Talking in Primary Care (TIP): Protocol for a cluster-randomised controlled trial in UK primary care to assess clinical and cost effectiveness of communication skills e-learning for practitioners on patients’ musculoskeletal pain and enablement

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# Abstract

## Introduction

Effective communication can help to optimise healthcare interactions and patient outcomes. However, few interventions have been tested clinically or subjected to cost-effectiveness analysis or are sufficiently brief and well-described for implementation in primary care. This paper presents the protocol for determining the effectiveness and cost-effectiveness of a rigorously developed brief eLearning tool, EMPathicO, among patients with and without musculoskeletal pain.

## Methods and Analysis

A cluster randomised controlled trial in GP surgeries in England and Wales serving patients from diverse geographic, socio-economic, and ethnic backgrounds. GP surgeries randomised (1:1) to receive EMPathicO e-learning immediately, or at trial end. Eligible practitioners (e.g., GPs, physiotherapists, nurse practitioners) are involved in managing primary care patients with musculoskeletal pain. Patient recruitment managed by practice staff and researchers. Target recruitment is 840 adults with and 840 without musculoskeletal pain consulting face-to-face, by telephone or video. Patients complete web-based questionnaires at pre-consultation baseline, 1-week and 1-, 3- and 6-months later. Two patient-reported primary outcomes – pain intensity and patient enablement. Cost-effectiveness considered from NHS and societal perspectives. Secondary and process measures include practitioner patterns of use of EMPathicO, practitioner-reported self-efficacy/intentions, and patient-reported: symptom severity, quality of life, satisfaction, perceptions of practitioner empathy and optimism, treatment expectancies, anxiety, depression, continuity of care. Purposive sub-samples of patients, practitioners, and practice staff take part in up to two qualitative semi-structured interviews.

## Ethics Approval and Dissemination

Approved by South Central – Hampshire B Research Ethics Committee on 1.7.22 and Heath Research Authority and Health and Care Research Wales on 6.7.22 (REC reference 22/SC/0145; IRAS project ID 312208). Results will be disseminated via peer-reviewed academic publications, conference presentations and patient and practitioner outlets. If successful, EMPathicO could quickly be made available at low cost to primary care practices across the country.

## Registration

ISRCTN18010240 registered 15 September 2022.

Strengths and Limitations of this Study

* Assessment of a brief online learning package which is evidence and theory-based and was rigorously developed with primary care clinicians.
* Practitioners (e.g., GPs, Physios, Nurses) consult as usual without needing to identify or consent patients within the consultation, as patient recruitment is done by administrative staff.
* Focussed on patients with musculoskeletal pain but including other patients as ‘all-comers’ enables efficient test of relevance to all primary care consultations.
* Feasibility work showed it is not practicable to record consultations in this trial, so there is no direct assessment of changes in practitioner communication behaviours after engaging with the e-learning package.
* ‘All-comers’ is a large and varied group of patients which enhances generalisability but is not suitably powered to plan sub-group analyses.

# Introduction

Approximately 1.7 billion people worldwide have musculoskeletal conditions, which are typically painful, limit peoples’ daily lives, and impair quality of life.[1] Musculoskeletal conditions including back, hip, knee and neck pain are commonly managed in primary care,[2-4] where patient-centred care, including excellent practitioner-patient communication, is an international priority.[5-7] In the UK, people with musculoskeletal conditions may be seen in primary care by GPs, practice nurses, physiotherapists, and other allied healthcare professionals.

Regardless of which treatment, therapy, or other intervention a patient receives, effective practitioner-patient communication can reduce symptoms and enhance quality of life, adherence to and satisfaction with care, producing benefits comparable to many pharmaceutical interventions.[8-10] Sub-optimal communication can lead to missed opportunities for benefit, worse quality of life and symptom management, unwanted prescriptions and non-adherence;[11,12] unnecessary economic costs;[12] deviation from guideline-recommended treatment;[13] and increased complaints and litigation.[14,15] Despite communication skills being taught in medical and allied health professional training, patients still report dissatisfaction with practitioner-patient communication,[16,17] the extent to which patients rate their practitioners as being empathic varies widely,[18] and medical students appear to exhibit broadly stable or declining levels of empathy during their degrees.[19,20] The need to enhance and expand communication skills is particularly pertinent since the COVID pandemic forced rapid introduction of remote consultations, bringing new opportunities and challenges for patients and staff not specifically trained to consult in this way.[21]

We focus on the communication of clinical empathy and positive messages within primary care consultations. Clinical empathy and positive messages are not routinely reliably optimised in clinical care but can have statistically and likely clinically significant effects on pain, patient satisfaction, and other outcomes with no evidence of adverse effects.[22] Our intervention planning determined that enhancing practitioners’ communication of clinical empathy and realistic optimism was feasible, measurable, and likely to have significant impact.[23,24] Even brief interventions can improve communication skills, including interventions concentrating on empathy skills such as active listening and expressing warmth at appropriate times[25-27] which take no additional time in the consultation.[27,28] However, few interventions have been tested clinically for effects on patients’ health,[29] have been subjected to formal cost-effectiveness evaluations,[30] or are sufficiently brief and well-described to facilitate implementation in the current primary care climate. Our work aims to address these limitations. We are evaluating the effects on patients’ health of brief, evidence-based, online training to enhance practitioners’ communication of clinical empathy and realistic optimism within everyday clinical consultations (“EMPathicO”).

## Aims and Objectives

The primary objective is to determine EMPathicO’s effects on (a) patient-reported pain and (b) patient enablement via repeated measures over 6 months following the index consultation, in patients presenting with musculoskeletal pain, compared to usual care control.

This clinical focus on musculoskeletal pain was chosen to align with the EMPathicO training, which includes modules on clinical empathy, realistic optimism, and how to communicate these better in the context of consultations for osteoarthritis. Including a condition-specific module permitted clear demonstration of communication skills in a particular context, which made the training better targeted and potentially more effective.[31] A painful musculoskeletal condition 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; osteoarthritis was chosen because it is a prevalent painful musculoskeletal condition in primary care.

Secondary objectives are:

* To estimate EMPathicO’s cost-effectiveness and effects on patient-reported quality of life and other secondary outcomes, over 6 months from index consultation, in patients with musculoskeletal pain.
* To test hypothesised mechanisms of action.
* To explore EMPathicO’s potential for implementation, by:
  + Determining EMPathicO’s effects on patient enablement, patient-reported quality of life and other secondary outcomes over 6 months from index consultation, in patients ineligible for the musculoskeletal pain group (i.e., presenting with other symptoms and/or very low levels of musculoskeletal pain, hereafter referred to as ‘all-comers’). This group was included because clinical empathy and realistic optimism may be beneficial for many different symptoms seen in primary care, and when practitioners adopt new communication behaviours within consultations for one type of condition these skills may ‘spill-over’ and also be implemented in consultations for other conditions. We wanted to evaluate any such additional benefits.
  + Identifying opportunities, barriers, and solutions for widespread implementation and impact, using the RE-AIM framework to explore EMPathicO’s Reach, Effectiveness, Adoption, Implementation, and Maintenance. [32,33]

# Methods and Analysis

This protocol reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Supplemental Material 1).[34] The first site was randomised on 31.10.22 and data collection is due to finish on 31.7.24.

## Patient and Public Involvement and Engagement (PPIE)

To ensure our work engages and is relevant to patients, we have worked with patients and members of the public throughout developing EMPathicO and this protocol. We continue working closely with our Patient Advisory Group, led by our PPIE lead, JB, who sits on our trial management group. This group comprises six patient and public contributors of varying ages, ethnic backgrounds (three from Black and Minority Ethnic backgrounds, three from White backgrounds), gender (three female, three male), and geographical locations within England. One member is neurodivergent, and all have lived experience of MSK pain as patients or carers. Our panel meet virtually for one hour bimonthly and contribute to specific activities including refining patient-facing documents and procedures, training qualitative interviewers, and interpreting data.

## Design

A cluster-randomised controlled parallel group superiority trial in primary care, with embedded qualitative and mixed methods process and implementation analyses.

Cluster randomisation was chosen because randomising individual practitioners risks cross-contamination within practices where practitioners share knowledge and patients; randomising individual patients risks contamination because practitioners cannot switch on/off communication skills in different consultations.

General practices constitute the clusters; practices are recruited and then randomised 1:1 EMPathicO: control. Randomisation is stratified (see below). All eligible practitioners within clusters are encouraged to undertake EMPathicO training (intervention) or consult patients as usual (control). The control was chosen to enable pragmatic assessment of benefits and costs of adding EMPathicO training to usual care.

Patient recruitment commences at least two weeks after the general practice is randomised (enabling time for intervention sites to complete the intervention training whilst maintaining consistent set up timelines across both arms). All adults (18+) verbally consulting a participating practitioner are invited to participate in the trial (see exclusions below).

Two groups of patients are recruited. The musculoskeletal group comprises patients consulting participating practitioners about musculoskeletal pain. The ‘all-comer’ group comprises patients consulting about symptoms other than musculoskeletal pain (or reporting very low levels of musculoskeletal pain). At pre-consultation baseline and repeatedly up to 6 months later patients complete questionnaires assessing pain, enablement, and secondary outcomes.

## Setting

General practices in England and Wales, recruited and supported by three recruitment hubs – Southampton, Keele, and Bristol.

## Target population

### GP Practice Eligibility Criteria

Eligible: NHS general practices in England and Wales, where a general practice is “an organisation which offers Primary Care medical services by a qualified General Practitioner who can prescribe medicine and where patients can be registered and held on a list.”[35]

Excluded: Practices involved in intervention development/feasibility work (18 from Wessex, 5 from West Midlands), practices where clinical members of the Trial Management Group/Trial Steering Committee see patients.

### Practitioner Eligibility Criteria

Eligible: practitioners from any discipline who are working within participating GP surgeries and seeing patients with musculoskeletal pain (e.g., GPs, Practice Nurses, Physiotherapists, Pharmacists, Physician Associates).

Excluded: Practitioners unwilling to undertake the intervention/trial procedures.

### Patients with Musculoskeletal Pain Eligibility Criteria

For the musculoskeletal pain group, eligible patients are adults (18+); verbally consulting a participating practitioner about new, recurrent, or ongoing musculoskeletal pain (e.g. back, hip, upper/lower extremity, neck pain - consistent with ICD-11’s diseases of the musculoskeletal system[36]); reporting average pain in the last week as 4 or more on numerical rating scale at baseline (0 = no pain; 10 = pain as bad as you can imagine); consulting face-to-face , telephone, or videoconference; able to give informed consent. The first consultation is the ‘index’ consultation, an initial triage interaction does not constitute an ‘index’ consultation. People without English as a first language are eligible, interpreters are available to support access to trial paperwork and patient-reported measures, and their use is recorded; informal interpreters (e.g., family) may also support.

Excluded: patients consulting solely in written forms (e.g., e-consult/email); pain caused by malignancy; unable to consent or to complete questionnaires (e.g., severe mental illness or distress, terminal illness); already enrolled in the trial (i.e., from a previous consultation); aged <18.

### All-Comer Patients Eligibility Criteria

For the all-comers group, eligible patients are adults (18+); verbally consulting a participating practitioner about something other than musculoskeletal pain or consulting for musculoskeletal pain and rating average pain in last week as less than 4 at baseline; able to give informed consent.

Excluded: As for patients with musculoskeletal pain.

## Interventions

### EMPathicO e-Learning Package

EMPathicO is an evidence-based theoretically-grounded digital e-learning package for practitioners routinely seeing patients frontline in primary medical care, including GPs, nurse practitioners and first-contact physiotherapists.[24] EMPathicO helps practitioners enhance their communication of clinical empathy and realistic optimism, is consistent with major consultation models including ‘ICE’ (Ideas, Concerns and Expectations),[37] and incorporates behaviour change techniques. Using the Behaviour Change Wheel, EMPathicO was designed to target users’ motivation (reflective, autonomic), capability (physical, psychological), and opportunity (environmental), through intervention functions of persuasion, incentivization, enablement, education, training, modelling, and environment restructuring. Multiple Behaviour Change Techniques were used to achieve these functions, including demonstration, information provision, goal-setting, action planning, and instruction. For a complete behavioural analysis of EMPathicO see supplementary material in our intervention development paper.[24]

The brief interactive e-learning modules are completed by practitioners and can be completed separately or together in less than 75 minutes and cover clinical empathy, realistic optimism, tailoring empathy and optimism for patients with osteoarthritis (a common cause of musculoskeletal pain), evaluating one’s own consultations, and goal-setting. Figure 1 summarises the structure and contents of the modules. EMPathicO was developed using LifeGuide open-source software for creating online interventions for health care, health promotion and training.[38]

*---Insert Figure 1 Here---*

The systematic process of developing EMPathicO using the person-based approach[39] involved multiple literature reviews, behavioural analysis, and extensive iterative qualitative research.[40-46] This work all contributed to the underpinning logic model (Figure 2).[24]

*---Insert Figure 2 Here---*

### Control: Usual Care

Practitioners in practices randomised to usual care control do not receive training and are asked to consult as usual. They are offered access to EMPathicO after all patient recruitment and follow-up is completed.

### Concomitant Interventions

All practitioners are discouraged from undertaking additional communication skills training during the study and must self-report any that does occur.

## Recruitment

### GP Practice Recruitment

Practices are recruited with local Clinical Research Network (CRN) support, seeking practices of different sizes (small-large) and locations (urban, rural) and those serving populations in areas of higher deprivation and greater ethnic diversity.

### Practitioner Recruitment

Practitioners within participating practices are recruited by that practice’s lead for this study (the local PI) with support from the trial team and materials including an infographic and one-minute video explaining the study.

### Patient Recruitment

Practices invite consecutive patients consulting participating practitioners within the recruitment period, after screening out any patients who do not have capacity for consent, or where there are medical grounds for excluding the patient (e.g., very unwell generally, severe mental distress). Patient recruitment methods are tailored to suit individual practices’ appointment booking systems. For patients with prebooked or same-day appointments, practices text, email, or post a brief invitation and link to the patient-facing study website up to 1 week before their consultation. Practices screen potential invitees for initial eligibility before sending invitations. Practices may display a poster in practice and/or on their website. Reception staff may introduce the study to patients attending in-person. Patients email or phone the patient-facing research team with questions.

Practices follow their usual procedures for contacting non-English speakers to invite them to take part e.g., contacting a designated friend, relative or support worker, arranging an interpreter, or adding a sentence in the patient’s own language on the initial study invitation.

The number of patient invitation emails/texts sent by each site is collected and recorded centrally. Qualtrics records instances of patients accessing the study website but declining consent and/or not meeting inclusion criteria.

The patient-facing study website is hosted on Qualtrics and shows the full study invitation and patient information sheet (PIS) (in languages requested by practices). After reading the PIS, patients complete a brief screening questionnaire, online consent and baseline measures. Supplemental Material 2 contains PIS and consent forms.

## Sample size

### Patients with Musculoskeletal Pain Sample Size

The minimum clinically important difference in the pain primary outcome is approximately one point,[47] standard deviation 3.3, consistent with a standardised effect size of 0.3. For 90% power, alpha of 0.025 to allow for two 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.[48] 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.

### ‘All-Comer’ Patients Sample Size

Recruiting 840 all-comers will give 90% power (based on alpha and ICC as per the musculoskeletal group above) to detect a standardised effect size of 0.3 in the enablement primary outcome, equivalent to a difference of 0.36 points (assuming SD=1.2[49]).

### Updated sample size calculation

Participants are being recruited from 53 practices rather than 42 practices as originally planned, which reduces the average cluster size. Assuming 14 patients per practice gives a design effect of 1.39. Under the same assumptions as above, the total sample size is (214\*2\*1.39)/0.8=744 participants.

## Outcomes

### Questionnaires, Data Collection and Participant Retention

Supplemental Material 3 summarises outcome and process variables, measurement timings, and questionnaire measures. We considered core outcome sets, questionnaire properties (e.g., validity, reliability, length), and acceptability to participants when choosing specific measures.

Patient-reported measures are completed on web-based questionnaires hosted on Qualtrics (Qualtrics, Provo, UT); to support inclusive access patients may request an interpreter and/or paper versions. £10 vouchers are sent at 1-month and 6-month follow-ups to incentivize completion.

Practitioner-reported measures are completed on LifeGuide[38] (measures completed by intervention group only) and Qualtrics (measures completed by all practitioners).

For practitioners and patients, automated follow-up emails are sent to non-responders at all timepoints. Researchers personally contact persistent non-responders who haven’t withdrawn and offer to resend questionnaires or complete primary outcomes by telephone.

### Primary Outcomes

For the musculoskeletal pain group, the two primary outcomes are pain intensity and patient enablement, each analysed over 6 months using a repeated measures approach. Pain intensityis the severity of pain sensation and is included in core outcome sets for chronic pain,[50 51] OA,[52] and low back pain.[53,54] Patient enablement refers to patients’ feelings, after a consultation, of confidence and empowerment to cope with their symptoms, to keep healthy and to help themselves. Our PPIE work highlighted enablement as at least as important as pain. Two primary outcomes help capture more holistic effects on patients’ health. The outcomes will be reported separately and our PPIE and embedded qualitative work will help explore, interpret and explain how they relate to each other.

For the all-comers group, patient enablement is the single primary outcome. Pain intensity is measured as a secondary outcome if pain is present.

#### Pain Intensity

Pain intensity is measured as average pain in the last week using the 4-item pain intensity subscale from the Brief Pain Inventory (BPI).[55]

#### Patient Enablement

The 6-item Patient Enablement Index (PEI) captures patients’ feelings, after a consultation, of confidence and empowerment to cope with their symptoms, to keep healthy and to help themselves.[56] To increase sensitivity, versions with more response options than the original four (much better/never/same or less/not applicable) have been reported.[57-59] Following our feasibility study we use a modified 7-point agree-disagree Likert response scale with a Not Applicable option.

### Secondary Outcomes

#### Symptom Severity and Global Impression of Change

Overall perceptions of symptom severity and change are important for musculoskeletal patients given the high prevalence of multi-morbid conditions and for all-comers because they apply to any condition and provide a symptom-focused pre-consultation baseline. Two single item 7-point[60] measures of Patient Global Impression of Symptom Severity and Patient Global Impression of Change are collected.[61]

#### Patient Satisfaction

The version of the 21-item Medical Interview Satisfaction Scale[62] (MISS) adapted and revalidated for UK primary care[63] is used to measure patient satisfaction with the consultation.

#### Pain Interference

Pain interference is measured with the 7-item pain interference scale from the BPI.[55]

#### *Health-Related Quality of Life*

Health status is measured using the 5-item EQ-5D-5L and the EQ-VAS.[64]

### Health Economics Outcomes

Cost effectivenesswill be assessed from NHS and societal perspectives including personal expenses and productivity over 6 months. Utility values will be estimated from EQ-5D-5L scores using the NICE-recommended approach at the time of analysis. Quality-adjusted life-years will be estimated by combining utility values, with length of time in each health state, using the area under the curve approach.[64-66] 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, is also collected.[67,68]

Practitioner time spent on EMPathicO training is captured by LifeGuide. Resource-use data is collected using ModRUM[69] (patient self-reported healthcare utilization) and bespoke questions (costs outside the healthcare sector e.g., personal expenses). The Work Productivity and Activity Impairment Questionnaire: General Health is used to collect information on productivity, including time off work.[70] NHS resources include primary, community and secondary care, and prescribed medications; they will be valued using the national unit costs.[71-73] Personal expenses will be presented as reported. Sick leave from employment will be valued using Annual Survey of Hours and Earnings.[74]

### Process Variables and Covariates

Potential mediators and moderators of intervention effects on pain, specified in the logic model, are included as process variables. Practitioner-reported self-efficacy, outcome expectancy, and intentions for conveying empathy and optimism in consultations are assessed using bespoke items developed in our feasibility work based on standard item stems, relevant guidelines and theory.[75-78] They demonstrated acceptable internal consistency (Cronbach’s alphas ranged 0.69-0.98) and were fully completed by practitioners (n=11).

Intervention usage data captured on LifeGuide includes, for each practitioner-participant, time spent on (different sections of) the intervention and patterns of access.

Patient perceptions of practitioner clinical empathy are assessed using the 10-item CARE[79] used extensively in UK primary care settings to assess patient perceptions of clinical empathy. Patient perceptions of practitioner response expectancies are assessed using a bespoke single item tested in our feasibility study. Patient treatment outcome expectancies are measured using the 15-item 6-subscale, Treatment Expectation Questionnaire (TEX-Q).[80] Patient anxiety and depression are assessed using the 7-item subscales from the Hospital Anxiety and Depression Scale (HADS).[81,82] Continuity of care is assessed using the 9-item Patient-Doctor Depth of Relationship Scale,[83] modified for non-doctor practitioners.

Practitioner characteristics collected are age, gender, ethnicity, years qualified, profession. Practice-level data collected from the practice and supplemented with data from national general practice profiles ([National General Practice Profiles - Data – OHID, phe.org.uk)](https://fingertips.phe.org.uk/profile/general-practice/data#page/8) are: list size, deprivation score, staffing.

Patient characteristics collected are age, gender, ethnicity, postcode (for calculating index of multiple deprivation, IMD), reason(s) for consulting (coded using the ICPC-2), comorbidities, and index consultation modality.

### Qualitative Interviews

A subsample of patients (up to n=45 with musculoskeletal pain and n=45 all-comers) and practitioners (up to n=40) take part in qualitative semi-structured telephone interviews. Participants are purposively sampled to capture diversity in index-consultation mode (telephone/video/face-to-face), ethnicity, age, gender, baseline pain severity. Participants are interviewed twice each, to explore short-term and longer-term implementation of EMPathicO skills (practitioners) and experiences of the index and subsequent consultations (patients). Practitioners are interviewed after (1) patient recruitment and (2) follow-up is completed at their practice. Patients are interviewed within approximately 7-14 days of their index consultation and again approximately 6 months later. Topic guides comprising open-ended questions and prompts are used flexibly and modified iteratively as necessary to explore emerging avenues of inquiry within scope of the trial. Field notes are taken, interviews are transcribed verbatim, identifying details are replaced (e.g., using pseudonyms), and transcripts are checked and imported to NVivo (Lumivero, Denver, CO) for analysis.

## Timelines

Tables 1 and 2 show practitioner and patient timelines for enrolment, questionnaires, and interviews.

---Insert Tables 1 and 2 Here ---

## Assignment of Interventions

### Sequence Generation, Allocation Concealment and Implementation

A computer-generated allocation sequence is used with random block sizes of 4 and 6. Blocks are stratified by practice-level high/low deprivation (IMD 1-5 / IMD 6-10) and large/small practice size (list size>7900 / <7900; 7900 = median practice list size in England). The allocation sequence is implemented using the randomisation function in LifeGuide and is not visible to users. The trial manager (or their delegate) inputs each eligible practice to the randomisation function on LifeGuide which then displays the allocation. Practitioners and patients can withdraw from the study without giving a reason, but they cannot request modification to their allocated intervention.

### Blinding

Patients and the trial statistician are masked to intervention allocation. Patients are not told in the PIS that as part of this study their general practice has been randomly allocated to intervention or control. This was approved by the ethics committee and is appropriate in this cluster-randomised trial where the communication-skills training intervention is very low risk and within the broad scope of usual practice. After all data collection is complete, patients will be debriefed in writing (email/mail) and told that “at the start of the TIP study some of the GP practices taking part had communication skills training (intervention practices) and some GP practices did not have any training (control practices).” They will also be told whether their practice did or did not receive the enhanced communication skills training. Efforts are made to mask researchers supporting patient data collection to intervention allocation; for example, the researchers collecting patient outcomes are not the same researchers who liaise with practices about the intervention. Efforts are made to mask practitioners to which patients are taking part; for example, the patient PIS includes the instruction to “please do not discuss your participation in the study with your GP, nurse, physiotherapist, or any other primary care practitioner”. In the unlikely event that patient unblinding is deemed necessary for patient care this will be done by the general practice and notified to the research team.

## Data Analysis

### Data Management

Web-based questionnaire data stored securely on Qualtrics servers (see <https://www.qualtrics.com/security-statement/>). Questionnaire data collected by telephone or paper entered into Qualtrics by one researcher and checked for accuracy by a second researcher.

Personal data stored on a secure server at University of Southampton in compliance with General Data Protection Regulations and the Data Protection Act 2018.

### Statistical Methods

Musculoskeletal and all-comers groups will be analysed separately. For the two primary outcomes, a linear mixed model will use all the observed data, and implicitly assumes that missing outcome scores are missing at random given the observed data. The BPI and PEI will be reported and analysed using post-intervention scores, adjusting for baseline score. 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 other covariates 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 formal pre-planned subgroup analyses.

Intention to treat analysis (as randomised) will be undertaken regardless of any practice-level non-adherence to the intervention. All available data will be used, 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. A full and detailed statistical analysis plan will be developed prior to final trial analysis and approved by Trial Steering Committee.

Interim analyses of outcomes are deemed unnecessary in this low-risk trial.

### Health Economic Analysis

An NHS perspective will be taken in the primary analysis; a wider perspective is taken in secondary analyses including impacts on patients and productivity. Analysis will be intention to treat. Relevant covariates, including baseline EQ-5D-5L, potentially skewed data and the cluster design will be accounted for using appropriate regression models.[66] Cost-consequences will tabulate costs from each perspective to a range of outcomes. Cost-effectiveness will be estimated in a cost-utility analysis combining QALYs and NHS costs. The incremental net monetary benefit 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

A process analysis will focus on mechanisms of impact and test hypotheses derived from the logic model about relationships among variables, including mediators and moderators. Intervention usage data, captured by LifeGuide, will be incorporated using the AMUsED framework for Analyzing and Measuring Usage and Engagement Data.[84]

### Qualitative and Mixed Methods Analysis

EMPathicO’s potential impact post-trial will be evaluated by using the RE-AIM framework to explore Reach, Effectiveness, Adoption, Implementation, and Maintenance. [32,33] Drawing on data from the main trial, the all-comers group and the qualitative interviews we will assess EMPathicO against the RE-AIM components using the approaches described in Table 3.

*---Insert Table 3 Here---*

# Ethics and Dissemination

## Safety, Adverse Events, and Insurance

This trial is classed as low risk following a risk assessment and there are no provisions for post-trial care. The team do not expect any adverse events (untoward medical occurrence in a trial participant) or Serious Adverse Events (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). However, adverse events are being collected (primarily via self-report), recorded and reported where necessary in accordance with the principles of ICH Good Clinical Practice and the requirements of the research ethics committee, sponsor, and trial steering committee.

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.

## Approvals, Oversight and Monitoring

The sponsor is the University of Southampton (rgoinfo@soton.ac.uk). Approval was received from South Central – Hampshire B Research Ethics Committee on 1.7.22 and the Heath Research Authority and Health and Care Research Wales on 6.7.22 (REC reference 22/SC/0145; IRAS project ID 312208). Protocol amendments are submitted for approval as required to the study sponsor and ethics committee and notified where necessary to all those concerned.

The Trial Steering Committee (TSC) provides trial oversight and advice through its independent Chairperson to the Trial Management Group and the funder on all aspects of the trial. The TSC assumes responsibilities of the Data Monitoring Committee and reviews information on the progress and accruing data; online Supplemental Material 4 presents the TSC Charter; Supplemental Material 5 presents stopping criteria). Annual and interim progress reports submitted to the funder.

## Dissemination

Patient recruitment commenced on 16.11.2022 and is ongoing at the time of manuscript submission. Results will be communicated to participants and disseminated to academic, practitioner, and public audiences via peer-review journal articles, conferences, and other appropriate formats e.g. blogs. Our public collaborators will co-lead dissemination activities. Results will be reported in accordance with CONSORT guidelines extensions for cluster-randomised trials[85] and trials of non-pharmacological interventions,[86] and the American Psychological Association Journal Article Reporting Standards for qualitative (JARS-QUAL) and mixed methods (JARS MMARS) research.[87] We will adhere to the ICMJE (<https://www.icmje.org/>) criteria for authorship and use the CRediT taxonomy (<https://credit.niso.org/>). Supplemental Material 6 summarises data access plans.

# Tables and Figures

### Table 1. Practitioner Timelines

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Allocation** | | **Post-allocation (wk)** | | | | | **On completing patient recruitment** | **On completing patient follow-up** |
| **TIMEPOINT** | **0** | **+1d** | **1** | **2** | **3-8** | **8** | **34** |  |  |
| **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 | X1 |
| **PATIENT RECRUITMENT** |  |  |  |  |  |  |  |  |  |
| Prepare invitations |  |  |  |  |  |  |  |  |  |
| Recruit patients |  |  |  |  |  |  |  |  |  |

1 Intervention-arm practitioners only

### Table 2. 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 |

## Table 3: 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 | All-comers group | Apply analysis plan from main trial to test intervention effectiveness in all-comers group. |
| Qualitative data (patients and practitioners) | Compare experiences of EMPathicO across in-person, telephone and video consultations, and for musculoskeletal 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 [88](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). |

## Figure Captions

Figure 1. Schematic Summary of Empathico Structure and Contents

Figure 2. Logic model showing how EMPathicO is hypothesized to affect patient outcomes.

# Authors’ Contributions

Allocated using CRediT categories. Conceptualisation (study idea) and Funding Acquisition: HE, FB, JH, PL, BS, GL, LM, JV, JB, CM, LC, MRi, KG, HA. Methodology (designing, planning and developing study methods): FB, HE, PL, GL, BS, LM, JV, CM, LC, MR, KG, JH, HA, JB, NC, ET, SP, RDH, JN, NI, PHL, TB, AH, MR. Investigation (data collection): NC, RDH, ET, AH, MRo, SP. Data Curation (study management data and data cleaning): NC, RDH, ET, AH, MRo, SP. Project Administration (managing and co-ordinating research activity plans and execution): FB, HE, NC. Software (implementation and support for the e-learning intervention): SP. Supervision (oversight, leadership, mentorship): FB, HE. Visualisation (creation and presentation of figures): SP, LM, FB. Writing (original draft): HE, FB, JH, BS, TB, MRi, KG, HA, JB. Writing (review, revisions, and editing): FB, HE, PL, GL, BS, LM, JV, CM, LC, MR, KG, JH, HA, JB, NC, ET, SP, RDH, JN, NI, PHL, TB, AH, MR.

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# Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: financial support for the submitted work from the NIHR; CDM is Director of the NIHR School for Primary Care Research; HA has received research grants from NIHR and Research Council of Norway, payment for delivering lecture to GPs in training about remote consultations, travel expenses to attend Scientific Foundation Board meeting; HA is chair of a steering committee at University of Leeds, member of advisory boards at Imperial College London and University of Manchester, and vice-chair of the Scientific Foundation Board Royal College of General Practitioners; HA is Officer at Prof Andrew Beggs Ltd. No other relationships or activities that could appear to have influenced the submitted work.

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