Talking in Primary Care: A cluster-randomised controlled trial in primary care to test the effectiveness and cost-effectiveness of communication skills e-learning for practitioners on patients' musculoskeletal pain and enablement

Short Title/Acronym: The TIP Trial

Version Control

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Trial Registration

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Abbreviations

BCT	Behaviour Change Techniques
BPI	Brief Pain Inventory
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease
CRN	Clinical Research Network
GP	General Practitioner
ICE	Ideas, Concerns and Expectations
iNMB	incremental Net Monetary Benefit
LBP	Lower Back Pain
MISS	Medical Interview Satisfaction Scale
MSK	Musculoskeletal
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NICE	National Institute for Health and Care Excellence
OA	Osteoarthritis
PBA	Person based approach
PCP	Primary Care Practitioner
PEI	Patient Enablement Index
PIS	Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
QALY	Quality-Adjusted Life-Year
QOF	Quality and Outcomes Framework
SMD	Standardised mean difference
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

Plain English Summary

Musculoskeletal pain – pain that relates to muscles, bones and joints - is a common problem for patients and is likely to increase as the population ages. Back, hip, knee and neck pain are common, and are often related to conditions such as osteoarthritis. Musculoskeletal pain can be difficult to treat and can affect

peoples' social life, wellbeing and employment. Pharmacological treatments often have very small effects and some carry the risk of dependence. Many primary care appointments involve patients who have musculoskeletal pain and it can be tricky for Primary Care Clinicians (GPs, nurses, and primary care physiotherapists) to know how best to help.

Previous research we conducted shows that it is possible to improve the way GPs communicate with patients with a brief training package. Our reviews of other published research also show that changing GP communication can help reduce pain and improve patients' quality of life and satisfaction with their care. Better communication is likely to also increase patients' confidence to self-manage their health conditions and help reduce the impact of their symptoms on their lives. This in turn could reduce the need for further treatments and appointments. Thus, enhancing communication could both improve symptoms and reduce costs for the NHS.

This research study aims to assess a communication e-learning training package that we developed with patients and clinicians previously. The training package is quick, easy to access, and received good feedback from the GPs, nurses and physiotherapists who tried it. The idea is to help primary care clinicians (GPs, nurses, doctors, physiotherapists) communicate with patients in a way that is positive and empathic within both remote (telephone and video) and in-person primary care consultations. In this study we will recruit 42 GP surgeries from England and Wales. Half of the GP practices will receive the training, the other half will not. We will compare outcomes in GP practices that have received the communication training with practices ones that have not to see which, if either, improves patients' symptoms, confidence in managing their symptoms, satisfaction with their consultation, and quality of life. We call this type of study a 'randomised controlled trial'. We will also see what, if any, impact there is on costs to the NHS. We hope this enhanced communication might benefit all patients, not just those who have musculoskeletal pain, and so we will also include patients who have appointments for other conditions/symptoms. In total we will involve 1680 patients in this study.

If shown to be successful, this enhanced communication training could quickly be made available at low cost to primary care practices across the country.

Expert Summary

Approximately 1.7 billion people worldwide have painful activity-limiting musculoskeletal (MSK) conditions including back, hip, knee and neck pain. Osteoarthritis is a common cause. Approximately 1 in every 7 GP consultations is about an MSK problem. Clinical guidelines recommend patient education and patient-centred care offering a range of different (ideally non-pharmacological) interventions. Regardless of which therapy a patient receives, excellent practitioner-patient communication has the potential to enhance such patient-centred care and can improve outcomes that are important to patients. Doctors communicating clinical empathy and realistic optimism about treatment outcomes can lead to reductions in pain and improvements in patient satisfaction with consultations. However, few interventions have been tested clinically for effects on patients' health, few have been sufficiently well described to allow implementation, and (where details are available) most interventions are prohibitively complex, expensive, and time-consuming. This makes engagement and uptake of current interventions extremely unlikely, particularly in the current climate of exceptionally high demand for primary care services and staff shortages. Furthermore, the COVID-19 pandemic has changed the landscape of primary care. Telephone consultations are much more widespread and present both challenges and opportunities to practitioners and patients. The pandemic has highlighted and exacerbated health inequalities and disparities in access and outcomes

and emphasized the need to ensure high quality communication optimised for patients from diverse ethnic backgrounds.

We have recently developed EMPathicO, an engaging, feasible, brief, evidence-based and theoretically grounded e-learning package for primary care practitioners. To develop this high-quality e-learning package we conducted 2 systematic reviews, 1 meta-ethnography, a behavioural analysis, extensive qualitative studies and a mixed methods feasibility study. The feasibility study involved 51 primary care practitioners across 26 practices, and 470 patients. Our feasibility study, and an earlier pilot trial of some EMPathicO components ('KEPE-Warm') strongly suggest that (1) EMPathicO could help practitioners enhance their communication of clinical empathy and realistic optimism and (2) EMPathicO is ready to be evaluated in a cluster-randomised trial in primary care.

Building on our successful development and feasibility work we now want to determine the clinical and cost effectiveness of EMPathicO training for primary care practitioners, primarily in patients presenting with MSK pain. We also aim to maximize the potential future impact of EMPathicO by also testing the effect of training practitioners on outcomes in patients with other conditions.

This protocol describes a cluster-randomised trial in primary care to test EMPathicO's clinical and cost effectiveness, with embedded qualitative research and a process evaluation to maximize its potential for widespread implementation and impact for patient benefit. We will conduct a multi-centre cluster-randomised controlled two parallel group superiority trial in primary care. General practices constitute the clusters (practice n=42). Individual practitioners (e.g., GPs, nurse practitioners, primary care physiotherapists) will undertake EMPathicO e-learning (intervention practices) or consult as usual (control practices). Patients consulting participating practitioners about MSK pain will complete patient reported baseline and repeated outcome measures assessing pain, enablement, and secondary outcomes up to 6 months after the index consultation (patient n=840). Alongside the MSK participants, we will also recruit a non-MSK pain ('All-comers') participants (n=840 patients with a range of symptoms other than MSK pain). A subsample of patients (approximate n=45 with MSK pain and n=45 without MSK pain) and practitioners (approximate n=30) will take part in qualitative interviews. Patients and the trial statistician will be masked to intervention allocation; we will also attempt to mask researchers supporting patient data collection. Effects of EMPathicO on pain and enablement among patients with MSK pain will be assessed using two co-primary outcome measures. Cost-effectiveness will be considered from an NHS and societal perspective. A process analysis will assess EMPathicO's underpinning logic model. The potential impact of EMPathicO will be considered through qualitative, quantitative, and mixed methods analyses guided by the RE-AIM framework (widespread Reach, Effectiveness for non-MSK pain ('All-comers') patients, Adoption, Implementation, and Maintenance of effects).

If the promising feasibility work translates into positive outcomes from this trial, our brief e-learning package could rapidly have a clinically meaningful impact with large reach, potentially enhancing care for patients with a range of conditions and thus impacting thousands of clinicians and patients.

Introduction

This protocol has been prepared in accordance with the SPIRIT statement (https://www.spirit-statement.org/).

Background and rationale

Approximately 1.7 billion people worldwide have musculoskeletal (MSK) conditions with back, hip, knee and neck pain being common. These conditions affect the joints, bones and muscles and can be local or widespread. Osteoarthritis (OA) is a common cause. They are characterised by pain, which typically interferes with activities and can limits peoples' daily lives, leading to reduced quality of life.[1] One in seven GP consultations in 2006 were for MSK problems, the most common of which were back problems followed by knee problems.[2] Primary care for patients with MSK problems is increasingly delivered by professionals other than GPs including practice nurses and physiotherapists who will be included in this project. The National Institute for Health and Care Excellence (NICE) provides numerous condition and joint-specific guidelines for MSK conditions.[3] A systematic review of high quality international guidelines for MSK pain (including the NICE guidelines for osteoarthritis and low back pain) identified the following 11 common recommendations: "ensure care is patient centred [sic], screen for red flag conditions, assess psychosocial factors, use imaging selectively, undertake a physical examination, monitor patient progress, provide education/information, address physical activity/exercise, use manual therapy only as an adjunct to other treatments, offer high-quality non-surgical care prior to surgery and try to keep patients at work".[4] According to the best and largest studies, most over the counter oral painkillers, like paracetamol and ibuprofen, are barely better than placebos for reducing MSK pain yet may have serious side-effects.[5-7] Some topical analgesics may be more effective at reducing acute and chronic pain and are associated with fewer adverse events.[8]

Regardless of which therapy a patient receives, excellent practitioner-patient communication has the potential to enhance patient centred care,[9] patient education, and discussions around other interventions; indeed, excellent communication significantly improve patients' symptoms, quality of life, adherence to and satisfaction with care, producing benefits that are comparable to many pharmaceutical interventions.[10-12] However, significant shortcomings in practitioner-patient communication remain and improving communication and person-centred care is an important goal in healthcare worldwide.[13] Furthermore, sub-optimal consultations represent missed opportunities for benefit and can even be harmful, causing: worse quality of life and symptom management, unwanted prescriptions and non-adherence;[14 15] unnecessary economic costs;[15] deviation from guideline-recommended treatment;[16] and increased complaints and litigation.[17 18] Despite communication skills being essential in medical and allied health professional training, medical students appear to exhibit broadly stable or declining levels of empathy during their degrees[19 20] and patients still report dissatisfaction with practitioner-patient communication.[21 22] The need for enhancing and expanding communication skills is particularly pertinent now since the COVID pandemic forced a rapid radical change to telephone and – to a lesser extent – video consultations, bringing new challenges for communication for staff who often haven't received specific training on consulting in this way.[23] Thus now more than ever, accessible brief effective communication skills training is needed to maintain and promote empathy during consultations. Fortunately, many primary care practitioners are willing to engage in further communication skills training. Even very brief interventions can successfully improve communication skills, including interventions concentrating on skills such as active listening and expressing warmth at appropriate times[24-26] which take no additional time in the consultation and so are likely to be very efficient.[26 27] While formal cost-effectiveness evaluations are very rare, it seems that effective interventions to enhance empathy may have more benefits than costs.[28] However, few interventions have been tested clinically for effects on patients' health,[29] few have been sufficiently well described to allow implementation, and (where details are available) most interventions are prohibitively complex, expensive, and time-consuming, which makes commissioning, engagement and uptake in the current primary care climate extremely unlikely.

Our research work addresses these limitations. We aim to improve patients' health outcomes by enhancing practitioners' communication of clinical empathy and realistic optimism via brief, engaging, digital training which can be undertaken and implemented within everyday clinical consultations using any medium, including face to face, telephone or video - even within the current pressured primary care context.

Rationale: Clinical Empathy and Realistic Optimism

A systematic review conducted by team members demonstrated the potential benefits of communicating clinical empathy and positive messages; empathy and positive messages showed statistically and likely clinically significant effects on pain (standardised mean difference, SMD, for empathy -0.18, SMD for positive messages -0.43), patient satisfaction, and other outcomes with no evidence of adverse effects.[30]

Clinical empathy involves the practitioner putting themselves in a patient's position, acknowledging their feelings, concerns and expectations and behaving in a way that communicates that understanding.[31 32] A compassionate, friendly consultation style using appropriate verbal and non-verbal cues can enhance the treatment of pain and related conditions and has been associated with greater patient satisfaction, adherence to treatment, and quality of life and health outcomes.[33-35] Clinical empathy is also beneficial to practitioners in reducing stress and burnout.[36] Empathic communication might even be an essential prerequisite for enabling people to better cope with, understand, and self-manage their health.[37] However, the extent to which practitioners express clinical empathy in consultations is typically low and varies widely: a systematic review of 64 studies using the CARE[38] measure of patient-rated practitioner empathy reported a weighted average mean score of 40 out of a possible 50 (range 29-50)[39] suggesting an ongoing need for training.

Conveying positive messages to patients helps them develop positive expectancies about treatment outcomes; positive expectancies are associated with better outcomes in laboratory and clinical studies of diverse symptoms, especially pain[40-42] and are an important part of the neuropsychological processes underpinning placebo effects.[43 44] For example, positive expectancies of analgesia alter pain perception via effects on central nervous system processing[45] and trigger a cascade of neurological changes very similar to those triggered by pharmaceutical analgesics.[46] However, some methods used in placebo experiments to impart positive outcome expectancies, such as short verbal statements that an intervention is a potent painkiller, may be unconvincing for patients with chronic pain in clinical practice.[47 48] Furthermore, for practitioners 'expectancies' and 'expectations' are terms associated with 'expectation management' which typically involves encouraging patients to have more realistic beliefs about the outcomes of treatment.[49] For example, a patient may expect a hip replacement within a few months of experiencing moderate OA pain, and continue in high-impact sports. 'Expectation management' in this context involves reducing the patient's expectations of treatment (they will be offered lifestyle advice and pain killers initially) and outcome (reduced mobility, waiting lists, and pros and cons of surgery). Our work aims to promote effective ways of encouraging patients to have positive outcome expectancies, within the context of their clinical situation – hence our focus on clinically *realistic* optimism, within an empathic interaction.[50]

Our Intervention: EMPathicO

We have recently developed EMPathicO, an engaging, feasible, evidence-based and theoretically-grounded digital e-learning package for practitioners.[51] We developed EMPathicO with and for the range of professionals now routinely seeing patients frontline in primary medical care, including not only GPs but also nurse practitioners and first-contact physiotherapists. EMPathicO helps practitioners enhance their communication of clinical empathy and realistic optimism and is consistent with major consultation models including ICE (Ideas, Concerns and Expectations).[52] It uses behaviour change techniques (BCTs) to support practitioners to adopt new verbal and/or non-verbal behaviours to better communicate clinical empathy

and realistic optimism to their patients. These BCTs include: persuasive messaging with scientific evidence and testimonials about the effects of clinical empathy and realistic optimism; instruction and examples of specific verbal and non-verbal behaviours to communicate clinical empathy and realistic optimism; and support for practitioners to reflect on their own consultations and select a small number of specific communication behaviours to work on by setting goals and planning how to accomplish them.

To develop EMPathicO we used the systematic multi-component person-based approach (PBA) which puts intervention users and beneficiaries at the heart of design and development to ensure relevant evidence and theory are integrated in a meaningful and engaging way.[53] The Behaviour Change Wheel and the COM-B model (Capability, Opportunity, Motivation - Behaviour) guided our behavioural analysis and complemented the PBA's focus on intervention users.[54] We conducted systematic reviews to identify the components of 7 empathy[55] and 22 optimism[56] interventions, and included promising components in EMPathicO prototypes. This confirmed our preliminary decision to base the prototype Empathy module on KEPE-Warm, a very brief evidence-based intervention developed by team members PL and HE; KEPE-Warm was itself based on a large observational study of non-verbal communication in primary care.[25] It effectively modified practitioner behaviour and produced significant benefits for patient satisfaction (MISS 0.23 higher, 95% CI 0.06 to 0.41), when compared to usual care in a cluster-randomised trial with 16 GPs.[26] We also conducted a meta-ethnography (26 studies including 557 patients and 199 practitioners) to synthesize, compare, and contrast patients' and practitioners' concerns and priorities for communication in primary care consultations about OA. Findings confirmed the need for improved communication in primary care consultations about OA and highlighted the potential benefits from encouraging greater working in partnership to foster a shared understanding of OA.[57] We conducted extensive qualitative research with 39 practitioners and 33 primary care patients, iteratively modifying EMPathicO prototypes based on emerging findings and testing these modifications with subsequent interviewees. This work all contributed to the underpinning draft logic model (Figure 1).[51]

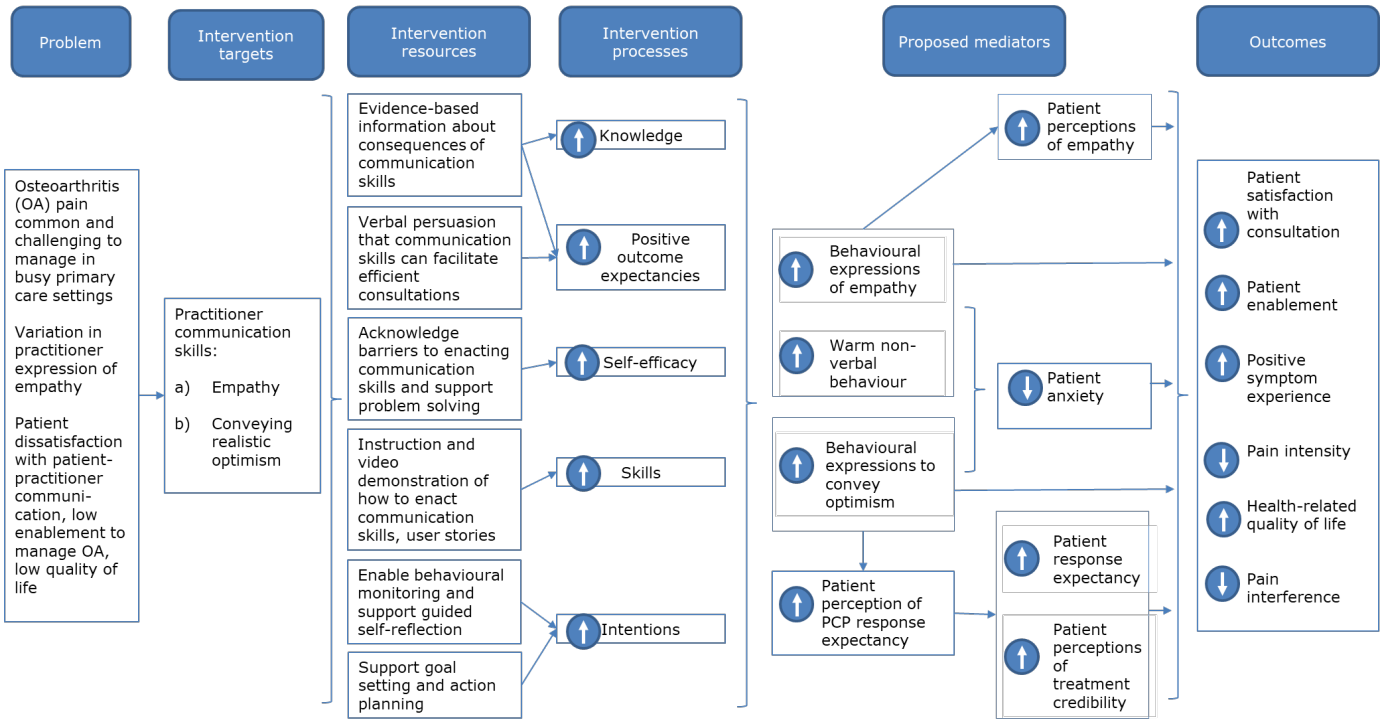

Figure 1. Draft logic model showing how EMPathicO is hypothesized to affect patient outcomes; this model is subject to ongoing refinements at this time.

EMPathicO includes brief interactive e-learning modules on clinical empathy (~12min), realistic optimism (~15min), tailoring these for patients with OA pain (~18min), and guidance for reflecting on one's own consultations (~8min) and goal-setting (~4min) (reported timings based on intervention usage data from 12 GPs). This clinical focus on OA was chosen because much (but not all) of the evidence that underpins the importance of clinical empathy and realistic optimism for patient outcomes is derived from studies of pain and painful conditions including but not limited to OA and other MSK pain. And interventions targeted to specific audiences and conditions are likely to be more relevant (to recipients) and possibly more effective.[58] Our extensive development and feasibility work with 39 practitioners (28 GPs, 4 GP trainees, 4 nurses, and 3 physiotherapists) confirmed that EMPathicO includes the necessary content in an easily accessible format to allow practitioners to tailor their new skills for use in OA and other painful MSK consultations. Importantly, it also has the potential to be broadly applicable across a range of other primary care consultations. We will explore this further in our trial.

During 2020, we completed a feasibility study of methods for evaluating EMPathicO in a cluster-randomised controlled trial in primary care.[59] Despite the first COVID-19 lockdown occurring a few weeks after commencing our feasibility trial, we worked in an agile way and amended our plans so that we could still collect relevant data. Before lockdown (Jan-March 2020), we had secured service support and excess treatment costs, worked with local CRNs to establish a recruitment pipeline for practices including first contact physiotherapists, and successfully set-up 5 practices. We had also identified barriers to practice recruitment that we will address and mitigate in this trial (seeing insufficient patients with OA during COVID-19, not wanting to film all consultations, using telephone consultations for pain management, and being too busy during January-February, e.g., with winter pressures). During and after lockdown (July-Sep 2020) practices had no capacity to recruit patients; therefore, we looked separately at feasibility of the intervention (intervention usage analysis with 12 practitioners and qualitative interviews with 11 practitioners) and patient outcomes (web-based survey of 437 patients with 30 purposively sampled qualitative interviews). Practitioners were keen to reflect on and further improve their communication skills and were prepared to undertake online training (even during the pressures of COVID). They found EMPathicO accessible, sufficiently brief, relevant and engaging and felt they were able to learn and implement the techniques for communicating clinical empathy and realistic optimism. They began implementing techniques immediately after completing training and found the techniques relevant to patients consulting for painful and non-painful conditions. Patients found the planned outcome and process measures acceptable and were willing to complete them online. We easily remedied minor problems with funnelling (e.g., 'if answer YES to question 8 then skip to question 10' type logic) and patients were keen to take part in research that could improve primary care consultations.

EMPathicO During and After COVID-19 Pandemic: Remote Consultations and Patient Diversity

The COVID-19 pandemic has changed how patients engage with primary care. Remote consultations, especially telephone consultations, are much more widespread: e.g. across 21 practices in West of England the proportion of telephone consultations rose from 30-31% in April-July 2019 to 83-89% in April-July 2020.[23] Survey data from England in early 2021 showed that 47% of consultations with the GP were via the telephone, and 0.5% conducted online (which includes video), a large increase compared to data from pre-pandemic early 2020 which suggested only approximately 10% of GP consultations were via the telephone.[60] Remote consultations present challenges to practitioners and patients; the nature and extent of these challenges may differ between groups. For example, in 2019 awareness and use of telephone consultation among patients in primary care has been shown to be associated with higher education,

having internet access, having a long-term condition, and being a frequent attender at general practice.[61] Health inequalities in access and outcomes[62] highlight the importance of high quality communication with patients from diverse ethnic backgrounds.[63] Practitioners are delivering care differently, with more reliance on remote methods. Patients are navigating new ways of accessing appointments. These changes mean it has never been more crucial to ensure care is delivered with empathy and communication optimised for all patients.

Our focus when developing EMPathicO (October 2018-December 2019) had mainly been on in-person consultations, but as the COVID-19 pandemic emerged in early 2020 it became imperative to ensure EMPathicO addressed different modes of consultation delivery; therefore, we explored in our feasibility study patients' and practitioners' experiences and perspectives on remote consultations. This was particularly important given compelling existing evidence that telephone consultations in general practice contain less rapport-building than face-to-face consultations, even after accounting for number of problems presented and duration of consultation.[64] And our feasibility data suggested EMPathicO should explicitly address clinical empathy in telephone consultations. Patients in our feasibility study survey (conducted in summer 2020) perceived practitioners to be slightly less empathetic during telephone consultations (total CARE 37.3 vs 39.8; n=254; a difference the developer of the CARE considered to be potentially clinically meaningful (personal communication). Patients in our interviews (n=30) reported slightly less rapport and more difficulty managing turn-taking in telephone consultations but inferred empathy and optimism from verbal behaviours that were already included in EMPathicO and can readily be expressed over the telephone. No telephone-specific ways of communicating empathy were identified from patients' perspectives.

We also undertook a rapid systematic review of 8 qualitative and quantitative studies of empathy as expressed in telephone consultations (studies included 527 patients and 20 practitioners). These studies suggested that empathy can be communicated within telephone consultations and there are no major barriers to doing so, but nevertheless some practitioners have concerns about communicating empathy without using visual aspects of non-verbal communication.[65] Echoing other practitioners' experiences of the accelerated move to remote consulting due to COVID-19,[23] practitioners in our feasibility study interviews (n=11) adapted quickly to telephone consultations but found them tiring and stressful and missed 'the nuances of human communication'. They highlighted the use of language and tone of voice as even more important because of the paucity of non-verbal cues. Of particular relevance to EMPathicO, practitioners suggested empathy might be inadvertently overlooked in the context of remote consultations and that some additional EMPathicO content to highlight skills for telephone and video consultations would be highly valued. Similar issues were raised concerning the paucity of non-verbal cues and the additional interactional 'work' involved in face-to-face consultations while wearing Personal Protective Equipment. Although in this context practitioners were more confident in still being able to express empathy by adapting the techniques covered in EMPathicO and focusing on those that could still be readily implemented (e.g., around eye contact and positive messages).

Health inequalities in access and outcomes[62] highlight the importance of high quality communication with patients from diverse ethnic backgrounds who are less likely to be able to adequately access general practice.[63] When developing EMPathicO, to supplement our meta-ethnography of 26 qualitative studies[57] we conducted a primary study on patients' perspectives with 33 patients but unfortunately struggled to recruit participants from diverse ethnic backgrounds.[66] To address this shortcoming, we worked with David Truswell (consultant in community engagement, equality and diversity) to discuss EMPathicO with two groups of people from Black Caribbean and South Asian ethnic backgrounds. This highlighted some features of EMPathicO that could be optimised to cater for diversity and we have now adapted these accordingly. For example, our evidence-based recommendation that practitioners convey optimism by saying that

"other patients like you have found this treatment helpful" was found to be problematic due to possible racist, sexist and ageist connotations. This phrase has therefore been removed from EMPathicO.

Patient and Public Involvement and Engagement (PPIE)

Our PPIE lead, co-investigator Jennifer Bostock (JB), has reviewed and co-written this protocol. Jennifer provided advice and input during our development and feasibility work for EMPathicO. She is a patient with osteoarthritis and has considerable experience in Patient and Public Involvement and Engagement including co-authoring a PPI intervention to boost recruitment and retention in trials which is of particular value to this study (https://www.phc.ox.ac.uk/research/health-experiences/developing-a-patient-and-public-involvement-intervention-to-enhance-recruitment-and-retention-in-surgical-trials-pirrist). We will also benefit from Jennifer's expertise as a REC Chair and will utilise her expertise and that of other PPI advisors to ensure that our study design, recruitment methods and participant facing materials are ethical and acceptable to patients.

In preparing this protocol, we consulted with a further 8 public contributors to explore their views and perspectives about our planned full trial. Contributors ranged in age from 25 to 66 years, 4 were female and 4 were male, represented a range of ethnic backgrounds (White British, British Asian, Black British and mixed cultural heritage) and described having MSK problems or symptoms. The public contributors took part in either an online discussion forum chaired by our PPIE lead (JB), or an individual telephone discussion with an experienced researcher. Public contributors were consulted on the outcomes that they considered most important from consulting with their primary care professional about MSK symptoms. Patient Enablement, the ability to understand and cope with their symptoms, was described as a high priority for most participants. Pain was also described as important but considered an individual experience that can fluctuate and consequently difficult to quantify. Impact of symptoms on daily life was also raised as an important outcome for people living with MSK pain, and the affect it could have on daily activities. This consultation has informed our selection of co-primary outcomes for the study: patient enablement and pain intensity. Public contributors also reviewed and gave feedback on our patient recruitment strategy and provided important recommendations for encouraging trial participation and completion of trial outcome measures. These recommendations have helped to inform our trial design and promote recruitment of a diverse range of participants into the trial.

We will continue to work with public contributors as we conduct and disseminate this trial. Jennifer will attend regular trial management team meetings, contributing to management decisions to optimise recruitment and follow up of participants in the trial. The team benefits from JB's ethical expertise and together with the other public contributors this will aid our ethical approvals and also ensure that the research is conducted ethically and sensitively. We will invite additional public contributors with experience of MSK pain (personally or as a carer) to assist with developing trial documents (participant information sheets, topic guides) and trial processes. We plan to include a wide demographic of participants in our trial including those from harder to reach communities. Consequently, we will aim to involve at least two contributors from a non-white background and at least two contributors from a deprived background, to help ensure our trial materials and processes have a broader relevance and can help facilitate recruitment of a more ethnically and socio-economically diverse group of participants. We will invite our public collaborators to co-lead dissemination activities including providing lay summaries and co-presenting findings with researchers to healthcare professionals, the scientific community and a wider public audience.

We will offer our public contributors training in public involvement through the Wessex Public Involvement Network and NIHR School for Primary Care Research PPIE initiatives. We will also support the public

contributors in acquiring new skills to foster ongoing enthusiasm for and to add value to research for this project and future studies. The PPI co-app and project team will provide support and training where necessary for example bite size methodology or ethics sessions. We shall capitalise upon the skills and experience of our lay advisors in order that we create a reciprocal shared learning environment. They will also be invited to join the Southampton Primary Care Research Centre's PPIE database and support network (lead by our PPIE Officer Sonia Newman) which can also provide opportunities for training, peer support and further contribution to research.

Finally, we will invite an independent public contributor to join our Trial Steering Committee to provide expert oversight of the trial from the patient perspective.

Our PPIE collaborators will be paid in line with national guidelines including funds to cover individual needs such as carers where necessary. Our approach to PPIE is to use NIHR guidance as a model but to tailor them to the needs of the project and our individual advisors.[67]

Objectives

The primary aim is to determine the clinical and cost-effectiveness of EMPathicO training in Clinical Empathy and conveying realistic Positive Messages for practitioners in patients presenting with MSK pain. The associated objectives are to:

a. Determine the effects of EMPathicO on (a) patient-reported pain and (b) patient enablement based on repeated measures over 6 months following the index consultation, in patients presenting with MSK pain.
b. Compare the costs and consequences and estimate the cost-effectiveness of EMPathicO versus usual care, over the 6 months following the index consultation, for patients with MSK pain.
c. Determine the effects of EMPathicO on patient-reported quality of life and other secondary outcomes across the 6 months following the index consultation.
d. Test the hypothesized mechanisms of action of EMPathicO, including intervention usage and effects on patient-perceived practitioner empathy and optimism (as per our logic model).

The secondary aim is to explore EMPathicO's potential for impact on conditions other than MSK pain and ways to maximise wide-spread adoption, implementation, and maintenance of effects. We will do this by assessing effects of EMPathicO training on patients presenting with any symptoms other than MSK pain since the impact of EMPathicO will potentially be in all consultations not just MSK consultations; testing how and in what circumstances EMPathicO changes practitioner communication behaviours and patient outcomes for in-person, telephone, and video consultations; and analysing a diverse range of patients' and practitioners' experiences of adoption and longer-term implementation. The associated objectives are to:

e. Determine the effects of EMPathicO on patient enablement, patient-reported quality of life and other secondary outcomes across the 6 months following the index consultation, in patients presenting with symptoms other than MSK pain.
f. Identify opportunities, barriers, and solutions for widespread implementation and impact, using the RE-AIM framework to address issues related to EMPathicO's Reach, Effectiveness, Adoption, Implementation, and Maintenance. [68 69]

Trial design

A cluster-randomised controlled two parallel groups superiority trial in primary care; general practices constitute the clusters, which will be randomised 1:1 to EMPathicO training versus usual care. All eligible practitioners (see below) within each cluster will be encouraged to undertake EMPathicO training (intervention) or will consult patients as usual (control); patients who present to participating practitioners will complete patient reported outcome measures at baseline and at four subsequent timepoints, assessing pain, enablement, and secondary outcomes. The major limitation of cluster RCTs is the potential for patient selection bias and for this to favour the intervention arm: to mitigate this we will work with reception staff and practice managers to automate patient study invitations and we will not involve practitioners in this process as far as possible; we will also collect and monitor patient baseline pain intensity. We cannot randomize individual practitioners: cross-contamination would occur within practices where practitioners share knowledge and patients. We cannot randomize individual patients: practitioners cannot switch on/off communication skills in different consultations.

Methods: Participants, interventions and outcomes

Study setting

General practices in England and Wales. Three recruitment hubs – Southampton (Wessex), Keele (West Midlands), and Bristol (West of England) – are well-positioned to recruit general practices serving patients from diverse geographic, socio-economic, and ethnic backgrounds. While the intervention is probably broadly applicable beyond England and Wales, it was developed within the context of English general practice so assessment of effect is planned in England and Wales in the first instance with the potential for wider dissemination if positive results are found.

Eligibility criteria

Practices

Inclusion criteria: All general practices serving NHS patients in England and Wales are eligible. Each hub will work closely with local CRNs to target practices in areas of high deprivation indices and serving patients from diverse ethnic backgrounds. Practices that are part of large multi-practice primary care networks will be eligible but the unit of randomisation will be considered on a case-by-case basis (i.e., randomise as a group or as individual practices). The degree and type of integration and likelihood of contamination between the practices will be considered.

Exclusion criteria: the 26 practices (18 from Wessex CRN, 5 from Keele area) that were involved in the intervention development and feasibility work. Practices where clinical members of the Trial Management Group/Trial Steering Committee see patients are also excluded. This is because they have already seen and/or used the intervention.

Practitioners

Inclusion criteria: All practitioners working within participating general practices and seeing people with MSK pain are eligible and will be encouraged to undertake the EMPathicO training; practitioners should be making management/treatment decisions concerning these patients; this may include GPs, physiotherapists, practice nurses, nurse practitioners, physician's assistants.

Exclusion criteria: Unwilling to undertake the intervention and the trial procedures.

Patients: MSK pain group

Inclusion criteria: Adult (18+); verbally consulting a participating practitioner about new, recurrent, or ongoing MSK pain (e.g. back, hip, knee, neck pain - consistent with ICD-11's diseases of the MSK system[70]); reporting their average pain in the last week as 4 or more on the numerical rating scale from the Brief Pain Inventory at the index consultation (where 0 = no pain; 10 = pain as bad as you can imagine); consulting face-to-face in surgery, via the telephone, or via videoconference, even if those consultations were initiated via e-consult / email/ or initial triage call; has capacity to give informed consent.

Patients may have serial consultations within the recruitment period, for example, a telephone consultation may lead to a face-to-face consultation, on the same or later day, with the same or another clinician. In this situation, the first consultation will serve as the 'index' consultation for the purposes of the trial. Some surgeries initially triage patients for example by a very short telephone call before providing a consultation. An initial triage interaction – e.g., a phone call in which patients are merely triaged to a subsequent consultation - will not count as an 'index' consultation, and patients will not be recruited solely on the basis of a triage interaction.

To support wider access to participation in research and improve sample representativeness, people who do not speak or read/write English will be eligible. We will capture on the first post-consultation questionnaire whether patients used an interpreter during the index consultation (including professional or informal, e.g., family member, interpreters). If numbers permit, we plan to test for any differences in intervention effectiveness for patients requiring an interpreter during their consultation. We are aware that some of the nuance of the communication approaches we are training practitioners to use may be diluted or 'lost in translation' but this is most representative of how the intervention would be used in usual clinical care after the trial so most informative for widespread generalisability in NHS clinical settings.

A professional interpreter will be made available over the telephone to support non-English speakers to access the trial paperwork and complete the patient-reported measures; we will also include people who wish to have a family member or other informal interpreter support their participation in the trial. The use of interpreters to support trial paperwork and patient-reported measures has the advantage over providing written translations of questionnaires in that it also makes the study more accessible to those with poor literacy levels in their first language. We believe the advantages of using interpreters in terms of increasing research access and representativeness outweigh the disadvantage of potentially reducing questionnaire validity/reliability in this subsample of participants.

Exclusion Criteria: Consulting solely in written forms, e.g., via e-consult / emails (these patients will not be invited into the study); has pain known to be caused by malignancy; unable to consent; unable to complete questionnaires (for example, because of severe mental illness or distress, terminal illness) (these patients will be screened out pre-invitation by practice staff); already enrolled in the trial (e.g., if they consulted a participating practitioner twice within the recruitment window).

Patients: non-MSK pain ('All-comers') group

Inclusion criteria: Adult (18+); verbally consulting a participating practitioner about something other than MSK pain; has capacity to give informed consent. We will also include in this arm patients who are consulting for MSK pain and reporting their average pain in the last week as less than 4 on the numerical

rating scale from the Brief Pain Inventory at the index consultation (where 0 = no pain; 10 = pain as bad as you can imagine).

Exclusion Criteria: Consulting solely in written forms, e.g., via e-consult / emails (these patients will not be invited into the study); has pain known to be caused by malignancy; unable to consent; unable to complete questionnaires (for example, because of severe mental illness or distress, terminal illness) (these patients will be screened out pre-invitation by practice staff); already enrolled in the trial (e.g., if they consulted a participating practitioner twice within the recruitment window).

Who will take informed consent?

Informed consent will be taken by the researchers; in most cases this will be done remotely but a face-to-face option will be used if necessary e.g., for patients recruited in-surgery. We anticipate that all practitioners and most patient participants will have internet access and so for these participants informed consent will be taken electronically via Qualtrics. Hard copies will be available for patients who prefer hard copies and/or who do not have internet access.

For all participants, consent will be itemized separately for: participation in the trial; use of anonymized data for future research and education activities; pseudonymized data deposit in a data archive; and to re-contact about taking part in a qualitative interview. All participants may withdraw from the study without giving a reason; data can be withdrawn on request up to the point of data cleaning. Informed consent for each qualitative interview will be taken verbally by the interviewer and recorded immediately prior to commencing the interview.

Practitioner Consent Process

As part of study initiation procedures, the research team will direct potentially eligible practitioners in participating practices to the practitioner-facing study website (hosted on Qualtrics online survey software) which will include a study invitation letter, an electronic copy of the PIS, a brief screening questionnaire, and an electronic consent form. The research team will be available to answer questions remotely (phone, email). Consent is required from practitioners who will be asked for self-report data e.g., practitioner-reported process measures shown in Table 2.

Patient Consent Process

As part of recruitment procedures, the researchers and/or practice staff (see Recruitment below) will direct patients to the patient-facing study website (hosted on Qualtrics online survey software). The patient-facing website will show the full study invitation letter and Patient PIS. After reading the Patient PIS, patients will have the opportunity to ask questions (by phone, email), will be asked to complete a brief screening questionnaire and - if eligible – will be asked to complete an electronic informed consent form.

For participants without internet access (or who prefer hard copies), hard copies of participant information sheets and consent forms will be provided in person and/or via post, for completion and return to the research team in person and/or via freepost. Whether this is done in person or via post will depend on the recruitment methods used at each practice. Participants will have the opportunity to ask the researchers questions (via phone and/or email).

Interventions

Explanation for the choice of comparators

The comparator is Usual Care. Practitioners in practices randomised to Usual Care will not receive the EMPathicO training during the trial. The usual care comparator enables us to test the clinical and cost-effectiveness of adding our intervention to practitioners' post-qualification training. A 'placebo' or 'inactive' comparator would not enable a test of clinical effectiveness and would not be consistent with our pragmatic approach. It would be very difficult to design such a comparator for communication skills training that would not be theoretically meaningful but would be plausible to practitioners and would be ethically acceptable.

Intervention description

Empathico

Practitioners in practices randomised to receive EMPathicO will be given access to the training via the LifeGuide online platform. EMPathicO includes brief interactive e-learning modules on clinical empathy (~12min), realistic optimism (~15min), tailoring these for patients with OA pain (~18min), and guidance for reflecting on one's own consultations (~8min) and goal-setting (~4min). Figure 2 summarises the prototype e-learning package, which is currently being finalised ready for trial.

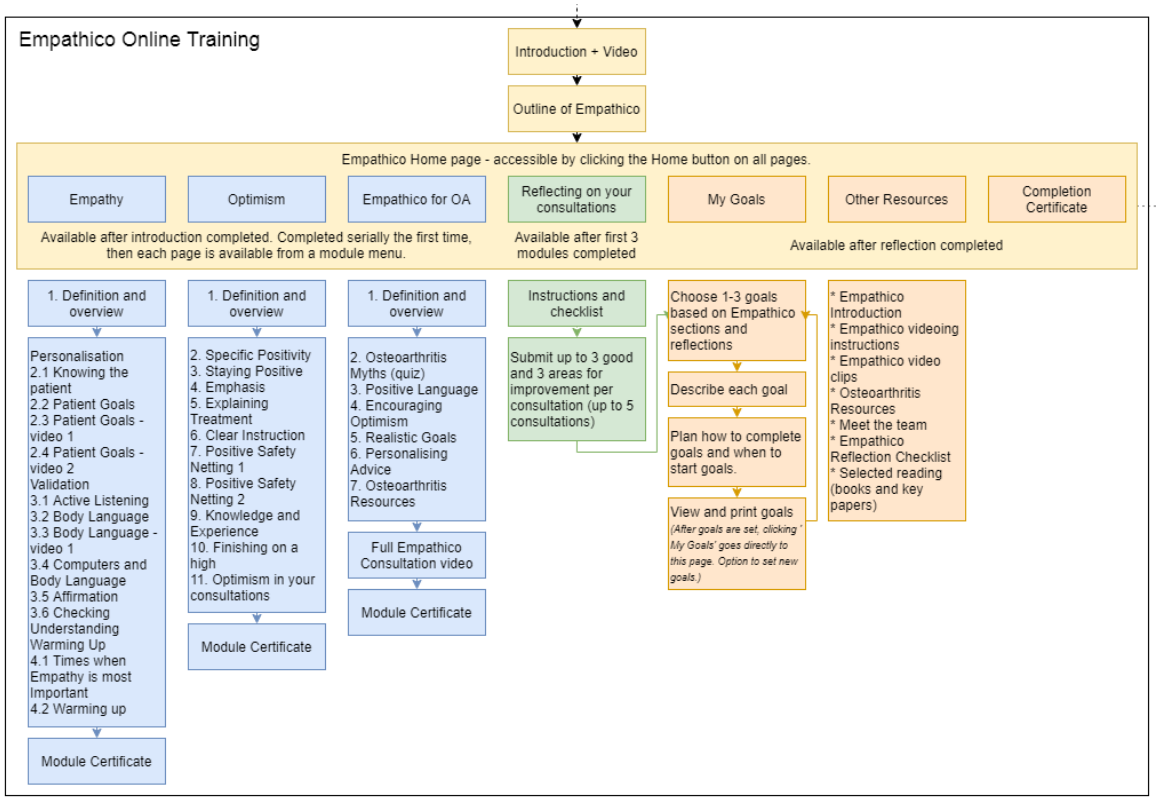

Figure 2. Overview of penultimate version of Empathico structure and contents (currently being finalised).

Usual Care Control

Practitioners in practices randomised to Usual Care control will not receive training. They will be offered access to the EMPathicO training when they have completed patient recruitment and follow-up.

Criteria for discontinuing or modifying allocated interventions

Practitioners and patients can withdraw from the study without giving a reason, but they cannot request modification to their allocated intervention.

Strategies to improve adherence to interventions

The extensive work already completed when developing the EMPathicO intervention and the automated email reminders built into EMPathicO increases the likelihood that practitioners will engage with the intervention and will implement the training in practice. Automated emails are sent at key points as reminders and to support timely progression through the training; for example, emails encouraging goal-setting are sent 7 and 9 days after initially logging on to users who have not yet submitted their goals on EMPathicO. The practice-facing researchers will regularly monitor practitioner engagement with the intervention via LifeGuide and technical support will be available from SP and other members of the practice-facing research team. We will collect and analyse detailed intervention usage data via LifeGuide (see Intervention Usage Data).

Relevant concomitant care permitted or prohibited during the trial

We will discourage practices in intervention and control groups from undertaking additional communication skills training during the study recruitment period and will collect data on any such engagement via self-report questionnaire at 34 weeks.

Provisions for post-trial care

There is unlikely to be any harm from this online intervention to enhance practitioner communication. Therefore, there are no provisions for post-trial care. Any adverse events that occur during the trial will be recorded and reviewed. Trial oversight will be provided by the Trial steering committee to ensure that if any harms are identified appropriate measures are put in place to address them. Individual practitioners are responsible for maintaining appropriate cover with a medical defence organisation. University of Southampton insurance may also apply where the cause of harm was not due to clinical negligence.

Outcomes and Measures

Outcomes and plans for assessment and collection of outcomes

Patient reported outcome and process measures and practitioner-reported process measures will be primarily collected via online survey software Qualtrics, which we used successfully in our feasibility study. Paper copies and telephone administration will be offered where needed to support inclusive access to research participation. Table 1 lists and summarises the timing and measures of patient-reported primary and secondary outcomes and process variables. In our feasibility study the patient-reported post-consultation and process measures were acceptable to patients and took participants on average 19 minutes (SD=14) to complete, which was acceptable to our qualitative interviewees and PPI advisors. According to Jordan et al[2] one in seven GP consultations in 2006 were for musculoskeletal problems, the most common of which were back problems followed by knee problems. Core outcome sets for chronic musculoskeletal pain[71 72], back pain[73 74], and hip/knee osteoarthritis[75] were therefore consulted to inform our selection of outcomes. These sets require measures of pain intensity, pain interference/physical function, emotional function, health-related quality of life, patient global impression of change, adverse

events, as well as data to report on participant flow for CONSORT, all of which we have included. The assessment of joint-specific symptoms is also required by OMERACT-OARSI [75] for trials in hip/knee osteoarthritis, but is not appropriate for our mixed MSK sample.

Table 2 lists and summarises the timing and measures of practitioner-reported process variables. Our feasibility study indicated that these measures were acceptable to practitioners and quick to complete. Table 3 lists the trial management data that will be collected and analysed.

Table 1. Patient-Reported Characteristics, Outcomes and Process Variables

Variable	Measure	Items	Measurement Timings				
			<-7d	<7d	+1m	+3m	+6m
Primary Outcomes							
Pain intensity (pain sample)	Pain intensity subscale from the BPI[76]	4	x	x	x	x	x
Patient enablement	Modified PEI[77]	6		x	x	x	x
Secondary Outcomes							
Patient global impression of symptom severity	Single item[78]	1	x	x	x	x	x
Patient global impression of symptom change	Single item[78]	1		x	x	x	x
Pain interference	Pain interference subscale from the BPI[76]	7			x		X
Patient satisfaction	MISS for UK general practice[79]	21		x			
Adverse events	Bespoke self-report item	1			x	x	x
Health Economics							
Health-related quality of life	EQ-5D-5L and EQ-VAS[80]	6	x		x		x
Capability wellbeing	ICECAP-A[81 82]	5	x		x		x
Healthcare utilization	ModRUM core module[83]	12		x		x	x
Prescribed medications	ModRUM depth questions[83]	1				x	x
Personal expenses	Bespoke self-report item	3				x	x
Productivity	WPAI:GH	6				x	x
Process Measures							
Perceptions of practitioner empathy	CARE[38]	10		X			
Perceptions of practitioner optimism	Bespoke item	1		X			
Treatment expectations	Treatment expectation questionnaire TEX-Q[84]	15		X			
Anxiety	HADS[85 86]	7		X			
Continuity of care	Patient-Doctor Depth of Relationship Scale[87]	9		X			
Depression	HADS[85 86]	7		X			
Sociodemographic Characteristics							
Age, gender, ethnicity		3	x				
Index of Multiple Deprivation	Postcode	1	x				
Health Characteristics							
Reasons for consulting		1		x			
Comorbidities		1		x			
Index consultation modality		1		x			

Table 2. Practitioner-Reported Characteristics, Outcomes and Process Variables

Practitioners	Variable	Measure	Items	Measurement Timings			
				Baseline	+2wk	+8wk	+34wk

All	Characteristics (age, gender, ethnicity, years qualified, profession)	Bespoke	5	x		
All	Practitioner self-efficacy for conveying clinical empathy	Bespoke, from feasibility study	7	X	X	x
All	Practitioner self-efficacy for conveying realistic optimism	Bespoke, from feasibility study	5	x	X	x
Intervention arm only	Practitioner outcome expectancy for implementing goals set during EMPathicO training	Bespoke, from feasibility study	16	X	X	x
Intervention arm only	Practitioner intentions to implement goals set during EMPathicO training	Bespoke, from feasibility study	3	X	X	x
Intervention arm only	Practitioner intervention usage	LifeGuide data	N/A		X	X
All	Practitioner-reported other training	Bespoke	1		x	x

Table 3. Trial Management Data

Variable	Measure
Practice characteristics	List size; Staffing; Deprivation score
Practice uptake	Proportion of expressions of interest converted Reasons for decline
Practitioner uptake	Proportion of eligible practitioners consenting Reasons for decline
Patient uptake	Proportion of eligible patients consenting Reasons for decline
Practice retention	Attrition rate Reasons for drop-out
Practitioner retention	Attrition rate Reasons for drop-out
Patient retention	Attrition rate Reasons for drop-out

Primary Outcomes

For the MSK group, the co-primary outcomes are **pain intensity and patient enablement**, each averaged over 6 months using a repeated measures approach, and we have allowed for co-primaries in our sample size calculations. Pain intensity is important because one of our intended pathways to change is for the EMPathicO training to enable practitioners to increase patients' response expectancies which should in turn reduce patients' symptom severity; as reflected in our logic model, evidence from placebo studies suggests that increasing patients' response expectancies associated with specific interventions and symptoms should reduce symptom intensity and much (but not all) of this evidence derives from pain. Patients have highlighted that Enablement is at least as important as pain, if not more important to them, as an outcome measure. Our PPIE input revealed a strong want for a 'coping with your illness' or 'enablement' outcome in addition to a symptom-based measure such as pain. Assessing both pain intensity and enablement as co-primaries will help to capture not only the effect enhanced clinical empathy and realistic optimism might be expected to have on pain based on previous literature, but also a more holistic effect on patients' ability to understand their illness, cope with it and minimize the impact it has on their lives. The outcomes will be reported separately and our PPIE and embedded qualitative work will help explore, interpret and explain how these co-primaries relate and impact on each other.

For the non-MSK pain ('All-comers') group, patient enablement will be the single primary outcome. We will also measure pain intensity in this group but will treat it as a secondary outcome.

Pain Intensity

Pain intensity is defined as the severity of pain sensation and is included in core outcome sets for chronic pain,[71 72 88] OA,[75] and Low Back Pain.[73 74] Pain intensity will be assessed before the index consultation to provide a baseline, then again immediately (within 1-week), 1-month, 3-months, and 6-months post-consultation.

Pain intensity will be measured using the 4-item pain intensity subscale from the BPI,[76] as recommended in core outcome sets by IMMPACT[88] and the Veteran's Health Administration.[72] We used an 11-point pain intensity numerical rating scale in our feasibility study and this worked well but some patients felt it captured only a small component of their pain experience and found it difficult to rate fluctuating pain levels; the Pain Intensity subscale on the BPI addresses this as it aggregates multiple 11-point pain intensity numerical rating scales assessing worst, least, average, and current pain. Following IMPAACT[88] and LBP core outcome set[73 74] recommendations, we will use average pain in the last week as the co-primary measure of pain intensity. The 4-item aggregated pain intensity subscale will be used as a secondary measure of pain intensity.

Patient Enablement

Patient Enablement is the extent to which patients feel confident and empowered by a consultation to cope with their illness(es), to keep healthy and to help themselves. Our PPIE work suggested this is a very important outcome for patients and it was included in our logic model as an important consultation outcome that is likely to produce improvements in patient self-management and reduced healthcare utilization over time; ultimately these benefits may also generalise beyond the patient's MSK pain to their self-management of other comorbid conditions. Enablement will be assessed immediately (within 1-week), 1-month, 3-months, and 6-months post-consultation.

The Patient Enablement Index (PEI) captures the extent to which patients feel confident and empowered by a consultation to cope with their illness, to keep healthy and to help themselves.[77] The original scale has six items with 4 response options (much better/never/same or less/not applicable). To increase sensitivity, versions with more response options have been reported.[89-91] In our feasibility study we used a modified 7-point agree-disagree Likert response scale and retained the Not Applicable option; participants used the full range of this extended response scale and, consistent with previous literature, PEI scores strongly correlated with scores on the MISS (r=.62) and the CARE (r=.58) but did not correlate with scores on the HADS-A (r=.06) or HADS-D (r=.08). We will use our modified 7-point version again in this trial.

Secondary Outcomes

Secondary outcomes capture patient satisfaction with the consultation (within 1 week immediately post-consultation) and health and quality of life changes (at 1-, 3- and 6-months post-consultation, see Patient Timelines Table). Secondary outcomes and measures have been selected based on the changes likely to result from our intervention according to our logic model, relevant core outcome sets, psychometric properties, PPIE input, brevity, and our feasibility study.

Symptom Severity and Global Impression of Change

Two single item 7-point[92] measures of Patient Global Impression of Symptom Severity and Patient Global Impression of Change will be administered at baseline (symptom severity item only) and all post-consultation timepoints (both items).[78] These items capture overall perceptions of symptom severity and change which are important for the MSK patients given the high prevalence of multi-morbid conditions. Capturing symptom severity and change is also important for non-MSK pain ('All-comers') group patients; this is because they are applicable to any conditions and provide a symptom-focused pre-consultation baseline.

Patient Satisfaction

Patient satisfaction with the consultation is important for patients and will enable comparisons with existing trials of empathy and optimism interventions. The 21-item Medical Interview Satisfaction Scale[93] (MISS) measures patient satisfaction with the consultation and detected post-intervention group differences in the KEPE-Warm study.[26] We have chosen the MISS version adapted and revalidated for UK primary care, which we used successfully in our feasibility study.

Pain Interference

Pain interference is included in core outcome sets for chronic pain,[71 72 88] OA,[75] and Low back pain LBP[73 74] and was important to our PPIE consultants. Pain interference will be measured with the 7-item pain interference scale from the BPI,[76] as recommended in core outcome sets by IMMPACT[88] and the Veteran's Health Administration.[72]

Health-Related Quality of Life

Health-related quality of life is in hip and knee OA[75] and LBP[73 74] core outcome sets. We will use the 5-item EQ-5D-5L to capture health-related quality of life and the EQ-VAS to capture global self-reported health (a vertical visual analogue scale from 0 (worst imaginable health) to 100 (best imaginable health)).[80]

Health Economics Outcomes: Healthcare Utilization and Associated Measures

Cost-effectiveness will be assessed from an NHS perspective and a societal perspective including personal expenses and productivity over a 6-month time horizon. As recommend by NICE, quality-adjusted life-years will be estimated by combining utility values estimated from the 5-item EQ-5D-5L, with the length of time in each health state, using the area under the curve approach.[80 94 95] The 5-item ICECAP-A, which was designed to capture broader aspects of quality-of-life and has been found to complement the EQ-5D in economic evaluations, will also be collected.[81 82] The EQ-5D-5L and ICECAP-A will be collected at baseline, 1- and 6-months.

Practitioner time spent on EMPathicO training will be captured by LifeGuide. Resource-use data will be collected via patient report. Self-reported healthcare utilization will be collected using ModRUM at <7days (for baseline), 3 months and 6 months.[83] Bespoke questions will be used at 3 and 6 months to collect resources outside the healthcare sector including data on personal expenses. The Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) will be used at 3 and 6 months to collect information on productivity, including time off work. NHS resources will include

primary, community and secondary care contacts, and prescribed medications. NHS resources will be valued using the national unit costs.[96-98] Personal expenses will be presented as reported. Time off work will be valued using Annual Survey of Hours and Earnings.[99]

Process Variables, Covariates, and Measures

EMPathicO aims to improve practitioners' communication of clinical empathy and realistic optimism. According to our logic model, the key precursors to practitioners' behaviour change are changes in practitioners' self-efficacy, outcome expectancy, and intentions for conveying empathy and optimism in consultations. Any changes in practitioners' communication of clinical empathy and realistic optimism - to be clinically meaningful - should be noticed by patients. Therefore, patients' perceptions of clinical empathy and practitioners' optimism are important components of the logic model. Finally, we hypothesize that for practitioners' optimism about treatment outcomes to reduce patient pain intensity then patients' treatment outcome expectations should themselves be more positive. Reductions in anxiety may also mediate the effects of clinical empathy and realistic optimism on pain. These constructs are all therefore included as process variables.

Practitioner-Reported Measures

Practitioner Self-Efficacy, Outcome Expectancy, and Intentions

Practitioner self-efficacy (all practitioners), outcome expectancy and intentions (intervention group only) for conveying clinical empathy and realistic optimism in consultations will be measured using bespoke items developed in our feasibility work based on standard item stems and following relevant guidelines and theory.[100-103] They demonstrated acceptable internal consistency (Cronbach's alphas ranged 0.69-0.98) and were fully completed by practitioners (n=11). They will be completed at baseline, 8-weeks (end of patient recruitment) and 34-weeks (end of patient follow-ups).

Intervention Usage Data

Intervention usage data will be captured on LifeGuide. This will include, for each practitioner-participant, data such as time spent on (different sections of) the intervention, patterns of use, order of accessing different sections, and any repeated use of sections.

Demographic and Professional Characteristics

Practitioners will be asked for their demographic and professional characteristics at baseline: age, gender, ethnicity, years qualified, profession. Practice-level data will be collected from the practice at the site initiation visit supplemented with data from national general practice profiles (National General Practice Profiles - Data – OHID, phe.org.uk): list size, deprivation score, staffing.

Case Report Form

A Case Report Form is not needed for this trial, as we will screen patients for eligibility based on responses to the screening questions on Qualtrics.

Patient-Reported Measures

Patient completed process measures will be completed immediately post-consultation only (ideally within 7 days).

Patient perceptions of practitioner clinical empathy

Patient perceptions of practitioner clinical empathy will be assessed using the 10-item CARE[38] a validated, reliable, questionnaire used extensively in UK primary care settings to assess patient perceptions of clinical empathy. The CARE was explicitly developed to be meaningful to people across the range of socio-economic backgrounds. It was used successfully in our feasibility study.

Patient perceptions of practitioner response expectancies

Patient perceptions of practitioner response expectancies will be assessed using a bespoke single item tested in our feasibility study (we found no existing measure of this construct). As expected, when measured within 2 weeks of consultation this bespoke item correlated with the established Credibility Expectancy Questionnaire[104] (CEQ) patient expectancy subscale (r=.40).

Patient treatment outcome expectancies

We will assess patient treatment outcome expectancies with a recently developed 15-item 6-subscale questionnaire designed to assess patient expectations about medical treatment outcomes, the Treatment Expectation Questionnaire (TEX-Q).[84] We used the English translation in our feasibility study (n=231) and confirmed its acceptability and psychometric properties for UK primary care: it demonstrated good internal consistency ($0.76<\alpha<0.94$), good congruent validity (moderate correlations with CEQ: $.4<r<.8$, except subscales measuring expectations of adverse effects which are not captured by CEQ) and good divergent validity (small correlations with Hospital Anxiety Depression Scale: $.02<r<.18$). We chose the TEX-Q with its 6 subscales over the CEQ with its 2 subscales as the former offers a more nuanced measure of multiple aspects of patient expectations and these are important in our logic model.[105]

Patient anxiety and depression

Patient anxiety will be assessed using the 7-item anxiety subscale from the well-validated in primary care Hospital Anxiety and Depression Scale (HADS).[85 86] Depression is included as a potential moderator and is assessed using the 7-item HADS Depression.

Continuity of care

Continuity of care is included as a potential moderator and will be assessed using the 9-item Patient-Doctor Depth of Relationship Scale,[87] modified for non 'Dr' practitioners.

Demographic and Clinical Variables

Items to be completed pre/post-consultation include age, gender, ethnic background, postcode (for calculating deprivation index), reason(s) for consulting (to be coded using the ICPC-2 as we did in our feasibility study), comorbidities, and index consultation modality.

Qualitative Interviews

Semi-structured interviews will be conducted and audio-recorded on MS Teams (using Teams to ring the participant's telephone) with practitioners and patients in both the MSK and non-MSK pain ('All-comers') trial groups. Participants will be purposively sampled for interview to capture diversity along dimensions including index-consultation mode (telephone/video/face-to-face), ethnic background, age, gender, baseline pain severity. Each participant will be interviewed twice, to explore their experiences of short-term and longer-term implementation (practitioners) and experiences of the index consultation and subsequent health/consultations (patients). Practitioners will be interviewed approximately 9-10 weeks post randomisation (on completing patient recruitment) and again approximately 34 weeks post-randomisation (when patient follow-up is completed). Patients will be interviewed within 7 days of their index consultation and again approximately 6 months later. As far as possible the same researcher will interview the participant at both time-points, to facilitate rapport. Researchers will make field notes on completing each interview, to include for example observations of participant affect and initial reflections on the interview. Up to 30 practitioners and 45 patients from the MSK pain group and 45 patients in the non-MSK pain ('All-comers') group will be interviewed. Interviews will be transcribed verbatim and identifying details will be replaced (e.g., using pseudonyms), transcripts will be checked and imported into NVivo for analysis (see below).

Adverse event, safety reporting and harms

This trial has been classed as low risk following a risk assessment. No adverse events (AEs) or Serious Adverse Events (SAEs) are expected; however, SAEs be collected, recorded and reported in accordance with good clinical practice and the requirements of the research ethics committee. Adverse events are included in core outcome sets for chronic pain[71 72 88] hip-knee OA[75] and LBP.[73 74] An adverse event (AE) is any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom or disease. A serious AE is any AE that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, consists of a congenital anomaly or birth defect, or other medically important condition. Patients may experience new or worsening symptoms during the trial period and a small number may, for example, have referrals for joint surgery. We will capture patient-reported adverse events using a single open-ended question with brief follow-ups adapted from the ACTIB trial[106] and used successfully in our feasibility study.

We will also ask GPs to report SAEs including deaths during the trial period. If the GP or other primary care practitioner suspects that an SAE resulted from use of the intervention it should be reported to the trial team immediately via the University's secure and encrypted SafeSend service using the trial SAE form. The causality of the event will be assessed by the practice clinician and a delegated clinician working within the TIPS trial team. If the event is deemed to be probably or definitely related to the intervention the SAE will be reported to the Research Ethics Committee and sponsor according to the expedited timescales. Safety information will be submitted to the TSC and to the REC in an annual progress report. The TIP trial SOP for SAEs will be followed.

Participant timelines

Table 4. Practitioner Timelines

	Allocation		Post-allocation (wk)					Close
TIMEPOINT	**0**	**+1d**	**1**	**2**	**3-8**	**8**	**9-10**	**+34wks**
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Site initiation visit	X							
Allocation		X						
INTERVENTIONS:								
EMPathicO training								
No training (control)								
ASSESSMENTS:								
Demographic and professional characteristics	X							
Self-efficacy for empathy and optimism	X					X		X
Expectations, intentions for EMPathicO skills [1]				x		x		X
Practitioner-reported other training						x		X
Qualitative interview							X	X[1]
PATIENT RECRUITMENT								
Prepare invitations								
Recruit patients								

[1] Intervention-arm practitioners only

Table 5. Patient Timelines

	Enrol	Consultation	Post-consultation			
TIMEPOINT	***<-7d***	**0**	***<7d***	***+1m***	***+3m***	***+6m***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ASSESSMENTS:						
Primary Outcomes						
Pain intensity	X		X	X	X	X
Patient enablement			X	X	X	X
Secondary Outcomes						
Global impression of symptom severity	X		X	X	X	X
Global impression of symptom change			X	X	X	X
Pain interference				X		X
Patient satisfaction			X			
Health economics: EQ-5D & ICECAP-A	X			X		X
Adverse events				X	X	X
Healthcare utilization	X				X	X

Prescribed medications, personal expenses, productivity					X	X
Process Measures						
Perceptions of empathy			X			
Perceptions of optimism			X			
Treatment expectations			X			
Anxiety			X			
Continuity of care			X			
Depression			X			
Sociodemographic characteristics	X					
Health characteristics			X			
Qualitative interview			X			X

Sample size

MSK pain Group

The minimum clinically important difference in the Brief Pain Inventory is around one point,[107] with a standard deviation of 3.3. This is consistent with a standardised effect size of 0.3. For 90% power, alpha of 0.025 to allow for co-primary outcomes, and a correlation between the 4 repeated measures of 0.7, a sample size of 214 per group is required. We assume a conservative ICC of 0.03, at the upper 75% of what has been observed in previous primary care trials.[108] Assuming 20 patients per practice gives a design effect of 1.57. Allowing for 20% loss to follow up gives a total sample size of (214*2*1.57)/0.8=840 participants to be recruited from 42 practices.

Non-MSK pain ('All-comers') group

840 non-MSK pain ('All-comers') patients will give us 90% power (based on alpha and ICC as per the MSK group above) to detect a standardised effect size of 0.3 in the PEI, which is equivalent to a difference of 0.36 points (assuming SD=1.2, based on feasibility study[59]).

Recruitment

GP Practice Recruitment

GP practices will be recruited with support from the local CRNs. Wessex CRN has agreed to be lead CRN and has worked with the trial team to approve the SOeCAT form for practice reimbursement for their service support costs and research activities. The trial team will present the trial at local research initiative days to generate interest in the trial and expressions of interest will be forwarded from the CRNs to the research team. The aim will be to recruit 42 practices (approximately 14 per recruitment hub area). We will aim for a range of practice demographics – from small to large practices; rural and urban practices and including those from areas with higher deprivation and will aim for practices serving populations with a range of ethnic diversity.

Patient Recruitment

The research team will support patient recruitment by selecting from the same recruitment procedures in all practices, regardless of intervention allocation. A range of patient recruitment methods will be used to

suit the diversity of current primary care appointment booking systems after detailed discussion with each recruiting practice. We have budgeted for reception and practice manager time to undertake patient recruitment activities and will integrate these activities into usual workflows as far as possible. Our range of patient-facing messaging and recruitment procedures have been and will continue to be developed with our PPI collaborators and diversity consultant to maximise accessibility to diverse patients. We have been and will continue to be guided in our approach and procedures by the INCLUDE roadmap[69] and the INCLUDE ethnicity framework[70] and associated resources.[71] The rapidly evolving nature of primary care access arrangements in the current COVID affected environment will necessitate agile recruitment methods and adaptation to a changing primary care landscape. We showed that we were able to do this in the feasibility study and are aware that this will likely be necessary for this trial. Our team (GL, PL, HE), has extensive experience using a range of methods to successfully recruit patients to other communication skills trials in primary care.[21,72]

For patients with appointments booked in advance, practices will text, email, or post a brief invitation and link to the patient-facing study website up to 1 week before their consultation and may follow this up with one reminder (by text, email, post, phone, or in person for patient with consultations in practice). For patients with same-day appointments, practices will text or email a link to the patient-facing study website. We have chosen to send invitations by text and/or email, as our pre-grant PPI work suggested younger patients may prefer to receive this via text while older patients may prefer email. We may need to send a small number of invitations by post for patients who do not have text and/or email registered with their practice. Patients will be able to email or phone the patient-facing research team with any questions.

Practices will screen potential invitees for initial eligibility before sending out invitations. Practices will be asked not to invite into the study any patients who do not have capacity for consent, or where there are medical grounds for excluding the patient from the TIP trial (e.g., very unwell generally, severe mental distress). Practices will be asked to check for patients who usually use an interpreter (formal or informal) at their consultations or who have literacy difficulties that would preclude reading study documents. We will ask each GP practice to follow their usual procedures for contacting non-English speakers to invite them to take part in the trial e.g., contacting a designated friend or relative or support worker, or arranging an interpreter, or adding a sentence in the patient's own language on the initial study invitation. Requests for interpreter and/or researcher support may be made by patients directly to the research team or via practice staff. The research team will then make the necessary arrangements to go through study documents with the patient, with or without an interpreter (as necessary), on the phone and/or in person in the GP practice.

For patients who have the necessary language and technical skills to access the study without support, the patient-facing study website (hosted on Qualtrics) will show the full study invitation and PIS. After reading the PIS, patients will be asked to complete a very brief screening questionnaire and will be informed that completing this screening questionnaire will be taken as consent for the research team to use these data for the purposes of determining and recording eligibility for the trial. The screening questionnaire will determine eligibility for both the MSK pain group and the non-MSK pain ('All-comers') group of patients and will capture whether the patient uses an interpreter (formal or informal) for consultations and whether the patient might need assistance to take part in the trial (e.g., difficulty reading and writing). We will closely monitor patient recruitment by practice and if we reach our target numbers for MSK pain patients or non-MSK pain ('All-comers') group patients, we will switch to amended invitations with the current inclusion criteria (MSK and/or non-MSK) clearly stated in accessible language and will make corresponding changes to the algorithm for determining eligibility on Qualtrics. The screening questionnaire on Qualtrics will be programmed such that those who are not eligible will be

shown a debriefing message that thanks them and explains they are not eligible to take part. Individuals who are eligible will be shown the informed consent items for completion. The informed consent items will be programmed such that those who do not give consent will be shown a debriefing message that thanks them and explains they are not eligible to take part. Individuals who do consent will be presented with the baseline outcome measures (4-item Brief Pain Inventory[73] (BPI) Pain Intensity subscale, the single item Patient Global Impression of Symptom Severity (PGI-S)), and baseline health economic measures (the 5-item EQ-5D-5L with EQ-VAS and the 5-item ICECAP-A: the ICEpop CAPability measure for Adults).

For patients attending in-surgery appointments the study invitation email/text/mail may be supplemented by reminders from reception staff and a researcher available in the waiting room, if infection control measures permit. Reception staff and researchers will remind the patient that the study is taking place and offer electronic and/or hard copies of the study invitation letter, information sheet, screening, consent, and baseline measures, if they have not yet signed up but are interested. Reception staff may also introduce the study to patients attending in-person if for some reason they have not received the initial invitation email/text/mail. We will work with practices to provide researchers in-person when and where needed to support recruitment. For example, practices may invite patients to attend 15 minutes before their scheduled appointment, to speak with a researcher about the study in the waiting room or a vacant office and to complete consent and baseline measures on paper or on Qualtrics using the researcher's internet-connected device or their own personal device. We will also offer practices a poster / infographic to display in practice and/or on their website, to raise awareness that the practice is taking part in the study and to reassure patients who receive an invitation e.g., by text message, that this is legitimate.

Electronic check-in is currently suspended in many practices due to COVID. If electronic check-ins are being used at any participating practices during the recruitment period, we will also work with practices to offer patients the option of using electronic check-in to complete screening, consent and baseline measures.

To minimise the risk of sample bias through selective recruiting in this cluster-randomised trial, we will work with reception staff and practice managers to automate patient invitations as far as possible and to integrate them with existing processes. While practitioners will necessarily be aware of the weeks and specific surgeries during which patient recruitment is happening, we will attempt to minimise the chances of practitioners knowing before or during their consultation that a specific patient is taking part in the trial. We will ask patients, reception staff, and practice managers not to disclose this information to practitioners. Any researchers supporting patient recruitment in waiting rooms will try to avoid identifying individual participating patients to their treating practitioners.

Recruitment Rates

For each morning or afternoon surgery session of approximately 15 to 20 patients, we estimate that at least 2 will be presenting with MSK pain (based on feasibility study, published consultation rates,[2] and correspondence with local GP research champions). A 6-week recruitment period in each GP practice, encompassing approximately 60 half-day surgery sessions across several practitioners, should therefore be sufficient to recruit the required 20 patients presenting with MSK pain. We will stagger recruitment of practices, access to EMPathicO and patient recruitment to ensure a manageable workload. This means that while each practice will follow the timelines shown in Table 4, the start of the timeline (day 0) will differ by practice and will be spread across approximately 9 months (approximately October 2022-June 2023). With each of the three hubs recruiting 14 practices, and allowing for holiday periods, we aim to

complete patient recruitment in 10 months (approximately November 2022 – August 2023) and data collection including 6-month follow-ups and reminders in 15 months (approximately November 2022 – February 2024). Recruitment can be more challenging for control practices and we will increase researcher support for recruitment in these practices if necessary.

Assignment of interventions: allocation

Sequence generation

A computer-generated allocation sequence with random block sizes of 4 and 6 and stratification by high/low deprivation and practice list size will be produced.

For the purpose of this trial, practices with a list size of less than 7900 persons are defined as 'small' practices and practices with a list size of 7900 persons and above are defined as 'large 'The figure of 7900 persons represents the median practice list size in England. High deprivation is defined as a General Practice Index of Multiple Deprivation (IMD) decile between 1 and 5; low deprivation is defined as a GP IMD decile between 6 and 10.

Concealment mechanism

The allocation sequence will be implemented using the randomisation function in LifeGuide and will not be visible to users.

Implementation

The trial manager, assisted by the researchers, will enrol practices and practitioners. On completing the site initiation visit and receiving practitioner consents, the trial manager (or other appropriately delegated member of the team) will randomise practices using a bespoke randomisation tool that was developed for the trial (hosted on the LifeGuide platform and based on its randomisation function). The trial manager and practice-facing researchers will then notify practices and practitioners to their intervention.

Assignment of interventions: Blinding

Who will be blinded?

Patients and the trial statistician will be masked to intervention allocation. Researchers will be split into two groups: practice-facing (to include the trial manager) or patient-facing. Practice-facing researchers will enrol practices and practitioners, interview practitioners, and communicate with practices about interventions; they will not be masked. Patient-facing researchers will support practice recruitment up to the point of randomisation and will lead on patient recruitment and patient-reported data collection; they will be masked as far as possible. Because we have a small team of researchers delivering this trial, it might be necessary (e.g., in cases of absence) for researchers to occasionally switch between the practice-facing and patient-facing roles, but we will endeavour to minimise this. Practices and practitioners cannot be masked to intervention allocation and will be instructed not to discuss the EMPathicO training (or lack thereof) with the patient-facing researchers.

Procedure for unblinding if needed

Unblinding of patients is permissible if it is deemed necessary for patient care but is very unlikely to be required in this trial. The patient's general practice will already know their allocated intervention. Practices will be instructed to inform the practice-facing research team if they unblind any patients.

Data collection and management

Plans to promote participant retention and complete follow-up

Patient retention and follow-up

The PIS will offer patients the opportunity to request an interpreter and/or a paper version of questionnaires and the screening questionnaire will also highlight patients who may need these options. £10 e-vouchers (paper vouchers if requested) will be sent at the 1-month and 6-month timepoints to incentivize completion. Automated follow-up emails will be sent to non-responders at all timepoints. Researchers will personally contact persistent non-responders who haven't withdrawn and offer to (re)send questionnaires or complete primary outcomes over the telephone. Team members have successfully achieved >70% retention in previous similar studies;[26 109-112] our feasibility study achieved 73% retention with no incentives or personal contacts. We have had patient input to our choice of measures (via feasibility study and PPIE groups) and are confident our carefully selected measures are appropriate; while a large number of individual measures are being used, it is important to note that the measures are not all completed at every measurement point (see Table 5). In our feasibility study the post-consultation and process measures took participants on average 19 minutes (SD=14) to complete, which was acceptable to our qualitative interviewees and PPI advisors.

Practitioner retention and follow-up

Incentives for practitioners to participate include certificates evidencing engagement with EMPathicO training for use in appraisals and other Continuing Professional Development (CPD) excess treatment, research, and service support costs to be paid to practices. As for patients, automated follow-up emails will be sent to non-responders to practitioner-reported measures at all timepoints. Researchers will personally contact persistent non-responders who haven't withdrawn and offer to (re)send questionnaires or complete them over the telephone.

Data management

Expression of interest

Expressions of interest will be saved to the University of Southampton secure network project folder (accessible only by members of the study team and University of Southampton IT Services) and destroyed on study completion.

Practitioners' own recordings of consultations

As part of the intervention practitioners will be encouraged to record some consultations in order to facilitate their reflective learning. The researchers will not have access to these recordings and they do not form part of the research data. Practitioners will be responsible for using their usual procedures (e.g., around consent, data protection, storage and destruction) for recording consultations for CPD. The researchers will provide guidance if requested.

Audio-recordings of participant interviews

Audio-recordings of participant interviews will be collected using the recording function on MS Teams. If any participants prefer to do the interview on MS Teams with cameras on (as opposed to being called by the researcher using MS Teams to audio-call their telephone) we will have to record the video and the audio but we will create an audio-only version of the recording and delete the video version on verifying the audio-only version. Following each interview, the audio-recordings will be saved to the University of Southampton secure project folder (accessible only by members of the study team and University of Southampton IT Services) and then deleted from the MS Stream on Sharepoint server. The audio recording file and transcript will be identified by assigning a participant identifier code (PIC) which will be used to identify the participant during the study. Transcribing will be facilitated through a member of the research team or a University-approved third party, using only the PIC. Transcribers will sign a confidentiality agreement to keep the data confidential; store the data securely; and delete the data when the transcription has been completed and receipt confirmed. Researchers will check transcripts for accuracy against original recordings will disguise details (e.g., names of people or places) that might render a participant identifiable (e.g., 'Dr Smith' would be changed to 'Dr 1'). The audio-recordings and transcripts will be pseudonymised through being associated with individual participants using PICs and will be subject to the procedures outlined below for Personal Data.

Screening, consent, process and outcome measures

Screening, consent, and patient and practitioner self-reported process and outcome measures will predominately be collected electronically via Qualtrics which was found to be acceptable in the feasibility study. However, as noted above, paper copies and telephone administration will be offered where needed to support inclusive access to research participation. When study paperwork and measures are administered via telephone, the telephone call will be audio-recorded via MS Teams, the researcher will enter data contemporaneously into Qualtrics, and this data entry will be checked against the audio-recording. When study paperwork and measures are completed on paper, the researchers will enter data into Qualtrics and this will be checked for accuracy by a second researcher.

During data collection, data will be stored securely on Qualtrics servers (see https://www.qualtrics.com/security-statement/).

When we finish data collection, Qualtrics data will be downloaded and saved to the University of Southampton secure drive project folder. Paper questionnaires will be scanned then hard copies will be securely destroyed. Audio-recordings of telephone administered measures and questionnaires, downloaded Qualtrics data, and scanned questionnaires will be pseudonymised through being associated with individual participants using PICs and will be subject to the procedures outlined below for Personal Data.

Intervention usage data

Data collected on practitioner participants' use of the online intervention will be collected by the LifeGuide platform and stored on secure, firewall protected servers, hosted by the University of Southampton. Only trained research personnel with specific roles within the project will have access to this server. Upon download, usage data will be saved to the University of Southampton secure drive project folder. Usage data will be pseudonymised through being associated with individual participants using PICs and will be subject to the procedures outlined below for Personal Data.

Data quality

Coding of entries will be double checked, and variables and values labelled. Duplicates will be checked to avoid double entry of data. Descriptive statistics will be used to identify out of range values and potential outliers.

Confidentiality

Personal data

Personal data will be collected and stored on a secure server at University of Southampton in compliance with the requirements of the General Data Protection Regulations and the Data Protection Act 2018. Research data will be pseudonymised using PICs and saved to the University of Southampton secure drive project folder (accessible only by members of the study team and University of Southampton IT Services) as described above. Participant names and contact details required to conduct the trial (e.g., email, phone, postal address – depending on participant-chosen modes of contact) will be kept in a password-protected electronic file and saved to the University of Southampton secure project folder (accessible only by members of the study team and University of Southampton IT Services). To keep participants' contact details up to date, we will prompt participants to update their contact details with us at the 3 month and 6 month data collection point (for patients) and the 34 week data collection point (for practitioners). It is necessary to ensure current contact details even at this final data collection point so that we can communicate trial results to participants.

Only trained research personnel with specific roles assigned will be granted access to the research data and/or the participant names and contact details. During the trial, the research team including investigators and researchers external to University of Southampton will be able to access research data as needed for the effective conduct of the trial, data analysis and publication.

If participants withdraw from the trial and request their data be withdrawn, their data will be deleted up to the point of data cleaning after which point it will only be possible to delete patient names and contact details. We will retain limited trial management data necessary for trial reporting (e.g., which arm they were in, when they withdrew, and any reason given for withdrawing).

Pseudonymised research data and participant names and contact details and the trial master file will be retained for 10 years after the study has finished in accordance with the procedures agreed by the sponsor. After this time, participant names and contact details and the trial master file will be destroyed along with any research data for which consent was not given for deposit in a secure data archive.

The results of the study will be written up in reports and publications. Anonymised quotations provided by participants during the interviews may be used to illustrate the findings, but participants will not be identifiable.

During analysis and write-up (approx. 2 years) all data will be saved to the University of Southampton project folder on a secure server, after which it will be stored off site at an approved storage facility that has been agreed by the sponsor.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

N/A

Statistical methods

Statistical methods for primary and secondary outcomes

For the co-primary outcomes, a linear mixed model will used. This will use all the observed data, and implicitly assumes that missing outcome scores are missing at random given the observed data. The primary analyses for the BPI and PEI scores will be performed using a generalized linear mixed model (GLMM) framework with observations at 3 days, 1-. 3-, and 6-months (level 1) nested in participants (level 2) and participants nested in practices (level 3). Unadjusted results will be reported as well as results adjusting for baseline values, stratification variables and potential confounders as appropriate. As there may not be a constant treatment effect over time, a treatment/time interaction will be modelled and included if significant, with time treated as a random effect. An unstructured covariance matrix will be used.

For secondary outcomes, the analyses will use a similar modelling approach, with mixed logistic/linear regression models as appropriate, a random effect for practice, controlling for baseline values, stratification variables and potential confounders.

No subgroup analyses planned. A full and detailed statistical analysis plan will be developed prior to final trial analysis and approved by Trial Steering Committee. Results will be reported in line with CONSORT.

Interim analyses

Interim analyses and progression criteria are based on recruitment rates 6 months after commencing patient recruitment:

- GREEN: Recruited 21 practices and 420 patients, with a good pipeline. Continue as planned.
- AMBER: Recruited 15-20 practices and at least 150 patients, with a good pipeline. Discuss with TSC and funder possible mitigating actions, e.g., increase staff time on recruitment activities, expand to other CRNs, shorten patient follow-up period.
- RED: Recruit <15 practices and <150 patients. Discuss with TSC and funder to explore all possible avenues to save the trial. If none deemed feasible, then stop.

Following initial discussion with our TSC, we do not believe it is necessary to conduct any interim analyses of outcomes in this low-risk trial.

Methods for additional analyses (e.g. subgroup analyses)

Health Economic Analysis

An NHS perspective will be taken in the primary analysis; with a wider perspective taken in secondary analyses including impacts on patients and productivity. Relevant covariates, including baseline EQ-5D-5L and the cluster design will be accounted for.[95] Cost-consequences will relate costs from each perspective to a range of outcomes. Cost-effectiveness will be estimated in a cost-utility analysis comparing QALYs to costs incurred to the NHS. The incremental net monetary benefit (iNMB) statistic will be presented at standard NICE thresholds and if appropriate, incremental cost-effectiveness ratios will be estimated. Uncertainty will be addressed by bootstrapping, plotting cost-effectiveness acceptability curves and in sensitivity analyses.

Process Analysis

The process analysis will focus on mechanisms of impact and test hypotheses derived from the logic model about relationships among variables, including mediators and contextual moderators.[110] Intervention usage data, captured by LifeGuide, will be incorporated using the AMUsED framework for Analyzing and Measuring Usage and Engagement Data.[111]

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Analysis will be by intention to treat (as randomised) regardless of any practice-level non-adherence to the intervention. All available data will be analysed, with a sensitivity analysis using multiple imputation if appropriate. Linear mixed models and multiple imputation both assume the data are missing at random, therefore sensitivity analyses to data missing not at random will also be explored. Further detail will be provided in the Statistical Analysis Plan.

Plans to give access to the full protocol, participant level-data and statistical code

The protocol will be published in an open access journal. We will seek patient and practitioner consent to deposit data in a data archive e.g., for secondary analysis. For participants who consent for their data to be deposited in a data archive, we will take the necessary steps to pseudonymize the data prior to deposit. Data will be deposited in Pure, the University of Southampton's online data repository, where access will be restricted through gatekeepers (the chief investigators) to suitably qualified individuals with appropriate protocols in place. Statistical code will not be deposited as the pseudonymisation process alters the dataset in a way that impacts the applicability of the statistical code.

Qualitative and Mixed Methods Analysis

This analysis aims to evaluate EMPathicO's potential impact post-trial. The RE-AIM framework involves addressing an intervention's Reach, Effectiveness, Adoption, Implementation, and Maintenance. [68 69] Drawing on data from the main trial, the non-MSK pain ('All-comers') group and the qualitative component we will assess EMPathicO against the RE-AIM components as shown in Table 6.

Table 6: Qualitative and Mixed Methods Data Analysis to Evaluate Intervention

RE-AIM	Data source	Analysis
Reach	Management data	Proportion and characteristics of practitioners and patients taking part. Reasons for declining.
Effectiveness	Non-MSK pain ('All-comers') group	Apply analysis plan from main trial to test intervention effectiveness in non-MSK pain ('All-comers') group.
	Qualitative data (patients and practitioners)	Compare experiences of EMPathicO across in-person, telephone and video consultations, and for MSK pain vs other conditions (framework analysis).

Adoption	Management data	Proportion and characteristics of invited practices taking part. Reasons for declining.
Implementation	LifeGuide usage & qualitative data	Assess patterns of usage and 'effective engagement' with EMPathicO. Explore barriers and facilitators to implementation in practice, drawing on Normalization Process Theory[113] (framework analysis).
Maintenance	Qualitative data (patients and practitioners)	Explore opportunities to embed EMPathicO in existing training structures. Examine longer term maintenance of practitioner behaviour change and effects on patients (reflexive thematic analysis).

The reach of the intervention (i.e., who participated or was exposed to the intervention) will be determined by analysing the proportion (frequency/percentage) and demographic characteristics of the practitioners and patients who take part in the trial collected as part of the trial management data. We will also summarise and describe practitioners' and patients' reasons for declining to take part and explore in the qualitative interviews factors that may contribute to participation/non-participation.

Effectiveness of the intervention (ability to change the desired outcomes of patient pain and enablement) will be analysed as part of the main trial. We will also explore practitioners' and patients' experience of the intervention in our qualitative interviews, in particular experiences of the intervention for different groups of people or in different contexts (e.g., remote vs. in person consultations, MSK pain vs. other conditions).

Adoption of the intervention will be assessed by summarising and describing the proportion of invited GP practices that take part in the trial and their characteristics as well as reasons for declining to take part collected as part of the trial management data.

We will analyse the implementation of the intervention (how well the intervention was used as designed) by evaluating intervention usage (e.g., which parts of the intervention were used when, how often, and how long practitioners used the intervention). Objective measures of intervention usage are automatically recorded by LifeGuide (with informed participant consent), allowing evaluations of usage patterns, such as time spent on intervention, number of visits, pages visited and engagement with specific modules and features (such as audio-visual tools). We will also explore in our qualitative work which parts of the intervention participants found helpful/unhelpful, perceived barriers and facilitators to using the intervention and views around implementing the intervention in everyday practice as well as contextual factors (e.g., pre-existing user beliefs, knowledge, skills) that may influence user engagement. We will draw on Normalisation Process Theory[113] as a theoretical framework for this qualitative analysis and will use Framework Analysis to code and map our data to the theoretical framework.[114]

We will explore processes and factors involved in the maintenance of the intervention using qualitative data from practitioners and patients. A reflexive thematic analysis[115] will focus on longer term maintenance of practitioner behaviour change from practitioners' and patients' perspectives, exploring barriers, facilitators, and processes, within and beyond the immediate context of the consultation. We will also explore opportunities to embed EMPathicO in existing training structures.

Together, these analyses will inform the future implementation of EMPathicO (if the trial is positive) and (regardless of trial outcome) will generate useful lessons for other, similar, interventions.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The TSC Charter is available on request. In broad terms, the TSC will provide oversight for the TIP study. It will also provide advice through its independent Chairperson to the Trial Management Group (TMG) and the funder (NIHR-SPCR) on all aspects of the trial. The TSC will also assume responsibilities of the Data Monitoring Committee (DMC) and review information on the progress and accruing data of this trial and provide advice on the conduct of the trial. Members of the TSC are Professor Joanne Reeve (chair) – Independent member; Dr Philip Pallmann – Independent member; Dr Ines Rombach – Independent member; Mr Ian Dickerson – PPI contributor; Dr Felicity Bishop – Co-Chief Investigator; Professor Hazel Everitt – Co-Chief Investigator.

Composition of the data monitoring committee, its role and reporting structure

An independent data monitoring committee is not indicated for this study due to the nature of the intervention, study endpoints, study duration and study population. The decision whether to review interim safety and efficacy will be made by the Trial Steering Committee (TSC).

Frequency and plans for auditing trial conduct

The study may undergo inspection and audit by the UoS (under their remit as Sponsor) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Protocol amendments will be submitted for approval as required to the study sponsor and the REC and notified where necessary to all those concerned, e.g. CRNs.

Dissemination plans

Results will be communicated to participants (practitioners and patients). Results will be written up and disseminated to academic, practitioner, and public audiences via peer-review journal articles, conferences, and other appropriate formats e.g. blogs. We shall encourage creative dissemination and take an holistic approach to publicising the results utilising our clinical, academic and PPI lay advisors to ensure maximum Impact.

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The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Availability of data and materials

Investigators and researchers on the trial who are external to University of Southampton will have honorary contracts enabling access to relevant folders within the University of Southampton secure drive project folder. Data sharing within the trial team is governed by the SPCR contract for SPCR partners (Keele, Bristol, Oxford) and separate data sharing agreements between Southampton and other partners (Warwick).

Ethics approval and consent to participate

Ethical approval will be sought from the HRA National Research Ethics Service. Informed consent will be obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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