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BMJ Open Persistent Physical Symptoms Reduction Intervention: a system Change and Evaluation (PRINCE) - Integrated GP care for persistent physical symptoms: protocol for a feasibility & cluster randomised waiting list, controlled trial

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ABSTRACT

Introduction: Persistent physical symptoms (PPS), also known as medically unexplained symptoms (MUS), and are associated with profound physical disability, psychological distress and high health care costs. England's annual National Health Service costs of attempting to diagnose and treat PPS amounts to approximately £3 billion. Current treatment relies on a positive diagnosis, life-style advice and drug therapy. However, many patients continue to suffer from ongoing symptoms and general practitioners (GPs) are challenged to find effective treatments. Training GPs in basic cognitive behavioural skills and providing self-help materials to patients could be useful, but availability in primary care settings is limited.

Methods and analysis: A cluster randomised waiting list, controlled trial will be conducted to assess the feasibility of an integrated approach to care in general practice. Approximately 240 patients with PPS will be recruited from 8-12 GP practices in London. GP practices will be randomised to 'integrated GP care plus treatment as usual' or waiting list control. 'Integrated GP care plus treatment as usual' will include GP training in cognitive behavioural skills, GP supervision and written and audio-visual materials for both GPs and participants. The primary objectives will be assessment of trial and intervention feasibility. Secondary objectives will include estimating the intra-cluster correlation coefficient for potential outcome measures for cluster effects in a sample size calculation. Feasibility parameters and identification of suitable primary and secondary outcomes for future trial evaluations will be assessed pre-randomisation and at 12 and 24 weeks post randomisation, using a mixed methods approach.

Ethics and dissemination: Ethical approval was granted by the Camberwell St Giles Ethics Committee. Results will be disseminated via peer reviewed publications and conference presentations. This trial will inform researchers, clinicians, patients and healthcare providers about the feasibility and potential cost-effectiveness of an integrated approach to managing PPS in primary care.

Trial Registration Number: NCT02444520; Overall trial status: Active; Recruitment status (since May 2015): No longer recruiting.

Registry Name: ClinicalTrials.gov

Strengths and limitations of this study

- PRINCE Primary is a cluster, randomised waiting list, controlled trial, designed to evaluate the acceptability and feasibility of an integrated General Practitioner (GP) approach to care for adults with persistent physical symptoms (PPS).
- A new transdiagnostic approach to managing patients with PPS in general practice was developed, which includes offering a CPD-accredited basic cognitive behavioural skills training and audio visual and written learning materials for GPs. Participants of GP practices randomised to 'integrated GP care plus treatment as usual will receive tailored self-help materials.
- This feasibility study is not powered to evaluate efficacy or cost-effectiveness of integrated GP care but intends to identify suitable primary outcomes for an adequately powered future evaluation trial.

INTRODUCTION

Medically unexplained symptoms (MUS) is an umbrella term referring to persistent bodily symptoms, which cannot be adequately explained by organic pathology.[1] MUS are highly prevalent with approximately 10% to 49% of patients in primary care.[2, 3] MUS are associated with significant functional impairment, psychological distress and high health care costs.[4, 5, 6] Moreover, approximately 60% of patients have a comorbid psychiatric condition, including depression, anxiety and panic disorders.[7-9] The NHS in England is estimated to spend approximately £3 billion each year attempting to diagnose and treat MUS, which represented approximately 10% of the total NHS expenditure in 2008-2009.[10]

The term MUS is commonly used in health care and research. However, it has been argued that using the label persistent physical symptoms (PPS) may be more appropriate for a number of reasons. Firstly, recent surveys indicated that people with such symptoms and healthy respondents preferred the term PPS, as it avoids mind-body dualism and has cross-cultural relevance.[11, 12] Secondly, it includes symptoms associated with medically diagnosed long-term conditions, such as diabetes, rheumatoid arthritis and multiple sclerosis, which may present co-morbidly with MUS. Thirdly, it concurs with changes in the latest edition of the Diagnostic and Statistics Manual (DSM-5). The DSM-5 has consolidated previous terms including somatization disorder, conversion disorder, and hypochondriasis into a new diagnostic term – Somatic Symptom Disorder (SSD). This refers to persistent (6 months) and clinically significant somatic complaints accompanied by excessive and disproportionate health-related thoughts, feelings and behaviours regarding the symptoms.[13] In this paper, we will use the term PPS to refer to MUS.

There is an accumulating body of evidence showing that cognitive behavioural interventions can reduce levels of symptoms and improve overall functioning in patients with PPS. Cognitive behavioural therapy (CBT) has demonstrated both short-term and long-term efficacy with small to medium effect sizes for PPS.[14, 15] Larger treatment effects have been reported for specific PPS syndromes, including non-cardiac chest pain[16, 17] and Irritable Bowel Syndrome (IBS) [18-20].

Research indicates that the way health care professionals deliver interventions and offer treatment to patients with PPS significantly affects health outcomes. For instance, a previous randomised controlled trial (RCT) evaluated the effectiveness of an integrated approach in treating women with chronic pelvic pain in secondary care. This involved an assessment of pain sensation, nociception, pain suffering and pain behaviour, followed by a discussion about possible physical, psychological, dietary and environmental contributions plus physiotherapy, versus routine laparoscopy. The findings revealed that the integrated

approach was significantly more effective in reducing pelvic pain compared to routine laparoscopy.[21]

Evidence supporting the efficacy of psychopharmacological interventions for PPS is less clear. A previous Cochrane review on pharmacological interventions found low-quality evidence for the use of new-generation antidepressants (NGAs). No evidence was found for other psychotropic drugs, including tricyclic antidepressants and antipsychotics.[22] This suggests the need for further research investigating the effectiveness of non-pharmacological treatments in managing PPS, including psychosocial interventions.

General practitioners (GPs) play a major role in identifying and managing patients with PPS. The Royal College of General Practitioners (RCGP) emphasises the importance of GPs in helping patients with PPS to make sense of their symptoms by adopting a biopsychosocial approach to treatment.[23] A previous randomised parallel group pilot trial investigated the feasibility (i.e. recruitment, retention and acceptability) of implementing a primary care Symptoms Clinic for patients with PPS.[24] The Symptoms Clinic comprised a structured set of consultations delivered by a specially trained GP with a strong interest in PPS. The intervention included exploring potential biological mechanisms underlying the PPS condition, empathetic support, and training patients in symptom-management (i.e. medication or cognitive behavioural techniques). The results indicated that the Symptoms Clinic was acceptable to the majority of patients randomised to the intervention group and may have the potential to generate clinically significant benefits. However, this pilot study did not assess feasibility parameters referring to GPs' willingness to participate in the study and undergo specialised psychological training. Moreover, the intervention was carried out by only one GP, raising questions about the generalizability of the study.

Managing patients with PPS can be highly challenging in general practice. Although GPs recognise the treatment of PPS as a responsibility of primary care, previous studies show that GPs often feel powerless, frustrated and helpless when encountering these patients.[25, 26] One possible explanation for this is an epistemological incongruence between taught ideal

biomedical models of disease, and the reality of meeting patients presenting with subjective persistent physical symptoms, which cannot be fully explained by organic causes.[26] Furthermore, GPs frequently report that factors such as time constraints and the lack of psychological training prevents them from effectively addressing patients' psychosocial needs and developing appropriate doctor-patient communication skills.[25]

Taken together, there are four strands of evidence:

1. Psychological interventions may help patients with longstanding PPS;
2. The way in which investigations are carried out and offered to patients with PPS affects health outcomes and service costs;
3. Psychopharmacological interventions (i.e. antidepressants) have shown no or only small effects on alleviating PPS; and
4. GPs often feel helpless and ill-equipped to manage patients with PPS.

RESEARCH OBJECTIVES

This paper presents a study protocol for the Persistent Physical Symptoms Reduction Intervention: a System Change & Evaluation in Primary Care (PRINCE Primary) trial, which aims to assess the acceptability and feasibility of an integrated care approach in managing adult patients with PPS in primary care. Commissioning Support for London piloted an integrated service model for PPS, which largely focused on commissioning and cost saving.[27] We will build on this pilot study by

- a. Assessing the feasibility of trialling a new integrated approach towards the management of patients in primary care, using robust methods, namely a cluster randomised waiting list, controlled trial.
- b. Estimating the intra-cluster correlation coefficient (ICC) for potential outcome measures for cluster effects in a sample size calculation.
- c. Measuring patient satisfaction and patient reported outcomes;

- d. Including a broad range of patient groups in primary care, including those with non-cardiac chest pain, dizziness and fibromyalgia;
- e. Identifying suitable primary outcome measures for a future trial evaluation.

METHODS AND ANALYSIS

Study Design

Two arm cluster randomised waiting list, controlled trial.

Method

Approximately two hundred and forty patients with PPS will be recruited from eight to twelve GP practices. These GP practices will be randomised to either 'integrated GP care plus treatment as usual' or waiting list control. GP practices randomised to 'integrated GP care plus treatment as usual' will include (i) GP training in cognitive behavioural techniques, (ii) GP supervision, (iii) audio visual material for GPs and (iv) self-help materials for participants. GP practices randomised to the waiting list control arm will continue with treatment as usual. The waiting list control arm will be crossed over at 28 weeks to give 4 weeks to collect measures. This will not be part of the RCT but will contribute to a separate long term follow up. A selection of feasibility parameters will be investigated pre- randomisation. In addition, to identify suitable primary and secondary outcomes for future trial evaluations measures will be completed at 12 and 24 weeks. GPs who attend the offer of GP training will complete measures pre and post GP training.

Setting

GP practices and participants will be recruited from South London, England. GP training will take place at GP practices. Training will be delivered by clinicians based within King's Health Partners.

Study Population

GP Practices/GPs

GP practices within South London which fulfil the following eligibility criteria will be recruited into the study.

- (i) At least 50% of GPs within the practice express an interest in completing the training workshop
- (ii) The Practice Manager, Partner or other authorised individual is able to give consent for the practice to take part in the study
- (iii) The practice is not at risk of closure within the next year

Patients

Patients that fit the eligibility criteria will be invited to take part in the study. Patients will be considered eligible for inclusion in this study if they fulfil all the following criteria;

- (iv) have a PPS (which is medically unexplained)
- (v) are greater than or equal to 18 and less than or equal to 65 years old
- (vi) are registered with a GP practice in South London that has consented to taking part in PRINCE Primary
- (vii) have had 6 or more consultations in the last year (not necessarily for the same symptom or directly related to PPS)
- (viii) have given written informed consent, provided baseline data before randomisation and can speak and read English at a level adequate for participation in the trial.

Patients will be excluded from the study if the patient has

- (i) active psychosis
- (ii) drug or alcohol addiction as indicated in the patient's medical notes
- (iii) current benzodiazepine use exceeding the equivalent of 10mg diazepam per day

- (iv) had any psychotherapy treatment within the last year (not inclusive of general visits from community psychiatric teams)
- (v) dissociative seizures
- (vi) if they are at imminent risk of self-harm, after psychiatric/ psychological assessment
- (vii) taking part in the PRINCE Secondary study or the ACTIB Study.[28]

Recruitment

GP Practice Recruitment: Invitation letters will be sent out to GP practices located in South London. If a GP practice is interested, it will be asked to contact the research team for further information. GP practices that fit the eligibility criteria will be enrolled onto the study after providing consent to participate.

Patient Recruitment: GP informatics (i.e. EMIS Web) will be used to identify potential patients with PPS from GP practices that agreed to participate in the study. Prior to the study, the trial team liaised with GPs to ensure that the search criterion intended to be uploaded onto EMIS web included a range of persistent physical symptoms as well as incorporating elements of the trial's eligibility criteria. For those patients identified in the search, the GP practice administration team will send information packs regarding the study and patients will be asked to reply to say whether they are interested or not interested in being contacted by the research team. Patients who express an interest will be contacted.

Study Procedure

Patients who give their consent to be contacted will be further screened and checked for eligibility by the research team. If the research team is unsure about their diagnosis, they will contact their GP and ask for confirmation. To formally enrol, patients will be required to complete and return a signed consent form. Once consent is obtained, a baseline questionnaire pack will be sent to participants four weeks prior to a pre-specified randomisation

date. If participants complete the questionnaire pack before this date they will be fully eligible to take part in the study. Participants will be fully informed that if they do not complete the baseline pack before the randomisation date they will not be able to participate in the study. GP practices will be randomised on the pre-specified date to one of two arms: 'integrated GP care plus treatment as usual' or waiting list control (please see figure 1 and section on planned intervention for more details). Participants of GP practices randomised to 'integrated GP care plus treatment as usual' should be offered the self-help material within 1 week of randomisation and GP's should be offered the training within 2 weeks of randomisation. GP practices randomised to the waiting list control arm will continue with treatment as usual until they are crossed over at 28 weeks. Based on these timeframes a training date for all GP practices will be scheduled in advance. However, GP practices will be fully informed that the GP training session is dependent on the randomisation outcome i.e. only GP practices randomised to integrated GP care will be offered the GP training. Once randomisation is completed both GP practices and participants will be informed of the outcome and this will be week 0 and considered the anchor point for this trial for all the participants. Measures will subsequently be taken at 12 and 24 weeks.

The recruitment and study procedures will enable us to investigate a selection of feasibility parameters pre-randomisation and identify suitable primary and secondary outcomes for future trial evaluations. See Figure 1 for a flow diagram showing the study procedure.

< Figure 1: Flow Diagram of the Study Procedure about here >

Randomisation

Randomisation of the GP practice clusters will take place following recruitment and baseline assessments of patients within each GP practice. The randomisation method will be stratified randomisation at the level of the cluster (i.e. GP practice). The randomisation will be stratified

by size of GP practice (≤ 6000 registered patients or > 6000 registered patients). GP practice randomisation will occur in pairs; two GP practices will be randomised at the same time with one being randomised to the waiting list control and the other being randomised to 'integrated GP care plus treatment as usual'. Within strata (large or small practices) blocking is used to ensure that numbers allocated to either trial arm balance after each block. To avoid being able to predict the allocation of a GP practice, practices are randomised as pairs rather than sequentially. This ensures that forthcoming allocations cannot be predicted. Participants will have four weeks prior to randomisation to complete the baseline questionnaire pack. GP practice randomisation will be coordinated by an independent randomisation service at the UKCRC registered King's Clinical Trials Unit (KCTU).

Blinding

Patients and GPs will not be blind to treatment allocation due to the nature of the trial (i.e. therapy trial). The trial team member responsible for treatment allocation will be unblind. All outcome data are based on self-report and will be collected either by post or email. The research assistant(s) responsible for contacting participants who have not returned or completed follow-up questionnaires will be unblind. Moreover, the Data Monitoring and Ethics Committee (DMEC,) research workers and trial statisticians will remain blind to treatment allocation. If unblinding is deemed to be necessary, the trial manager will use the system for emergency unblinding through the DMEC.

Planned intervention: Integrated GP care plus treatment as usual

Our proposal seeks to develop new care pathways for patients with PPS.

The intervention 'Integrated GP care plus treatment as usual' will include:

- GP training in utilising cognitive behavioural skills during 10-minute consultations;
- GP supervision;
- Audio-visual and written materials/guidelines for GP's;

- Written self-help materials for participants;
- Animation to illustrate the approach;
- Integrated case management discussion prior to secondary care referral. GPs will be encouraged to consult with a colleague before making a referral;

GP Training

GP training will be delivered at GP practices by clinicians based within King's Health Partners. To inform our decision about length of training we discussed options with the GP's and offered them anything from 1 hour to 1 day training in behaviour change skills. Most reported that they could spare up to 90 minutes as a group given their other commitments. For this reason, this is what we settled upon. The session will involve a lecture, a role-play demonstrating engagement of a patient in a dialogue which focuses on a behaviour change technique and discussion. The specific content of the session will include background information about PPS and a three systems model of understanding how symptoms might be perpetuated regardless of cause. The link between symptoms, cognitions and behaviour will be described. The emphasis will be on engagement skills and behaviour change interventions, not cognitive restructuring, as this is more realistic for GP's with limited time. More specifically we will focus on techniques that improve sleep routines and the uptake of meaningful activities. In addition, we will demonstrate ways of negotiating the setting of goals that the individual values, as homework. We will ask GP's to utilise these skills and techniques in their consultations. We will not be encouraging the GP to see the participants for additional consultations. GPs will therefore use the approach during routine rather than study-specific consultations. To ensure that GPs are aware of which participants are taking part in PRINCE Primary we will upload a file note on the GP practice database for every patient that participates. This means that if a participant has an appointment, the GP will be aware that they are participating in this study. GPs will be provided with study-specific guidance on how to change the nature of consultations. Guidance notes and supporting manuals/documentation will be written which

are potentially sustainable and suitable for use in other NHS settings. Information will be tailored to the needs of the patient and will be focused on a range of clinical conditions. Examples include low back pain, dizziness and headaches.

A list of helpful responses in the consultation with patients will be provided. The training will be assessed (before and after) in terms of knowledge of PPS and confidence in diagnosing and managing these symptoms. Knowledge will be assessed via ten true- and false questions referring to the content of the training. GPs will also be asked to rate their confidence in working with patients with persistent symptoms by responding to a series of pre-specified questions, using a Likert scale ranging from 1 (not at all confident) to 7 (very confident). Satisfaction with training will be assessed after the training. Open-ended questions will be used to elicit feedback about the workshops. Optional supervision (individual face-to-face, Skype/phone and/or group supervision) will be provided to GPs who request additional support. We will assess the uptake of this. Hand-outs will be available for GPs to give to participants. These will be reviewed for ease of reading by service users before the trial starts. To summarise we have drawn upon Lee David's approach to GP education [29] and our training will include:

- How to make use of the cognitive behavioural model in their consultations;
- How to overcome barriers to using this approach;
- How to develop their consultation skills;
- How to use a three systems model to examine relationships between symptoms, thoughts and behaviour;
- How to set an agenda and homework;
- How to develop a partnership;
- How to set some behavioural goals;
- How to facilitate the patient in problem solving.

As this intervention does not encourage extra consultations, we recruited frequent attenders based on the likelihood that they are more likely to visit their GP, however we cannot be certain. This is one reason why 'integrated GP care plus treatment as usual' includes sending participants booklets (i.e. we are not just providing GPs with materials we are also providing self-help materials for participants).

Participant information booklets

Participants of GP practices randomised to 'integrated GP care plus treatment as usual' will be offered a series of booklets based on cognitive behavioural principles via the post. These include, (i) an introduction to PPS, (ii) how to juggle activities, (iii) improving sleep, (iv) living with uncertainty, (v) emotional well-being and (vi) goal setting. Participants will also be sent symptom booklets that include information focusing on their primary symptoms. Furthermore, they will also have access to an animation describing a patient's experience with chronic pain, via a website set up specifically for the PRINCE Primary trial.

Waiting list control: Treatment as Usual

GP practices randomised to the waiting list control will not be offered 'integrated GP care'. Participants of GP practices randomised to the waiting list control arm will continue with treatment as usual. Treatment as usual is defined as the continuation of standard GP medical care for PPS, including usual GP follow-up and pharmacological treatment. The GP practices in the waiting list control arm will be crossed over and offered 'integrated GP care plus treatment as usual'. The cross over will be at 28 weeks to give 4 weeks to collect measures. However, this will not be part of the RCT.

Feasibility Parameters, Measures and Data Collection Time-points

The aim of this study is to assess the feasibility of conducting a future evaluation trial to assess a new systems approach to PPS in general practice. Table 1 and Table 2 provide an overview

of data collection time-points. Based on the NIHE's definition of a feasibility study,[30] the PRINCE Primary trial will assess the following feasibility parameters:

1) Feasibility parameters:

- a) Willingness of GP practices to be contacted about PRINCE Primary (number of GP practices responding out of GP practices approached)
- b) Willingness of GP practices to consent and be randomised (number of GP practices consenting to participate out of GP practices that responded with an interest to participate)
- c) Availability of data needed and the usefulness and limitations of the general practice databases (Number of patients identified using GP informatics (search algorithm) out of patients registered with the GP practice)
- d) Interest of patients to be contacted about the study (Number of patients responding out of patients identified via the search algorithm)
- e) Rate of eligible participants (Number of patients meeting the eligibility criteria out of patients who responded with an interest to participate)
- f) Willingness of patients to consent to participate in PRINCE Primary (Number of patients consenting to participate out of patients who met the eligibility criteria.
- g) Willingness of participants to complete baseline measures before randomisation (Number of participants sending baseline forms back out of participants that provided consent)
- h) Interest of GPs to attend the GP training (intervention arm only): (Number of GPs attending the GP training out of number of GPs working at the GP practices offering training)
- i) Participants follow-up rates to questionnaires per group (Number of participants completing questionnaire packs at 12 and 24 weeks respectively out participants randomised)

2) Measures to identify suitable primary and secondary outcomes for future trial evaluations:

- a) *Psychosocial Functioning*: we will use the 5-item Work and Social Adjustment Scale (WSAS)[31] to measure patients' own perceptions of the impact of PPS on their functioning in terms of work, home management, social leisure and private leisure activities, and close relationships.
- b) *Physical Symptoms*: we will measure the number of symptoms with the PHQ-15[32] derived from the Patient Health Questionnaire which reflects DSM-IV diagnoses.
- c) *Psychological Distress*: mood will be assessed using the 9-item PHQ.[33]
- d) *Global Outcome*: the adapted Clinical Global Impression (CGI)[34] change score yields a self-rated global measure of change and has been used in previous trials of CBT interventions.
- e) *Satisfaction*: we will measure patients' self-rated satisfaction of the intervention via qualitative interviews (i.e. thematic analysis).
- f) *Cost Effectiveness (Service)*: health service use (including hospital attendances and admissions, GP contacts), informal care, lost work time and financial benefits will be measured via the self-report Client Service Receipt Inventory[35] and the EQ-5D.[36] GP medical records will be used as an objective measure to assess the number of consultations and medical examinations patients received.

3) *Process Measures*: the Cognitive Behavioural Responses Questionnaire (CBRQ)[37] will be used to assess potential mechanisms of change.

4) *GPs' knowledge and confidence*: GP training will be evaluated for knowledge, skills and confidence using self-reported measures. GPs who attend the offer of GP training will complete this pre and post GP training.

Qualitative Component

Participants who consented to participate in a semi-structured interview (approximately 45 mins) will be contacted after 28 weeks to give 4 weeks' time to collect measures. If the participant is still interested a time and date will be arranged to conduct the interview either via telephone or face to face.

The aim of the qualitative interview will be to discuss the participant's experiences and opinions of the intervention, in particular (i) what they thought of the intervention, (ii) how useful they found the resources, and (iii) whether they perceived any differences in treatment approach during their GP consultation. Interviews will be audio recorded and transcribed by members of the research team using thematic analysis.

GP's will also be invited to participate in a semi structured interview (group/individual). The aim of the interview will be to discuss GPs experiences of implementing the intervention as well as discussing any suggestions on how the intervention can be improved. Interviews will be audio recorded and transcribed by members of the research team using thematic analysis.

Table 1 Overview of participant assessment moments and outcome measurements

| | Instrument | Pre-randomisation | Baseline | 12 weeks | 24 weeks |
|--|-----------------|-------------------|----------|----------|----------|
| Feasibility Parameters | | | | | |
| Interest of patients to be contacted about the study | | x | | | |
| Rate of eligible trial participants | | x | | | |
| Willingness of patients to consent to participate in PRINCE Primary | | | | | |
| Willingness of participants to complete baseline measures before randomisation | | x | | | |
| Participants follow-up rates to questionnaires per group | | | | x | x |
| Measures to Identify Suitable Primary Outcomes | | | | | |
| Psychosocial Functioning | WASAS | | x | x | x |
| Physical Symptoms | PHQ-15 | | x | x | x |
| Psychological Distress | PHQ-9 | | x | x | x |
| Global Outcome | CGI | | | x | x |
| Service Use | CSRI & EQ-5D-5L | | x | | x |
| Potential Mediators | | | | | |
| Treatment outcome | CBRQ | | x | x | x |

WSAS Work and Social Adjustment Scale, PHQ-15 Patient Health Questionnaire 15, PHQ 9 Patient Health Questionnaire 9, CGI Clinical Global Impression, CSRI Client Service Receipt Inventory EQ-5D-5L EuroQual 5 Level, CBRQ Cognitive Behavioural Responses Questionnaire

Table 2 Overview of GP's/GP Practices assessment moments and outcome measurements

| Outcomes | Instrument | Pre-randomisation | Pre-training | Post Training |
|--|-------------|-------------------|--------------|---------------|
| Feasibility Parameters | | | | |
| Willingness of GP practices to be contacted about PRINCE Primary | | x | | |
| Willingness of GP practices to consent and be randomised | | x | | |
| Availability of data needed and the usefulness and limitations of the general practice databases | | x | | |
| Interest of GPs to attend the GP training (intervention arm only) | | | x | |
| GP Training Outcomes | | | | |
| Knowledge and Confidence | Self-report | | x | x |

Data collection plan: retention

Retention rates will be maximised by providing participants with the option of completing questionnaires via post, telephone or email. Furthermore, thank you cards will also be sent at various stages of the trial.

Proposed sample size

A selection of 8-12 GP practices stratified by size (<6000 or > 6000) (clusters) will be recruited, with an expected patient sample size of 240. This would mean that 120 patients will receive the integrated GP care by 24 weeks and will complete measures. As this trial is a feasibility study, no formal power calculation has been carried out. Instead the number of GP practices was chosen, such that we have sufficient replicates to estimate feasibility parameters at the practice level.

Data Management

Data will be collected on paper source data worksheets. Data will then be entered onto the InferMed MACRO online data entry system, on a study-specific database designed and hosted at the King Clinical Trial Unit (KCTU). The system is compliant with Good Clinical Practice and FDA 21 CFR Part 11. Data exports will be provided to the trial statistician upon request.

The web-based randomisation system will maintain an accurate record of randomisations and data can be exported from this system for reports. Post-randomisation data can be readily extracted from the MACRO trial database for the preparation of DMEC reports and a front-end search function is available to support data checking and cleaning.

Central data entry and data cleaning will be undertaken by a designated research worker. Major issues in staff training or data quality will be raised with the trial manager, who will perform source data checking against the data collection forms. Discrepancies can be raised in the system for resolution by site staff. Source data verification will be recorded on the system and any changes to data subsequent to verification will automatically generate an

alert in the system. Individual user access to the InferMed MACRO system will be co-ordinated via the trial manager, who will submit requests to the KCTU. No direct requests from sites will be accepted.

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to; (i) patient data will be pseudo-anonymised (allocation of a unique personal identification number (PIN)) and (ii) all pseudo-anonymised data will be stored on a password-protected computer. All trial data will be stored in line with the General Data Protection Regulation (GDPR) and archived in line with Sponsor requirements. Consent forms and other paper records will be stored in swipe-card accessed offices in locked filing cabinets.

Statistical Analysis

A CONSORT diagram will be constructed including various feasibility parameters: the number of eligible practices and patients, number of practices and patients agreeing to enter the trial, number of GP practices randomised, then by treatment arm: the number of patients continuing through the trial, the number withdrawing from the study at various time points. The feasibility parameters will be estimated using the CONSORT diagram and will be presented as proportions accompanied by 95% confidence intervals (CI) to provide a measure of estimator precision.

Inferential analyses will be used to estimate intervention effects in terms of outcome variables. The formal statistical analyses will estimate the difference in mean outcomes between patients from GP practices randomised to 'integrated GP care plus treatment as usual' and waiting list control by intention to treat at 12 and 24 weeks follow up. We will provide estimates of trial arm differences with associated 95% confidence intervals and will also translate these effects into standardised effects sizes to enable comparisons across measures and time points. This information can help the planning of a future evaluation trial by providing guidance as to promising outcome measures and likely effect sizes. No formal significance testing will be carried out. Standardised effect sizes will be calculated by dividing estimated

mean differences by the respective baseline standard deviations (SDs). Analysis will be based on the intention-to-treat principle and we plan to use linear mixed modelling with maximum likelihood (ML) estimation. A random effect for participant will be entered in the model to account for correlations between repeated measures. Additionally, a random effect for cluster will also be included to allow for correlations between patients within a practice. Bias in estimates of trial arm differences will be avoided by use of randomisation and blinding of the outcome assessors.

All efforts will be made to avoid missing baseline data (i.e. requiring completion of baseline data before randomisation), but missing values will be imputed according to current recommendations.[38] Missing scale item data will be handled as per questionnaire specific recommendations. We will aim to support participating practices to minimise loss to follow-up by encouraging a number of approaches: adopting other evidence-based procedures for recruiting and maintaining participation in the study and encouraging patients to return outcome measures (e.g. contacting people before sending out questionnaires, sending personalised cover letters using colour printing, and keeping measures short in terms of completion time).[39, 40]

Health Economics

The main objective of the health economic aspect of the feasibility study is to assess what services are being used and this will inform the collection of service use data in a full trial.

Data Monitoring

The Programme Management Group (PMG) will be responsible for ensuring the appropriate, effective and timely implementation of the study. The Data Monitoring and Ethics Committee (DMEC) and Programme Steering Committee (PSC) have been formed as independent committees to oversee the study. The committees will be responsible for the independent

oversight of the progress of the trial, the investigation of Serious Adverse Events (SAEs) and for determination of trial progress.

Procedures for Recording and Reporting Serious Adverse Events

Adverse events are any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial. Any SAEs, Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) will be recorded by the research worker at 12 and 24 weeks post baseline. An adverse event is defined as serious if it:

- results in death;
- is life-threatening (with an immediate not hypothetical risk of death at the time of the event);
- requires hospitalisation (but not including elective hospitalisation for pre-existing condition);
- results in a new persistent or new significant disability or incapacity defined as:
 - i. Severe = a significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound);
 - ii. Persistent = 4 weeks continuous duration;
- Any other important medical condition which, though not included in the above, may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed;
- Any new episode of deliberate self-harm.

We will require two clinically trained scrutinisers to review all serious adverse events and reactions, independently from the trial team. They will be blind to the treatment group and will

be required to establish whether events reported constituted serious adverse events. The scrutinisers would then be unblinded to treatment allocation so that they can then establish whether any serious adverse events were serious adverse reactions to the system approach.

Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the DMEC/PSC or Research Ethics Committee (REC) concerned. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the PSC (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

Auditing

The investigator(s) will permit trial-related monitoring, audits and REC review by providing the sponsor(s) and REC direct access to source data and other documents. Monitoring of this study will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team. The study will be compliant with the research governance framework and MRC Good Clinical Practice Guideline.[41] We will institute a rigorous programme of quality control. The trial manager will be based at the Institute of Psychiatry, Psychology and Neuroscience, King's College London and line-managed and supervised by the chief investigator. The trial manager will prepare study specific Standard Operating Procedures (SOPs) for the study. The trial manager will supervise a designated research worker to undertake data management/cleaning, so that they can provide regular reports on data quality to the chief investigator and the other co-applicants. Quality assurance checks will be undertaken by the trial team to monitor the level of missing data and timeliness of data entry and check for illogical or inconsistent data. The trial manager will monitor data collection

procedures, ensure that study data entry procedures are followed and undertake source data verification against the paper data collection forms. The trial statisticians will be affiliated with KCTU, and will be responsible for producing DMEC reports, drafting of the Statistical Analysis Plan (SAP) and for carrying out primary analyses. We will ask the DMEC to take on this role of monitoring participating GP practices at recruitment. Our KCTU has SOPs that guide the trial statistician's reporting to the DMEC.

Patient and Public Involvement

In the early stages of this study we developed links with key stakeholders including patients with persistent physical symptoms, commissioners and a national charity. The first meeting entailed an open discussion to ensure that the trial was not burdensome for patients and to also gain a better understanding of what GP's felt was possible. We continue to involve these stakeholders during the study. Patients were not involved with the recruitment of participants into the study. Peer reviewed results will be disseminated to participating GP practices and study participants.

ETHICS AND DISSEMINATION

Ethical and Research Governance Approval

This feasibility study is funded by Guy's and St Thomas' Charity. Ethical approval has been granted by the Camberwell St Giles Ethics Committee (Reference 15/LO/0057) and King's College London and South London and Maudsley (SLaM) Hospital will act as sponsors for the research. The study will be managed via a central co-ordinating team. The study was also submitted to NHS Clinical Research Network, South London for research governance and approval was received on 13th April 2015.

Confidentiality

All patient data will be pseudo-anonymised. All pseudo-anonymised data will be stored on a password-protected computer. All trial data will be stored in line with the Data Protection Act. Consent forms and other paper records will be stored in locked filing cabinets within swipe-card access offices.

Insurance / Indemnity

Standard procedures for insurance of University and NHS employees and sites, and NHS patients will apply.

Dissemination Policy

We anticipate that there will be different target audiences for our dissemination activities:

- a. *Professionals*: we will disseminate findings to healthcare professionals (e.g. rheumatologists/ neurologists/cardiologists, psychiatrists, GPs, nurses, psychologists, CBT Therapists) via papers in high impact peer reviewed journals and presentations at local, national and international scientific meetings. We will also disseminate findings via the recently established UK Functional Neurological Symptoms (UKFNS) group. Findings will also be presented at the British Association of Behavioural and Cognitive Psychotherapies (BABCP) conference and GP Conferences within the UK. We will make available written materials and offer training workshops for other NHS clinical services, and at meetings if appropriate.
- b. *Service planners and commissioners*: if our study is successful, we anticipate that our findings will have relevance for the provision of care for patients with PPS, and therefore we will disseminate our findings to those who plan and commission care for people with PPS.
- c. *Voluntary sector*: we will make our findings available to PPS charities, which already disseminate information on PPS. We will offer summaries of our findings to websites for

the public which already provide information on PPS and to charities offering information on other MUS but not currently PPS,

DISCUSSION

This cluster randomised waiting list, controlled trial aims to investigate the feasibility of an integrated GP care approach plus treatment as usual for patients with PPS in primary care versus waiting list control. The intervention primarily operates at the GP practice (cluster) level and hence a cluster randomised trial design is employed. This means GP practices randomised to 'integrated GP care plus treatment as usual' will include (i) GP training in cognitive behavioural skills, (ii) GP supervision, (iii) audio visual material for GPs and (iv) self-help materials for participants. GP practices randomised to the waiting list control arm will continue with treatment as usual (i.e. GP practices will not be offered the intervention' initially but will be crossed over and offered the intervention at 28 weeks to give 4 weeks' time to collect measures). Cluster randomised trials can be subject to selection bias when patients are recruited after allocation of the intervention to the clusters (GP practices). Hence our design ensures that patients are recruited before their GP practice is randomised so their decision to take part in the trial cannot be informed by knowledge of whether the GP practice receives the intervention. To avoid participants having to wait a long time only those who frequently attended their GP will be eligible to participate in this study (please see eligibility criteria). Patients will not be dropped if they are not seen by a trained GP as the integrated care approach also includes self-help materials for patients. This study aims to mimic a real-life setting in which a patient may not see the same GP on a regular basis.

Given the prevalence of PPS and their costs to health services, there is an urgent need to develop easily accessible and affordable treatments for this patient group. Although previous studies have examined the efficacy of CBT-based approaches in treating patients with PPS, most studies were conducted in secondary care and focused on specific conditions.[14, 15] Taken together, evidence suggests positive effects of CBT-based group intervention on PPS. However, group interventions and bringing in secondary care healthcare professionals may not always be feasible and time-efficient. The present trial attempts to address these challenges by evaluating the feasibility of training GPs in delivering behaviour change interventions in a 10-minute consultation and providing patients with self-help materials.

There are limitations to this study. It is unlikely that all GPs will attend all of the training. However, we will organise the training at times that suit as many GPs as possible. We cannot be sure in any case that GPs will utilise the skills they may have acquired during the training. GPs consultations will not be recorded as GP's themselves feel it is too burdensome. In order to mitigate these shortcomings, we will conduct semi-structured qualitative interviews with a random selection of patients to assess whether they had seen a GP and whether they felt that a behaviour change intervention had been delivered.

In conclusion, this RCT aims to assess the feasibility of an integrated GP approach for treating patients with PPS. Based on the results of the study, a fully-powered RCT will be considered in order to assess the clinical effectiveness of this approach in changing identified health-related outcomes.

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Author Contributions TC, RM-M, MA, PMC, MHotopf, AD, SL were involved in the design of the study and were co-applicants for funding. TC led the grant application and is chief investigator. TC, M Husain, MP, MA, NF and RM-M developed the intervention (i.e. integrated GP care). PMC and IM lead on the Health Economic evaluation. SL and KJ lead on statistical analysis. NF and PF leads on the qualitative component. All the authors read and approved the final manuscript.

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Conflicts of interests MH reported grants from Innovative Medicines Initiative and European Federation of Pharmaceutical Industries and Associations, outside the submitted work. In addition, TC and RMM declared the following; Organisational financial interests: TC received ad hoc payments for conducting workshops on evidence-based treatments for persistent physical symptoms. TC has received grants from NIHR programme grants, HTA, RfPB, Guy's and St Thomas Charity, King's Challenge Fund, Muscular Dystrophy, Multiple Sclerosis Society. KCL received payment from Taylor and Francis for editorial role. RMM currently receives grant funding from NIHR programme grants, Breast Cancer Now, Crohn's and Colitis UK, and National MS Society. In the previous 36 months, RMM received funding from MS society UK and NIHR HTA. In 2019, payments from Taylor and Francis to KCL for RMM's role as Editor of Health Psychology Review. Payments for adhoc lectures and workshops on Long term conditions. Personal financial interests: TC is the author of several self-help books on chronic fatigue and received royalties in the past. TC received expenses and ad hoc payment for role as external examiner NUI Galway and Waterford Institute of Technology. TC received expenses for keynote speeches at UK Society for Behavioural Medicine, BABCP Conferences (travel and accommodation). TC received ad hoc payments for conducting workshops on evidence-based treatments for persistent physical symptoms. RMM received payments for her role as National Advisor to NHS England for Increasing Access to Psychological Therapies (IAPT) for People with Long Term Conditions from 2011-2016. RMM received ad hoc payments for workshop training in IBS in 2017 and 2018 and this will continue in 2019. RMM receives ad hoc consultancy payments from Mahana therapeutics and this is likely to continue in 2019. RMM has stock options in Mahana therapeutics. RMM

received travel expenses for keynote speech to Internal Society of Behavioural Medicine. In 2019 RMM will be a keynote speaker for Association for Researchers in Psychology and Health (the Netherlands), European Health Psychology Society Annual Conference (Croatia), and the 9th World Congress of Behavioural and Cognitive Therapies (Germany). Travel and accommodation expenses will be reimbursed

Ethics approval Camberwell St Giles Ethics Committee REC 15/LO/0057

Data Sharing Statement

No consent was provided for sharing data with third parties. Once papers have been published, data will be anonymised and deposited in a repository. Bona-fide researchers can apply to use the data but are required to clearly specify the research question a priori.

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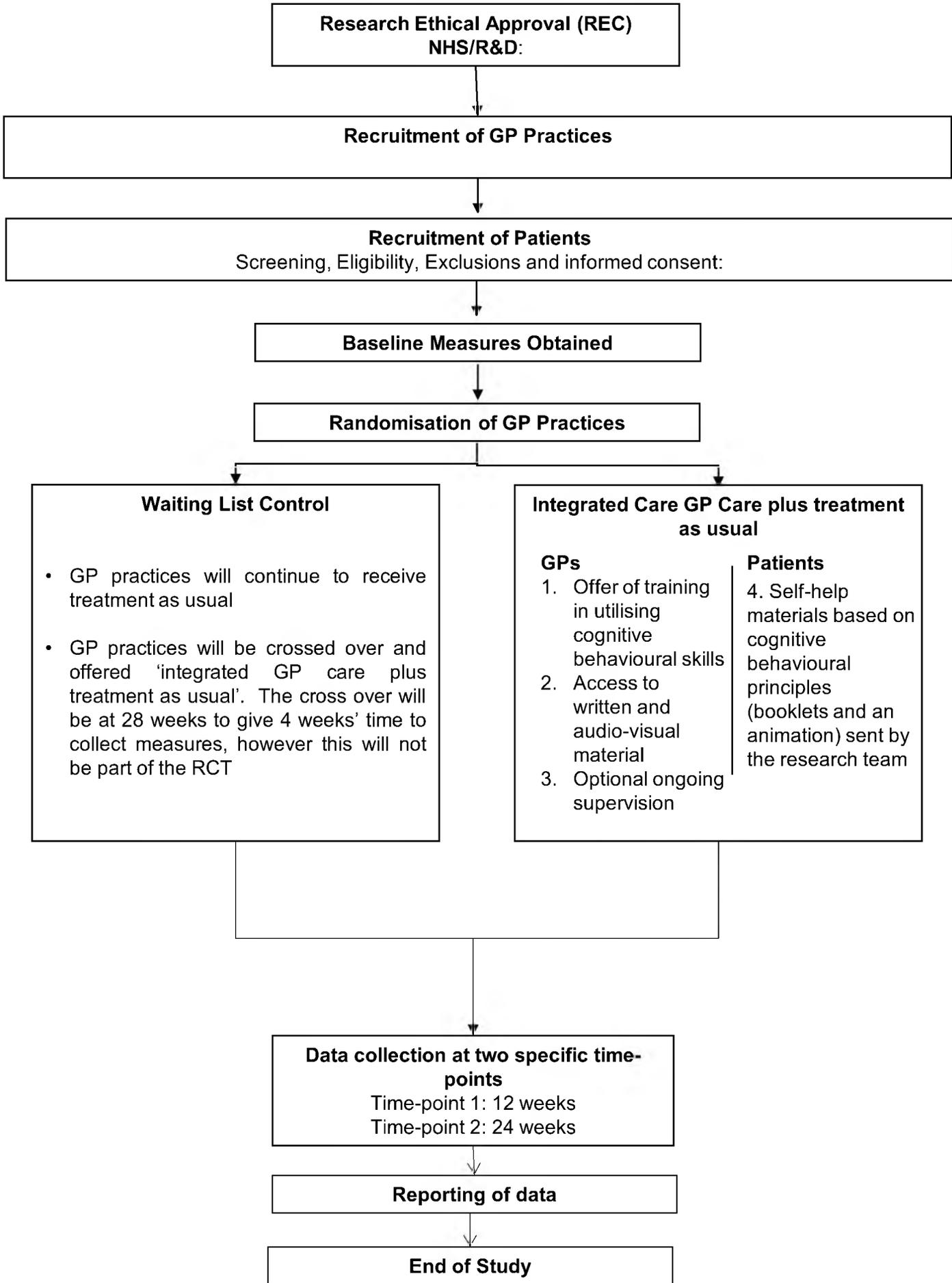


Figure 1: Flow Diagram of Study Procedure