Multiple Symptoms Study 3: pragmatic trial of a community based clinic for patients with persistent (medically unexplained) physical symptoms

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Multiple Symptoms Study 3: pragmatic trial of a community based clinic for patients with persistent (medically unexplained) physical symptoms

Multiple Symptoms Study 3

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients.

Contents

Abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
ER-GP	Extended-role GP
GAD-7	Generalised Anxiety Disorder Assessment
HLS EU-6	European Health Literacy survey
HRA	Health Research Authority
HS&DR	Health Services and Delivery Research
MRC	Medical Research Council
MSS3	Multiple Symptoms Study 3
MUS	Multiple Unexplained Symptoms
NIHR	National Institute for Health Research
PGIC	Patient Global Indicator of Change
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PROMIS	Ability to Participate in Social Roles and Activities
QALY	Quality Adjusted Life Years
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCI	Symptoms Clinic Intervention
SSD-12	Somatic Symptoms Disorder – B criteria scale
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

General information

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Protocol amendments since Version 1.0

1. Introduction (page 9)
'Syndrome' removed from chronic fatigue to more accurately reflect the inclusion criteria
3.1 Internal pilot (pages 11 &12)
Internal pilot criteria details removed as not required in the protocol as a trial procedure
4. Selection of participants (page 13)
Updated to clarify what details will be collected on the expression of interest form
Exclusion criteria 6 updated to state 'at time of screening telephone call' instead of computer search **5. Randomisation and enrolment (page 14)**
Section update to state that block randomisation will be done rather than minimisation
7.3 Process and related measures (page 18)
Section updated to remove the PAM-13 outcome measure
7.4 Measurement of outcomes (pages 18, 19, 20 & 21)
The method of contacting participants has been updated as we will no longer collect the preferred method of contact.
Outcome measures updated to remove the PAM-13 outcome measure and to collect participant reported healthcare resource use at 6 and 12 months only
9. Safety Assessments (pages 23-26)
Section updated to clarify which AEs will be collected for this trial and how they are defined and reported.
20. Appendix 1 (page 39)
Appendix updated to be consistent with above changes

Protocol amendments since Version 2.0

4. Selection of participants (page 12)
Repeat prescriptions for Irritable Bowel Syndrome medication in last year has been added to the GP computer searches.
5. Randomisation and enrolment (page 13)
Community or research facility have been added as an option for the enrolment visit to take place to ensure that accessible locations are used
7.4 Measurement of outcomes (page 18 & 20)
Table 1 and Figure 1 updated to include the PHQ-9 at the 26 week data collection time point
20. Appendix 1 (page 38 & 49)
Appendix updated to be consistent with above changes

Protocol amendments since Version 3.0

4. Selection of participants (page 12 & 13)
The number of PIC sites has been increased to approximately 112 and Doncaster has been listed as a research site.
A reminder invitation pack has been added in to the process for identifying potential participants.
7.4 Measurement of outcomes (page 21)
A £10 high street voucher at the baseline appointment has been added
20. Appendix 1 (page 38, 39, 41, 44 & 55)

Appendix updated to be consistent with above changes

Protocol amendments since Version 4.0

General Information (pages 5 and 6)
Contact details of co-applicants and trial team updated
Trial Summary (Page 9)
Changes to text to allow for remote delivery of the Symptoms Clinic appointments via video consultations.
3. Trial Design (page 12)
Change to text to state that the Symptoms Clinics will take place via video consultations.
4. Selection of participants (page 12 and 13)
Increased number of GP practices acting as PIC sites, addition of inclusion criteria stating the access requirements participants must have to be enrolled in to the study. Extended inclusion criteria 2b from 3 years to 42 months
5. Randomisation and enrolment (page 14 and 15)
Changes made to text to allow remote enrolment appointments and link to appendix for remote consent process added.
6.1.2 Symptoms Clinic Consultation content (page 16)
Added that leaflets can be emailed or posted to participants
6.1.3 Symptoms Clinic delivery (page 16)
Changes made to text to change to remote delivery of the Symptoms Clinics
7.4 Measurement of outcomes (page 20 and 21)
Updated to include COVID-19 related questions at enrolment and 52 weeks.
Flow chart updated to reflect remote consent and Symptoms Clinic delivery
12. Data handling and record keeping (page 30)
Added recording and storage of verbal consent on Dictaphones.
20. Appendix 1. (pages 35 – 64)
Inclusion of remote consent flow diagram as appendix 1
MSS3 SWAT protocol moved to appendix 2, changes made throughout to reflect the above changes in relation to recruitment and delivery.

Trial Summary

Multiple Symptoms Study 3 is a large randomised controlled trial to test the effectiveness of a Symptoms Clinic for people with persistent “medically unexplained” physical symptoms. Persistent physical symptoms affect around 1 million people (2% of adults) in the UK. They affect patients’ quality of life and account for at least one third of referrals from GPs to specialists.

Setting
The trial will take place across at least three centres in the north of England. In each centre, GPs will deliver the intervention to patients from all participating practices. The Symptoms clinics will be held via video consultations.

Participants
Participants will be adults aged 18 – 69 years, recruited from GP practices using a combination of records search and postal questionnaire. They will have multiple physical symptoms which impair their quality of life to a moderate extent and will have had diagnostic tests or specialist opinion which did not show serious disease. Participants will be randomised to either receive the Symptoms Clinic Intervention or to continue with their usual care.

Intervention
The Symptoms Clinic is an extended-role GP intervention which has gone through several stages of development and piloting. The Symptoms Clinic is a service delivered by specially trained GPs which uses a psychologically-informed medical consultation model developed for patients with persistent physical symptoms. The clinics are designed to allow patients to describe the nature and impact of their symptoms and help them find new ways of understanding and managing those symptoms drawing on current scientific knowledge. Each patient receives one 50 minute consultation and up to three structured 15 minute follow-ups.

Outcomes
The primary outcome will be physical symptoms (PHQ-15) at 52 weeks after randomisation. Secondary outcomes at 52 weeks include healthcare use (GP consultations, specialist referrals and investigations) and quality of life in order to estimate cost per QALY. Process evaluations will include analysis of consultations, and interviews with patients and key stakeholders.

1. Introduction

Persistent physical symptoms which cannot be adequately attributed to physical disease affect approximately 1 million adults in the UK (2% of the adult population) [1-3]. Many patients with such symptoms receive repeated referral and investigation [4] which give them little benefit [5] but has real costs to health services in terms of time and diagnostic resources [6]. When patients are told that medical tests do not show a cause for their symptoms they are commonly disappointed in their interactions with clinicians [7, 8]. Patients with symptoms want to have those symptoms explained in acceptable ways [9, 10] in order to feel that their symptoms are legitimate [7], to adapt to them and to manage them. Without explanation many patients seek further healthcare use while at the same time losing confidence that it will help them.

Persistent physical symptoms are known by several names, none of which is optimal [11]. The commonest (at least among professionals and researchers) is “medically unexplained symptoms” (MUS). Some persistent physical syndromes are grouped into clusters (syndromes) such as irritable bowel syndrome, fibromyalgia and chronic fatigue. Psychiatric classifications such as DSM5 include “somatic symptom disorders” but these are limited to patients with relatively severe symptoms. Newer classifications have been proposed which include milder persistent symptoms but none is widely used in the UK [12]. “Persistent physical symptoms” is more acceptable to patients than MUS and is less likely to lead doctors into the trap of viewing symptoms as either physical or psychological rather than a combination of both. The term “medically unexplained symptoms” implies either that symptoms cannot be explained at all, or that they cannot be explained by disease and are therefore “psychosomatic” – caused by psychological distress. However it is now possible to explain persistent physical symptoms using models such as central sensitisation [13] which integrate biological, psychological and social phenomena. Central sensitisation describes a set of processes by which symptoms are amplified and persist, that can be viewed at psychological and neurobiological levels.

We have developed a model of “rational explanation” [14] which enables clinicians to integrate knowledge from central sensitisation with patients’ reported experiences to develop explanations for symptoms. These rational explanations make sense of symptoms in terms of brain and body processes and are acceptable to doctor and patient [15, 16]. They leave room for psychosocial influences without placing them as the cause, and they provide opportunities to guide self-management. In rational explanations, psychological factors such as heightened vigilance to symptoms or persistent worry about symptoms are presented as understandable mechanisms by which symptoms persist rather than signs that symptoms have a “psychosomatic” cause. In contrast, previously advocated explanatory models such as somatisation are rejected by patients as too simplistic [9, 10] and leave patients with persistent physical symptoms dissatisfied with the explanations they receive.

Improving persistent symptoms has the potential to have a substantial effect on health and on its impacts in terms of lost productivity and increased care needs. Physical symptoms not explained by disease account for very substantial costs [6]. They are the reason for between 40% and 60% of all referrals across a range of specialties [5] and have been estimated to cost £3bn annually to the NHS and £14bn to the wider economy [3].

If effective, the Symptoms Clinic has the potential to both improve the health of individual patients and also to improve the efficiency of the NHS by reducing their healthcare use, particularly the need for specialist referrals and further diagnostic testing. This research takes a service delivery perspective by evaluating a new service provided at an intermediate level between primary and secondary care. We have taken this approach in order to concentrate training and skill in a few individuals per centre and optimise delivery of the intervention. The intervention uses enhancements to the skills of a general practitioner in simultaneously handling clinical diagnosis and psychosocial factors and is deliberately provided within a medical rather than psychiatric paradigm. It thus responds to patients' requests to provide explanation in a way which includes symptoms (rather than just diagnosis) within the ambit of mainstream medical care. In sitting between primary and secondary care, it draws on the example of other GP with Special Interest clinics (e.g. in musculoskeletal medicine) and consultation letter models of care for persistent symptoms in Europe and USA [17]. If this study finds that Symptoms Clinics are an effective and sustainable addition to the care delivery landscape, there are likely to be additional benefits. First, Symptom Clinics will act as a focus for the development and refining of further interventions and possibly for trials of new medical therapies as they become available. Second, they will act as centres for the diffusion of skills into wider practice. Third, they will have an important public education function about the nature of persistent physical symptoms.

This study builds on successful preliminary studies which have shown the feasibility, transferability and acceptability of the Symptoms Clinics.

The focus of this study is adults who have persistent physical symptoms of a level which impairs quality of life and is associated with substantial healthcare costs in terms of secondary care referral and diagnostic tests. Using existing classifications, they can be considered as falling within the spectrum of somatic symptom disorders. We will exclude both the most severely affected individuals, for whom more intensive specialist treatment is appropriate and milder cases (for whom the prognosis is good [18]). The aim of the research is to test an intervention which uses an extended medical consultation to reach an explanation of persistent symptoms in a way which (a) recognises and validates the patient's distress and concern (b) explains the symptoms in terms of body and mind processes which are modifiable (c) proposes action – which may include cognitive and behavioural techniques – aimed at managing symptoms or their impact in order to improve patient wellbeing and reduce costly specialist referrals.

The study will be conducted in compliance with the protocol, Good Clinical Practice and regulatory requirements.

2. Aims and objectives

The aim of this study is to determine the clinical and cost-effectiveness of the "Symptoms Clinic", a new service for patients with persistent ("medically unexplained") physical symptoms. The Symptoms Clinic is a locality based service delivered by specially trained GPs which uses a psychologically-informed medical consultation model developed for patients with persistent physical symptoms.

The study has 4 key objectives:

1. To conduct a pragmatic randomised controlled trial, with internal pilot, of the Symptoms Clinic compared to usual care, in people with persistent ("medically unexplained") physical symptoms and increased healthcare use.

2. To establish Symptoms Clinics for the purposes of the research study, train GPs for the role of GPs with Special Interest in each centre and provide them with supervision; to systematically recruit patients from primary care, and ensure satisfactory trial procedures and follow up.

3. To compare patient outcomes in terms of experience of physical symptoms and quality of life at 52 weeks post randomisation, and their healthcare use over those 52 weeks, between participants allocated to the Symptom Clinic plus usual care and those allocated to usual care alone.

4. To understand the processes of change associated with attending the Symptoms Clinic by (a) conducting qualitative interviews with a subsample of patients (b) recording and coding key elements of the clinical intervention (c) interviewing key participants and stakeholders.

3. Trial design

The Multiple Symptoms Study 3 is a pragmatic, multi-centre, parallel group, individually randomised controlled trial, with an internal pilot phase. Symptoms Clinics will be delivered by specially trained GPs via video consultation across at least 3 areas of the UK. The primary outcome will be symptoms measured by the PHQ-15 at 52 weeks after randomisation. Outcomes will also be measured at 13 and 26 weeks. A process evaluation will be informed by three nested observational studies.

4. Selection of participants

Potential participants will be identified from approximately 120 GP practices acting as Participant Identification Centres (PIC) across research sites including Sheffield (and surrounding areas), Manchester, Gateshead/Newcastle and Doncaster. PIC sites will be recruited through local Clinical Research Networks (CRN) and Sheffield CTRU.

A three-stage identification process will be adopted using computer searching, GP record screening and postal questionnaire.

Stage 1
The GP PIC sites will complete a computer search on the practice clinical system to identify patients whose records include: (a) at least one code for an MUS syndrome (e.g. irritable bowel syndrome, fibromyalgia) or at least two codes for negative investigations (e.g. CT Scan normal); (b) at least 2 referrals for specialist opinion or diagnostic investigations in the last 3 years; (c) no codes to indicate serious disease (e.g. cancer, coronary heart disease, inflammatory or

connective tissue disease) which might account for a substantial number of symptoms; (d) repeat prescriptions for Irritable Bowel Syndrome medication in last year. Detailed instructions for how to complete the searches on each clinical system will be provided by the CTRU.

Stage 2
Once the computer search has produced a list of patients a GP at the practice will screen the patient names (and where necessary their medical records) to exclude any patients with major medical conditions causing their symptoms which were not picked up on search and those for whom invitation by the practice may be inappropriate.

Stage 3
The GP practice will then send an invitation letter, Participant Information Sheet (PIS) and screening questionnaire to the patients identified in stages 1 and 2. Interested patients will return an expression of interest form, which includes patient contact details, sex and age as well as a completed PHQ-15 to Sheffield CTRU. Sheffield CTRU will screen the PHQ-15 for eligibility. If the PHQ-15 score indicates that the participant is not eligible then the CTRU research team will contact the participant using an ineligibility letter via post or email which explains that the study would not be suitable for them.

Approximately three weeks after the initial mailing the GP practice will send a reminder invitation pack to participants that have not yet responded.

The above stages will be adopted to identify patients who meet the below inclusion and exclusion criteria:

Inclusion criteria:

1. Aged between 18 – 69 years (inclusive) at the time of the computer search
2. Current physical symptoms which meet the below criteria
    a. clinical records suggest MUS (presence of at least one code for an MUS syndrome or at least two codes for negative investigations)
    b. records show at least 2 referrals for specialist opinion or diagnostic investigations in the last 42 months
    c. records show no evidence of any previous or current major illnesses likely to cause multiple symptoms
    d. doctors in the GP practice do not believe that the majority of the patient's symptoms can be currently explained by other pathology;
    e. the score on the self-completed PHQ-15 symptoms scale is between 10 and 20 (inclusive)
3. Access to a mobile phone with video calling capability or an email address and computer with video conferencing capability (Capability requirements are: microphone, camera and internet connection)

Exclusion criteria:
Patients will be excluded if any of the following apply:

1. A score of 3 on question 9 on the PHQ-9 completed at the baseline appointment*

2. Difficulty conducting a healthcare consultation in English without either a professional or family interpreter or other assistance (either indicated in GP records, or becoming apparent during the enrolment and consent process)
3. The GP regards inviting them to participate as inappropriate (e.g. recent bereavement)
4. Severe symptom-related disability (e.g. requiring help with daily personal care or severely impaired mobility)
5. Undergoing active multidisciplinary rehabilitation, IAPT programme or specialist psychological treatment including specialist pain, fatigue or other symptom clinic at the time of screening.
6. Currently pregnant** or less than 6 months postnatal at the time of the screening telephone call

*If a score of 3 is identified at any time point during the study the suicide protocol will be triggered
**if a participant becomes pregnant after the screening telephone call they will remain in the study and continue to attend the Symptoms Clinic Intervention if allocated to the intervention group.

Following stages 1-3, the details of interested and potentially eligible patients will be passed on to a local research nurse/delegated member of the research team who will contact the patient to discuss the study further, answer any questions from the patient and discuss a timetable for further participation. If a potential participant wishes to proceed, the researcher will complete screening checks by enquiring directly about the exclusion criteria relating to personal care, active multidisciplinary rehabilitation, and current specialist psychological treatment. They will also ensure that the participant has access to the appropriate technologies to take part in video consultations as required for delivery of the Symptoms Clinic intervention. When discussions are complete the researcher will make an appointment with the patient for study enrolment. If the patient wishes to have more time to consider participation then a second phone call can be arranged.

5. Randomisation and enrolment

Enrolment will take place via video conference or telephone call. The research nurse or delegated member of the research team will discuss the study with the patient, complete the informed consent process (see appendix 1 for remote consent process) and collect baseline data. Details of whether the participant has experienced COVID-19 will also be collected. It must be made completely and unambiguously clear that participation in the study is entirely voluntary and that consent to participate in the study can be withdrawn at any time without affecting their future care.

The research nurse or delegated member of the research team taking consent will ensure that the participant has a copy of the PIS and will also provide the participants with a copy of the researcher completed consent form. The consent form will be filed in the Investigator Site File along with the audio consent recording.

Randomisation will be completed after consent has been obtained and baseline data collected (details of baseline measures in section 7.4). Patients will be individually randomised (1:1) and will be allocated to the Symptoms Clinic plus usual care or usual care alone using a computer generated pseudo-random list, stratified by study centre with random permuted blocks of varying

sizes. Randomisation will be via SCRAM, the Sheffield CTRU-hosted web-based randomisation system and will be in accordance with their Standard Operating Procedures (SOPs). The sequences will be held on a secure server and will be concealed until recruitment, data collection and analyses are complete.

The research nurse or delegated member of the research team will enter the participant demographic details, PHQ-15 score and confirmation of consent directly into the randomisation system. If internet access is not available there will be a reserve method to contact the central trial team at the University of Sheffield by telephone and provide these details for a member of the core team to enter into the randomisation system. The research nurse will then inform the participant of their allocation, and if assigned to the intervention will collect participants NHS number (required for linkage to video consultation software) and make a first appointment to attend the Symptoms clinic. All participants (intervention and control) will be advised to continue to use healthcare services as and when they deem appropriate. Sheffield CTRU will confirm the allocation and appointment details (if applicable) in a letter to the participant.

6. Trial treatment

6.1 Intervention

6.1.1 Symptoms Clinic

The intervention being assessed is a psychologically-informed medical consultation (Symptoms Clinic) delivered by a specially trained ER-GP. The consultations include detailed medical history taking, explanation (including discussion of appropriate diagnosis) and advice about management. Consultations will be delivered remotely via video consultation or telephone. The Symptoms Clinic involves an initial long consultation of approximately 50 minutes followed up by two or three medium length consultations of 15-20 minutes.

6.1.2 Symptoms Clinic Consultation content

The ER-GP will follow a detailed Symptoms Clinic manual which describes a range of optional components as well as an overall structure.

The initial consultation will collect a detailed account from the patient of their current symptoms, and the ways in which those symptoms impact the patient and their situation. It includes medical history and targeted questions in relation to psychosocial matters. The consultation will be conducted in a way which aims to ensure that the patient recognises they have been heard and their experience validated. The latter part of the initial consultation involves the GP proposing and negotiating explanations for the patient's symptoms using the principles of "rational explanation"[14] within one or more of the explanatory models developed from our preliminary studies.

The subsequent consultations aim to build on the initial consultation and the explanations proposed therein. They focus on (usually) one key cognition and one behaviour in order to suggest ways of self-management that the patient can follow. The clinic resources include a range of self-management leaflets, which can be posted or emailed to the participants, describing techniques

for symptom management (e.g. sensory grounding). The final consultation aims to tie together the components of treatment and set a plan for the patient to follow.

6.1.3 Symptoms Clinic delivery

The initial consultation will be delivered via video consultation. Subsequent consultations are offered via video consultation but may be conducted by telephone where the patient prefers.

For a participant to be considered as having completed the intervention there must be an initial consultation and at least 1 follow up consultation. The clinic model specifies an initial consultation and 3 follow-up consultations, but this is optional and will be at the discretion of the ER-GP and participant. The decision as to the number of follow up appointments will be considered on a case by case basis taking into account the progress made during the consultations, how much more can be achieved through further consultations and the suitability of the intervention to the participant. Details of each consultation can be found in the MSS3 GP manual.

Symptoms clinic consultations may be observed by investigators responsible for the process evaluation component to gain an understanding of the context of the consultations in preparation for qualitative analysis and interviews, consent will be obtained from the participant.

If a participant misses a Symptoms Clinic appointment then one new appointment will be offered. If this appointment is missed then the participant will be informed that no further appointments will be made and to continue with their usual care, attending their GP when required.

6.1.4 Communication between the Symptoms Clinic and patients' usual GP

After the first and final consultation for each patient the Symptoms Clinic doctor will write to the patient's GP (copying in the patient) summarising findings, explanation and plan. The patient's GP will not be expected to do anything specific with the content of the letter.

While the aim of the consultation is to focus on symptoms which are not due to disease, we estimate that in around 1 in 25 cases, a previously unrecognised disease may become apparent: if that is the case, the GP conducting the clinic will refer the patient back to the usual GP for further management / referral. The ER-GP and participant will discuss whether they wish to continue attending the symptoms clinic. If they withdraw from the intervention we will continue to collect follow up data (see section 7.5 for further details).

6.1.5 Fidelity of the intervention (Symptoms Clinic)

All participants will be asked that their Symptoms Clinic consultation be audio-recorded as part of the consent process. These will be archived for quality assurance purposes and a sample (50% during the first 6 weeks, 25% thereafter) will be transcribed, with selected sections such as dialogue relating to explanation highlighted for review by members of the research team.

Fidelity will be assessed from consultation transcripts or recordings against standards developed in the preliminary studies in three ways: (a) proportion of consultation time spent on different components of the intervention [19], (b) number and type of explanations for symptoms proposed [15], (c) nature and outcome of discussion about explanations [16].

6.1.6 Recruitment, training and supervision of practitioners to deliver the intervention

ER-GPs will be recruited to deliver the Symptoms Clinic in each centre. They will undergo six days of training during the set-up phase of the study and deliver one clinical session per week during the delivery phase.

Local investigators will advertise for and recruit GPs to be trained in and deliver the intervention. Shortlisted candidates will be interviewed and 3 or 4 GPs per location identified for initial training. Following the initial training two will be appointed as ER-GPs for the study.

Once appointed, the ER-GPs will receive further training as follows: (1) two days of training at the University of Sheffield; (2) supervised practice in the ER-GP's own practice in which the GP will see patients following the symptoms clinic model, record the consultations and review them with the local investigator; (3) at least two further half-day training sessions at their local centre. The content of training is defined in the GP manual and follows that used in the second preliminary study.

Towards the end of the training period, ER-GPs will record a set of three consultations for review, quality assessment and constructive feedback by a panel comprising the CI and two other investigators. Patient consent will be obtained for the recording of training consultations, and supervision / review from the CI and local investigators.

During the study, ER-GPs will receive clinical supervision. This will take place approximately monthly with a local investigator within their contracted sessions. The supervision will include review of consultation content and encourage reflective learning and consolidation of skills.

6.1.7 Separation of Symptom Clinic intervention from routine care

There is the potential for participants allocated to the usual care arm of the trial to be exposed to the intervention and the ER-GP. We will minimise the risk of participants receiving routine care from the ER-GPs (of whom there will only be two in each of the three study centres) as follows: (1) where a ER-GP conducts all his or her routine clinical work in one small-medium sized practice (<12,000 patients) we will not recruit participants from that practice; (2) where a ER-GP conducts routine clinical work either in a large practice (≥12,000 patients) or in a portfolio fashion across several practices, we may enrol patients from those practices but will ensure that these participants are not seen in the Symptoms Clinic by a ER-GP who might see them in routine care.

To minimise the risk of ER-GPs using the consultation techniques outside of the trial, all ER-GPs will undertake not to conduct extended consultations using the SCI model in their usual practices (after the training period).

7. Assessments and procedures

7.1 Primary outcome measure

The primary outcome will be physical symptoms (PHQ-15) [20] at 52 weeks after randomisation. PHQ-15 comprises 15 physical symptoms, with each accorded 2,1 or 0 points based on how much they have bothered the patient over the last 4 weeks (bothered a lot, bothered a little, not at all). In our preliminary studies a change of 3 points between baseline and 13 weeks (from a mean baseline score of 15) was associated with at least one grade of improvement (out of seven) on the Patient Global Indicator of Change (PGIC). We therefore regard this 3 point change as clinically important to individual patients.

7.2 Secondary outcome measures

Secondary outcomes will include quality of life (EQ-5D-5L, SF-6D, and ICECAP [21] capabilities based measures) over 52 weeks after randomisation and healthcare use over the 52 week period (GP consultations, referrals & diagnostic tests including imaging and endoscopy). In particular, we will record referral to / involvement with other symptom management services such as for pain or fatigue. We will measure participants' overall impression of change with the PGIC. We will also collect the Ability to Participate in Social Roles and Activities (PROMIS) measure to capture social functioning. There will also be data collection time points at 13 and 26 weeks to examine short and mid-term treatment effects (see *Table 1* for details).

7.3 Process and related measures

To understand factors associated with participants symptoms; depression, anxiety and health related concerns will be measured using the PHQ-9 [22], the Somatic Symptoms Disorder – B criteria scale (SSD-12) [23] and the Generalised Anxiety Disorder Assessment (GAD-7). We will also measure patients' health literacy using the HLS EU-6 which was developed for the 2011 European Health Literacy survey and captures health literacy skills across a range of understanding and self-management areas.

7.4 Measurement of outcomes

Self-report measures will be collected by questionnaire at the enrolment interview and follow up measures by post at 13, 26 and 52 weeks. Non-responders will be followed up using contact details provided by the participant to check that the outcome measures have been received by the participant and to prompt them to return the outcome measures. We will attempt to contact on all contact details provided by the participant, this may include telephone contact, email, text message and postal letter. At all contact points details of how the participant can contact the research team will be included and an offer to complete the questionnaires over the telephone will be made. The research team will adhere to the data collection procedure document when following up non-responders.

Details of whether the participant has experienced COVID-19 will be collected at baseline and 52 weeks.

Healthcare use data will be collected from primary care records. If primary care records cannot be accessed then the participant self-report questionnaire data will be used. Timing of outcomes are shown in *Table 1.*

Table 1.

Outcome Measures	Source	Time			Post randomisation	
		Screening	Recruitment*	13 weeks	26 weeks	52 weeks
Physical Symptoms (PHQ-15)	PQ					
Health profile SF12	PQ					
NHS primary and secondary health care use	CR					
Self-reported healthcare use	PQ					
PHQ-9 & SSD-12	PQ					
GAD-7	PQ					
EQ-5D-5L & ICECAP	PQ				EQ-5D-5L	
Patient Global Impression of Change	PQ					
HLS EU-6	PQ					
PROMIS	PQ					

To avoid the risk of bias researchers collecting and handling outcome measures will be blinded to allocation of the participant. The extraction of health resource use data from medical records will be completed after all other measures have been collected from the participant as it is possible that the outcome assessor will be unblinded through exposure to correspondence in the notes. The health resource use data collection form and record review guidance will outline the order in which data is to be collected so correspondence is the last section to be reviewed.

Searches & invitation:
PIC site GP's

GP record search: CTRU will provide practice with search strategy. The GP will screen list of identified patients and exclude any that are not suitable. The practice will post out invitation pack (including PHQ-15)
n= 5980

Patient reply:
CTRU team

Patient reply: Reply forms and PHQ-15 returned to CTRU. CTRU research team will review PHQ-15 score
n= 920

If PHQ-15 <10 or >20

CTRU to send ineligibility letter

If PHQ-15 between 10 and 20

CTRU inform local CRN nurse of interested patient

Screening and Randomisation:
Local CRN Nurse / delegated researcher

Telephone screening: discuss study and check for eligibility. Baseline appointment arranged if applicable

Baseline appointment: complete informed consent, confirm eligibility and complete baseline measures
Measures collected: PHQ-15, Health profile SF12, PHQ-9, SSD12, GAD-7, EQ-5D-5L. ICECAP. HLS EU-6. and PROMIS

Randomisation: completed using the University of Sheffield online randomisation system

Usual care
n= 188

Usual care & symptoms clinic
n=188

Book appointment for first Symptoms Clinic Consultation and collect NHS number

Typically, within 1-2 weeks

Symptoms Clinic Delivery:
ER-GP

Initial Symptoms Clinic: ER-GP conducts 1st Symptoms Clinic via video consultation adhering to the GP manual
All consultations will be audio-recorded. ER-GP sends letter to the participant and their usual GP outlining the explanations used and their implications for treatment / self-management

Follow up appointments made by local CRN nurse, practice receptionist, CTRU or ER-GP (to be agreed locally)

Follow up Symptoms Clinic: ER-GP conducts 2-3 follow up consultations adhering to the GP manual (can be video consultation or via telephone)
All consultations will be audio-recorded. ER-GP sends letter to the participant and their usual GP following the final appointment

Qualitative interviews and analysis of patient experiences

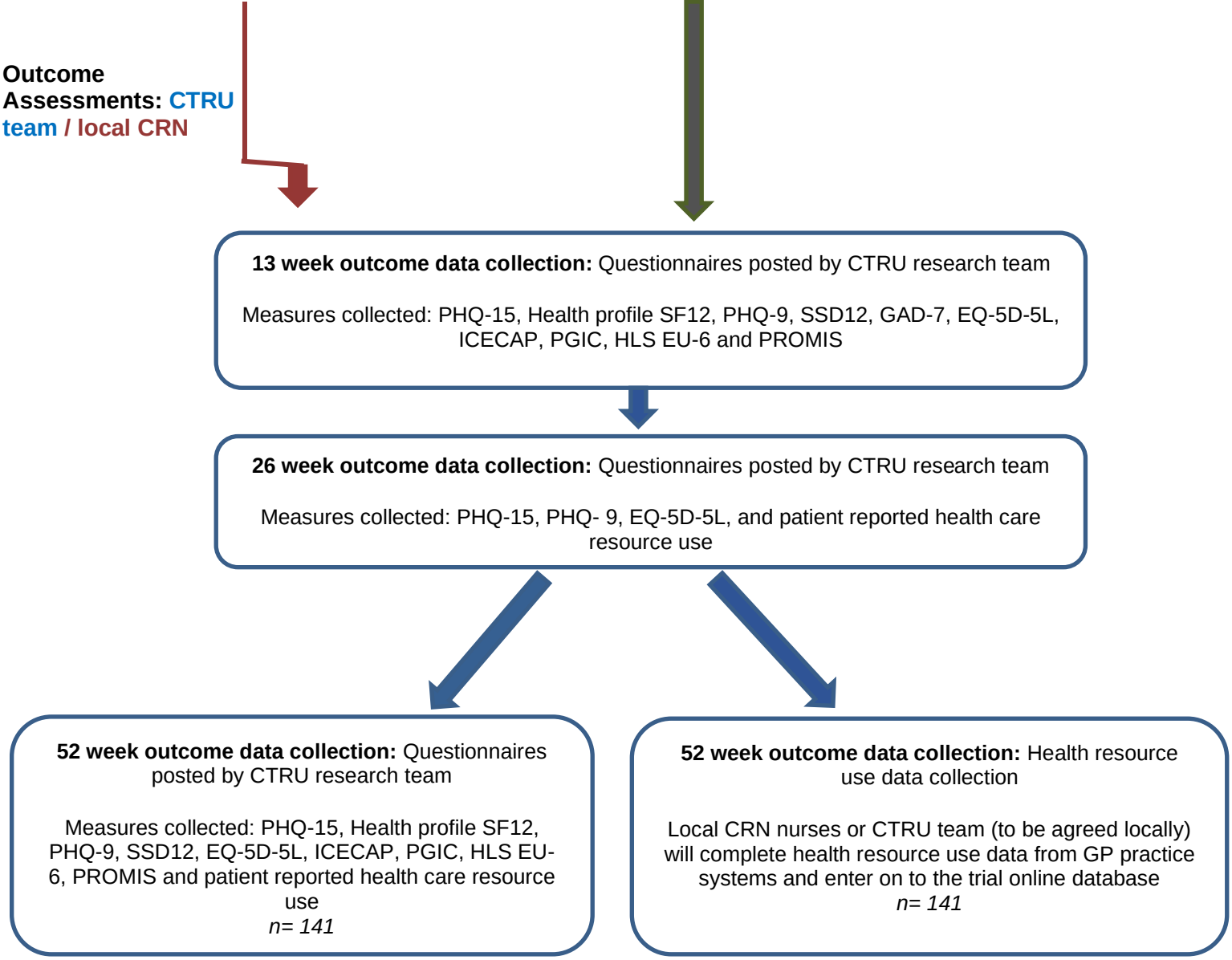

Figure 1: Flow chart of assessments and follow-up.

The total trial period is at least 56 months. Participants will be in the study for approximately 52 weeks. This will include a baseline appointment, initial Symptoms clinic consultation and up to three follow up appointments. Follow up outcome measures will be collected at 13, 26 and 52 weeks post randomisation as described in *Figure 1.* This will be collected through postal questionnaires or the option of telephone completion.

Participants will receive a £10 high street voucher following the baseline appointment and a further £10 voucher on completion of the 52 week questionnaires.

7.5 Participant withdrawal, discontinuation and loss to follow up

Participants may withdraw from active participation in the study on request. Individuals withdrawn from the intervention will not be replaced and will be followed up for all outcomes, unless they specifically request to be withdrawn from follow up data collection. We will ask permission to collect their healthcare resource use from their GP practice at 52 weeks; participants will have the opportunity to opt out of this on withdrawal. The reason for withdrawal from the intervention/study, if known, will be recorded on a Case Report Form (CRF). However, data up to the time of consent withdrawal will be included in the data reported for the study.

If an enrolled patient is found to have a new clinical condition causing their symptoms, the ER-GP will report this to the usual care GP and CI. A decision about further study appointments will be discussed on an individual case basis; guided by the participants' choice as to whether they wish to continue attending the appointments. If a participant is withdrawn from the intervention on this basis follow up data will still be collected and included in the intention to treat analysis.

A participant will be considered lost to follow up if they do not return the participant completed outcome measures at 52 weeks after all reminder options have been utilised, according to the outcome data follow up guidance, ie. no response to telephone contact, reminder letter or email. If a participant does not respond to earlier follow up questionnaires (at 13 and 26 weeks) we will still approach at subsequent follow up time points.

7.6 Site & trial closure procedures

The end of the trial is defined as completion of all follow-up data for the last participant.
Sites will be closed once all CRFs have been entered on to the database and data cleaning has been completed. The Research Ethics Committee (REC) will be informed of trial closure.

8. Statistics

8.1 Sample size

8.1.1 Definition of effect size

In the pilot trial we observed an average 3.2 point clinically important change in the intervention group from baseline to 13 weeks, compared to a 1.4 point change in the control group. We have thus powered the trial on a between group difference of 2 points on PHQ-15 (equivalent to a clinically important 3 point change from baseline)

We have based calculations of effect size on a pooled standard deviation of 5; this is larger than that seen in our preliminary studies owing to their restricted eligibility range and more in keeping with observational studies. This results in a standardised effect size of 0.4, which is similar to that seen in two small European studies of extended GP consultations for broadly comparable patients [25, 26].

8.1.2 Calculation of sample size

Allowing for 25% loss to follow up, and a further pragmatic 6% inflation to allow for minor treatment centre imbalances or differences, a sample of 188 patients per arm has 90% power (alpha =0.05) to detect this effect. Therefore 376 participants will be recruited.

8.2 Statistical analysis

Full details of all analyses will be provided in the Statistical Analysis Plan, which will be reviewed by the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC) prior to analysis.

The primary outcome will be analysed using a general linear model correcting for baseline PHQ-15. Secondary outcomes will be analysed in a similar manner within a generalised linear modelling framework using appropriate link functions for the outcomes' distributions. The primary outcome will be analysed using observed data with no imputation for missing data, but we will assess the amount and patterns of missing data and test the sensitivity of estimates of treatments effects using an appropriate imputation strategy. We will explore potential modification of the treatment effect by including treatment-by-subgroup interactions in models. All treatment effect estimates will be presented with 95% confidence intervals.

A single main analysis will be performed at the end of the trial when all follow up has been completed. Interim analyses will be performed if requested by the DMEC and Standard Operating Procedure (SOP) ST004 will be adhered to maintain the integrity of the trial.

9. Safety assessments

There are a number of anticipated adverse events due to the nature of the participant group being studied. The participant group are regular users of healthcare resources and may be frequently referred to specialist services or undergo investigational tests. Current mental health illness and previous trauma are prevalent in patients with Persistent Physical Symptoms, and there is some potential for the intervention to temporarily exacerbate mental distress. However in our previous feasibility study we found no major unexpected changes in physical or mental health [19].

9.1 Definitions

Adverse event (AE)
A standard definition of an AE is "any untoward medical occurrence in a study participant".

The MSS3 patient population – who by definition have multiple symptoms and at least moderate healthcare use - are likely to experience many 'medical occurrences'. It is difficult to identify which medical occurrences are 'untoward' but fall short of the serious adverse event criteria. The multiple and complex symptoms of this population mean that the link of causality between the intervention and the event will be difficult to interpret. In addition, due to the data collection

methods employed in the trial, we anticipate differential identification of adverse events between arms, as those attending the symptoms clinics will be having regular contact with a GP over the first months of the trial. We expect any non-serious adverse events reported via participant-completed questionnaires or contained in GP records to be less reliable than those collected by the ER-GP and contain incomplete information.

For this study we therefore consider the collection of all non-serious adverse events both problematic and of limited utility. We will therefore only collect the following AEs:
(a) significant exacerbation of mental distress defined as a PHQ-9 score of 20 or more and/or a score of 2 or 3 on question 9 (suicidality item), representing at least a 1 point score change (i.e a change from 2 to 3 from their previous measure)
(b) self-harm, which may be identified by the ER-GP during consultations or where volunteered by the participant to a member of the research team or through review of medical notes
(c) any emerging serious mental illness or substance use disorder identified after randomisation

Serious Adverse Event (SAE)

An SAE is an event that:

(a) results in death;

(b) is life-threatening* (subject at immediate risk of death);

(c) requires hospitalisation or prolongation of existing hospitalisation**;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect

(f) is otherwise considered medically significant by the investigator***

* 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Expected SAEs

Serious adverse events that are expected or have the potential to be experienced by the patient population: (a) diagnosis of cancer, (b) diagnosis of a serious medical condition, (c) admission to hospital with an exacerbation of persistent physical symptoms [1](d) self-harm (resulting in hospitalisation or otherwise meeting the definition of a serious adverse event); (e) suicide attempt; (f) death from suicide.

Related Unexpected SAEs

These are SAEs that have not been listed in this protocol as expected and are suspected to be "related" to any aspect of the research procedures.

9.2 AE and SAE identification

There a number of routes through which an AE or SAE may be identified, these include:

- Participant self-report
- Health resource use data collection
- ER-GP identification

Participant Self-report

Self-report questionnaires will be collected at baseline, 13 weeks, 26 weeks and 52 weeks post randomisation. The PHQ-9 will identify exacerbation of mental distress and current suicidal thoughts. If a patient scores 3 on question 9 of the PHQ-9 at baseline then they will not be randomised in to the study and the suicide protocol will be triggered. This can be triggered at any point during the study if a score of 3 is identified and the event will be reported as an AE. The health resource use questionnaire will include questions about A&E attendance and hospital admissions.

Whilst it is unlikely that participants will report SAEs between data collection points they will be provided with contact details of the CTRU research team on which they can contact to inform them of an event.

Self-reported SAEs will be flagged to the Trial Manager (or delegated member of staff in the absence of the Trial Manager). The patient completed PHQ-9 and SAE data will be monitored by the CTRU research team to allow efficient identification and reporting of events. Where an event has been identified by the CTRU research team but more information is required they will contact the participant (by telephone in the first instance) to obtain more detailed information about the event.

[1] E.g. Abdominal pain admission in a patient with Irritable Bowel Syndrome or a neurological admission in a patient with functional neurological symptoms.

ER-GP identification

During a Symptoms Clinic consultation an ER-GP may identify an AE or SAE through the participant's account of recent clinical events or through their expressed concerns. ER-GPs will use their clinical experience to assess and manage changes in patients' clinical conditions, working within the policies of the study.

If the ER-GP has a concern for the mental distress of a participant they will administer the PHQ-9 to determine if the participant meets the threshold for an adverse event.

The ER-GP will be trained in what constitutes an AE and SAE.

Health resource use data collection

Health resource use will be collected from medical notes by the research team after the final outcome assessments have been completed at 52 weeks. All health resource contacts will be collected at this time point, including GP appointments, out-patient appointments, accident and emergency attendance, in-patient events and service contact or attendance such as NHS 111 and out of hours or walk in centre.

Any of the above events which result in a hospital admission, and have not previously been identified through patient report or ER-GP identification will be reported as an SAE.

9.3 Reporting procedures

AEs as defined in this protocol will be recorded on the study database.

All SAEs will be reported to CTRU within 1 working day of identification on the standard reporting document. If a full clinical assessment cannot be made at that time it should still be sent to CTRU and an assessment made as soon as feasible and forwarded to CTRU. The local PI and/or CI, in collaboration with the ER-GP (where the event has been identified during a Symptoms clinic consultation) will assess SAEs for relatedness and expectedness.

All SAE report forms will be stored in the Local Site File and Trial Master File. SAEs will be reported in the periodic safety reports to the REC, TSC and DMEC.

Reporting Related Unexpected SAEs
Suspected Unexpected SAEs related to the intervention will be reported to the REC within 15 days of being reported to the CTRU, using the HRA safety report form for non-CTIMPs.

10. Ancillary sub-studies

10.1 Economic evaluation

We will complete a cost-effectiveness analysis of the Symptoms Clinic plus usual care compared to usual care alone. The cost-effectiveness analyses will be based on resource use and outcome

data collected during the trial. This will take the format of a within-trial cost-effectiveness analysis and use a cost-utility framework in order to estimate cost per Quality Adjusted Life Years (QALY).

The effects of the intervention will be estimated as gain in QALYs at 12 months using health related quality of life data collected at baseline, 13, 26 and 52 weeks and the area under the curve method. Published UK tariffs will be used to convert these data to quality of life weights.

We will measure quality of life for this analysis using the EQ-5D-5L and the SF-6D. In addition we will also use the newer ICECAP measure in order to examine their relative responsiveness to change in this patient population.

Data from GP electronic records in the 12 months after randomisation will be collected and used to estimate health care resource use costs. We will also administer a self-reported healthcare resource use questionnaire; this data will be used In the event that participant medical records cannot be obtained.

The data to be extracted include:

- GP contacts (excluding those specifically for chronic disease management or preventive care),
- diagnostic tests (e.g. blood tests, imaging),
- referrals to specialists in physical and mental health including psychologists,
- prescription for psychotropic and pain-related medications.

This data will be extracted directly on to the CRF which will detail the order and level of detail required from the patients' electronic medical records. The CRF will standardise the data being collected across the sites and reduce the risk of the outcome assessor becoming unblinded to the treatment arm until the final stages of outcome data collection.

Use of health care resources will be valued and the associated costs estimated by assigning unit costs from standard published UK sources. The costs related to the intervention delivery will be estimated using trial records and will take into account:

- face-to-face/video consultation clinic time,
- clinic-related administration (letters, appointments, etc.),
- clinician training,
- clinical supervision.

10.2 Process evaluation

We will conduct three nested observational studies:

Analysis of consultation content

Approximately 30% of consultations will be transcribed and available for analysis. These will be used to examine the intervention content using the classification of consultation content, explanations and response to explanation which we have developed from the preliminary studies [16, 27, 28]. We will use this data to conduct exploratory analysis relating explanation type, content and negotiation to patient outcomes in order to develop better understanding of the mechanisms by which the intervention affects outcomes.

Qualitative study of processes of change within patients
We will conduct semi-structured interviews with a purposive sample of 20 participants at different stages of the intervention. These will be analysed thematically, recognising that there are likely to be changes in intra-personal understanding and interpretation (for which an interpretive phenomenological approach is likely to be valuable) and inter-personal or social understanding and interaction. We will pay particular attention to patients' views on what aspects of the Symptoms Clinic were particularly valuable to them and how these translated into perceived changes in thoughts, behaviours and symptoms.

Stakeholder study of clinic delivery
The patient interviews will be supplemented by professional stakeholder interviews including GPs delivering the intervention, investigators providing supervision to the GPs, local commissioners and GPs from practices whose patients had taken part. Interviews will examine acceptability of the clinic concept and processes, skills learned and knowledge transferred value for GPs and perceived value to patients.

Conduct of the process evaluation
The process evaluations will be conducted by the research fellow. Supervision of this work will be handled by investigators: specifically, Dr Sanders (consultation content), Professor Greco (patient interviews), and Professor Rowlands (stakeholder interviews). Towards the end of the process evaluation we will bring the separate process evaluation strands together in order to identify key lessons for future implementation.

Relationship between process evaluation and intervention delivery
Recent MRC guidance on process evaluation highlights the importance of considering the relationship between process evaluation and intervention delivery[27] including whether the process evaluation is allowed to inform the intervention or the two are independent of each other. For this study we will permit information to flow from the process evaluation to the intervention during the first three months of the Symptoms Clinics. These can be considered as the time of professional learning curves for both the GPs delivering the intervention and for the supervising investigators. During this time, we will permit early lessons to be learned and shared. After three months, the process evaluations will be conducted in relative isolation from intervention delivery in order to maintain intervention fidelity.

10.3 PROMETHEUS in MSS3

Data from an embedded sub-study will contribute to a programme of research funded by the Medical research council (MRC) to expand the evidence base on an important issue concerning the recruitment of participants to trials. The embedded sub-study ('PROMETHEUS in MSS3') aims to evaluate the impact on participant recruitment of a pen incentive and a brief participant information sheet. This will be implemented using a factorial embedded randomised controlled trial design. Each patient being invited into MSS3 will be randomised to one of the following: 1) A pen with the trial logo printed on, in addition to the standard trial invitation materials; 2) A pen with the trial logo printed on, in addition to a brief PIS, and the standard trial invitation materials; 3) A brief PIS, and the standard trial invitation materials; 4) The standard trial invitation materials alone. We will evaluate whether receiving the

pen incentive and/or brief PIS is associated with higher levels of recruitment into MSS3. The full protocol for PROMETHEUS in MSS3 is attached as Appendix 2.

11. Trial supervision

The NHS Sheffield Clinical Commissioning Group will act as sponsor for the trial. Three committees have been established to govern the conduct of the study: the TSC, the Trial Management Group (TMG) and the DMEC. These committees will function in accordance with Sheffield CTRU standard operating procedures.

11.1 Trial Steering Committee

The TSC consists of independent clinicians (including an independent Chair as required by Sheffield CTRU), an independent statistician, an independent health economist and a PPI representative. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals as outlined in the TSC terms of reference. The TSC can prematurely close the trial following advice from the sponsor, funder, DMEC or TMG.

11.2 Trial Management Group

The TMG consists of the CI, other site PIs, collaborators and staff from CTRU. The CI will chair the meetings at regular intervals as agreed by the group and will oversee the day to day implementation of the trial in accordance with the terms of reference.

11.3 Data Monitoring and Ethics Committee

The DMEC consists of an independent statistician and two independent clinicians. The DMEC will work in accordance with an agreed Charter, reviewing reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. No formal interim analyses and stopping guidelines are set in advance but the DMEC can request that an interim analysis is performed.

11.4 Local Advisory Groups

We will convene local advisory panels at each centre including at least local investigator(s), a local GP commissioner, a patient partner and at least one of the locally trained GPs delivering the intervention. These panels will each meet 3 times during the study and will be tasked with identifying local successes, problems and solutions in delivering the intervention both in order to ensure the smooth running of the study and to inform future implementation. Information from them will be included in the process evaluation.

12. Data handling and record keeping

Data management will be provided by the University of Sheffield CTRU who adhere to their own SOPs relating to all aspects of data management including data protection. Data quality is the responsibility of the Sheffield CTRU Trial Manager and the CTRU Data Management Team. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP DM009 and a Monitoring plan will ensure the quality of the data in accordance with SOP QA001.

Participant confidentiality will be respected at all times. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties. All participants will be assigned a unique study ID number to identify them on all data collection forms and to link all of the clinical information held about them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Data entry will be completed by the research team at the central office or by delegated members of the team at participating centres. Data will be entered onto a bespoke study database residing on Prospect, CTRU's in-house web-based data capture system, hosted on University of Sheffield servers. Prospect uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS.

Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature will be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data: only members of the research team who are responsible for contacting participants (for example, to send out follow up questionnaires or arrange a symptoms clinic appointment) will have access to participant names and contact details.

Verbal consent and Symptoms Clinics consultations will be audio-recorded on to a dictaphone and then transferred to the access-restricted folder on the University's networked filestore following completion of the enrolment appointment or Symptoms clinic session. Once it is stored on the network drive the recording must be securely erased from the dictaphone. If the dictaphone needs to be taken away from the primary care facility for any purpose prior to transferring the file, an encrypted dictaphone must be used to record the consultations.

Original CRFs will be retained in an investigator site file. Patient identifiable data on CRFs may need to be transferred between the research site and the CTRU in order to perform data entry, undertake monitoring activities or if secure storage is not available at the research site. Data will be transferred via post (recorded delivery for sensitive data) or secure electronic transfer. Participant consent will be obtained for this transfer of data.

Study records will be stored for a period of 6 years after the completion of the trial before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived at site during the retention period and information supplied to the Chief Investigator.

13. Data access and quality assurance

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained.

The data management system described in section 11 provides validation and verification features which will be used to monitor study data quality, in line with CTRU SOPs and the DMP. Discrepancy reports will be generated to show where data clarification is required. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

A DMP and Site Monitoring Plan will detail the level and type of monitoring required to ensure the quality of data and compliance with study procedures as detailed in SOPs DM009 and QA001.

14. Publication

The MSS3 publication policy will be adhered to for all publications.
Dissemination will be undertaken through peer reviewed scientific journals and clinical and academic conferences. We will also ensure regular dissemination to the patient groups and provide periodic project bulletins to interested parties via the study website. No report, either verbal or written may be made without the approval of the core publications group. A publications policy will describe the process for approving papers and how authorship will be determined.

The study team are obliged, by the terms of its contract, to notify the NIHR HS&DR programme of any intention to publish the results of NIHR funded work at least 28 days in advance of publication in a journal. This also applies to public oral and poster presentations. The TSC will be also be notified of publications which report the final output of the study

15. Finance

The study has been funded by the National Institute for Health Research's (NIHR) Health Service and Delivery Research (HS&DR) programme and the details have been drawn up in a separate agreement.

16. Ethics approval

Ethics approval will be obtained for the trial including approval of the protocol, all informed consent forms, and information materials to be given to the participants prior to initiation at sites. Any further amendments will be submitted and approved by the REC. The CTRU research team will communicate these changes to investigators and participating sites.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

17. Regulatory approval

This study will be submitted for approval by to the local CRN participating practices. The Statement of Activities will be approved by the HRA and used by sites to confirm their capacity and capability to undertake the research.

18. Indemnity / Compensation / Insurance

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this research project. In addition the investigators supervising the symptoms clinic delivery and the ER-GP will have medical malpractice/clinical negligence insurance or indemnity cover in place.

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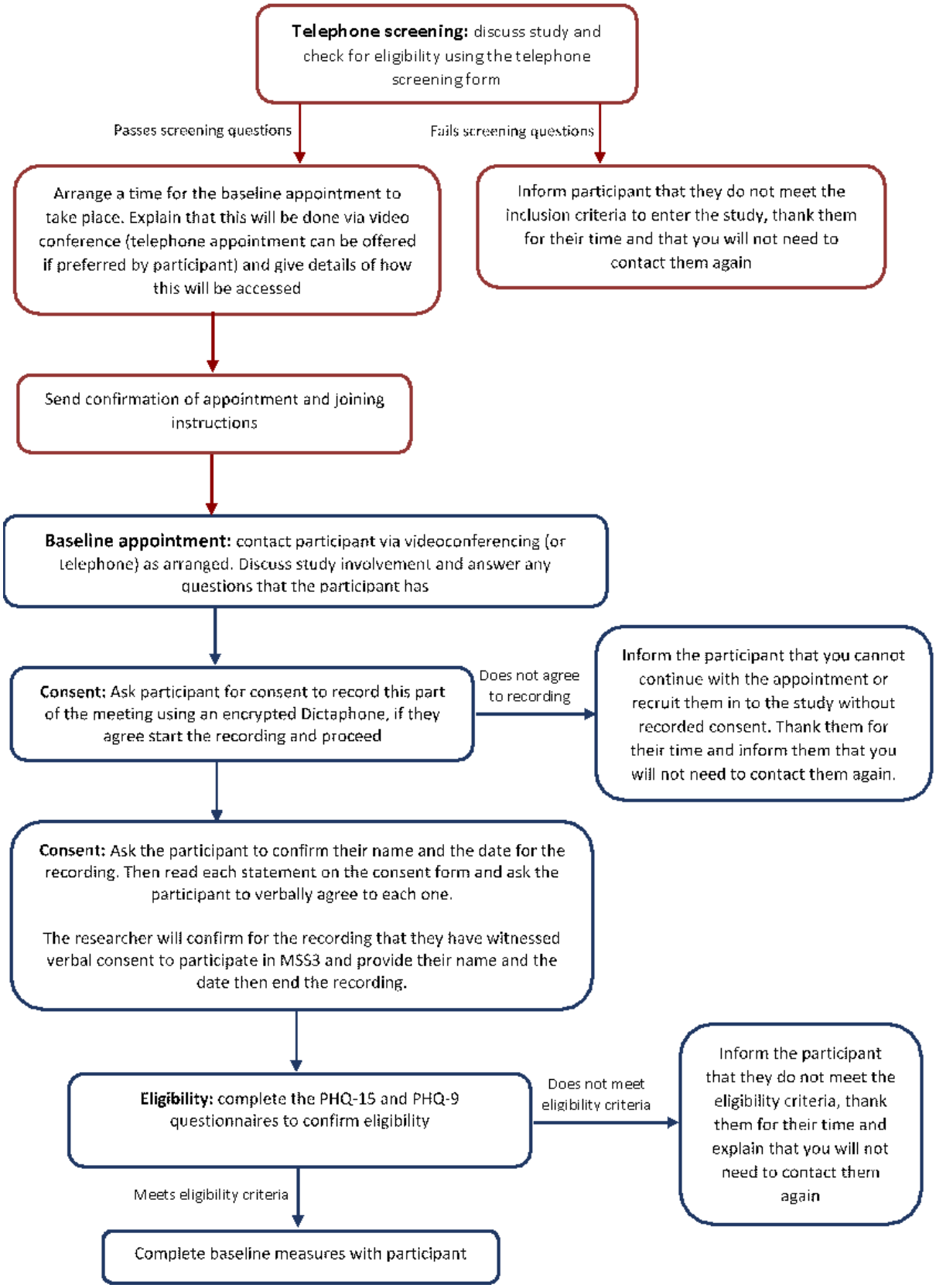
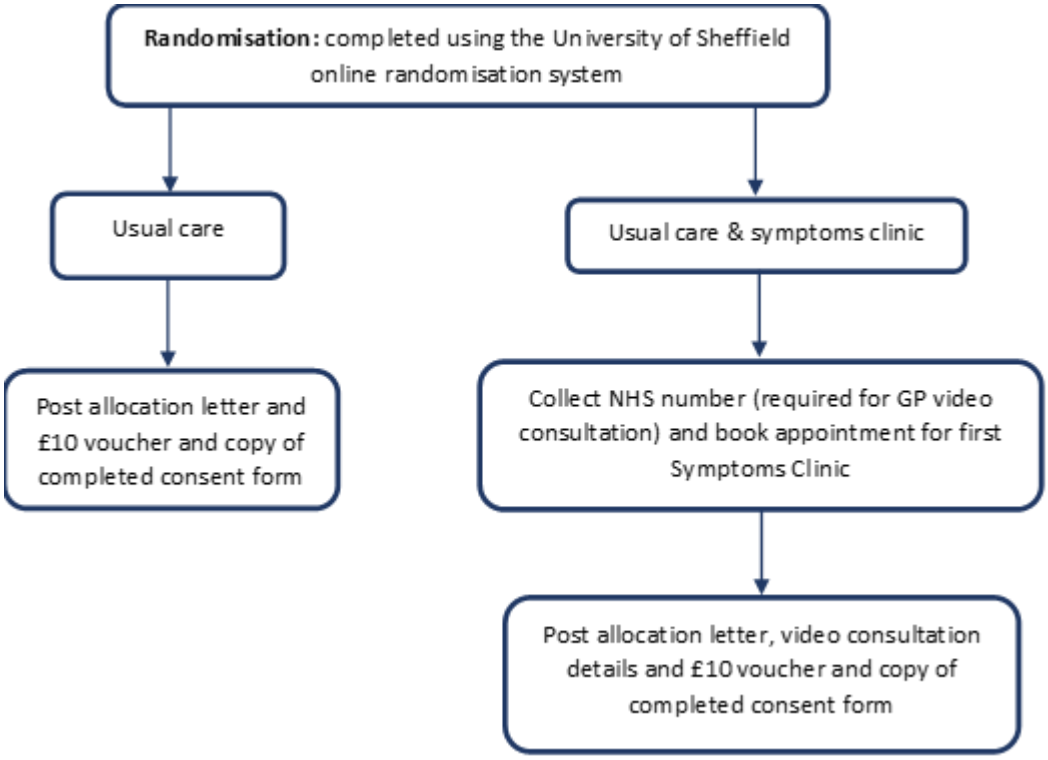
20. Appendix 1

MSS3 Screening and remote consent process




Randomisation: completed using the University of Sheffield online randomisation system
Usual care
Usual care & symptoms clinic
Post allocation letter and £10 voucher and copy of completed consent form
Collect NHS number (required for GP video consultation) and book appointment for first Symptoms Clinic
Post allocation letter, video consultation details and £10 voucher and copy of completed consent form

Appendix 2

PROMETHEUS in MSS3: What is the impact on recruitment of a pen incentive and a brief participant information sheet? A factorial embedded randomised controlled trial

SWAT Intervention: 1) Pens (SWAT 37); and 2) and brief participant information sheet (To be registered on SWAT database)

Host trial name: Multiple Symptoms Study 3 (MSS3): pragmatic trial of a community based clinic for patients with persistent (medically unexplained) physical symptoms

Host Trial Start date: 1st February 2018

REC application submission date: 1st May 2018

Participant recruitment start date: 1st October 2018

Protocol version: 4.0

Background

The need for evidence based recruitment interventions

Randomised controlled trials are crucial for evidence based healthcare. Despite substantial amounts of money being invested by funders in the UK and internationally, many trials fail to recruit on time and to budget. The latest estimates show that only 56% of trials achieve their planned sample size (1); the costs of poor recruitment can be huge (2). This constitutes significant research waste (3,4). Other consequences of poor recruitment include sampling bias, reduction in statistical power, delays in the generation of evidence and the subsequent adoption of effective interventions, as well as in some cases the continued use of interventions that are ineffective and/or harmful to patients. Many strategies are used by trialists to improve recruitment; however few such interventions have been rigorously evaluated in real-life trials (5,6). A priority setting exercise placed recruitment as the top priority for methodological research (7).

Trials embedded in real-life, ongoing 'host' trials (also known as 'Studies within A Trial' [SWATs]) are the most robust way of evaluating interventions for improving participant recruitment and retention in trials. However, common recruitment strategies have a largely low-quality evidence base. There are many uncertainties about the effects of different recruitment strategies and the use of some (and, conversely, the non-use of others) is adding to waste in research (4).

The PROMETHEUS programme, funded by the Medical Research Council (MRC), is designed to identify effective and cost effective methods to improve recruitment to and retention in trials, and to identify if it is possible to routinely embed this activity in trials, using SWATs. The aim of PROMETHEUS is to make embedding SWATs standard practice across multiple clinical trials units and centres undertaking trials.

The interventions

Pen incentives

There is some evidence that using a pen as a nonmonetary incentive increases response rates and time to response for trial follow-up questionnaires (6,8). The theoretical basis underlying the use of pen incentives is that of *reciprocation*, where people feel obligated to respond with positive behaviour received, with positive behaviour in return (9–12). In the context of trial recruitment, offering a potential participant a gift such as a pen may make the person more likely to take up the trial invitation to enrol. It is also possible that the convenience of having a pen to hand upon receipt of the invitation may increase the likelihood of the forms being completed. One trial in the U.S. embedded in an observational study, showed that including a pen with the study logo to a

questionnaire mailed to women who had previously not responded significantly improved recruitment rates (13). However to our knowledge, there have been no trials which have evaluated the impact of using a pen to increase recruitment.

Brief participant information sheets

A common method of recruiting participants from general practices and other registries into trials is to send letters to potentially eligible patients inviting them to participate in the trial, along with the trial Participant Information Sheet (PIS). However PISs are lengthy, and increasingly complex - often about 8 pages long (14). There is a hypothesis that being asked to read such a large document in one go may act as a deterrent to potential participants becoming involved in the research (15). A shorter PIS may be more appealing to patients initially as it is likely to provide more manageable volume of information, which may encourage more potential participants to contact the trial team to be screened and subsequently recruited into the trial (15). The latest Cochrane review of recruitment interventions identified two trials that have evaluated a brief PIS compared with a full PIS (5,15,16), and found the brief PIS makes little or no difference to recruitment compared with a full PIS. RD = 0% (95% CI = -2% to 2%); GRADE: moderate. However, it would be useful to replicate this trial in a SWAT in different populations, in order to end uncertainty about whether to use a brief or standard PIS when initially contacting participants to invite them into a trial.

SWAT aims

This SWAT aims to evaluate the effectiveness and cost effectiveness of a brief PIS (provided in addition to a standard length PIS), with or without the addition of a trial logo branded pen on recruitment and response rates in the Multiple Symptoms Study 3 (MSS3) host trial.

Methods

MSS3 is acting as a host trial in PROMETHEUS. This protocol details the work that will be undertaken for PROMETHEUS in MSS3. An embedded factorial randomised controlled trial design will be used to evaluate the effectiveness of a brief PIS (provided in addition to a standard length PIS), with or without the addition of a pen branded with the trial logo on recruitment of participants. The general methodology of the SWAT will be guided by methodology developed and published by the MRC-funded START programme (17). To assist with final reporting, this protocol is written in line with the guidelines for reporting embedded recruitment trials (18).

The MSS3 host trial

MSS3 aims to recruit 376 patients with persistent physical symptoms from 120 general practices in the UK. Persistent physical symptoms, which are disproportionate to biomedical disease affect

around 1 million people (2% of adults) in the UK. These 'medically unexplained' symptoms (MUS) cause distress to patients and account for over one third of referrals to specialists. Although most persistent symptoms can be explained, many patients do not receive adequate explanations for their symptoms.

The MSS3 team have rigorously developed the Symptoms Clinic treatment model, to focus on explaining symptoms and guide self-management. In preliminary studies it was acceptable to patients and showed promising results.

The MSS3 trial aims to examine the effectiveness of a Symptoms Clinic Intervention (SCI) by conducting a pragmatic trial to test the primary hypothesis that compared to usual care alone, the Symptoms Clinic plus usual care leads to a clinically meaningful improvement in patients' symptoms. Potential participants aged 18-69 will be recruited from GP practice lists. Patients will be randomised to receive the Symptoms Clinic plus usual care or usual care alone. The SCI comprises extended psychologically-informed medical consultations. Patients receive an initial 50 minute consultation and 2-3 follow ups of 20 minutes. Clinic doctors explain symptoms as understandable bodily processes, and aim that patients feel understood and more able to self-manage.

The primary outcome will be symptoms (PHQ15) at 52 weeks after randomisation. Secondary outcomes will include healthcare use over 52 weeks, symptoms at 13 weeks and quality of life at 13 and 52 weeks. Outcomes will be analysed on an intention to treat basis. Pre-specified content analysis of consultations and interviews with selected patients and stakeholders will inform detailed process evaluations. Within-trial cost-effectiveness analysis will estimate cost per QALY.

Recruitment to the MSS3 host trial

Potential participants will be identified from approximately 120 GP practices acting as Participant Identification Centres (PIC) across research sites in Sheffield (and surrounding areas), Manchester, Gateshead/ Newcastle and Doncaster. PIC sites will be recruited through local CRNs and Sheffield CTRU. A three-stage identification process will be adopted using computer searching, GP record screening and postal questionnaire.

Stage 1: The GP PIC sites will complete a computer search on the practice clinical system to identify patients whose records include: (a) at least one code for an MUS syndrome (e.g. irritable bowel syndrome, fibromyalgia) or at least two codes for negative investigations (e.g. CT Scan normal); (b) at least 2 referrals for specialist opinion or diagnostic investigations in the last 3 years; (c) no codes to indicate serious disease (e.g. cancer, coronary heart disease, inflammatory or connective tissue

disease) which might account for a substantial number of symptoms; (d) repeat prescriptions for Irritable Bowel Syndrome medication in last year.

Stage 2: Once the computer search has produced a list of patients a GP at the practice will screen the patient names (and where necessary their medical records) to exclude any patients with major medical conditions causing their symptoms which were not picked up on search and those for whom invitation by the practice may be inappropriate.

Stage 3: The standard recruitment pack will be posted to potential participants by their general practice. All those invited will receive: (1) an 'invitation to participate' letter, printed on the practice headed paper, (2) a standard length PIS (Appendix B outlines the standard length PIS), (3) an 'expression of interest' form, (4) a PHQ-15 questionnaire, and (5) a prepaid envelope addressed to Sheffield CTRU. Interested patients will return an expression of interest form and completed PHQ-15 to Sheffield CTRU, who will screen the PHQ-15 for eligibility.

Approximately three weeks after the initial mailing the GP practice will send a reminder letter to participants that have not yet responded.

Inclusion criteria – MSS3:

1. Aged between 18 – 69 years (inclusive) at the time of the computer search
2. Current physical symptoms which meet the below criteria
    a. clinical records suggest MUS (presence of at least one code for an MUS syndrome or at least two codes for negative investigations)
    b. records show at least 2 referrals for specialist opinion or diagnostic investigations in the last 42 months
    c. records show no evidence of any previous or current major illnesses likely to cause multiple symptoms
    d. doctors in the GP practice do not believe that the majority of the patient's symptoms can be currently explained by other pathology;
    e. the score on the self-completed PHQ-15 symptoms scale is between 10 and 20 (inclusive)

3. Access to a mobile phone with video calling capability or an email address and computer with video conferencing capability (Capability requirements are: microphone, camera and internet connection)

Exclusion criteria – MSS3:

1. A score of 3 on question 9 on the PHQ-9 completed at the baseline appointment
2. Difficulty conducting a healthcare consultation in English without either a professional or family interpreter or other assistance (either indicated in GP records, or becoming apparent during the enrolment and consent process)
3. The GP regards inviting them to participate as inappropriate (e.g. recent bereavement)
4. Severe symptom-related disability (e.g. requiring help with daily personal care or severely impaired mobility)
5. Currently undergoing active multidisciplinary rehabilitation or specialist psychological treatment including specialist pain, fatigue or other symptom clinic.
6. Currently pregnant or less than 6 months postnatal at the time of the screening telephone call

Following stages 1-3, the details of interested and potentially eligible patients will be passed on to a local research nurse who will contact the patient to discuss the study further, answer any questions from the patient and discuss a timetable for further participation. If a potential participant wishes to proceed, the research nurse will complete screening checks by enquiring directly about the exclusion criteria relating to personal care, active multidisciplinary rehabilitation, and current specialist psychological treatment. They will also ensure that the participant has access to the appropriate facilities to attend video consultations as required for delivery of the Symptoms Clinic intervention. When discussions are complete the researcher will make an appointment with the patient for study enrolment. If the patient wishes to have more time to consider participation then a second phone call can be arranged. Appendix A outlines the flow of participants in MSS3.

Trial design: the factorial recruitment SWAT

Recruitment into the SWAT is planned to occur between October 2018 and November 2019 until recruitment into the MSS3 host trial ceases. The SWAT will adopt a factorial design, with patients randomised to one of four interventions. Potential participants invited by post to take part in MSS3

will receive the full contents of the standard recruitment pack (described at Stage 3 above), with the addition of the following:

- **Intervention 1**: A pen with the trial logo.
- **Intervention 2:** A pen with the trial logo and a brief PIS (provided in addition to the standard length PIS).
- **Intervention 3:** A brief PIS (provided in addition to the standard length PIS).
- **Intervention 4:** The standard contents only – no additional interventions.

A code will be added to each expression of interest form identifying which of the above interventions were included in the pack.

Reminder letters sent to patients who have not responded within three weeks of the initial mail-out will be labelled as such to allow the research team to identify which replies have been returned as a result of the reminder letter. Reply forms returned from the reminder letter will not be included in the SWAT analysis.

Inclusion and exclusion criteria– The SWAT

The SWAT will include all patients identified as potentially eligible for the MSS3 trial: there are no additional inclusion or exclusion criteria.

The recruitment interventions

The control intervention – the standard length PIS

The standard length PIS (Appendix B) was developed by the MSS3 host trial team, based at Sheffield CTRU, following National Research Ethics Service (NRES) guidance and will be reviewed by an NHS REC as part of the ethics application for the MSS3 study. The content of the PIS includes; general information about the purpose of the trial, how and why the participant might be involved, key trial concepts, such as randomization, the interventions being tested, and the potential risks and benefits of those interventions, participant's right to withdraw, trial team contact information, confidentiality information, and details on who is funding and monitoring the research. The information has been reviewed by the patient representative member of the MSS3 Trial Management Group and will also be reviewed by the Trial Steering Committee which also includes a patient representative. The standard PIS is 6 A4 pages in length. The accompanying GP invitation letter, the expression of interest form and the PHQ-15 will all be on single A4 sheets (Appendix D).

The brief PIS

The brief PIS will consist of an A4 sized sheet printed on high quality paper in colour and folded into three, in a leaflet style. It has been designed to provide a more succinct and easy to read summary of the MSS3 trial than the standard PIS. The information has been reviewed by the patient representative on the MSS3 Trial Management Group. It will be provided alongside the standard PIS in the recruitment pack. The invitation letter will explain that the brief PIS is there in order to provide the patients with a summary of the research in order to decide if they might be interested in participating and that the standard PIS provides more details should they wish to read this before returning the form, but that they will have the opportunity to discuss the study with a nurse and ask questions later.

Appendix C is the brief PIS.

The pen intervention

The pens will be branded with the MSS3 "brief" logo and colours (see below). The pens will be black ink, of a good standard (mid-price) and similar to those used previously as promotional items on clinical trials managed by Sheffield CTRU.

Randomisation

The type of intervention included in each invitation pack (whether a brief PIS and/or a pen is to be included or not) will be determined by random allocation. Patients will be randomised in a 1:1:1:1 ratio, stratified by GP practice. Block randomisation with random varying block sizes will be used, with the block sizes being determined by a statistician and not shared with other researchers. The allocation lists will be generated by a CTRU statistician and shared only with the CTRU staff preparing the invitation packs, who will be independent of the CTRU staff who will process the invitation responses. All recruitment materials will be placed in envelopes which will be pre-stamped, ready for the practice to post out to patients. The packs will be placed in order of the random allocation list and then numbered sequentially before being sent to the practice. By numbering the packs, the researcher will have a record of which interventions are in each pack, which will enable the trial team to monitor if packs are sent out in the correct randomised order.

Practice staff will be informed to label the recruitment packs with patient addresses in the sequential order that the researcher had placed them in. Patients will not know that they are part of a trial testing recruitment interventions so will be blind to the SWAT hypothesis. CTRU staff undertaking trial recruitment will be blind to the group to which patients are allocated. It will not be possible to entirely blind practice staff to the interventions as it will be clear that some packs have pens in and some do not.

Outcome measures

Primary Outcome

1. The primary outcome is the effectiveness of the recruitment interventions. This is defined as the recruitment rate, being the proportions of participants in each intervention group who are randomised into the host trial.

Secondary Outcomes

1. The proportion of patients in each intervention group who return an expression of interest form
2. The cost-effectiveness of the interventions for each host trial
3. The proportion of patients who return an expression of interest form but do not go on to be randomised due to a) ineligibility or b) non-consent, according to each intervention group
4. The time taken to respond to an invitation to participate in MSS3

Statistical methods

Sample size calculation

The sample size calculations for the MSS3 trial have been outlined in the main trial protocol. As is usual with a study within a trial, we did not undertake a formal power calculation to determine the sample size (19), since the sample size is constrained by the number of patients being approached in the MSS3 host trial. The sample size will therefore be the total number of patients invited into the MSS3 trial. Based on response rates achieved in two preliminary studies we estimate we will need to invite 4888 patients in order to recruit 376 to the trial, representing a recruitment rate of about 8%. This would provide 80% power to identify a 3% difference between the groups in recruitment rate if one existed. A simple multiple comparison adjustment was applied, using a significance level of 2.5%, which would allow us to test both interventions.

Statistical analyses

Analyses will be conducted on an intention to treat basis, including all randomised participants identified from the initial invitation letter on the basis of the groups to which they were

randomised. Reply forms returned following the reminder mail out will not be included in the analysis. Analysis will be conducted using 2 sided significance tests at the 5% significance level. For analysis of the primary outcome, logistic regression will be used to produce odds ratios and their associated 95% confidence intervals and p-values. Cost effectiveness will be presented as a cost-per-additional recruited participant.

Results from this SWAT will ultimately be combined in a meta-analysis with response rate data from other host trials participating in the PROMETHEUS study.

Anonymised data from MSS3 will be sent to the PROMETHEUS study team in accordance with the PROMETHEUS study data sharing agreement (Appendix E).

Ethical issues

Research Ethics Committee (REC) and Health Research Authority approval for the host trial was sought from Greater Manchester Central Research Ethics Committee on 25th June 2018. This SWAT was submitted as part of the main trial, to enable the recruitment interventions to be implemented in the host trial setting.

Patients will not be informed about this recruitment SWAT and so will not have the opportunity to give informed consent. Patients will therefore be blind to the SWAT allocation. In this case of evaluating whether a pen and/or brief PIS impact on recruitment rates, seeking individual patient consent prior to sending the invitation is not appropriate. This is because it may confuse patients as to what they are consenting to, and may impact on their behaviour if they are aware that different recruitment methods are being tested, confounding the evaluation (20).

SWAT registration

The pen SWAT has been registered on the MRC SWATs database as SWAT 37. The brief PIS will also be registered as a sub-study on the MRC SWATs database.

Financial and Insurance Issues

The SWAT is funded as part of the PROMETHEUS programme, which is sponsored by the University of York. It forms a sub-study to the MSS3 trial, which is sponsored by NHS Sheffield Clinical Commissioning Group.

Project Timetable

Date	Action

27th April 2018	Documentation for the SWAT agreed & signed off
11th May 2018	Submission to REC of application
1st October 2018	Recruitment to the SWAT begins
1st November 2019	Recruitment to the SWAT ends
1st February 2020	Data cleaning and submission of data set to PROMETHEUS team
1st April 2020	Collation of results and analysis, begin write up of trial level paper

Dissemination of research

The results of this SWAT will be published in a peer-reviewed journal to further improve the evidence base regarding effective recruitment strategies in trials. This publication will be led by the MSS3 team, with input from PROMETHEUS members. In addition the data will be included in a meta-analysis of all studies of the same intervention conducted by the PROMETHEUS programme led by the PROMETHEUS team. Dissemination of research findings will be conducted in line with the PROMETHEUS authorship arrangements (Appendix F).

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Appendices

Appendix A: Flow of participants through MSS3

Appendix B: Standard participant information sheet

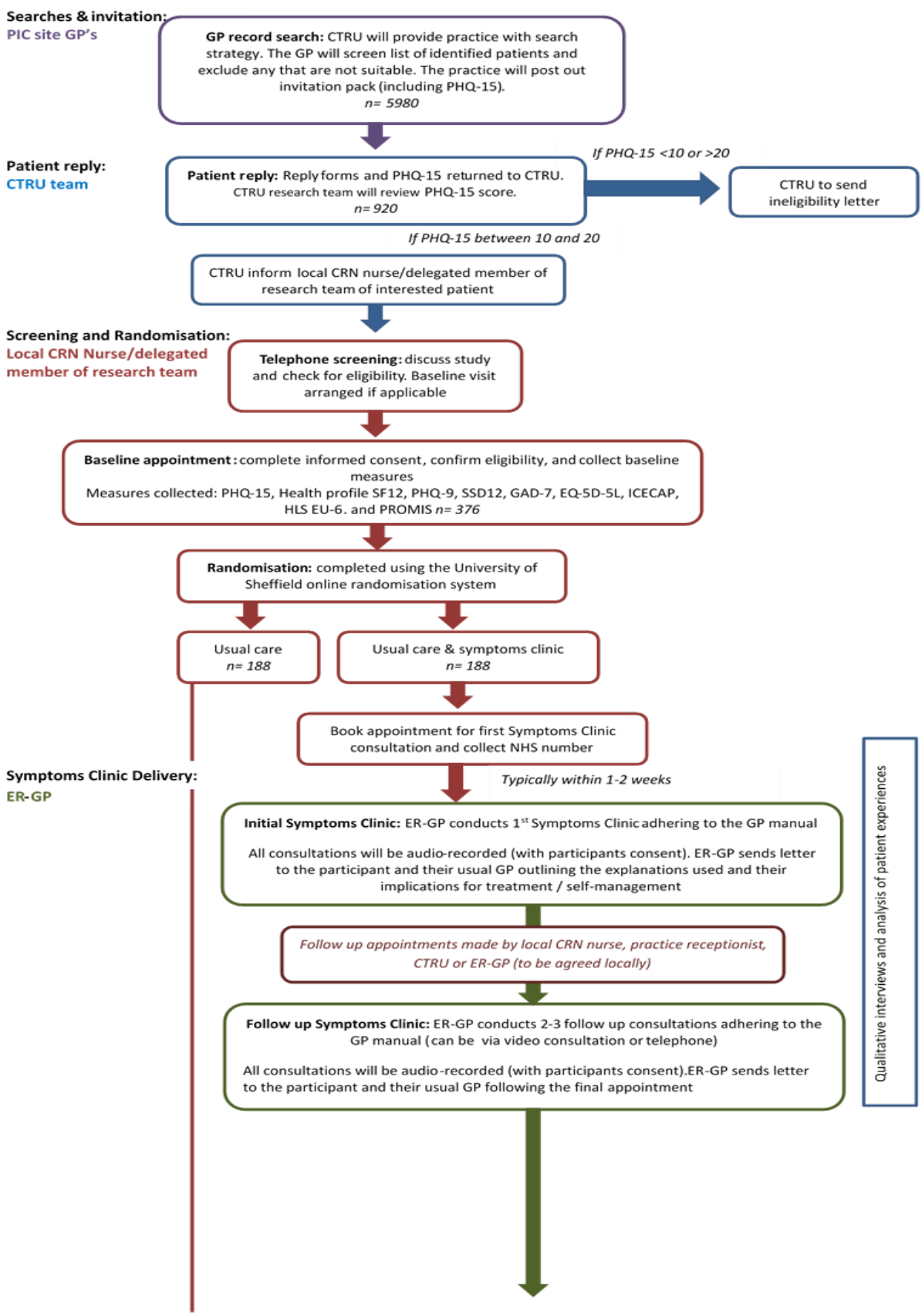
Appendix C: Brief participant information sheet

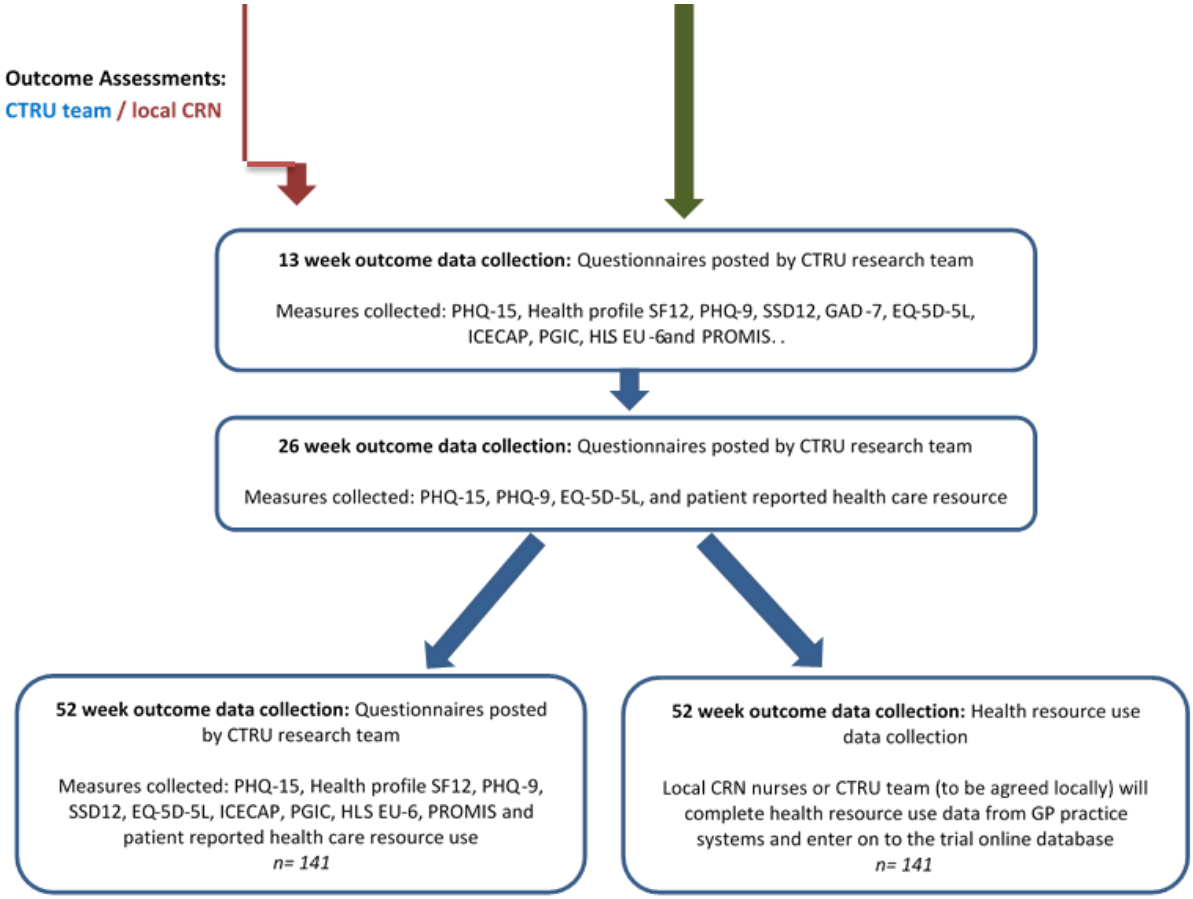
Appendix D: GP invitation letter, the expression of interest form and the PHQ-15

Appendix E: PROMETHEUS Data sharing agreement

Appendix F: PROMETHEUS publications & authorship arrangements

Appendix A: Flow of participants through MSS3


Searches & invitation:
PIC site GP's
GP record search: CTRU will provide practice with search strategy. The GP will screen list of identified patients and exclude any that are not suitable. The practice will post out invitation pack (including PHQ-15).
n= 5980
Patient reply:
CTRU team
Patient reply: Reply forms and PHQ-15 returned to CTRU. CTRU research team will review PHQ-15 score.
n= 920
If PHQ-15 <10 or >20
CTRU to send ineligibility letter
If PHQ-15 between 10 and 20
CTRU inform local CRN nurse/delegated member of research team of interested patient
Screening and Randomisation:
Local CRN Nurse/delegated member of research team
Telephone screening: discuss study and check for eligibility. Baseline visit arranged if applicable
Baseline appointment: complete informed consent, confirm eligibility, and collect baseline measures
Measures collected: PHQ-15, Health profile SF12, PHQ-9, SSD12, GAD-7, EQ-5D-5L, ICECAP, HLS EU-6. and PROMIS n= 376
Randomisation: completed using the University of Sheffield online randomisation system
Usual care
n= 188
Usual care & symptoms clinic
n= 188
Book appointment for first Symptoms Clinic consultation and collect NHS number
Typically within 1-2 weeks
Symptoms Clinic Delivery:
ER-GP
Initial Symptoms Clinic: ER-GP conducts 1st Symptoms Clinic adhering to the GP manual
All consultations will be audio-recorded (with participants consent). ER-GP sends letter to the participant and their usual GP outlining the explanations used and their implications for treatment / self-management
Follow up appointments made by local CRN nurse, practice receptionist, CTRU or ER-GP (to be agreed locally)
Follow up Symptoms Clinic: ER-GP conducts 2-3 follow up consultations adhering to the GP manual (can be via video consultation or telephone)
All consultations will be audio-recorded (with participants consent).ER-GP sends letter to the participant and their usual GP following the final appointment
Qualitative interviews and analysis of patient experiences


Outcome Assessments:
CTRU team / local CRN
13 week outcome data collection: Questionnaires posted by CTRU research team
Measures collected: PHQ-15, Health profile SF12, PHQ-9, SSD12, GAD-7, EQ-5D-5L, ICECAP, PGIC, HLS EU-6and PROMIS. .
26 week outcome data collection: Questionnaires posted by CTRU research team
Measures collected: PHQ-15, PHQ-9, EQ-5D-5L, and patient reported health care resource
52 week outcome data collection: Questionnaires posted by CTRU research team
Measures collected: PHQ-15, Health profile SF12, PHQ-9, SSD12, EQ-5D-5L, ICECAP, PGIC, HLS EU-6, PROMIS and patient reported health care resource use
n= 141
52 week outcome data collection: Health resource use data collection
Local CRN nurses or CTRU team (to be agreed locally) will complete health resource use data from GP practice systems and enter on to the trial online database
n= 141

Appendix B: Standard participant information sheet (over page)

Multiple Symptoms Study 3

Participant Information Sheet

We would like to invite you to take part in the Multiple Symptoms Study 3. Before you decide if you would like to take part, it is important to understand why the research is being done and what it will involve for you. Please read the following information carefully; if anything is unclear or if you would like more information then please do not hesitate to ask us. Please take time to decide whether or not you are willing to take part in the study. Thank you for reading this information.

Important things you need to know

- We want to find out if a new Symptoms Clinic delivered by video consultations is helpful for patients with persistent physical symptoms. By "persistent physical symptoms" we mean symptoms (such as pain, fatigue, or other feelings that your body is not working properly) which are there most days and which interfere with daily life.

- We are recruiting people with persistent physical symptoms to Multiple Symptoms Study 3 which has been set up to test the Symptoms Clinic. People who take part in the study will either be invited to receive video consultations at the Symptoms Clinic as well as their usual care, or will continue with their usual care alone.

- We will ask everyone in the study to complete some questionnaires about their health and its impact on their daily life at the beginning of the study and after 3, 6 and 12 months.

- If you change your mind about taking part in the study, you can stop at any time without having to give a reason.

How to contact us

If you have any questions about this study please contact:

Cara Mooney, Trial Manager
Telephone: 0114 222 4308
Email: multiple.symptoms.study3@sheffield.ac.uk
Address: School of Health and Related Research, CTRU,
University of Sheffield,
Regent Court, 30 Regent Street,
Sheffield, S1 4DA

Why is this study happening?

Many people have troublesome physical symptoms such as pain, fatigue, or feelings that their body is not working properly. Patients often find that doctors and medical tests tell them that they don't have a serious disease, but don't explain why they still have symptoms or what they can do about it.

The purpose of this study is to find out if receiving Symptoms Clinic consultations via video call is helpful for people with persistent physical symptoms. The Symptoms Clinic is a set of consultations with a specially trained doctor. It aims to help people understand their symptoms and find ways to manage them better in order to reduce the impact of symptoms on daily life.

How will the study do this?

This study is a "randomised controlled trial": half the people who join the study will get an appointment for the Symptoms Clinic and half will not. We will ask everyone who joins the study to answer sets of questions about their symptoms and how they affect their daily life. These questions will be asked at the start, and 3, 6 and 12 months later. We will use the results of the questionnaires to decide if the Symptoms Clinic is effective.

How will the study decide who gets a Symptoms Clinic appointment?

Whether you get a Symptoms Clinic consultation or not will be decided by a computer. It uses a process called randomisation (which is a bit like tossing a coin). This means that each person who joins the study has an equal (50/50) chance of being invited to receive the Symptoms Clinic or not. It also means that the research team cannot choose which group you are put into or change the group you are allocated to.

Everyone who joins the study will also be asked to complete each set of questionnaires, whether they are allocated a Symptoms Clinic appointment or not.

What will the study tell us?

The study is designed to provide reliable information for health service planners and managers. It will mean they can decide whether a service like the Symptoms Clinic is helpful and affordable within the NHS.

Who is running this study?

Multiple Symptoms Study 3 is being led by health researchers at the University of Sheffield. We are working in partnership with researchers at the universities of Manchester, Newcastle, Northumbria, Aberdeen and Goldsmiths, London. The study is sponsored by Sheffield Clinical Commissioning Group and has been funded by the National Institute of Health Research, part of the NHS. No commercial organisations are involved in the running of this study or the intervention being studied. The research has been approved by Greater Manchester Central Research Ethics Committee (reference 18/NW/0422).

Why have I been invited to take part?

Your GP practice is involved in the study and their record system has identified you as someone who may have persistent physical symptoms and be suitable for our study. Unfortunately GP records cannot easily identify exactly who has persistent physical symptoms so you may find that this invitation pack doesn't apply to you.

However, if you have physical symptoms which

are there most days and interfere with your daily life you may well be eligible to take part if you wish to.

We are aiming to recruit a total of 376 people to this study from three different areas of England.

Do I have to take part?

No. It is completely up to you whether you take part in the study or not. Should you change your mind then you can withdraw from the study at any point without giving a reason. If you withdraw from the study, we will keep the information about you that we have already obtained but we will not collect any further information. A decision to withdraw or not to take part will not affect the other care you receive.

How can I know if I am suitable to take part?

If you are interested in taking part in Multiple Symptoms Study 3, please complete the enclosed questionnaire and reply slip and return this to the research team in the prepaid envelope provided.

The research team will get in touch to let you know if you are suitable or not. If your answers suggest that you may be suitable to take part, then a member of the research team will contact you (by phone using the number and preferred time you give us) and check if you are eligible to take part in the study by asking you some brief questions.

At this point you will also have the opportunity to ask the researcher any questions you might have about the study. You do not have to enter the study unless you feel completely happy with what you are being asked to do.

What will happen to me if I take part?

If you are eligible to take part and you are happy to proceed with the study the researcher will arrange a study call at a time that suits you. This will be either a video call (which we will set up for you) or an ordinary phone call. You will be sent further instructions on how to attend this. During this study call we will discuss the study further with you to ensure that the study is suitable for you and to confirm that you are happy to take part. If that is the case we will record your consent by asking you to state aloud that you agree to take part in the study. We will keep a recording of this part of the study call so that it is clear we have your agreement. This is similar to asking a person in a face to face meeting to sign a consent form. We will also ask you to complete some more questionnaires.

This study call will take around 1 hour. Near the end, the researcher will use the computer system to carry out the randomisation.

If you are allocated to receive the Symptoms Clinic, the researcher will make your first Symptom Clinic appointment (which will usually be a few weeks later) and will remind you that you should continue to use your usual healthcare as needed. If you are not allocated to the Symptoms Clinic, the researcher will remind you that you should continue to use your usual healthcare as needed.

What happens in the Symptoms Clinic?

The Symptoms Clinic is a set of up to four remote medical consultations designed to help people make sense of persistent physical symptoms (especially if medical tests have been negative) and to reduce the impact of symptoms on daily

life. Consultations will take place remotely (video or telephone call) with a doctor who has had special training for the Symptoms Clinic Intervention.

Your first consultation will last around 50 minutes. This consultation will involve the doctor taking a medical history and finding out about your current symptoms, and how they impact on you. Following this, you will have two or three shorter consultations which will be around 15- 20 minutes.

All consultations will be audio-recorded and some will be transcribed for research purposes. Data will be kept completely confidential - further details of this can be found in the '**What will happen to information you collect about me during the study?'** section of this sheet.

Following the first and last consultations in the Symptoms Clinic Intervention, the doctor will write to your usual GP to summarise the consultations; you will be sent a copy of these letters.

We may also invite you to take part in an optional interview with a member of the research team to find out your views of the Symptoms Clinic intervention.

Will there be any follow up?

Approximately three months after your first appointment when you were entered into the study, the researcher will send you a questionnaire pack; this pack will include similar questionnaires to those you completed for us at that first study call appointment.

The information provided in these questionnaires will help us to know whether the Symptoms Clinic consultations have been helpful. It is really important that this data is collected from those in the usual GP care group as well as those in the Symptoms Clinic Intervention group as it will allow us to compare the groups and look for any differences. We will also contact you at 6 months and 12 months after your first visit to ask you to complete the questionnaires.

At the end of the study we will also look at your medical records to collect information about the number and type of healthcare visits and appointments you have had during the study.

What are the possible risks and burdens of taking part?

Taking part involves at least one video or telephone appointment with our researcher which will last around 1 hour. If you are allocated to the Symptoms Clinic Intervention group it will involve a number of remote consultations with a doctor who will not be your usual GP. There is a small risk that you might find consultations about your symptoms difficult or distressing. In total the four consultations will take around two hours of your time.

As detailed above we will also be contacting you to complete questionnaires at 3 months, 6 months and 12 months after entering the study.

What are the possible benefits?

Some people who took part in our previous studies found that the Symptoms Clinic helped them to make sense of their symptoms and reduced the impact of symptoms on daily life. Taking part will help to give us more information about whether the Symptoms Clinics do benefit people with persistent physical symptoms. You will be offered a £10 high street voucher at the end of your first study call appointment with our researcher and after completing the final study questionnaire as a thank you for your time.

What will happen to information you collect about me during the study?

We will be using information from you and your medical records in order to undertake this study. NHS Sheffield Clinical Commissioning Group is the Sponsor of this study and will act as the data controller. This means that they are responsible for looking after your information and using it properly. NHS Sheffield Clinical Commissioning Group will keep identifiable information about you for 6 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at: https://www.sheffield.ac.uk/scharr/sections/dts/ctru/mss3

We will collect information from you and your medical records for this research study in accordance with the Sponsors instructions. All data obtained in the study will be kept confidential. All information provided by you or recorded by the research team will be identified using a code number and will only be linked together with your name and contact details where the research team at the University of Sheffield, (insert local site) or our specially trained GPs need to contact you about the study, such as to make an appointment or collect follow up data, and to make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

Individuals from Sheffield Clinical Commissioning Group and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in Sheffield Clinical Commissioning Group who will have access to information that identifies you will be people who need to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, or contact details.

We will keep identifiable information about you from this study for 6 years after the study has finished.

All information will be kept in a locked room at the Clinical Trials Research Unit in the University of Sheffield or on secure university networks. Information may also be held at your local research centre which is supporting the study. Members of the research team may need to post your study documents to the University of Sheffield for storage and monitoring purposes. This will be stored in a locked filing cabinet.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

What will happen to the results of the study?

When the study is complete we will present the results in scientific journals and conferences. None of your personal details will be identifiable in any publication or presentation. We will also provide you with a summary of our findings from the study and share this among health professionals and patient groups.

What if something goes wrong?

If you have a concern about any aspect of this study you should contact the Trial manager, Cara Mooney (0114 222 4308). Alternatively you could speak to the Chief investigator Prof. Chris Burton (0114 222 2216). Alternatively you can contact (insert local contact details)

If you are harmed by taking part, or if you are harmed due to someone's negligence, then you may be able to take legal action.

Who can I contact for further information?

If you have any questions about the study or want more details about how you might get involved you can contact the research team on: multiple.symptoms.study3@sheffield.ac.uk

Or any of the details below:

Trial Manager

Cara Mooney
School of Health and Related Research, CTRU,
University of Sheffield,
Regent Court,
30 Regent Street,
Sheffield,
S1 4DA
Tel: 0114 222 4308
Email: c.d.mooney@sheffield.ac.uk

Chief Investigator

Prof. Chris Burton
Academic Unit of Primary Medical Care
Samuel Fox House
Northern General Hospital
Herries Road
Sheffield
S5 7AU

Tel: 0114 222 2216
Email: chris.burton@sheffield.ac.uk

Thank you for taking the time to read this information sheet

Appendix C: Brief participant information sheet

Who are we looking for?

We are looking for people with persistent physical symptoms to take part in this research study.

By "persistent physical symptoms" we mean symptoms which are there most days and which interfere with daily life. These can include:

- Pain, fatigue, or other feelings that your body is not working properly
- Conditions such as IBS, Fibromyalgia, Tension-Type Headache, and Pelvic Pain.

If you have troublesome physical symptoms affecting several parts of your body, you may be suitable to join Multiple Symptoms Study 3.

Why are we doing this?

We have done small studies of the Symptoms Clinic and it seems to be useful to patients. Multiple Symptoms Study 3 will tell us how worthwhile the Symptoms Clinic really is for patients and for health services.

We are doing it as a trial, where only half the people get to receive the Symptoms Clinic because that is the best way to find out how effective a treatment or clinic is.

Who are we ?

We are a group of health researchers, led by a team at the University of Sheffield, with partners in Manchester and Newcastle.

If you have any questions or want more details about how you can get involved you can contact the team on:

multiple.symptoms.study3@sheffield.ac.uk

OR

Trial Manager

Cara Mooney
c.d.mooney@sheffield.ac.uk
0114 222 4308

Chief Investigator

Prof. Chris Burton
chris.burton@sheffield.ac.uk

The University Of Sheffield. | Clinical Trials Research Unit.

NHS Sheffield Clinical Commissioning Group

Multiple Symptoms Study 3

A new 'Symptoms Clinic' for people with persistent physical symptoms.

Participant Summary Leaflet

Funded by the National Institute for Health Research's Health Services & Delivery Research Programme

VERSION 2.0, 09.07.2020

What is the Symptoms Clinic?

The Symptoms Clinic is a set of medical consultations with a doctor who has been specially trained. The consultations will be completed over video call.

We know that many people with persistent physical symptoms feel frustrated that doctors can't explain their symptoms. The Symptoms Clinic is designed to help find explanations for symptoms and to reduce the impact of symptoms on daily life. It aims to help people to:

- ✓ **make sense** of,
- ✓ **adapt** to,
- ✓ and **manage** their

persistent physical symptoms.

What will happen to me if I take part?

EVERYONE who takes part in the study will be asked to have an appointment with a researcher by video call or over the telephone and answer questions about their health.

HALF OF THE PEOPLE who take part will also get remote appointments to receive the Symptoms Clinic. No-one will know whether you are in the half of people who get Symptoms Clinic appointments or not until you have joined the study.

EVERYONE who takes part in the study will still be able to get their usual healthcare.

EVERYONE who takes part in the study will be asked to complete questionnaires about their health and its impact on daily life after 3, 6 and 12 months.

If you want to find out more information about how or why the study is set up, please read the detailed Participant Information Sheet

What do I do now?

If you are willing to take part then **please complete the enclosed reply form and questionnaire** and return these to the research team in the pre-paid envelope provided.

When we have received your reply we will get back in touch with you. If we think you might be suitable for the study, a researcher will arrange to discuss this with you in more detail before you decide whether you want to take part.

We have also enclosed a Participant Information Sheet which gives you more details about what the study will involve.

Appendix D: GP invitation letter, the expression of interest form and the PHQ-15

INSERT GP practice header / study logo

Dear Sir / Madam,

Multiple Symptoms Study 3

We would like to invite you to take part in a research study. The study is looking at the treatment of patients who are affected by persistent physical symptoms. We are working with researchers at the University of Sheffield to help find patients for this study. The practice has agreed to send this letter to you but we have not given your name or other personal details to the research team.

The first stage of this study is to identify people who would be suitable to take part. [*If randomised to standard PIS only:* We have included a participant information sheet which includes more details about what taking part in the study would involve and a questionnaire which will help the researchers to know if the study would be suitable for you.]

[[*If randomised to brief PIS:* We have included a participant leaflet which provides a summary of the research to help you to decide whether or not you would like to take part and a questionnaire which will help the researchers to know if the study would be suitable for you. We have also included a longer participant information sheet which contains more detailed information which you may also want to read.]

If you are willing to take part or think you might be interested, please complete the questionnaire and reply form and post them to the research team in the envelope provided. It is completely up to you whether or not you would like to be involved. You will have the chance to discuss the study in more detail with a member of the research team before making a final decision. Should you change your mind, you can stop taking part in the study at any time without having to give a reason.

If you do not wish to take part, you do not need to do anything, no information about you will go to the researchers and your medical care will not be affected in any way.

Thank you for taking the time to read this letter and enclosed documents. If you wish to make any enquiries or ask any questions about this invitation or taking part in the study then please contact the Trial Manager, Cara Mooney on 0114 222 4308 or you can email the research team on multiple.symptoms.study3@sheffield.ac.uk

Yours sincerely,

[Insert practice name]

The University Of Sheffield. | Clinical Trials Research Unit.

INSERT LOCAL CCG LOGO

Multiple Symptoms Study 3

Reply form: Multiple Symptoms Study 3

Thank you very much for taking the time to reply to our letter of invitation. Please complete the below form including your contact details. Please return your completed form and physical symptoms questionnaire to the research team using the envelope provided.

Acceptance: I confirm that I have read and understand the information sheet for the above study and I am happy for the research team to contact me on the details provided below about taking part.

Full Name _____ Age (in years) ☐☐

Address _____

_____

Postcode ☐☐☐☐ ☐☐☐

Home phone ☐☐☐☐☐☐☐☐☐☐☐ Mobile No ☐☐☐☐☐☐☐☐☐☐☐

Email address _____

The best times to contact me are:

OR ☐ No preference

Sex ☐ Male ☐ Female ☐ Prefer not to answer

How many times have you been to your GP about your symptoms in the past year? ☐ Not at all ☐ Only once ☐ 2 or 3 times ☐ 4 or 5 times ☐ 6 or more times

How many times have you had tests or been to a specialist about your symptoms? ☐ Not at all ☐ Only once ☐ 2 or 3 times ☐ 4 or 5 times ☐ 6 or more times

Signature _____ Date _____

MSS3 Reply form v2.0, 24.07.2018

Practice ID: [insert practice and SWAT randomisation identifier]

PHYSICAL SYMPTOMS (PHQ-15)

During the <u>past 4 weeks</u>, how much have you been bothered by any of the following problems?

	Not bothered at all (0)	Bothered a little (1)	Bothered a lot (2)
a. Stomach pain	☐	☐	☐
b. Back pain	☐	☐	☐
c. Pain in your arms, legs, or joints (knees, hips, etc.)	☐	☐	☐
d. Menstrual cramps or other problems with your periods ***WOMEN ONLY***	☐	☐	☐
e. Headaches	☐	☐	☐
f. Chest pain	☐	☐	☐
g. Dizziness	☐	☐	☐
h. Fainting spells	☐	☐	☐
i. Feeling your heart pound or race	☐	☐	☐
j. Shortness of breath	☐	☐	☐
k. Pain or problems during sexual intercourse	☐	☐	☐
l. Constipation, loose bowels, or diarrhea	☐	☐	☐
m. Nausea, gas, or indigestion	☐	☐	☐
n. Feeling tired or having low energy	☐	☐	☐
o. Trouble sleeping	☐	☐	☐

(For office coding: Total Score T_____ = _____ + _____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix E: PROMETHEUS Data sharing agreement

PROMETHEUS Data sharing agreement

This document specifies the data management and data sharing agreement between the PROMETHEUS programme and the Multiple Symptoms Study 3 (MSS3) trial. In this document, the 'PROMETHEUS programme team' refers to researchers named on the PROMETHEUS protocol. 'PROMETHEUS collaborators' refers to those providing 'host' trials for the PROMETHEUS programme.

PROMETHEUS roles and responsibilities

The MSS3 team agrees to:

(a) Conduct the PROMETHEUS study in the MSS3 trial, and randomly allocate patients who are being invited to take part in MSS3 to receive a pen incentive and/or a brief participant information sheet, in addition to the standard MSS3 invitation materials.

(b) Collect data on the numbers of patients approached using each recruitment method and data on the numbers randomised.

(c) Collect and provide data on the following demographic characteristics of patient enrolled into MSS3: age and sex in addition to aggregated data on ethnicity.

(d) Provide collected data in an anonymised form (labelled data set in STATA, SPSS, or a database suitable for import to STATA) to the PROMETHEUS programme team for analysis within six months of the SWAT finishing. Any data provided to the PROMETHEUS team must be rendered anonymous by the MSS3 team by removing identifiers such as date of birth (e.g. recoding it to 1st January of the birth year or simply putting age) and participant identity number and then randomly sorting the data. This aims to ensure that it would not be possible

to re-identify participants in the dataset, in line with General Data Protection Regulation (GDPR) requirements.

(e) Not introduce the recruitment interventions in a non-randomised fashion during the conduct of the PROMETHEUS study.

(f) Seek permission from the PROMETHEUS research team to introduce the recruitment interventions after the end of the PROMETHEUS study period.

(g) To invoice the PROMETHEUS study team at York Trials Unit for costs incurred during the conduct of the PROMETHEUS study, in accordance with funding as agreed on [DATE/REFERENCE].

It is possible that host trials may wish to withdraw from the PROMETHEUS programme before the end of the study. In this case, data collected up to that point would still be required to be provided to the PROMETHEUS programme team.

Data protection and publication issues in the PROMETHEUS programme

The University of York has strict guidelines for data storage, access to study data and adherence to the principles of data protection (including the Data Protection Act 1998). The link to relevant information is: https://www.york.ac.uk/records-management/dp/

Data transfer policy

Datasets will be accepted from PROMETHEUS collaborators in electronic format (the University of York can translate datasets in various formats through *Stat Transfer*). In addition, PROMETHEUS collaborators will provide written details of the coding of variables in the dataset to allow consistent analysis (see PROMETHEUS study protocol).

All datasets will be anonymised by PROMETHEUS collaborators *before* transfer to the University of York, removing all identifiable patient information such as names and addresses. Data may be encrypted before transmission to ensure security.

Data storage

Datasets from PROMETHEUS collaborators will be transferred to a combined database on a secure server at the Department of Health Sciences, University of York. All data received will be treated in the strictest confidence. Analysis of the data will be undertaken at York Trials Unit, University of York. Professor David Torgerson will act as custodian for the combined dataset. The combined dataset will be stored by the University of York in a secure location. Data from individual datasets will remain the property of PROMETHEUS collaborators.

Environment

The PROMETHEUS research project is led by the York Trials Unit, University of York (www.york.ac.uk/healthsciences/research/trials/), a UKCRC registered Clinical Trials Unit (Registration: 40) which undertakes national, rigorous randomised controlled trials of health care, education and criminal justice interventions.

Signature

I _____on behalf of the MSS3 host trial agree to the roles and responsibilities in relation to the PROMETHEUS study conduct and sharing of data.

Signature: _____

Date: _ _ / _ _ / _ _ _ _

I _____on behalf of the PROMETHEUS programme agree to the roles and responsibilities in relation to the PROMETHEUS study conduct and sharing of data.

Signature: _____

Date: _ _ / _ _ / _ _ _ _

Appendix F: PROMETHEUS publications & authorship arrangements

PROMETHEUS in MSS3 publication and authorship agreements

PROMETHEUS has the potential to generate a large number of publishable datasets, which will include embedded trials of PROMETHEUS interventions run in single trials ('single datasets'), and the combined datasets of PROMETHEUS interventions run in multiple trials ('combined datasets').

This document describes the ground rules for publishing and authorship for applicants and researchers on the PROMETHEUS grant ('PROMETHEUS programme team') and researchers providing 'host' trials for the study ('PROMETHEUS collaborators'), in this case the Multiple Symptoms Study 3 (MSS3) host trial.

Core principles

The core principle governing authorship are:

- Clear communication.
- No surprises.
- No waiting to publish, and
- Access to an independent adviser.

Ground rules

1. All publications arising from the 'combined datasets' will include the PROMETHEUS programme team and representatives from PROMETHEUS collaborators (normally host trial Chief Investigator and/or Trial Manager).

a) Where PROMETHEUS collaborators request more than two representatives, nominations for authorship will be discussed among the PROMETHEUS programme team.
b) Requirements for authorship are those of the International Committee of Medical Journal Editors (http://www.icmje.org/).
c) If author numbers become excessive, papers may be authored under a collaborative name or a combination of named authors (PROMETHEUS programme team) and a group collaborative name (PROMETHEUS collaborators) (http://www.councilscienceeditors.org/i4a/pages/index.cfm?pageid=3373).

2. The PROMETHEUS research team are keen to encourage publication from single datasets where possible.
    a) Publication of the final PROMETHEUS data takes precedence – we cannot delay publication, for example, to allow single datasets to be published first, or for publication of the host trial main results to be published first.
    b) We would expect that PROMETHEUS collaborators would look for opportunities to involve members of the PROMETHEUS research team as authors in publications arising from individual datasets, either as individuals or under a collective name.
    c) The PROMETHEUS research team will be able to provide materials for papers on the development of the interventions, as well as general background and criteria for reporting standards in embedded trials developed as part for the MRC START project.

3. All other publications arising from PROMETHEUS (i.e. not based on the combined datasets) remain in the authorship of the PROMETHEUS programme team.

4. PROMETHEUS collaborators need to sign up to the PROMETHEUS authorship arrangements.

5. We will appoint an independent adviser to whom the PROMETHEUS research team or PROMETHEUS collaborators can go for advice or independent arbitration in the event of a disagreement about authorship.

Agreed publication strategy for PROMETHEUS in MSS3

The MSS3 host trial team have expressed a preference to complete the analysis and write up of the SWAT, with involvement from the PROMETHEUS programme team. Relevant members of the PROMETHEUS team will be involved as co-authors.

The MSS3 team will share a copy of the anonymised individual patient level data (IPD) with the PROMETHEUS team to allow IPD meta-analysis of each intervention to be undertaken. Where IPD sharing is not possible, summary data will be shared.

Signature

I _____on behalf of the Multiple Symptoms Study 3 (MSS3) host trial agree to the PROMETHEUS authorship arrangements.

Signature: _____

Date: _ _ / _ _ / _ _ _ _

I _____on behalf of the PROMETHEUS programme, agree to the authorship arrangements.

Signature: _____

Date: _ _ / _ _ / _ _ _ _