Stratified primary care for musculoskeletal consultations compared with usual care: study protocol for the STarT MSK cluster randomized controlled trial.

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Abstract

Background: Musculoskeletal (MSK) pain from common conditions such as back pain and osteoarthritis is a major cause of pain and disability. We previously developed a prognostic tool (STarT Back Tool) specifically for use in primary care to guide the management of patients with low back pain. Prognostic stratified care models involve matching treatments to the patient's prognostic profile to support clinical decision-making in an effort to maximize treatment benefits, reduce harm and increase health care efficiency. A logical next step is to determine whether a similar model of prognostic stratified care might also have benefits for primary care patients with a much broader range of MSK pain presentations (back, neck, knee, shoulder and multi-site pain).

Objective: The primary objective is to determine, in patients presenting with one of the five most common MSK pain presentations in UK primary care, whether stratified care involving use of the Keele STarT MSK Tool to allocate individuals into low, medium and high risk subgroups and matching these subgroups to recommended matched clinical management options, is more clinically and cost effective compared to usual non-stratified primary care.

Methods: We are conducting a pragmatic, two parallel-arm (stratified versus non-stratified care), cluster RCT, with a linked health economic analysis and mixed methods process evaluation. The setting is UK primary care, and the trial will include approximately 24 average-sized general practices randomized (stratified by practice size) in a ratio of 1:1 (approx. 12 practices per arm) with blinding of trial statistician and outcome data-collectors. The units of randomization are the general practices and the units of observation are adults consulting for MSK pain without indicators of serious pathologies, urgent medical needs, or vulnerabilities. Potential participant records will be tagged and individuals sent postal invitations using a GP point-of-consultation electronic medical record (EMR) template. The intervention is supported by an EMR template housing the Keele STarT MSK Tool (to stratify into low, medium and high-risk prognostic subgroups of persistent pain and disability) and recommended matched treatment options. The primary outcome using intention-to-treat analysis is patient-reported pain intensity, measured monthly over 6-months. Secondary outcomes include measures of physical function and quality of life and an anonymized EMR audit will capture clinician decision-making. The economic evaluation will focus on the estimation of incremental quality-adjusted life years (QALYs) and MSK pain-related healthcare costs. A mixed-methods process evaluation is planned to explore a range of potential factors that might influence differences between trial arms, as well as to better understand how stratified care is used and perceived by patients and clinicians involving quantitative analyses focussing on a priori hypothesized intervention targets, and qualitative approaches using focus groups and interviews. The sample size target is 600 patients per arm (1200 in total) from 24 general practices.

Results: Recruitment to the trial commenced on 18th May 2018 and ended on 15th July 2019, after a recruitment period of 14 months in 24 GP practices. It is anticipated that all follow-up and interview data collection will be completed by February 2020.

Conclusions: This study protocol describes the detail of the STarT MSK trial, which aims to investigate the clinical and cost effectiveness of stratified primary care for patients with the five most common MSK pain presentations compared to usual non-stratified care. The intervention was designed to improve patient outcomes including pain intensity, physical function and quality of life, and also clinician decision-making in order to reduce treatment variability and improve adherence to best practice. This

trial is the first attempt, as far as we know, at testing a prognostic stratified care approach for primary care patients with MSK pain. The results of this trial should be available by the summer of 2020. Clinical Trial: ISRCTN15366334

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Title: Stratified primary care for musculoskeletal consultations compared with usual care: study protocol for the STarT MSK cluster randomised controlled trial.

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INTRODUCTION

Background

Musculoskeletal (MSK) pain from common conditions such as back pain and osteoarthritis is a major cause of pain and disability. Estimates from the most recent global burden of disease suggest it is the leading cause of disability adjusted life years (DALYS) in Western Europe and Australia [1]. Overall, it accounts for 6.8% of global DALYS, comparable to cancer (7.8%), ischemic heart disease (5.2%) and mental health disorders (7.4%). This burden is reflected in healthcare use, particularly in UK primary care where MSK pain accounts for around one fifth of all consultations [2-4]. It also accounts for 8.8 million physiotherapy consultations and over 3.5 million calls annually to emergency services [5]. Usual general practitioner (GP) care for MSK pain typically involves a long-term management approach carried out during short 10-minute face-to-face consultations during which patients are assessed and treated with advice, education and reassurance, analgesic medication, referral for investigation(s), referral to other services offering conservative treatments such as physiotherapist-led exercise, or referral to secondary care medical specialists such as orthopaedic consultants and rheumatologists. For many patients, primary care clinicians should reassure them that their MSK pain is not associated with serious underlying pathology, that the prognosis is usually good, and that further tests are not indicated, combined with advice and support to help them stay active [6]. However, evidence suggests substantial variability in clinical practice, with treatment often not in line with best practice recommendations in guidelines, particularly with respect to opioid medication and X-ray investigation [7].

Due to the high prevalence of these common symptoms, MSK pain has overtaken mental health issues such as stress as the number one reason why people take time off work in Europe and the USA [1]. The early identification and improved management of those at risk of severe disabling MSK pain in primary care, where the majority of these patients are managed, is therefore a high priority [8]. Patients with different MSK pain presentations (e.g. back, neck, knee, shoulder or multi-site pain) share common prognostic factors [9]. Co-occurrence of MSK pain located in more than one body region is common [10], with the risk of a poor outcome increasing for those with multi-site pain [11]. For example, the Chronic Pain Risk Score [12] has been shown to have predictive validity among patients with MSK pain in different body regions [13-15]. However, previous prognostic questionnaires such as the Chronic Pain Risk Score and the Orebro MSK Pain Screening Questionnaire [16] were not designed to guide primary care management and their use in primary care clinical practice is uncommon.

As a consequence, we previously developed a prognostic tool (STarT Back Tool) specifically for use in primary care to guide the management of patients with low back pain [17]. Prognostic stratified care models involve matching treatments to the patient's prognostic profile to support clinical decision-making in an effort to maximise treatment benefits, reduce harm and increase health care efficiency [18]. The STarT Back Tool consists of nine questions summed into an index score. It utilises cut-points to identify three prognostic subgroups (patients at low, medium, or high risk of persistent disabling pain). In two previous UK studies, stratified care for back pain, based on matching treatment to prognosis, led to superior clinical and economic outcomes compared to best current practice and usual primary care [19, 20]. The evidence suggested that patients at low risk received less investigations and referral to secondary care, and by contrast patients at medium or high risk were matched to treatments that could better meet their needs, leading to improved outcomes.

Rationale

A logical next step is to determine whether a similar model of prognostic stratified care might also have benefits for primary care patients with a much broader range of MSK pain presentations. The five most common MSK pain presentations in UK primary care are low back pain, knee pain, shoulder pain, neck pain and multi-site pain [2]. In a research programme with four workpackages (the STarT MSK programme) our team first developed and validated a new 10-item prognostic tool, the Keele STarT MSK Tool, to stratify patients with the five most common MSK pain presentations into subgroups (those at low, medium and high

risk of persistent pain and disability) [21]. Secondly, we agreed evidence-based recommended matched treatment options for patients in each subgroup following a systematic review [22], and expert consensus process [23]. Thirdly, we conducted an external feasibility and pilot randomised trial with 524 patients from 8 general practices (4 intervention, 4 control) [24,25]. The pilot trial confirmed the acceptability of using a stratified care approach in primary care consultations and also helped to refine our recruitment, retention and sample size estimates, ahead of the main trial. The findings informed the final wording of the self-report version of the STarT MSK Tool, led to a Clinician Completed version of the tool, and allowed us to simplify the recommended matched treatment options. All changes made to the main trial protocol following the pilot trial were discussed, shared and agreed with the trial funder the National Institute for Health Research (NIHR), the Trial Steering Committee and Data Monitoring Committee.

Aims and Objectives

Primary Objective

The primary objective of the STarT MSK main trial is to determine, in patients presenting with one of the five most common MSK pain presentations in UK primary care, whether stratified care involving use of the Keele STarT MSK Tool to allocate individuals into low, medium and high risk subgroups, and matching these subgroups to recommended matched clinical management options, is more clinically and cost effective compared to usual non-stratified primary care. The primary clinical outcome is average pain intensity over the past 2 weeks measured each month for 6 months.

Secondary Objectives

The secondary objectives of the trial include:

1. Examining differences in secondary clinical outcomes, clinical decision-making and behaviours and health economic outcomes at 6-months follow-up.

- Patient outcomes include physical function, confidence to manage their pain (pain self-efficacy), psychological distress, fear avoidance beliefs, patient perceived reassurance from their clinician, pain interference with sleep, hobbies/leisure activities, pain interference with work and daily routine, health related quality of life and patient satisfaction with care received.
- Clinical decisions and behaviours of interest include identifying whether stratified care changes the primary care management of MSK patients. We anticipate that primary care clinical management will become more consistent for patients within each risk group and be more in line with stratified care, where patients at low risk of persistent disabling pain are less likely to be referred for additional healthcare whereas patients at medium or high risk are more likely to be referred for additional healthcare in ways that match the recommended management options. Using the practices' medical record data we will examine differences between the trial arms in clinical decision-making and behaviours.
- Health economic evaluation will determine the cost-utility of stratified care in comparison to usual, non-stratified care. A cost-consequence analysis will initially be reported, with a subsequent cost-utility analysis from a healthcare perspective to determine cost per quality-adjusted life years (QALY) gained, calculated using EQ-5D-5L responses from the initial and 6-month questionnaires. A broader costing perspective will be considered in a sensitivity analysis, taking into account NHS/Personal Social Services costs and productivity costs associated with time off work. The outcome of interest for the economic analysis will be QALYs. Additional exploratory analyses will consider the cost-effectiveness of stratified care compared to usual non-stratified care for patients at low, medium and high risk of persistent disabling pain.

2. Undertaking a process evaluation to explore how stratified care, as a complex intervention, interacts with existing patterns of service organisation, professional practice, and professional-patient interaction. The evaluation will use mixed quantitative (e.g. including a mediation analysis) and qualitative methods, integrating data both at the collection and analysis stages, in order to generate more detailed and comprehensive findings.

METHODS

Study Design and Setting

The STarT MSK trial is a pragmatic, two parallel arm, cluster RCT, with a linked health economic analysis and mixed methods process evaluation. The setting is UK primary care, and the trial will include approximately 24 average sized general practices with a total registered adult population of approximately 120,000. General practices will be randomised to either the stratified care intervention (approx. 12 practices) or to continue with usual, non-stratified care (approx. 12 practices). The units of randomisation are the general practices and the units of observation are adults consulting for MSK pain with one of the five most common MSK pain presentations. The intervention in both arms of the trial will include an embedded template within the general practice computer system which will 'pop-up' during the first relevant Read-coded MSK pain consultation within the specified study period (termed the "MSK consultation"; this may be the first consultation, or a repeat consultation for MSK pain). However, the content of the template will differ in the two arms of the trial (see Figure 1); in the control arm it includes three questions; i) the eligibility of the patient to be invited to participate, ii) the location/site of MSK pain for which the patient is consulting, and iii) average MSK pain intensity in the past two weeks (primary outcome). In the intervention arm, in addition to these three questions, the template also includes Keele STarT MSK Tool and recommended matched treatment options (see Figure 2).

A cluster RCT rather than an individual patient RCT was chosen for both scientific and practical reasons. Stratified care is a new way of working and the tool, training and support is delivered at general practice level (e.g. the computer template once installed will 'pop-up' on all the computers in the practice). Primary care clinicians would likely find it difficult to behave differently towards individuals randomised to control and intervention arms, and therefore the probability of contamination between the two arms would be high using an individual patient randomised trial design. This trial can be thought of as a professional-cluster intervention type [26], in that the stratified care intervention involves changing the professional's behaviour during the consultation, in this case using a prognostic tool and matching patients to clinical management options. Although the patient can opt out of data collection, the intervention is still likely to have an effect on them since it involves introducing specific questions and recommendations about matched treatment options into the consultation.

Minimising Systematic Bias

The risk of selection bias, specifically of recruitment and participation bias, is a known concern in cluster RCTs [27]. A number of steps have been taken to minimise this, which were tested in the pilot RCT, where we observed no evidence of selection bias:

- The initial part of the computer template to help identify eligible patients is automated based on diagnostic codes entered during the consultation and operates in the same way in both arms of the trial.
- If the clinician deems a patient to be ineligible, they are asked to give a reason for this exclusion so that these reasons can be compared across intervention and control arms. This process is monitored during trial recruitment with monthly feedback provided to participating practices showing the frequency of template non-completion, and the proportions of different reasons for ineligibility recorded.
- Patients in both arms of the trial will receive identical study invitation packs comprising the same patient information leaflet (which does not mention stratified care, only that the study seeks to better understand how common aches and pains affect patients and how primary care can be improved), invitation letter, questionnaire, and consent form for data collection, minimising the risk of patients in intervention or control arms being more or less likely to participate (participation bias).

General practice recruitment and consent

It is anticipated that an estimated eligible target population of approximately 5,000 patients will be identified within a 6-month recruitment window from approximately 24 average-sized general practices (approx. 120,000 registered adults). Practices will include those that range in size (based on patient list size and number of GPs), and a range of settings (urban, semi-urban and rural). Practice eligibility criteria includes;

those that use the EMIS Web clinical system (most commonly used electronic medical record system in the UK); those proficient at using Read codes (diagnostic codes) during MSK consultations evidenced through an audit of their recent Read coding behaviour; willingness to undergo the training and support sessions needed to become familiar with the stratified care intervention; willingness to participate in anonymised aggregated medical record audits of MSK consultations during the trial recruitment period; and willingness to engage with the process evaluation.

The balance between scientific considerations and the need for consent is a known issue for cluster RCTs [26, 27]. Informed consent for practices to participate is formalised through written agreements led by the senior GP partner in each practice acting as 'guardian' for patients in their care, following agreement with their team to provide either usual care or stratified care for the period of the trial (dependent on random allocation). It is anticipated that practices will actively recruit patients for approximately 6-months, with practice recruitment periods staggered over a 12-month period. Reimbursement for practice time to recruit and participate in the training is provided.

Individual Patient Participants

Potential individual patient participants will consult at a participating practice with one of the five most common MSK pain presentations (back, neck, knee, shoulder or multi-site pain) as determined by the clinician at the point-of-consultation.

Patient inclusion criteria: aged 18 years and over, registered at the practice during the recruitment period, with a recorded relevant MSK pain Read code entered into the computer system (this may be the first, or a repeat consultation), a completed study template, consent to study data collection, consent for research team to have access to their medical record data, and completion of the initial postal questionnaire within 4 weeks of the first mailing.

Patient exclusion criteria: those with indications of serious 'red flag' pathology (eg. recent trauma with significant injury; acute, red, hot swollen joint; suspected fracture; joint infection; cancer; inflammatory arthropathy such as rheumatoid arthritis; spondyloarthropathy, polymyalgia rheumatic; crystal disease (gout); urgent medical care needs (e.g. Cauda Equina Syndrome); vulnerable patients (including any patients on the 'severe and enduring mental health register', or those who have a diagnosis of dementia, or those with a recent diagnosis of a terminal illness, or those who have experienced recent trauma or bereavement, or those nearing the end of their life); those unable to communicate in English (both in reading and speaking).

Patient recruitment for outcome data collection

As described above, an electronic computer template designed to automatically fire to help identify patients will be installed on participating practice computer systems, when one of around 200 different MSK pain related Read codes (symptom or diagnostic codes) is entered, as defined by Jordan et al. [2] and informed by our pilot RCT. Clinicians will be trained to use this system, but it is already standard practice in NHS primary care since 1985 for clinicians to use this standard vocabulary to record patient findings and procedures in health and social care IT systems across UK. In the consultation, when an MSK related Read code in entered onto the electronic medical record system, the trial specific template will be activated. Initially, it prompts the clinician to notify eligible patients about the research study by reading the following:

"Our practice is working with Keele University on a research study about ways to improve treatment for common aches and pains such as back, neck, knee and shoulder pain. As you have consulted today for one these conditions, we would like to share your contact details with the researchers so that they can send you details of the study. Is that ok with you?"

Patients who do not give this consent do not have their contact details shared with the research team. Individuals who have previously asked not to be part of any research within the practice are given a Read code that prevents the template from firing in the first place. Retention of identifiable patient data is restricted to the limited period of invitation only, after which time the data of subsequent non-consenters to the trial will be destroyed. Keele Clinical Trials Unit (CTU) operates this activity in compliance with the provisions of the Data Protection Act (1998) and adheres to appropriate standards of governance and security as outlined by the

Sponsor's (Keele University) Standard Operating Procedures (SOPs).

Practice staff supported by the NIHR Clinical Research Network (CRN) where possible, will regularly (typically weekly) send the contact details of patients for whom the template has been successfully completed to Keele CTU for the purpose of mailing patients their invitation letter, using a secure NHS.net email to transfer data including; name, address, Read code for pain site, date of consultation, and EMIS patient identification number. On a monthly basis the participating practices provide anonymised information about the numbers of patients for whom the study template is activated and of those how many are not fully completed. This facilitates the provision of a monthly report of their template completion rate and for intervention practices, additional detail about their fidelity to choosing recommended matched clinical management options for patients at low, medium and high risk.

Eligible participants (from both trial arms) will be sent identical study packs in the post containing: a letter from the patient's general practice introducing the study, a patient information leaflet (PIL), which describes the study and includes instructions of what to do if they wish to take part, an initial questionnaire, including a consent form to record consent for data collection, and a stamped addressed envelope. The following mechanisms will ensure only eligible and appropriate patients are invited; a) a list of relevant exclusion Read codes (e.g. recent cancer diagnosis) will be used to automatically prevent the template from firing, b) clinicians will be able to screen individual patients for their suitability at the point of consultation.

In the initial questionnaire sent to patients, participants will provide their written consent for researchers to use their data for this research. A study team member (blind to practice allocation) will support patients who telephone with questions or who need additional support to complete their postal questionnaires, monthly SMS texts or one-page questionnaires. The same set of MSK Read codes that trigger the automated template was successfully used as the identification method in our pilot RCT. The electronic identification method is designed to ensure the template 'pop-up' is only activated once per patient, so individuals can only be invited once to participate in this study. Eligible patients who do not respond within two weeks to their initial study invitation will be contacted again with another study pack. Patients who do not complete their initial questionnaire within four weeks of the initial mailing date will not be contacted again for follow-up data. Patients who return their initial questionnaire and consent to further data collection will be included in the study. The primary outcome (pain intensity) will be collected once a month for six months via SMS text or one-page postal questionnaire (depending on participant preference).

The procedures for reminders for the SMS text monthly communications are as follows: the initial contact will be sent on the next Sunday afternoon that is closest to a calendar month following their initial questionnaire mailing date. If there is no response to this initial contact, a reminder communication will be sent on Tuesday afternoon and if again there is no response after 48 hours, we will send the monthly one-page postal questionnaire. On the second consecutive month we will repeat this procedure but if there is no response, in addition to sending the monthly one page postal questionnaire, a study team member will telephone the patient to establish what the problem is, seek to resolve it, provide appropriate support and collect the data where possible. For those receiving the monthly one-page postal questionnaire, non-response after two weeks will lead to another one-page postal questionnaire. Non-response on a second consecutive month will lead to a study team member telephoning the patient to establish what the problem is, seek to resolve it, provide appropriate support and collect the data where possible. Participants will also receive a 6-month follow-up questionnaire to collect further outcomes. Non-responders to the 6-month follow-up questionnaire will be sent a reminder postcard at two weeks, a full questionnaire two weeks later (i.e. at four weeks), and for those who have not responded, a brief questionnaire will be sent after six weeks to collect key outcome measures. We will try to collect minimum data over the telephone from participants at eight weeks where needed. These follow-up methods have been used successfully in previous studies [28-31] including the pilot RCT.

Randomisation and blinding

Practices will be randomised in a ratio of 1:1 to intervention or control using stratified block randomisation [32] based on practice patient list size using a Keele CTU computer-generated random sequence and concealment by ensuring each practice has an anonymised code. The randomisation sequence/stratification will be carried out by the senior trial statistician. The block randomisation will follow Keele CTU's randomisation SOP and the data sequence will be held on a secure server. Blinding for individual clinicians is not possible but any staff involved in the collection or database entry of patients' outcome data will be blind to

allocation. Access to the allocation sequence will be restricted to those with authorisation. Allocation will be shared with the study team (except for the trial statistician and data entry staff who are to remain blind) who will then arrange to inform each practice about their allocation. Data cleaning/checking through stage 1 'data-freeze' and stage 2 'data-lock' reviews will be carried out by the trial statistician, thus maintaining blinding to allocation. The Trial Steering Committee (TSC) will also be blinded to allocation unless it becomes absolutely necessary to reveal allocation. The Data Monitoring Committee (DMC) trial statistician will be involved in the allocation assignment, and therefore will not be blinded throughout the study. These processes follow recommendations for cluster trials [27] to reduce selection bias where randomisation is prior to patient data collection.

Interventions

Practice Recruitment Template Installation

Following confirmation that a practice is eligible and willing to take part, an initial setup meeting will be held between the practice, study research team and a CRN member. This will take place for all practices in both arms of the trial and will be followed by training sessions where the computer template will be installed and demonstrated on the practice's EMIS clinical system. Once the template is installed, the practice is 'live' and potentially eligible participants will be identified in consultations.

Intervention Arm

The recommended matched clinical management options are not new but summarise available evidence-based options into those considered by expert consensus to be appropriate for patients at low, medium and high risk of persistent pain and disability.

The STarT MSK stratified care approach has two components i) prognostic tool and ii) matched options:

i) The Keele STarT MSK Tool (clinician completed version) © [is freely available at keele.ac.uk/startmsk] is used in the patient consultation [21], and is supported by being embedded in the practice's computer template, dedicated training and support sessions, regular audit, peer feedback and clinical mentoring opportunities using an evidence-based clinician support package to support clinician behaviour change [33]. The prognostic tool has ten questions from which the patient's score and subgroup (low, medium or high risk of persistent pain and disability) are calculated.

<insert Figure 2 here>

ii) Appropriate matched clinical management options based on an individual's prognosis on the Keele STarT MSK Tool will be displayed to support clinical decision-making. The matched clinical management options were identified by an evidence synthesis [22], followed by three expert consensus workshops [23], during an earlier phase of research and then further refined following the STarT MSK feasibility and pilot [24].

<insert Figure 3 here>

Per protocol treatment decision rules:
Patients at low risk will be considered to be treated "per protocol" if they receive only treatment options 1 or 2 (see Figure 3). Patients at medium risk will be "per protocol" if they receive any of options 3-6 (although option 5 for specific pain sites only). Patients at high risk will be "per protocol" if they receive option 3 or any options between 7-11.

It can be seen from Figure 3 that the matched options for patients at low risk include advice and education (using printed materials where possible), over-the-counter analgesics and avoidance of MSK investigations and referrals (where possible). Matched options for patients at medium risk, in addition to the low risk options include GPs being encouraged to refer patients to physiotherapy, to review their pain medication and to consider investigations where necessary. Matched options for patients at high risk, in addition to the medium and low risk options include, consider atypical analgesia if neuropathic pain is present, referral to specialist services (e.g. orthopaedics, rheumatology and pain clinics), imaging and/or booked reviews to manage complex clinical factors such as co-morbidities, polypharmacy, and frailty.

Clinician support to deliver stratified care

The training and support sessions provided to intervention and control clinicians are designed to equip them with the knowledge and skills to complete the study recruitment template and understand the study inclusion/exclusion criteria. In addition, for intervention practices a 2-hour intervention training session will be provided. This includes learning about previous stratified care research [19, 20], the rationale for developing this new intervention and for investigating whether it will benefit patients with a broader range of MSK pain. Training will describe the aim to reduce unnecessary healthcare for patients at low risk, whilst better targeting healthcare resources for patients at medium or high risk. Clinicians will have a demonstration of how to use the new approach and have the opportunity to try it out and ask questions and explore how it can be integrated into routine practice. The session will also include discussion and clarification about how the approach differs from usual care and each of the recommended clinical management options. We will also invite a representative from the local MSK physiotherapy service to the training sessions and discuss how best to ensure that patient referrals to physiotherapy include a record of the index consultation and the patient's STarT MSK Tool risk group and agree the best method for physiotherapists to communicate with referring GPs if they have a concern about a patient. A feedback meeting will be held with all participating practices (intervention and control) roughly 6 weeks after starting recruitment to discuss the report of their use and completion of the study specific IT template. For intervention practices, additional feedback on their fidelity to the recommended matched clinical management options will also be provided, comparing each clinician with their colleagues in the same practice and with other clinicians in the trial (anonymised). Monthly email feedback reports will be sent to participating practices.

Physiotherapists linked to intervention practices will also have the opportunity to attend a short training session about the trial and be required to avoid treating patients from control practices for the period of the trial to avoid contamination. However, other key features of physiotherapy care will be as similar as possible for patients irrespective of whether they come from intervention or control practices, including: physiotherapy waiting times, treatment session length and number, and the clinical grade of treating therapist. We will collect these process data from physiotherapy services using a mix of usual clinical record data and standardised case report forms for the study.

Control Arm

In the usual care control arm, patients will consult at their general practice, be assessed and receive advice and treatment as usual (e.g. advice and education, medication, referral for investigations or tests, or referral to other services such as physiotherapy, MSK interface clinics or secondary care specialists such as orthopaedics and rheumatology), without the use of formal stratification tools. In order to keep the control arm as close to "usual care" as possible, clinicians will be advised to follow their usual approach for responding to a patient's pain intensity rating for the presenting MSK problem. Asking a patient the intensity of their pain and where their pain is coming from is common practice [30] and therefore should have little impact on the "usual care" provided.

Data collection

There will be three different types of data collection:

a) Individual patient data, collected from:
   i) the practices' completed computer templates at the point of consultation
   ii) initial and 6-month postal questionnaires to participants (full and minimum data versions)
   iii) monthly SMS text or one-page postal questionnaire
b) Clinician decision-making and behaviours using data collected from medical records and case report forms
c) Practice level anonymised aggregated data of MSK Read codes and template use

a) Individual patient outcomes

i) General practice IT template

The first item on the template asks the primary care clinician to confirm if their patient gives consent to have their contact details shared with the research team. If the answer is Yes, then the clinician will record the location of the patient's MSK pain. How this is answered determines which study letter and questionnaire the

patient will be sent, as these are slightly different for patients with back, neck, knee, shoulder or multi-site pain. The item reads:

Please confirm the primary pain site the patient is consulting with today:
Possible response options include: 'back pain', 'neck pain', 'knee pain', 'shoulder pain', 'multi-site pain', or 'unable to complete template' (which leads to the exit screen).
The third question on the template asks the clinician to record the patient's MSK pain intensity by asking:
How intense was your pain, on average, over the last 2 weeks?
[Responses on a 0-10 scale, where 0 is "no pain" and 10 is "worst pain ever"]

ii) Initial and 6-month follow-up questionnaires

The initial and 6-month follow-up postal questionnaires are designed to collect information on descriptive characteristics of the participants, pain-related characteristics and primary and secondary outcome measures (see below). Patients are informed in their study invitation that they have been contacted because they recently visited their general practice (the date of their visit will be given) for their MSK pain, which will be pre-populated in the letter (e.g. knee pain, shoulder pain etc.) using information from weekly downloaded template codes.

Participants will also be told that it is important they think about their <*MSK pain*> as they answer the following question:

Thinking about your (e.g. neck) pain: Over the last 2 weeks, on average, how intense was your pain? [Responses from 0 = no pain to 10 = worst pain ever]

iii) Monthly SMS text or one-page questionnaire for 3 items including the primary outcome

In addition to the primary outcome (pain intensity), the monthly SMS text or one page questionnaire includes two potential mediating variables using the following single items for psychological distress and self-efficacy which are taken and adapted with permission from the validated Musculoskeletal Health Questionnaire [34]:

"How much distress have you been experiencing because of your pain, on average, over the last 2 weeks? [0 = no distress to 10 = extreme distress]"
"How confident have you felt about managing your pain by yourself e.g. medication, changing lifestyle? [0 = not at all confident and 10 = extremely confident]"

b) Clinician behaviours via linked medical records

Clinician decision-making and behaviours will be examined via a review of the practice computerised medical records for all patients who give consent for this (at the end of the initial questionnaire). This will allow data to be analysed from a) individual patient outcomes b) the initial patient-clinician consultation electronic template, c) further aspects of their medical record over 6-months following the MSK consultation. Variables of interest from the MSK consultation will include: the date of consultation, coded reason for the consultation, MSK pain intensity and location, STarT MSK Tool (clinician completed version) individual items and total score (intervention arm only), and information about the management decisions and other actions taken by the clinician. Other clinical behaviours of interest are described in the outcomes section. The information collected on the patient's risk subgroup and management options in the intervention practices will be audited and fed back to clinicians at regular intervals, allowing them to see how closely they have followed the matched clinical management options. At the end of the trial we will also report the fidelity of clinicians in the intervention practices in terms of completing the tool and choosing matched treatments options. The template MSK pain intensity score will also provide the initial score for the primary outcome for participants in both arms of the trial.

Physiotherapists treating patients referred from participating practices will complete their usual clinical records. At the end of the trial, we will collect details about the physiotherapy treatment provided for consenting trial participants to compare between intervention and control.

c) Practice level anonymised and aggregated data of MSK Read codes (n=~9,000).

Each participating general practice will provide anonymised medical record data from potentially eligible

patients for whom the template was activated through entry of an MSK Read code. We will compare:

- the characteristics of those patients in which the template is activated with those who respond to the initial questionnaire and provide individual level patient outcomes. The information examined will not involve any patient identifiable data and will not be linked to any other data unless prior patient consent has been.
- aspects of clinical behaviours for 6-months following the index consultation to compare intervention and control practices for key treatment processes for each risk subgroup. For example, this will include requests for:
  i) prescriptions (e.g. categorised into such as simple analgesics, non-steroidal anti-inflammatories (NSAIDs), neuromodulators, muscle relaxants, corticosteroid injections and opioids)
  ii) referrals (e.g. categorised into physiotherapy/MSK interface services, specialist services including orthopaedics, pain clinics, and rheumatology)
  iii) imaging (e.g. categorised into x-rays/MRI scans, MSK ultrasound scans and bone density scans)
  iv) sick certifications or fit-notes (e.g. categorised into number per patient and mean length in days)
  v) repeat MSK general practice visits

The collection of anonymised and aggregated medical record data is not uncommon within similar general practice research studies that examine potential recruitment bias [35] or for intervention studies examining clinician decision-making and behaviours during the consultation (e.g. POST cluster trial [29] and SWAP cluster trial [31, 36].

Patient and Public Involvement Engagement (PPIE)

This study was discussed and shaped with PPIE involvement through dedicated workshops prior to the funding submission. The PPIE group agreed with the importance of developing a more robust research base for treatments that can improve the primary care management of MSK pain. Their discussions informed the design and piloting of the text message system and one-page postal questionnaire, used to capture the primary outcome of pain intensity, they also reviewed and improved the patient facing documentation for the study. Members of the group have expressed an interest in being involved in the analysis of the qualitative data, and it is intended to include them in that process.

Further PPIE meetings were held following the feasibility and pilot trial to identify improvements for the main trial. Their recommendations included:

- Updating the invitation pack to provide greater clarity to patients about what is involved in taking part in the trial
- Simplifying the consent form in the initial patient questionnaire
- Removing the prize draw system we used for participants in the feasibility and pilot trial. This was considered to potentially be confusing for patients and did not appear to lead to a higher response rate to the questionnaires than those in similar research studies.

Outcomes

Primary Outcome:

The primary outcome for the trial is the patient reported clinical outcome of pain intensity, measured monthly over 6-months. Pain intensity is a recommended outcome for trials of MSK pain [37] and had strong face validity among members of the PPIE group. In addition, analysis of our previous MSK cohort data confirmed that this outcome is sensitive to change in this population.

Secondary Outcomes:

Secondary clinical outcomes captured at initial and 6-months stage include: body site specific physical functional measures, using the Roland-Morris Disability Questionnaire (RMDQ) for patients with back pain [38], the Neck Disability Index (NDI) [39, 40] for patients with neck pain, the Shoulder pain and disability index (SPADI) [41] for patients with shoulder pain, the Knee Injury and Osteoarthritis Outcome Score Physical Function Short-form (KOOS-PS) [42] for patients with knee pain and the Short Form 12v2 Physical

Component Scale [43] for patients with multi-site pain. Other clinical outcomes will include patients' risk of persistent disabling pain using the Keele STarT MSK Tool, the MSK pain symptom severity and impact using the Musculoskeletal Health Questionnaire [44] which includes measures of pain interference with sleep, physical activity level, hobbies/leisure activities, work and daily routine, and quality of life with items for patients' confidence to manage their pain (pain self-efficacy), emotional health, and understanding of how to deal with their condition. We will also collect fear avoidance beliefs using the 11-item version of the Tampa Scale of Kinesiophobia [45], and patient perceived level of reassurance from their clinician will be captured using the Holt and Pincus [46] reassurance scale, which has four sub-scales: information gathering, relationship building, generic reassurance and cognitive reassurance. Other outcomes will include health related quality of life using the EQ-5D-5L to calculate quality adjusted life years (QALYs) in the health economic evaluation [47] and single item questions to capture patient satisfaction with care received, receipt of written education material from their clinician, and overall rating of change in their MSK pain since their primary care consultation [48].

Baseline population descriptors:

To help describe the population recruited, additional baseline descriptors will capture: health literacy using the Single Item Literacy Screener (SILS) [49], episode duration of MSK pain by asking time since last whole month free from this pain, age, sex, employment and their most recent paid job title (to calculate their socio-economic status).

Healthcare resource use:

Questions on additional healthcare resource use and patient borne costs including MSK pain-related hospital inpatient stays, outpatient attendances (e.g. to physiotherapy), other NHS and private practice healthcare appointments and over-the-counter medicines and treatment will be included in the 6-month questionnaire. Work performance will be assessed through a single-item work presenteeism question, and time (days) off work will be aligned to occupational information to ascertain cost of absenteeism.

Table 1 summarises the patient reported data being collected.

<INSERT TABLE 1 Here>

Process evaluation

A process evaluation is planned to explore a range of potential factors that might influence differences between trial arms, as well as to better understand how stratified care is used and perceived by patients and clinicians. Following recent MRC guidance on process evaluations for complex interventions [50] we have designed a mixed method approach [51]. This will use quantitative analyses focussing on *a priori* hypothesised intervention targets, and qualitative approaches using focus groups and interviews.

A key aim of the process evaluation is to better understand the role of potential intervention targets (mediators) on differences in outcomes between the trial arms [52]. The evidence from our previous stratified care trial (for back pain, the STarT Back trial) suggested that the identification and targeting of psychological distress among patients at high risk led to improved outcomes [53]. In addition, a systematic review has recently summarised available evidence and identified pain self-efficacy as another potential mediator [54]. Evidence from the Keele IMPaCT Back study [20], which sought to implement our stratified care approach for patients with low back pain consulting in general practice, suggested that important clinical behaviour changes included more systematic identification of patients who are 'at risk' of persistent disabling pain who need additional support (leading to more referrals to physiotherapy). After careful consideration by the trial team, a number of potential treatment mediators have been identified *a priori*, including three potential factors at the patient level, (i) reduction in levels of psychological distress measured each month with a single item, (ii) increases in pain self-efficacy measured each month with a single item, (iii) increases in patient perceived reassurance following primary care consultation measured via the initial questionnaire. Changes in these potential patient level treatment mediators will be examined within a mediation analyses using causal modelling techniques (e.g. structural equation modelling) to confirm if they are in the causal pathway explaining any observed between arm differences in outcome with results also examined at each subgrouping level (low, medium and high).

In addition, one we have identified a number of *a priori* potential mediators at the level of clinical behaviour, measured using the medical record data, including the proportion of patients who receive: prescription medications for MSK pain, referrals to other services (e.g. physiotherapy and secondary care specialists), referrals for investigations (e.g. radiographs, MRI/CT scans, blood tests), sick certifications (fit notes), and further MSK related consultations. We will test if there are significant differences in these behaviours between intervention and control practices and whether any of these differences are associated with the results in terms of patients' pain intensity.

Sample size

In an average sized UK general practice (6,000 registered adults) we expect that about 800 potentially eligible patients will consult with the musculoskeletal pain sites of interest per year, or 400 over 6-months. The feasibility and pilot trial showed that on average the template was activated 375 times over 6-months in each practice, and clinicians fully completed it in 41% of cases (154 times or 6 times per week), leading to a letter inviting the patient to participate in the data collection. From this, we expect 40% of patients invited will return their initial questionnaire in the main trial, be eligible and consent to further data collection (or 62 over 6-months in one practice). However, to be more cautious, given general uncertainty in data and in generalisability of pilot estimates, we have conservatively estimated the average number of participants recruited per practice within 6-months in the main trial to be around 33% of those invited (or n=50 in 6-months or n=9 per month per practice).

The trial is powered at 90% to test the hypothesis of overall superiority of stratified primary care versus usual care based on an alpha of 5% (two-tailed) to detect a small 'effect size' (standardised mean difference) of 0.2 [55] in the primary outcome (pain intensity). An effect size of 0.2 was considered to be appropriate based on information from the feasibility and pilot trial, in which the proportion of responders in the three risk subgroups was: 32% at low risk, 55% medium risk, and 13% high risk. Our previous trial of stratified care for patients with low back pain (the STarT Back trial) found an effect size of 0.3 and 0.4 in the primary outcome (back pain-related physical function) in patients at medium and high risk respectively and so we have assumed these standardised differences in this new trial [19]. Also, the minimal clinically important difference for the NRS-pain scale in MSK pain has been reported to be 1-point [56], which equates to an effect size of about 0.4 relative to an expected SD of about 2.5 [55]. We expect that there would be little or no difference between stratified care compared to usual care for patients in the low risk subgroup. Hence, through multiplying these effects by the expected proportion within each of the subgroups, the overall effect size of interest is 0.2 (equating to an absolute mean difference of about 0.5 in pain intensity on a 0 – 10 scale).

The sample size calculation takes account of clustering of individual participants by practice and likely participant dropout over 6-months follow-up (inflationary effects on sample size requirement) as well as repeated measurements and adjustment for corresponding baseline pain intensity score (deflationary effects). We have allowed for an ICC of 0.01 based on previous patient-level data from primary care trials [57] as well as expected variation in recruitment per practice using a guideline coefficient of variation of 0.65 [58], and together with an expected loss to follow-up across all time-points of approximately 25%, these factors combine to give a sample size inflation factor of ×2.3 (based on an average cluster size of about 50 participants per practice in 6-months). Correlation of data within 6 repeated measurements and correlation of follow-up scores with baseline score are typically 0.7 and 0.5, respectively [59], which combine to give a sample size deflation factor of ×0.5). The product of inflation and deflation effects results in a magnification of 1.15 compared to a conventional, individual-patient, single follow-up comparison, whereby the sample size requirement would be 525 per trial arm (or 1050 in total). The adjusted sample size target is therefore 600 patients per arm (1200 in total) from 24 general practices (12 per arm).

Statistical reporting

Data will be reported according to the Consolidated Standards Of Reporting Trials (CONSORT 2010) statement [60, 61], including extensions to cluster randomised trials [62] and pragmatic trials [63].

Final analysis will be carried out after all the data are collected, entered and cleaned according to Keele CTU SOPs. A flow diagram will show the flow of participants through the trial including reasons for not taking part and loss to follow-up (split by trial arm). For trial participants, summaries of continuous variables will comprise the number of observations used, mean, median, SD, inter-quartile range as appropriate for the

distributional form of the data (in total and split by treatment arm). Summaries of categorical variables will comprise the number of observations used, and the number and percentage of observations in each category.

Inferential analyses will include reporting of the main (point) estimate for the mean between-arm difference (numerical outcomes) or odds ratio (categorical outcomes) along with 95% confidence intervals and P-values (two-tailed). Odds ratios will also be converted to absolute risk differences (using the usual care prevalence as the base-reference in any conversion). Hypothesis tests will use a two-sided 5% significance level. Main analyses will be performed independently by the trial statisticians using the protocol and statistical analysis plan agreed with the TSC. For any results discordance(s) if consensus agreement cannot be reached then a third (independent) statistician will be asked to review and resolve any differences.

Methods of analysis

Descriptive statistics: Baseline characteristics

The baseline demographics and clinical characteristics of general practices and individual participants will be reported. CONSORT guidelines generally do not recommend statistical significance testing of baseline imbalances between trial arms. However, a more recent publication suggests baseline testing of individual level characteristics for cluster RCTs to examine the level of selection bias as indicated by potential imbalances in baseline covariates between arms [64].

Main analysis of primary outcome

To avoid any potential bias in the analysis, intention to treat (ITT) will be the primary analysis population (including primary, and secondary outcomes) unless otherwise stated in the detailed Statistical Analysis Plan (available from the authors). This is defined as general practice-clusters (and affiliated participants) being analysed as they are randomised regardless of the intervention. Data for individuals who withdraw consent to participate in data collection will be included up to the point of withdrawal. Primary analysis will compare mean difference in pain intensity scores between trial arms over 6-months follow-up using a hierarchical linear mixed regression model evaluating repeated measures data at 1, 2, 3, 4, 5 and 6 months follow-up (level-1) within individuals (level-2) and taking into account clustering of individuals within general practices – the unit of randomisation (level-3). The analyses will be adjusted for age, sex and baseline pain intensity score (recorded from the IT template at the point of consultation) at the individual-patient level, and general practice size. This analysis fulfils the ITT principle with analysis as randomised and missing data being accounted for under the missing at random assumption. Although the primary analysis will focus on the ‘average’ intervention effect across 1-6 months follow-up, we will also use treatment by time interaction terms to evaluate between-arm differences in mean responses across each of the individual time-points of 1, 2, 3, 4, 5 and 6 months. Model fit will be assessed across difference covariance structures (unstructured, independence, exchangeable, autoregressive) to ascertain the best-fit model that will be implemented (i.e. the model that gives the lowest BIC, AIC and highest log-likelihood statistics). The monthly pain intensity scores will be used but if, for any individual, the last monthly SMS/brief questionnaire response is missing but they have completed the corresponding pain intensity question in their returned 6-month questionnaire (if completed within 20 days of the date of issue of their monthly SMS/brief questionnaire) then the available pain intensity score response will be used (as the 6-month score) for purposes of the primary outcome evaluation.

Analysis of secondary outcomes

Analysis of secondary outcomes will similarly be carried out following the ITT approach and using a linear mixed model for numerical outcomes and generalised mixed logistic models for categorical outcomes (adjusted for age, sex, baseline pain and corresponding baseline score (where applicable) at the individual-patient level, and general practice size). For monthly follow-up measures of distress and confidence in managing pain, the analysis will follow that of the primary analysis with initial focus on ‘average’ scores over the 6-months of follow-up and then the time-specific between-arm estimates. The focus of the other secondary measures is on 6-month follow-up data only, with the exception of perceived reassurance which is captured in the baseline questionnaire.

Sensitivity analysis of primary outcome

A sensitivity analysis will be carried out using a complier average causal effect analysis (CACE) to provide an

unbiased estimate of intervention effect for patients treated according to the stratified care protocol i.e. for the intervention arm 'protocol' is taken as clinical management in line with the recommended matched treatment options for each risk subgroup. CACE analysis will be performed using a 2-step instrumental variable regression modelling approach where the first step relates to model prediction of 'compliance' (at level 2 (individual patient level)) using trial arm only as a fixed-effect predictor and practice and participant IDs as random-effects, and the second step estimates the between-arm difference in outcome ('average' pain intensity) based on predicted compliance – the endogenous (instrumented) variable (from the first step) and the exogenous (instrumental) variables of trial arm, age, sex and point-of-consultation pain score using a mixed effects model as used in the primary analysis.

Subgroup exploratory analysis of primary outcome

Subgroup exploratory analysis of the primary outcome ('average' pain intensity) will be carried out by modelling intervention arm-interaction terms within the regression models for: (i) risk subgroups (low (reference category), medium and high risk); (ii) single MSK pain (reference) site versus multi-site pain; (iii) pain site (back (reference), shoulder, knee, neck). Subgroup analysis will be performed regardless of the results of the primary analysis. The mean between-arm difference (and 95% CI and P-value) will be computed for each subgroup comparison and visually displayed via a forest plot. The main focus will be on the 'average' pain intensity rather than on 3-way interactions of intervention-subgroup-time – but the 3-way interaction results will also be examined (and descriptive results produced by subgroup).

Exploratory mediation analyses

If there is a significant between-arm difference in the primary outcome (overall pain intensity) then we will carry out exploratory mediation analysis by structural equation modelling to examine (i) which potential mediators are 'causal' in effect; (ii) if psychological mediators (psychological distress or pain self-efficacy in months 1-5) are on the causal pathway for effect; (iii) if patient perceived reassurance mediates direct/indirect associations of 6-month pain intensity outcomes.

Evaluation of process outcomes

Process outcomes will be evaluated through comparison of aggregated anonymised data at the level of the participating general practices, by examining, for example, re-consultation rates for MSK pain over 6-months and referral rates to other services between practices in the stratified care versus usual care arms. In intervention practices, we will also investigate the proportions of patients for whom the electronic template is completed, and matched clinical management options are selected overall and by risk subgroup.

A descriptive analysis will be undertaken of physiotherapist data by intervention arm (eg. waiting times, number of treatment sessions, clinical grade of treating physiotherapist).

Examination of bias

Selection bias will be examined through scrutiny of comparability of recruitment rates per trial arm and comparability in general practice and participant characteristics. Further, a comparison will be performed examining the characteristics of patients in which the electronic template is activated but who did not take part in the data collection (non-participants) with those who did participate in terms of practice distribution, pain intensity scores, location of MSK pain, and (within the intervention arm) the proportion of patients at low, medium and high risk of persistent disabling pain (from the practice consultation IT template). Both crude descriptive and inferential statistics will be reported.

Differential attrition between trial arms will be examined and reported descriptively: frequencies for responses by trial arm will be recorded in the descriptive tables. We will compare baseline socio-demographic and clinical variables and (for response ≥1) monthly NRS-pain intensity scores across level-of-completion of NRS-pain intensity (level of completion = 0 to 6, where 0=non-response, 1=responded once and 6=responded to all six monthly follow ups) to ascertain whether pattern of missingness is likely to be 'missing completely at random', 'missing at random' or 'not missing at random'. If the overall follow-up rate of the primary outcome is over 5% different between trial arms and the pattern of missing data is 'missing at random' then we will undertake a multiple imputation or MI (via chained equations) analysis inclusive of baseline variables that are observed to be statistically associated with follow-up response. Further, if the pattern of missingness is seen to suggest that it is non-ignorable, the MI sensitivity analysis will address missing data imputations with

additionally incremented or reduced value corresponding to the overall baseline SD (thereby mimicking the non-ignorable pattern).

Health Economics

The health economics analysis will determine the cost-effectiveness of stratified care in comparison to usual, non-stratified care over 6-months. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences. Subsequently cost-utility analysis will be undertaken from an NHS/Personal Social Services (PSS) perspective to determine the cost per additional QALY gained. A broader costing perspective will be considered in a secondary analysis, taking into account NHS/PSS costs, private MSK-related healthcare costs and productivity costs associated with time off work.

Costs

Resource use information will be obtained on primary care consultations (eg. general practitioners and practice nurses), secondary care consultations (e.g. hospital consultants, physiotherapists), prescriptions, hospital-based procedures (eg. diagnostic tests, injections, and investigations), length of inpatient stays, and surgery. Patients will be asked to distinguish between UK NHS and private provision. Cost data will be collected via participant questionnaire at 6-months. Unit costs will be obtained from standard sources and healthcare providers including the British National Formulary (BNF), Unit Costs of Health and Social Care and NHS Reference costs [65-67]. Given that MSK pain is associated with significant lost productivity, information will also be collected from participants on occupation status, time off work related to their MSK problem and reduced work performance (presenteeism). This will enable the calculation of productivity costs, allowing analysis from a broader societal cost perspective. The average wage for each respondent will be identified using UK Standard Occupational Classification coding and annual earnings data for each job type [68].

Outcomes

The outcome of interest for the economic analysis is quality-adjusted life years (QALYs) and will be generated from participant responses to the EQ-5D 5L questionnaire at baseline and at 6-months follow-up. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations.

Data analysis

The cost-utility analysis will be carried out on an ITT basis, with the aim of estimating the difference in costs and QALYs between the stratified care and usual, non-stratified care arms. Missing EQ-5D 5L and cost data will be imputed using MI techniques [69] in order to ensure that all trial participants are included in the final analysis. For each participant, a QALY score over the 6-month follow up period will be estimated using the area under the curve approach [70]. Imbalances in baseline utility (EQ-5D 5L) scores between the stratified care and usual non-stratified care arms will be controlled for using a regression approach [71].

Total healthcare costs over the study period will be calculated by multiplying the resource items used by the respective unit cost and summing over all items. Differences in mean costs and QALYs between the stratified care and usual non-stratified care arms will be estimated. The data for costs is likely to have a skewed distribution, therefore, a non-parametric comparison of means (e.g. bootstrapping) will be undertaken to estimate 95% confidence intervals around costs.

Due to the nature of the trial, methods are required to address clustering in both costs and outcomes, and to recognise correlation between individual- and cluster-level costs and outcomes. Methods currently suggested in the health economics literature are multilevel models (MLM) and the 2-stage non-parametric bootstrap (TSB) [72]. For the base case scenario, MLM will be used to estimate differential costs, differential QALYs and incremental net benefits. The analysis will also allow us to control for covariates. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial data itself as well as the methods employed to analyse the data. A cost-effectiveness acceptability curve (CEAC) will be constructed to assess the probability that stratified care is effective at different willingness-to-pay thresholds. In order to estimate productivity costs, self-reported days off work will be multiplied by the average wage rate. The analysis will use the human capital approach.

Planned sensitivity analysis will include: 1) a complete-case analysis as an alternative to using an imputed dataset 2) a broader societal perspective 3) Additional exploratory analyses that will consider the cost-effectiveness of stratified care versus usual non-stratified care for patients in the low, medium and high risk subgroups separately. All analyses will be performed using performed using Stata 15 software.

Linked qualitative study

Theoretical framework

Two theoretical frameworks will underpin the evaluation; firstly, the COM-B model [73], which offers a way of understanding behaviour in the context of complex interventions, around three key determinants: *capability* – the psychological or physical ability to enact the behaviour; *opportunity* – the physical and social environment that enables the behaviour; and *motivation* – the reflective and automatic mechanisms that activate or inhibit behaviour. Second, Normalisation Process Theory (NPT) provides a framework for understanding how/why some new healthcare interventions are accepted and taken up whilst others are less successful [74]. Both frameworks emphasise the broader socio-political contexts in which health behaviours and practices are situated, and the importance of taking these contexts into account in understanding the adoption of new interventions [74, 75].

Aim

To understand the ways in which stratified care is perceived and operationalised, from the perspectives of healthcare professionals and patients, taking into account individual, local and national contexts.

Objectives

i) Identify the acceptability and impact on the consultation of using the clinician completed version of the Keele STarT MSK Tool, and the extent to which the matched treatment options are viewed as being in line with clinical judgements on best practice

ii) Understand the impact of stratified care on: i) individual clinicians, ii) general practice and physiotherapy services, iii) inter-professional and professional-patient communication, and iv) patients at low, medium and high risk

iii) Document any variation in experiences or views across different practices and services in the trial.

Methods

An iterative, mixed methods approach will be adopted [51, 76], with the quantitative data informing the qualitative data collection, and analysis from both informing the overall findings and conclusions. Data will be drawn from:

Clinicians: GPs and physiotherapists involved in delivering stratified care will be invited to participate in up to 3 separate focus groups held at approximately 4 GP practices Where clinicians are unable to attend focus groups, arrangements will be made for individual interviews. Initial focus groups/interviews will explore clinicians' views and experiences of delivering stratified care during the course of the trial. Follow-up focus groups/interviews will be conducted at a later stage once trial results are available, to explore views on the trial results and, depending on these results, discuss potential implications for practice, policy and service provision beyond the trial.

Patients: one-to-one semi-structured interviews will be conducted to explore individual patient experiences. Patients at low risk will be interviewed approximately 2 months after their index primary care consultation, whereas patients at medium and high risk will be interviewed at approximately 4 months. This timescale will allow for participants to reflect on their experiences of clinical management (including time to access any treatments), communication with the clinicians involved in their care, and their healthcare resource use over time.

Sampling

Clinicians and patients will be sampled from the stratified care arm of the trial. GPs directly involved in the trial will be identified based on diversity of practice characteristics, including size and geographic location. A sample of physiotherapists in linked participating services will also be invited to participate. Patients will be

purposively sampled from baseline questionnaire responses to capture diverse characteristics, such as pain scores and health related quality of life, risk subgroup, co-morbidity, age, sex and socio-economic status.

Sample size of qualitative study

Data collection will continue until saturation is reached, defined as 'informational redundancy'– the point at which additional data no longer offer new insights [77]. We estimate around 20-30 clinicians and approximately 20-30 patients will be required.

Recruitment to qualitative study

Clinicians will be informed that as part of their participation in the trial, they may be approached to participate in focus groups or interviews. Additional information explaining confidentiality, anonymity, data storage and archiving will be distributed ahead of each focus group/interview, and individual written consent obtained prior to the start of the discussion.

Patients will be informed that, as part of their participation in the study, they consented to further research contact. An invitation letter and detailed interview information leaflet will be mailed to the patient, and after 2-3 days a researcher will telephone the patient to check if they are willing to participate and, if so, make arrangements for the interview. Interviews may be face-to-face or by telephone, based on participant preference, and will be arranged at a time/location convenient for the participant. Once an interview has been arranged a confirmation letter will be sent. Written consent will be obtained at the start of the interview, or audio-recorded if the interview is via telephone and checked again at the end. Interviews are estimated to last approximately one hour.

Trial management, Study Administration and Data Storage

The Trial Manager assisted by the Study Coordinator will oversee the day to day running of the trial. General practice staff assisted where necessary by the CRN will download details of patients who have a completed template (name, address, the MSK pain site, date of MSK consultation and EMIS patient identification number) on a weekly basis from each practice. Practice staff will arrange transfer of patient details to the dedicated research administrator in Keele CTU using nhs.net to nhs.net transfer for mailing of the study invite pack to potential participants. A unique study number will be applied to each potential participant. On return of a completed initial questionnaire, details will be entered into the research database to ensure no unnecessary reminders are sent. Details of informed consent will be stored on the research database including participants' names and contact details. In this database participants will be primarily identified by study number. Data will be entered into the research database by trained members of the administrative team who will be blinded to general practice allocation. Access to the database will be restricted to those members of the team that require access. The coding schedule for the questionnaires will be used to inform database design and to facilitate data entry. Details of data entry accuracy will be kept by the research data management lead and trial statisticians and reported.

Any requests for access to the anonymised data will follow our data sharing procedure. Requests for anonymised data will be reviewed by our Data Custodian and Academic Proposals Committee. The full statement on data sharing can be found at www.keele.ac.uk/pchs/datasharing. All information will be held securely and in strict confidence. Each person in this study will be given a study number so that data from the study will not have any identifiable information, such as names and addresses, and cannot be traced. On this basis, these **anonymised** data will be kept electronically and may be used in other research studies.

Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual participating practices or NHS services. One potential issue is that GPs in the intervention arm may feel that the recommended matched clinical management options are not appropriate for an individual patient, in which case they will need to choose a treatment that is not amongst the recommended options. The clinician training sessions will make it clear that despite being part of a clinical trial clinicians retain the responsibility to provide appropriate care to their patients. Clinicians will be encouraged to report to the research team where there are consistent difficulties

with the stratified care intervention.

Statement of Indemnity and Trial Sponsor

Keele University has in place Clinical Trials indemnity which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS organisation (general practices and other services involved) remain liable for clinical negligence and other negligent harm to patients under this duty of care. The Sponsor (Keele University) is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC.

Oversight/Trial Monitoring

Trial Management Group (TMG): comprising of the CI, AI, Keele CTU staff, and other key trial team members have responsibility for the clinical set-up, ongoing management, promotion of the trial, and for the analysis and interpretation of results. Specifically the TMG are responsible for the (i) protocol completion, (ii) study document development, (iii) obtaining Health Research Authority (HRA) approval, (iv) completing cost estimates and project initiation, (v) facilitating the TSC and DMC, (vi) reporting of serious adverse events, (vii) monitoring of recruitment, intervention and follow-up procedures, (viii) data collection, and database development. The group will meet on a regular basis, typically monthly, throughout the trial. The trial does not incorporate any a priori stopping rules, and hence no planned interim analysis of the outcome measures collected in the trial will be carried out.

Financial Arrangements

Clinicians participating in the focus groups/interviews will receive a reimbursement of their time using standard professional rates. Patients participating in an interview will be given a £10 Love to Shop gift token by way of thanking them for their participation and will only receive remuneration for travel if they participate in an interview at a site other than their home.

Serious Breaches of the Protocol and GCP

Keele CTU has systems in place to ensure that serious breaches of GCP are picked up and reported. A "serious breach" is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the participants of the trial; or the scientific value of the trial. All protocol deviations or breaches of GCP will be recorded and reported to the Sponsor according to the relevant SOP.

Serious Adverse Events

Serious adverse events (SAE) include death, hospitalisation, significant disability or incapacity, any life-threatening circumstance, or any other medically significant occurrence that are believed to be related to the trial or interventions. All participating practice staff and physiotherapists will be asked to report to the CI as soon as possible any identified and likely related serious adverse event (SAE) experienced by a trial participant. We have discussed this issue with the independent TSC and agreed that the potential harms of the study are considered to be minimal and the stratified care information and matched treatment options are considered not only to be evidence-based but also have strong clinical community endorsement and credibility. Any serious adverse events will be brought to the immediate attention of the trial team. The CI will then assess whether the event was related to or resulted from any of the trial procedures or interventions, according to the process laid out in Keele CTU's SOPs. Any unexpected SAE considered to be related to the trial procedures will be reported to the main Research Ethics Committee by the CI within 15 days of becoming aware of the event. In addition, all such events will be reported to the Trial Sponsor, Trial Steering Committee and Data Monitoring Committee.

Confidentiality and Anonymity

All information collected during the course of the trial will be kept strictly confidential. All identifying information will be anonymised before being used for analysis. Information will be held securely on paper and managed electronically by Keele University through Keele CTU. Keele CTU complies with all aspects of

the 1998 Data Protection Act. The trial data will be held on a database hosted on a secure server by Keele CTU. All research staff involved in this study adhere to robust data security procedures and have explicit duties of confidentiality. These practices are written into their employment contracts and are equivalent to the duty placed on NHS staff. If a participant withdraws consent from further collection of data their data collected to date will remain on file and will be included in the final study analysis unless requested otherwise.

Results

Recruitment to the trial commenced on 18th May 2018 and ended on 15th July 2019, after a recruitment period of 14 months in 24 GP practices. It is anticipated that all follow-up and interview data collection will be completed by February 2020.

Discussion

This study protocol describes the detail of the STarT MSK trial, which aims to investigate the clinical and cost effectiveness of stratified primary care for patients with the five most common MSK pain presentations compared to usual non-stratified care. The intervention was designed to improve patient outcomes including pain intensity, physical function and quality of life, and also clinician decision-making in order to reduce treatment variability and improve adherence to best practice. This trial is the first attempt, as far as we know, at testing a prognostic stratified care approach for primary care patients with MSK pain. The results of this trial should be available by the summer of 2020.

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Supplementary Files

Figures

Recommended matched treatment options MSK: Musculoskeletal NSAIDS: Non steroidal anti inflammatory drugs GP: General practice.

L=Low risk; M=Medium risk; H=High risk	Back			Knee			Multisite			Neck			Shoulder		
	L	M	H	L	M	H	L	M	H	L	M	H	L	M	H
1. Education and advice, inc. exercise, activity modification, weight loss etc.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Simple oral and topical medications limited to those available over the counter	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Refer to physiotherapy/MSK service		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
4. Consider weak opioid if acute pain as alternative to NSAIDs		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
5. Consider cortico-steroid injection					✓	✓		✓	✓					✓	✓
6. Refer to supported self-management or locally available community resources e.g. walking group, exercise on prescription/ personalised exercise programme, expert patient programme, dietician, slimming world, etc.		✓	✓		✓	✓		✓	✓		✓	✓		✓	✓
7. Consider atypical analgesia (e.g. amitriptyline, pregabalin, gabapentin) if neuropathic pain present			✓			✓			✓			✓			✓
8. Consider referral to pain management service			✓			✓			✓			✓			✓
9. Consider referral to secondary care			✓			✓			✓			✓			✓
10. Consider imaging			✓			✓			✓			✓			✓
11. GP management of comorbidities, distress, frailty, polypharmacy and pain management			✓			✓			✓			✓			✓

Multimedia Appendixes

Independent peer review comments on trial protocol.
URL: https://asset.jmir.pub/assets/c49c91139711696d4258492b125c5ec0.docx