sent to their home address, patients will be able to complete and return them in their own time. This is the same methodology used for the previous studies. The consent form will be checked, initialled and dated by a Vfrac study team member. The information will be logged onto the study database. The hardcopy will be scanned and then stored in a locked filing cabinet.

7.4. Baseline Assessments

WP1: Vfrac implementation within primary care
Baseline data will be collected from Practice Managers to describe their practice based on a proforma (see Vfrac Baseline Data Collection Form – Practices).
WP2: Nested qualitative assessment of acceptability
Patients - Qualitative focus group (1 per participant): Focus groups will be conducted either in person or remotely using video conferencing software. Focus groups will aim to understand and assess the perceived acceptability of Vfrac. A topic guide will be used to guide discussions, with flexibility to pursue emerging ideas[22]. Similarities and differences between participants views will be explored. The topic guide will be informed by the Theoretical Framework of Acceptability[17]. If F2F focus groups are not feasible due to Covid restrictions, or participants do not feel they have the necessary IT skills to participate in online group discussions, participants will also be given the option of taking part in one-to-one interviews. These will either be conducted F2F, by telephone or using videoconferencing software. This will ensure maximum diversity and inclusion.
Healthcare professionals – Qualitative focus group (1 per participant): Focus groups will be conducted remotely using video conferencing software. Focus groups will aim to understand and assess the perceived acceptability of Vfrac and identify factors that impact on implementation, including barriers and facilitators to delivery. During focus groups a topic guide will be used to guide discussions, with flexibility to pursue emerging ideas[22]. Similarities and differences between participants views will be explored. The topic guide will be informed by the Theoretical Framework of Acceptability[17] and implementation science theory[24]. Focus groups may not be feasible given the time constraints of healthcare professionals. If so, provisions will be put in place for individual interviews. These will be conducted by phone or using video conferencing software.

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Self-completion questionnaire (1 per participant): All participants will self-complete the Vfrac questionnaire plus questions on satisfaction and ease of use at home compared to during the consultation for back pain at their general practice. The questionnaire consists of the published Vfrac questions[12] plus questions on satisfaction and ease of use of self-completion questionnaire based on the framework on Quality in Healthcare developed by Huycke et al[25] to cover process, interpersonal and technical attributes, and relevant questions from the validated question on remote consultations by Mekhjian et al[26]. The method for self-measurement of the wall-to-tragus distance was based on a published method[27], and work with our experienced in-house musculoskeletal PPI group to produce easy to use instructions for measurement at home. Instructions for measurement of the wall-to-tragus distance are on a single side of A4 as our patient partners did not want it spread over two sides of paper.

Medical records review: Radiology data will be accessed by Prof Emma Clark to assess for the presence or absence of osteoporotic vertebral fractures. This is necessary, as there is a concern that people with vertebral fractures may find it difficult to measure their wall-to-tragus distance due to difficulty raising their arms above head height[28].

7.5. Subsequent Visits

WP1: Vfrac implementation within primary care

Data will be collected by electronic download from all 6 general practices every 3 months after recruitment. Data to be collected is based on the Vfrac development work and is described in the Follow-up Data Collection Form for Control General Practices, and Follow-up Data Collection Form for Intervention General Practices. From all general practices data will be collected to capture type of healthcare professional carrying out initial consultation for back pain, number and date of consultations by older women with back pain, resource use after initial consultation for back pain and new diagnoses since initial consultation for back pain. In addition, from intervention general practices data will be collected on proportion of consultations for back pain where Vfrac was used, other consultations where Vfrac was used, and results of the Vfrac tool recorded in the medical notes. Data collected will be anonymised at each general practice to remove patient identifiable details such as name, address and NHS number.

Data will also be collected from the online Vfrac tool. When healthcare professionals enter data into the tool after clicking on the URL, inbuilt analytics will be used to record length of time taken and completeness of data collection. For each individual patient, once the data has been submitted, the Vfrac result and recommendations will be available as a 'copy and paste', along with a unique Vfrac code (watermark). This will then be recorded in the individual patients medical records. Each practice will have their own URL allowing access to the online Vfrac tool, for security, and also to allow analysis of differences in data collection across practices. No patient identifiable data will be recorded by the online Vfrac tool, simply the answers to each question for every entry per practice. There will be no ability to link back any data to individual patients, only to practices. The Vfrac result and recommendation for individual patient will have been copied and pasted into the medical records at the time of the consultation, and will be captured during the electronic download from the general practices every 3 months using the watermark.

WP2: Nested qualitative assessment of acceptability

No subsequent visits for patients or healthcare professionals

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

After receiving the completed consent forms and questionnaire, the study team will provide practices with the names, identifiable data (date or birth and address) and Vfrac unique study identifiable number (IDN) of patients who have been recruited to this nested assessment of agreement. Electronic GP records will then be accessed by the practice team to identify the output from the Vfrac tool recorded by the healthcare professional for each patient recruited to this nested assessment of agreement. Outputs of the Vfrac tool recorded by the healthcare professional will be returned to the study team labelled with the Vfrac IDN only and no identifiable data.

7.6. Discontinuation/Withdrawal of Participants from Study

Each patient and healthcare professional has the right to withdraw from the study at any time. Withdrawal from the study will not result in exclusion of the previously collected data for that patient or healthcare professional from analysis. The reason for withdrawal will be recorded, if given. If a patient loses capacity to give informed consent during the study, they will be withdrawn but data to date will be kept.

7.7. Definition of End of Study

The end of study is 18 months after recruitment of the sixth (last) general practice.

8. STATISTICS AND ANALYSIS

8.1. Description of Methods

WP1: Vfrac implementation within primary care

This is mainly a narrative analysis with outputs being two manuals: one to aid future implementation (1B), and one to aid future data collection (1C).

1A Contribution to finalisation of future study design

1A-1 Training requirements for healthcare staff: List of types of healthcare professionals who carry out initial consultation for older women with back pain; description of questions and topics needed during osteoporosis update provided by the PI to all practices; and any other useful information.

1A-2 IT requirements and options for ideal integration within IT systems: Description of difficulties encountered during integration and solutions found; List of options for more easy integration; List of relevant staff to engage in this process; and any other useful information.

1A-3 Options for ideal integration within clinical pathways: Description of difficulties encountered during integration and solutions found; List of options for more easy integration; List of relevant staff to engage in this process; and any other useful information.

1A-4 Required length of follow-up for future study (one of the Stop/Go criteria): The length of follow-up required for any future definitive trial to capture most (≥90-95%) patient journeys.

1D Contribution to understanding of 'usual care': A description of what happens to patients consulting with back pain in the control practices where Vfrac is not being used.

WP2: Nested qualitative assessment of acceptability

All interviews will be audio-recorded, transcribed and anonymised, then imported into NVivo qualitative analysis software. Interviews will be transcribed through an approved company (The Transcription Company UK, https://www.thetranscription.co.uk/) with a confidentiality agreement in place between the company and the University of Bristol, using a standardised protocol used for all qualitative research at the University of Bristol. After the interview has been audio recorded on an encrypted device it will be uploaded to the University of Bristol's secure sever as soon as possible and then deleted from the audio recorder. The data file will then be uploaded to Transcription Company's website using an encrypted file transfer service. It will then be transcribed in full and returned. Transcripts will then be anonymised by the research team.

Data from patients and healthcare professionals will be analysed as discreet datasets, using an inductive thematic approach to identify themes and subthemes in the responses[29]. Themes from both datasets will then be synthesised. To help understand the perceived acceptability of Vfrac, an abductive approach will be used whereby codes will be transposed into the 'Theoretical Framework of Acceptability'[17]. Further factors that impact implementation will also be transposed onto implementation science theory[24]. To illustrate this process, data will be displayed on charts using the framework approach to data organisation[30]. Factors identified by mapping codes onto the 'Theoretical Framework of Acceptability' and implementation science theory, will be synthesised to form a taxonomy of barriers and facilitators to implementation. These will form the basis of recommendations to modify Vfrac and improve delivery in future trials (Manual 1B).

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Agreement: Outputs of the self-completed Vfrac (high risk vs low risk) will be compared to the face-to-face Vfrac (high risk vs low risk), and agreement will be assessed using Cohen's kappa. Standard classifications of Cohen's kappa will be used with 0.6 indicating substantial agreement.

Satisfaction and ease of use: Summary statistics for proportions of participants satisfied with process, interpersonal and technical attributes will be calculated. The free-text fields in the satisfaction and ease of use questionnaires will be used to modify the tool if necessary. Questions have been compiled using the framework on Quality in Healthcare developed by Huycke et al[25] to cover process, interpersonal and technical attributes, plus relevant questions from the validated question on remote consultations by Mekhjian et al[26].

Satisfaction/ease around process: includes questions on written information provided, and value of environment where questionnaire was completed

Satisfaction around interpersonal attributes: includes questions on comfort with completing at home, preference to be seen F2F, value of personal relationships, value of F2F communication

Satisfaction around technical attributes: includes questions on ease of carrying out self-measurements of height, weight and wall-to-tragus distance

Recommendations for completion of questionnaire by friends and family: includes asking whether they would recommend home completion, F2F completion by a nurse or either to friends and family

8.2. The Number of Participants

WP1: Vfrac implementation within primary care

A sample size of six has been chosen because discussions with primary care have identified three potential operational characteristics that may impact on uptake, ease of use and acceptability of Vfrac, and this number of practices will allow observation and explorations of aspects of feasibility within and across these various characteristics.

WP2: Nested qualitative assessment of acceptability

An estimated 4-6 participants will be included in eight focus groups, totalling 16-24 patients and 16-24 healthcare professionals. Final sample size will be determined by data saturation[21].

WP3: Nested assessment of agreement between use of Vfrac within general practices and self-completion at home

Based on assessment of agreement using Cohen's kappa, and assuming approximately 30% of Vfrac outputs should be classified as high risk, for a sample size of 60 (20 from each intervention practice), the margins of error from 95% confidence intervals around estimates of kappa in the range 0.8-0.6 (the definition of substantial agreement) would be from 0.16-0.22.

9. DATA MANAGEMENT

9.1. Access to Data

Dr Emma Clark is the data custodian for this study. Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. It is our intention to share the underpinning research data for work packages 2 and 3 to maximise reuse. Patients will be asked for permission to share anonymised data beyond the immediate project team. The data will be deposited at the University of Bristol Research Data Repository (as restricted data). A metadata record will be published openly by the repository and this record will clearly state how data can be accessed. The actual data is only made available to authenticated researchers upon application. The criteria we check applicants against is: the applicant has provided a verifiable institutional affiliation; the applicant has provided verifiable institutional contact details; the applicant has nominated an appropriate institutional signatory; the applicant has ethical approval in place (this may not be required, depending on the nature of the requested dataset). The request is referred to the University of Bristol Data Access Committee (DAC) for approval before data can be released. Again, the applicant's host institution must agree to a Data Access Agreement.

9.2. Data Recording and Record Keeping

The Chief Investigator, Dr Emma Clark, is responsible for data collection, recording and quality. All online data will be stored on the University of Bristol's secure database. All paper copies will be kept in locked cabinets in the study team's office (limited, secure access) until they are scanned. The computer will be kept in the University of Bristol. Data will be collected and retained in accordance with GPRD. Paper copies of the completed consent forms and baseline questionnaires will be scanned, and stored electronically. Back-up copies of electronic data will be also kept on the University of Bristol mainframe. Study documents (paper and electronic) will be retained in a secure location during and after the study has finished. All source documents will be retained for a period of 5 years following the end of the study. Anonymised data will be stored for 30 years in the data repository.

10. QUALITY ASSURANCE PROCEDURES

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

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Declaration of Helsinki

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

11.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3. Approvals

The protocol, informed consent form, patient information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4. Reporting

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

11.5. Participant Confidentiality

The study staff will ensure that the patients' anonymity is maintained. The patients will be identified only by a study ID number on all study documents and any electronic database, with the exception of the consent form and a linked, secure online file containing personal details, in order to be able to contact the participant during the study period. WP2 focus groups and interviews will be recorded on digital encrypted audio recorders and uploaded onto University of Bristol secure servers as soon as possible to transcribe and analyse. The audio-file will then be deleted from the recorder. Transcripts will be anonymised by removing participant identifiers. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the GPRD, which requires data to be anonymised as soon as it is practical to do so.

11.6. Expenses and Benefits

Patient participant travel for work package 2 will be funded via the research grant.

12. FINANCE AND INSURANCE

12.1. Funding

This study is funded by a National Institute for Health Research grant under the Research for Patient Benefit Scheme (NIHR203026)

12.2. Insurance

The University of Bristol has arranged Clinical Liability insurance to cover the legal liability of the university as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including the Trust's responsibility for University of Bristol employees acting in connection with their NHS honorary appointments).
The University of Bristol holds Professional Negligence insurance to cover the legal liability of the University, for harm to participants arising from the design of the research, where the research protocol was designed by the University.
Professor Emma Clark holds an honorary appointment with the Bristol North Somerset South Gloucestershire (BNSSG) Clinical Commissioning Group (CCG) giving her the protection of the NHS indemnity scheme.

13. PUBLICATION POLICY

On completion of the study, a report will be prepared for the Funder. We will post a short plain English summary on the study website.
The results will be published in peer-reviewed journals and presented at scientific meetings. The NIHR and the University of Bristol open access policies for publication of peer-reviewed papers will be followed.
The PI and Co-applicants will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by a National Institute for Health Research grant under the Research for Patient Benefit Scheme (NIHR203026). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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