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<https://doi.org/10.3310/kwgx2382>

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## Synopsis

# Multiple Symptoms Study 3 – An extended-role general practitioner clinic for patients with persistent physical symptoms: a Randomised Controlled Trial

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Published April 2025

DOI: 10.3310/KWGX2382

## Abstract

**Background:** People with multiple and persistent physical symptoms have impaired quality of life and poor experiences of health care. We aimed to evaluate the effectiveness of a community-based Symptoms Clinic intervention in people with multiple and persistent physical symptoms.

**Trial design:** Pragmatic multicentre individually randomised parallel group clinical trial.

**Methods:** Participants: Recruitment was between December 2018 and December 2021 in four areas of the UK. Eligibility was based on electronic health records, healthcare use and multiple physical symptoms (PHQ-15 between 10 and 20) which were not due to other medical conditions. Intervention delivery changed from face to face to online in 2020 in response to the pandemic.

Interventions: Participants were randomised to receive the Symptoms Clinic plus usual care (intervention) or usual care alone (control). The Symptoms Clinic is a short-term extended medical consultation-based intervention delivered over approximately 8 weeks.

Objective: To test the clinical and cost-effectiveness of an extended-role general practitioner 'Symptoms Clinic' for people with persistent physical symptoms.

Outcome: The primary outcome measure was the PHQ-15 at 52 weeks post randomisation.

**Randomisation:** Participants were randomised 1 : 1 using a centralised web-based system, stratified by study centre with random permuted blocks of varying sizes.

**Masking:** It was not possible to mask participants to their allocation. Outcome assessors who handled patient-reported questionnaires were masked to allocation.

**Results:** Numbers randomised: 354 participants were randomised into the trial: 176 to the usual care group and 178 to the intervention group.

Numbers analysed: 132 participants in the usual care group and 144 participants in the intervention group were included in the analysis representing 77.8% retention.

**Outcome:** Mean (SD) PHQ-15 at baseline was 14.9 (3.0) in the control group and 15.0 (2.9) in the intervention group. At 52 weeks it was 14.1 (3.7) in the control group and 12.2 (4.5) in the intervention group. The between-group difference, adjusted for age, sex, baseline PHQ-15 and clinician effect was  $-1.82$  (95% CI  $-2.67$  to  $-0.97$ ;  $p < 0.001$ ) favouring the intervention.

**Harms:** There were no significant between-group differences in the proportions of patients experiencing non-serious ( $-0.03$ , 95% CI  $-0.11$  to  $0.05$ ) or serious ( $0.02$ , 95% CI  $-0.02$  to  $0.07$ ) adverse events. All serious adverse events were deemed unrelated to trial interventions.

**Economic evaluation:** Cost-effectiveness analysis indicated an incremental cost-effectiveness ratio of £15,751/QALY.

**Process evaluation:** The intervention was delivered with high fidelity and was acceptable to patients. The intervention appeared to act through the hypothesised mechanism of explanation as a bridge from uncertainty about the cause to actions to manage symptoms.

**Limitations and further research:** The intervention was delivered by a small number of GPs in long consultations. Further research should examine wider implementation and how to integrate elements of the intervention into shorter consultations.

**Conclusions:** The Symptoms Clinic delivered by specially trained GPs leads to a clinically meaningful improvement in physical symptoms at 52 weeks and is likely to be a cost-effective addition to current care.

**Funding:** This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health and Social Care Delivery Research programme as award number 15/136/07.

A plain language summary of this synopsis is available on the NIHR Journals Library Website <https://doi.org/10.3310/KWGX2382>.

## Introduction

This report describes Multiple Symptoms Study 3 (MSS3): a pragmatic randomised controlled trial to evaluate the clinical-effectiveness and cost-effectiveness of the Symptoms Clinic, a new service delivered by specially trained GPs, for patients with persistent physical symptoms.

### *Rationale for research and background*

Persistent physical symptoms which are disproportionate to detectable physical disease are common in all clinical settings. They are present in up to 40% of primary care consultations<sup>1</sup> and account for a similar proportion of referrals from general practitioners to specialists.<sup>2</sup> Approximately 2% of adults experience multiple physical symptoms at a level which impacts significantly on their quality of life.<sup>3,4</sup> Persistent physical symptoms account for substantial costs to health services and society.<sup>5,6</sup>

Persistent physical symptoms can exist either on their own (e.g. palpitations or headache) or in clusters represented as syndromes (e.g. fibromyalgia or irritable bowel syndrome). While all medical specialties have their own syndromes, there are theoretical and pragmatic arguments for viewing persistent physical symptoms as overlapping and sharing common processes.<sup>7</sup> Although

persistent physical symptoms have often been referred to as 'medically unexplained symptoms', there is increasing evidence that they can be understood and explained. This understanding is multilayered, including neurological processes by which the brain senses, interprets and regulates the body,<sup>8,9</sup> psychological and social processes by which personal experience, emotions and interpretation influence perceptions of and responses to the body,<sup>10,11</sup> and bodily processes such as inflammation or disordered function which may precede or follow from these other layers. Considering these multilayered processes together permits an understanding of symptoms as entities in their own right<sup>12</sup> in a way which is analogous to current understanding of chronic pain.<sup>13</sup> This approach transcends binary divisions of 'medically unexplained'/explained<sup>14</sup> or organic/functional.<sup>15</sup> For these reasons and patient preference,<sup>16</sup> we use the term persistent physical symptoms.

When people with persistent physical symptoms are told that medical tests do not show a cause, any reassurance is typically transient<sup>17</sup> and patients are left feeling stuck, disbelieved and helpless.<sup>18,19</sup> Professionals' failure to provide explanations for persistent physical symptoms has been identified as central to the problem,<sup>18</sup> however persistent physical symptoms can be explained in ways

which are acceptable to patients<sup>20,21</sup> and there is some evidence this can facilitate improvement.<sup>22,23</sup>

Despite the prevalence of persistent physical symptoms in primary care, two recent reviews concluded that there are no effective primary care-based treatments.<sup>24,25</sup> We developed an extended consultation intervention for people with persistent physical symptoms using extended-role general practitioners (ER-GPs) to deliver a Symptoms Clinic.<sup>23,26</sup> The aim of the intervention is to recognise and validate the patient's experience, work with them to reach acceptable explanation(s) for their persistent physical symptoms<sup>20,21,27</sup> and use this to plan actions to manage symptoms or limit their impact.<sup>28</sup> Prior to the current study we carried out Multiple Symptoms Study 1<sup>23</sup> – a pilot randomised controlled trial (RCT) as proof of concept and Multiple Symptoms Study 2<sup>–26</sup> a non-randomised study which examined whether the treatment model could be taught and implemented. In MSS3, we evaluated the effectiveness of the Symptoms Clinic in a randomised controlled trial.

### Aims and objectives

The aim of MSS3 was to determine the clinical and cost-effectiveness of the Symptoms Clinic. To achieve this aim, we had four objectives:

1. Conduct a pragmatic RCT of the Symptoms Clinic plus usual care versus usual care alone, in people with persistent physical symptoms.
2. Establish trial-specific Symptoms Clinic, train ER-GP and provide them with supervision; systematically recruit patients from primary care, and ensure satisfactory trial procedures and follow-up.
3. Examine the effect of the intervention on patient outcomes, including symptom burden and quality of life across 52 weeks and use this data alongside healthcare use to evaluate the cost-effectiveness of the intervention.
4. Understand the processes of change associated with the Symptoms Clinic through qualitative interviews with a subsample of participants, recording and coding key elements of the intervention consultations, and interviews with stakeholders.

### Methods

#### Protocol and permissions

MSS3 was registered on the ISRCTN registry (ISRCTN57050216) on 2 October 2018. The protocol has been published<sup>29</sup> and the Statistical Analysis Plan was signed off before data collection was completed. NHS Research Ethics approval was received from Greater Manchester Central Research Ethics Committee, reference 18/NW/0422, on 25 June 2018.

#### Study design

MSS3 was a pragmatic, multicentre, parallel group, individually randomised controlled trial, with internal pilot phase.

The trial was initially conducted in local GP practices and community research facilities across three regions in the North of England, UK. In response to the COVID-19 pandemic, the trial was redesigned and moved to remote delivery with participants recruited from four areas of England (Yorkshire and the Humber, Greater Manchester, Newcastle and Gateshead, and Northwest London).

Full details of our methods including recruitment, data collection and analysis were published in our protocol paper.<sup>29</sup> The methods are summarised in [Figure 1](#) and described in subsequent sections.

#### Participants

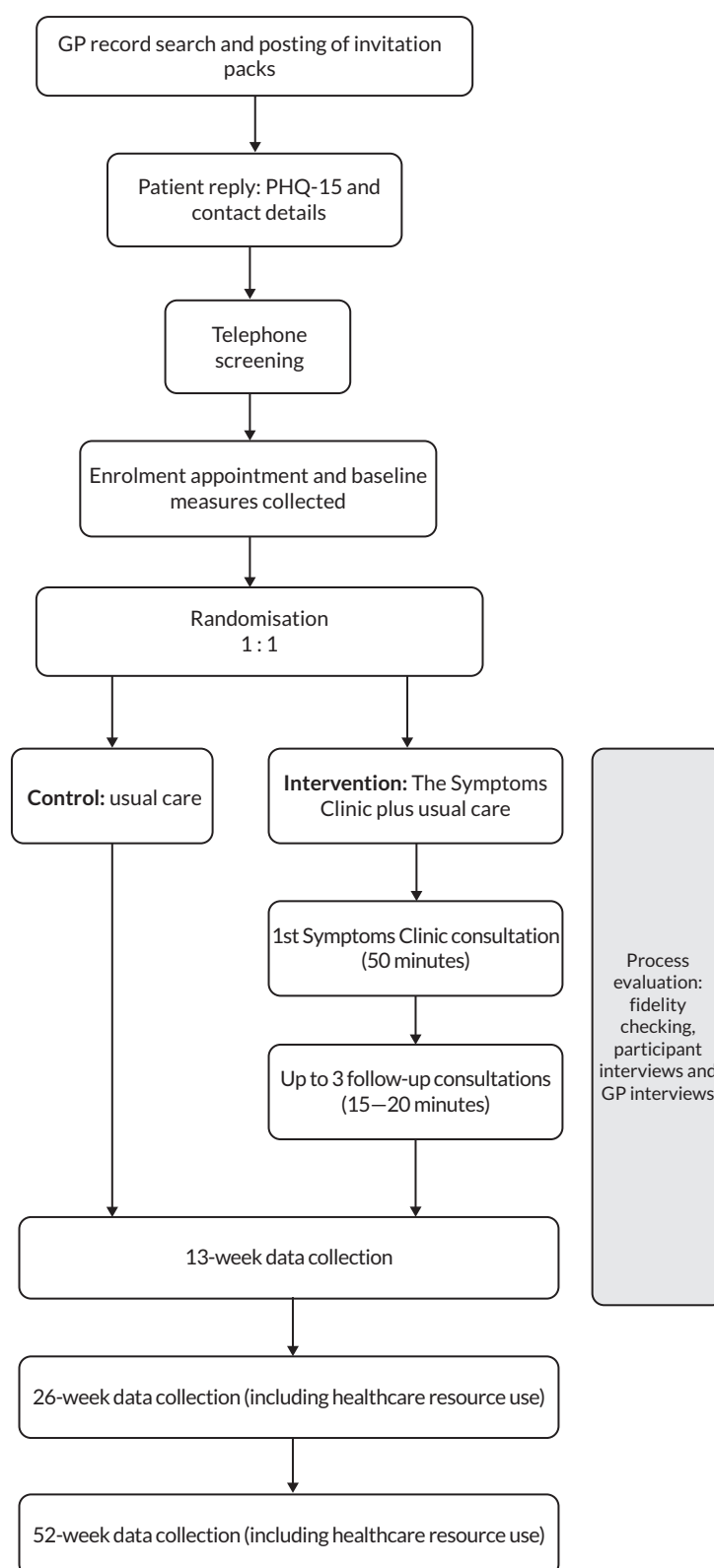
We recruited participants who were aged between 18 and 69 years (at the time of the computer search) and had current physical symptoms meeting the following criteria: (1) one or more codes suggesting a syndrome based on syndromes; (2) records show at least two referrals for specialist opinion in the last 36 months (extended to 42 months when restarting recruitment after the first pandemic wave); (3) records show no evidence of any previous or current major illnesses likely to cause multiple symptoms; (4) doctors in the GP practice do not believe that the majority of the patient's symptoms can be currently explained by other pathology and (5) had a score of between 10 and 20 (inclusive) on the Physical Health Questionnaire-15 (PHQ-15). Additional criteria are detailed in the protocol paper. Following the move to remote delivery of the trial, participants were also required to have the technology available to attend a video consultation.

Participants meeting these criteria were identified through a three-stage identification process. This involved computer searches, GP record screening and postal invitation. These stages were completed by GP practices acting as Participant Identification Centres.

**Stage 1:** GP practices conducted a computer search on their clinical system to identify potentially eligible participants. The full search strategy has previously been published.<sup>29</sup>

**Stage 2:** The list of patients produced by the search was screened by a GP at the practice, and those for whom invitation to the trial may be inappropriate were excluded.

**Stage 3:** The GP practices sent invitation packs to the final list of patients. Interested patients returned the reply form



**FIGURE 1** Multiple Symptoms Study 3 trial flow diagram.

and a completed PHQ-15 to the Clinical Trials Research Unit (CTRU) at the University of Sheffield in a pre-paid return envelope. Patients who did not respond within approximately 3 weeks of the first mailing were sent a reminder invitation pack.

### Recruitment and informed consent

The research team contacted patients who expressed an interest in the trial and were deemed potentially eligible to discuss the study further and answer questions. If the patient remained interested, screening checks were

completed and, if appropriate, an enrolment appointment was booked. At the enrolment appointment, informed consent was obtained, eligibility was confirmed and baseline data was collected. Randomisation also took place.

Initially, written informed consent was obtained during face-to-face appointments, and this was changed to audio-recorded verbal informed consent following the move to remote delivery.

### Randomisation

Participants were randomised (1:1) to receive the Symptoms Clinic intervention plus usual care (intervention) or usual care alone (control).

Randomisation was conducted using a computer-generated pseudo-random list, stratified by study centre with random permuted blocks of varying sizes. A centralised web-based randomisation system was used to conceal allocation.

### The Symptoms Clinic

The Symptoms Clinic intervention is a series of up to four medical consultations. The initial session is approximately 50 minutes followed by follow-up sessions of 15–20 minutes. Consultations are conducted one to one. The treatment model used in these clinics has previously been reported<sup>28</sup> and is summarised under four headings: Recognition, Explanation, Action and Learning (REAL). The Symptoms-Clinic intervention was delivered by GPs with an extended role. These are GPs in non-traditional roles which use the skills of holism and of managing complexity and uncertainty, which are central to generalism. The extended role is often done by practitioners in 'a setting outside their usual general practice and involves receiving referrals for assessment and treatment from outside their immediate practice'.<sup>30</sup> Extended-role GPs were trained (over 10 initial sessions and with 3 study update meetings) in the science underpinning the intervention and delivery of the clinics.<sup>28</sup>

Consultations before March 2020 were delivered face to face. Subsequently, consultations took place via video consultation using the clinical system Accurx or telephone.

### Fidelity of the Symptoms Clinic intervention

All Symptoms Clinic consultations were audio-recorded using an encrypted Dictaphone. A random sample from each of the ER-GPs was transcribed for quality assurance and process assessment (approximately one-third of consultations). The remaining audio-recordings have been archived for quality assurance purposes.

Fidelity was assessed from consultation transcripts or recordings. A framework of items in the intervention was used as a template and for each consultation the presence of each item was indicated and evidenced by using an extract or quote from the transcript. A traffic light system was used where clearly present was marked green, possibly present marked amber and absent marked red.

### Outcomes and data collection

All outcome measures were self-reported by participants with the exception of healthcare resource use obtained from medical case note review of GP records. Self-report measures were collected by questionnaire at the enrolment appointment and by post at 13, 26 and 52 weeks post randomisation. Medical case note review of GP records was completed at 52 weeks only and captured data for the full 52 weeks the participants were in the trial.

The primary outcome was the participant reported PHQ-15 at 12 months post randomisation.

The secondary outcome measures were:

- Quality of life measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).<sup>31</sup> This acted as our primary quality-of-life measure, however we also collected the SF-6D<sup>32</sup> derived from SF-12 and ICEpop CAPability measure for Adults (ICECAP-A)<sup>33,34</sup> to compare their performance in this study population
- Symptoms of depression using the Patient Health Questionnaire-9 (PHQ-9)<sup>35</sup>
- Symptoms of anxiety using the Generalised Anxiety Disorder-7 (GAD-7)<sup>36,37</sup>
- Healthcare utilisation over the 52-week period using both self-report and, where possible, medical case note review of GP records
- Patient-reported Global Indicator of Change (PGIC)
- Patient-reported Outcomes Measurement Information System-Ability to Participate in Social Roles and Activities (PROMIS-APS)<sup>38</sup>

We also collected:

- Somatic Symptoms Disorder – B criteria scale (SSD-12)<sup>39</sup>
- European Health Literacy Survey (HLS EU-6)<sup>40</sup>

Researchers collecting and handling outcome measures were blind to participant allocation.

All data was entered into the CTRU's web-based data management system (Prospect), by authorised members of the research team. All data are collected and retained



in accordance with the Data Protection Act 2018, the General Data Protection Regulation and trial unit standard operating procedures (SOPs).

### **Data analysis**

Primary and secondary outcomes were analysed using partially nested heteroscedastic mixed-effects regression models. Models included fixed effects for baseline values of the outcome measure, sex, age and allocation, and random effects for extended-role GP in the intervention arm only. Analyses followed the principle of intention to treat. Estimates of treatment effect were reported with 95% confidence intervals. No interim analyses were conducted and no adjustments were made for multiplicity.

Sensitivity analyses were conducted for the primary outcome to examine the robustness of the findings to different model specifications. Sensitivity models were as follows: (1) the main model was repeated excluding participants who had not completed their final questionnaire within the desired window of 2 weeks prior to and 1 month following the 52-week time point; (2) the main model was repeated with the inclusion of a fixed site effect; (3) to investigate potential COVID-19 pandemic effects the allocation factor was entered as usual care/in-person intervention/remote intervention; (4) missing data were imputed using multiple imputation with chained equations; (5) complier average causal effects were modelled using two-stage least squares regression using compliance as an endogenous regressor instrumented by allocation. Baseline patient-reported outcome measures were used alongside sex and age as predictors in the latter two models.

### **Process evaluation**

MSS3 included three nested observational studies to inform its process evaluation. These included consultation content analysis and interviews with study participants and with GPs.

### **Consultation content**

Approximately 30% of consultations were transcribed and used to examine the intervention content. This data was used to assess intervention fidelity by mapping findings to pre-specified elements of the Recognition Explanation Action Learning treatment model and using an evidenced checklist approach.

### **Participant and GP interviews**

Semistructured interviews were conducted with a purposive sample of 19 participants, at different stages of the intervention, to explore processes of change within participants. We also interviewed six of the study GPs

in relation to their training and subsequent experience. Delays in study recruitment and due to the pandemic meant that while we had intended to interview a small sample of other stakeholders towards the end of the study, this was not possible. All interviews were audio-recorded and transcribed prior to analysis.

### **Qualitative analysis**

Consultation transcripts and interviews were analysed using a reflexive thematic analysis approach. Initial coding by the researcher (KF) was followed by in-depth discussions among the qualitative research team (researcher, two senior sociologists and CI) to ensure that an appropriately wide range of theoretical perspectives were brought to the analysis.

### **Economic evaluation**

We conducted a cost-effectiveness analysis of the Symptoms Clinic plus usual care compared to usual care alone from the primary perspective of the UK NHS and Personal Social Services. This was based on healthcare resource use in both primary and secondary care. This included GP (and related staff) consultations both in and out of hours, diagnostic tests and investigations. This data also included use of community services and hospital outpatient and in-patient care (planned and unplanned), investigations including scans and endoscopies. Costs also included use of private health care. It used a cost-utility framework to estimate cost per quality-adjusted life-year (QALY) gained.

The effects of the intervention have been estimated as gain in QALYs at 52 weeks using health-related quality of life data collected at baseline, 13, 26 and 52 weeks in the primary analysis and the area under the curve method. Published UK tariffs were used to convert these data to quality-of-life weights. We measured preference-based health-related quality of life using the EQ-5D-5L and the SF-6D. We also used the newer capability wellbeing ICECAP-A measure to examine their relative responsiveness to change in this patient population. Participants completed a self-reported healthcare resource use questionnaire at 26 and 52 weeks post randomisation to estimate healthcare resource use costs.

Use of healthcare resources has been valued and the associated costs estimated by assigning unit costs from standard published UK sources [including Personal Social Service Research Unit (PSSRU) unit costs and NHS reference costs]. Costs related to intervention delivery were estimated using trial records, taking into account face-to-face/video consultation clinic time, clinic-related administration, clinician training and clinical supervision.

The analysis was performed on an intention-to-treat basis (for participants with complete data on resource use and health utilities across all follow-up time points). The results of the analysis are reported as incremental costs, effects and incremental cost-effectiveness ratios (ICERs) in terms of the incremental cost per QALY gained. Cost per QALY data was presented in the form of cost-effectiveness acceptability curves (CEAC) to show the probability that the intervention is cost-effective for different values of willingness to pay per additional QALY.

Results summary

To date, four results papers (in addition to the protocol paper) have been submitted for publication, with one published and the remaining three under editorial review. These are summarised in Table 1.

Recruitment and training of GPs

Seven GPs were trained in the intervention and six of them went on to deliver the REAL model in Symptoms Clinic either face to face or online.

Treatment model delivery

Fidelity assessment was carried out on 131 consultations from a total of 45 participants using the evidenced checklist. It found a high level of fidelity for all items with only a few exceptions.

Recruitment and retention of trial participants

The initial target enrolment was 376 participants. This was adjusted to 350 in the final year after discussion with the funder due to greater than predicted retention at 52 weeks. Ultimately 354 individuals were randomised of whom 87.6% in the intervention arm completed at least two clinic sessions. Primary outcome was completed by

77.8% of participants. Figure 2 shows the CONSORT flow diagram of participants at each stage of the trial.

Primary outcome

Mean (SD) PHQ-15 at baseline was 14.9 (3.0) in the control group and 15.0 (2.9) in the intervention group. At 52 weeks it was 14.1 (3.7) in the control group and 12.2 (4.5) in the intervention group. The between-group difference, adjusted for age, sex, baseline PHQ-15 and clinician effect was -1.82 (95% CI -2.67 to -0.97;  $p < 0.001$ ). Using a clinically important difference (CID) of 2.3 points on the PHQ-15,<sup>44</sup> the number needed to treat for a 1 CID beneficial change was 4.2 and for a 2 CID change was 5.

Secondary outcomes

All secondary outcomes showed a between-group adjusted difference in the same direction indicating benefit. The adjusted difference in EQ-5D was 0.072 (-0.001, 0.145) and for participation in social roles and activity was 2.1 (0.0, 4.2), both favouring the intervention. Sensitivity analysis found no meaningful differences in effectiveness between GPs and no difference between face-to-face and online intervention delivery.

Harms

We found no difference between allocation groups in serious adverse events and in both arms there was a low rate of new diagnosis of medical conditions and no instance of a new and serious cause being found for symptoms thought to be eligible for inclusion.

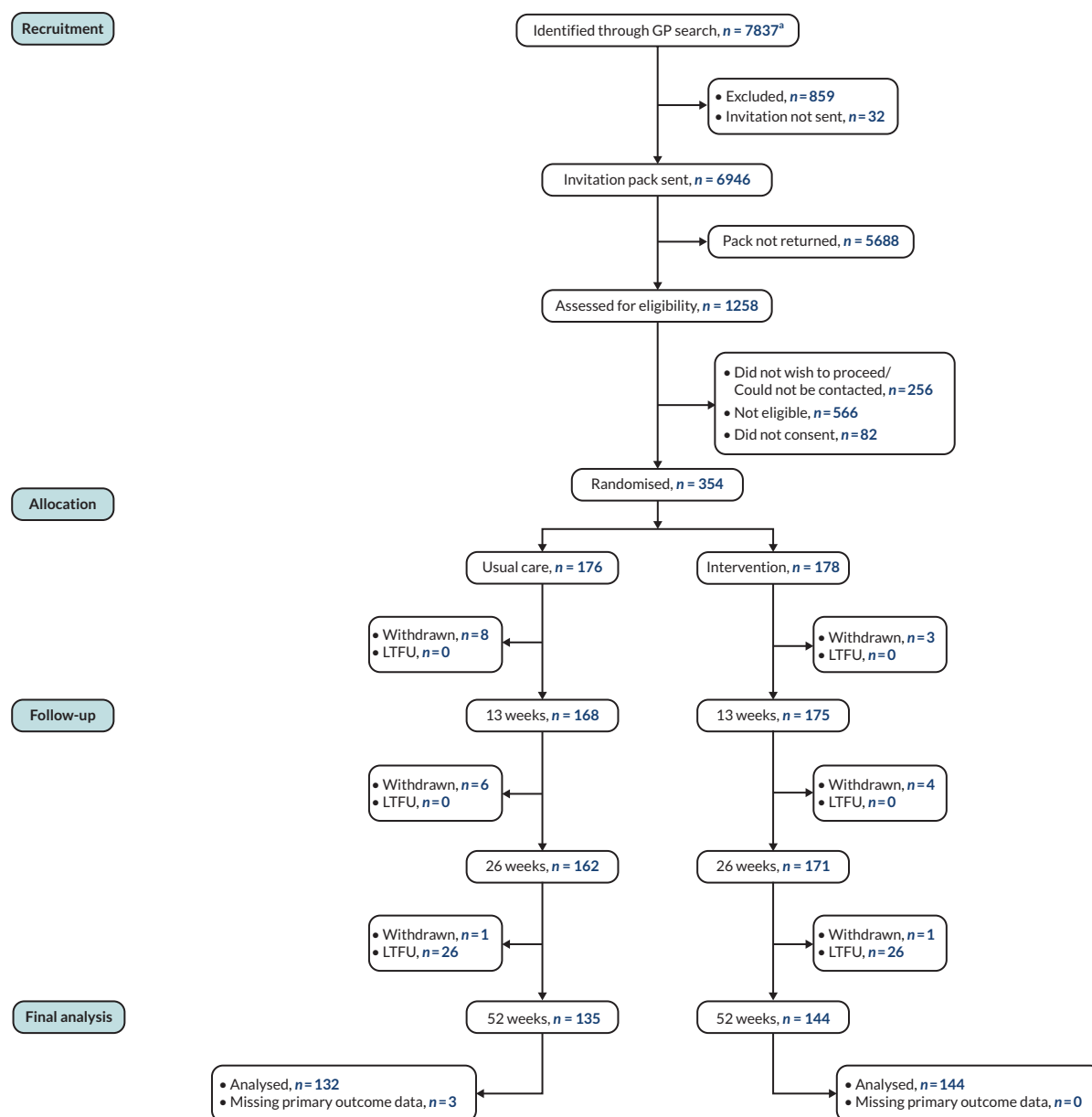
Healthcare use

We found no major differences between allocation groups in subsequent GP contacts, specialist referrals, diagnostic tests or prescribed medications.

TABLE 1 Results related papers being synthesised in this synopsis

Working title	Formal title	Publication/submission
Treatment model delivery	Recognition, explanation, action, learning: Teaching and delivery of a consultation model for persistent physical symptoms	Published, <i>Patient Education and Counselling</i> , 2023 <sup>28</sup>
Trial results	Effectiveness of a symptom-clinic intervention delivered by general practitioners with an extended role for people with multiple and persistent physical symptoms in England: the Multiple Symptoms Study 3 pragmatic, multicentre, parallel-group, individually randomised controlled trial	Published, <i>The Lancet</i> , June 2024 <sup>41</sup>
Economic evaluation	Cost-effectiveness of an extended-role general practitioner clinic for persistent physical symptoms: results from the Multiple Symptoms Study 3 pragmatic randomized controlled trial	Published, <i>Value in Health</i> , October 2024 <sup>42</sup>
Process evaluation	Explanation for symptoms and biographical repair in a clinic for persistent physical symptoms	Published, <i>SSM-Qualitative Research In Health</i> , 2024 <sup>43</sup>





**FIGURE 2** CONSORT flow diagram. <sup>a</sup> Missing total number returned by search imputed for four centres using total after exclusions. LTFU, lost to follow-up.

## Economic evaluation

Complete-case analysis showed that, compared with UC alone, SC+UC was more expensive [adjusted mean cost difference: £918, 95% CI £785 to £1049] and likely more effective [adjusted mean QALY difference: 0.058 (95% CI -0.012 to 0.127)], yielding an ICER of £15,751/QALY. In multiple imputation analysis, SC + UC yielded both lower incremental costs (£642, 95% CI £568 to £710) and QALYs [adjusted mean QALY difference: 0.040 (95% CI 0.004 to 0.077)], with similar ICER of £15,958/QALY. At a threshold value of £20,000 per QALY, SC + UC had probabilities of 70% and 68% of being cost-effective, respectively.

## Mechanism of change

We examined the process of change within the study using the concept of biographical repair. This begins with the premise that chronic illness has effects not just on a person's body and their participation in ordinary activities but also on their sense of self<sup>45</sup> and the narratives they recount to describe and construct that. Biographical disruption is a well-established theory of how illness introduces problems with the self<sup>46,47</sup> including restricted capabilities, being discredited, and having to rely more on others.<sup>46</sup> Biographical reconstruction<sup>48</sup> and repair<sup>49,50</sup> are then seen as ways in which individuals 'seek to cope with

the change in their life by reconstructing their identity and restoring a sense of normality'.<sup>49</sup>

We found that study participants had experienced biographical disruption and through the Symptoms Clinic underwent a process of biographical repair. They found a new balance between acceptance and agency in relation to their symptoms, regained some control over them, and moved to a new normality in which their old normality was clearly recognisable. The analysis found that all four stages of the clinic REAL model were necessary for that. While explanation was central, it was not possible to coproduce (rather than impose) an explanation without sufficient recognition and validation of the patient. Explanations then formed a rational bridge to actions and self-management strategies to reduce symptoms or lessen their impact. While biographical repair is not a new way of framing a process of recovery, it has not been described over such a short time frame as during the Symptoms Clinic.

In-depth analysis of how explanations facilitated biographical repair found that the explanations were able to view symptoms as multilayered; thus a previously insufficiently explained set of symptoms could be deconstructed into neurophysiological processes (of signalling between the body and brain); psychological and social responses to the symptoms and episodes in a complex life course. Using the expert generalist medical consultation ensured that the consultations could switch between specific layers and the 'big picture' and were able to include all elements simultaneously rather than splitting into arbitrary mind and body or functional and organic.

### Additional analyses in progress

Several additional analyses are in progress or planned. These include a substantial qualitative paper further examining the consultation process, provisionally titled 'Awakening the sense of the possible: the Symptoms Clinic as a liminal space' and analysis of the relationship between health literacy and the content and effectiveness of the intervention.

## Discussion/interpretation

### Principal findings

Multiple Symptoms Study 3 has four main findings:

First, we have demonstrated that the Symptoms Clinic intervention – a series of long semistructured consultations with a specially trained ('extended-role') GP – can be taught and delivered with a high level of fidelity, although

it requires substantial time and supervised rehearsal before it can be used even by experienced GPs.

Second, the intervention was effective in terms of the primary outcome measure. The adjusted between-group difference was a significant reduction of 1.8 points (95% CI –2.67 to –0.97) in PHQ-15 at 1 year after enrolment – and at least 9 months after completion of the intervention. While the average between-group difference of 1.8 points was less than the clinically important difference of 2.3 points,<sup>44</sup> the distribution of treatment effects was skewed. The number needed to treat to produce a substantial improvement of 4.6 points (twice the clinically important difference) was five.

Third, while the clinic increased costs, the gain in quality of life was such that the incremental cost-effectiveness ratio (ICER) was £15,765/QALY with a 69% probability of being cost-effective at a threshold value of £20,000 per QALY.

Fourth, the in-depth process analysis confirmed not just that the intervention was being delivered as intended but that the hypothesised underlying mechanism – clinical explanation as a way of correcting 'epistemic incongruence' – allows patients who are stuck in a state of biographical disruption to repair this disruption and acquire a sense of agency over their symptoms.

### Contribution to existing knowledge

The argument that persistent physical symptoms (often known as medically unexplained symptoms) are complex and multifactorial is not new,<sup>51</sup> nor is the argument that the lack of explanation is an important problem.<sup>18,52</sup> However, previous work on explanations has largely been observational<sup>53,54</sup> or theoretical.<sup>20,21</sup> Where interventions have been developed, they have relied on relatively simple explanation – such as reattributing physical symptoms to mental distress,<sup>55</sup> however this is ineffective<sup>56</sup> and the reasons for this have been outlined.<sup>18,57</sup>

This study took a much broader approach to the nature of persistent symptoms, building on existing biopsychosocial theories<sup>10</sup> and adding in more recent neuroscientific developments<sup>9,11</sup> in order to provide a range of mechanisms which could be used in discussion with the patient to coproduce a useful and good-enough explanation.<sup>20</sup> In this we drew on work from the two earlier multiple symptoms studies which developed a taxonomy of explanation<sup>21,27</sup> which was tested in MSS3. It also made the important inferential step of considering persistent physical symptoms as entities in their own right.<sup>12,58</sup> Thus they were no longer symptoms as indicators of disease (and if not physical disease, of something mental), but as indicators

of problems in the symptom processing pathways (both in the body and in the brain/mind). While this differs from most professional and lay discourses about symptoms, it is very similar to the recent changes in the conceptualisation of chronic pain.<sup>13</sup>

While the study emphasised the importance of explanation, it is likely that new information alone is not enough. A recent German trial provided explanatory information at the end of a single consultation and found no meaningful effect of the additional information.<sup>59</sup> In contrast MSS3 sought to combine GPs' skills as clinical generalists with explanation which could be personalised to the individual. This role accords well with the interpretivist aspect of general practitioners<sup>60</sup> skills but runs counter to the general trend of using GPs as a first-contact service with signposting/referral to more specialist services. In the context of persistent physical symptoms, it appears that the ability to comfortably operate in biomedical, psychosocial and biographical layers of a person's illness is important. Certainly the consultations within the Symptoms Clinic showed the GPs moving skilfully between these layers and able to simultaneously consider multiple causal mechanisms.

### **Strengths and limitations of the study**

The trial recruited participants from four UK centres and reached its target recruitment. There were high rates of intervention completion and low rates of withdrawal: primary outcome data was obtained from 78% of participants. Importantly, two of the study centres are in areas of high socioeconomic deprivation and this was reflected in the participant demographics. The study also measured health literacy and at baseline only 36% of participants met the cut-off for 'sufficient' health literacy. Delivery of the intervention was rigorously monitored and evaluated with good fidelity<sup>28</sup> suggesting that while the Symptoms Clinic involves complex consultations, it can be effectively delivered to a socioeconomically diverse population with favourable results. While the study recruited from primary care, the severity in terms of physical symptoms was comparable to that seen in large trials of specialised psychological interventions.<sup>61,62</sup>

An important limitation is that delivery was by a small number of extended-role GPs. However, none had worked with the investigators before, and they were selected by open competition. While the GPs varied in experience, and in confidence (at least initially), analysis showed no significant difference between them in terms of patient outcomes. Supervision of the ER-GPs was by the intervention developers (CB and VD) and training of further trainers will need to be addressed in further work.

Several limitations arose due to the pragmatic nature of this intervention and trial. Participant inclusion criteria were broad which means they are difficult to standardise, however, this reflects the idea of persistent physical symptoms as an umbrella concept<sup>7</sup> and the pattern of symptoms reported (in terms of their frequencies relative to each other) were similar to those in a population with physical symptoms attributed to burnout<sup>63</sup> and a general population survey<sup>64</sup> suggesting that the study population was broadly generalisable in terms of symptoms. There was no attempt to conceal allocation from participants, however all assessments were collected and processed with full concealment for research team members. As a pragmatic trial with a usual care control arm, the study cannot completely rule out the possibility of effects being due to non-specific (attentional) aspects of the intervention. However, one would expect any effects of this would be short term while the observed difference between groups increased between 6 and 12 months. Furthermore, there was strong qualitative evidence that the specific components of the intervention were central to patients' improvement. The full costs of training of the extended role GPs were included in the analysis and comprised almost 40% of the intervention cost. However, these were a 'one-off' for each extended role GP and in a clinical setting, the skills would be continued with perhaps only an annual refresher course. This would lower the actual delivery cost.

### **Relationship to other studies**

Two recent reviews of primary care interventions for persistent physical symptoms found no evidence for effective primary care-based interventions.<sup>24,25</sup> A previous review<sup>56</sup> had suggested that more intensive interventions<sup>65,66</sup> might be effective, particularly if involving explanations.<sup>22</sup> The treatment model and findings of the process evaluation in this study align well with the desirable characteristics of a primary care intervention outlined in a recent realist review.<sup>24</sup> In MSS3 we observed changes in our primary outcome that were at least comparable with those in a recent trial of transdiagnostic cognitive-behavioural therapy (CBT) in secondary care<sup>62</sup> and similar to those seen in a large trial of brief psychodynamic interpersonal therapy.<sup>61</sup> Recent primary care-based studies with broadly comparable patients to MSS3 have evaluated brief CBT and signposting by GPs,<sup>67</sup> mental health nurse-led care with<sup>68</sup> and without<sup>69</sup> physical therapy and referral to psychosomatic therapists.<sup>70</sup> All had smaller effects on physical symptoms than the Symptoms Clinic intervention.

A recent study examined the types of explanations being used to explain persistent physical symptoms in different

settings.<sup>71</sup> Explanations often had both neuroscientific and personal components although they varied in the extent to which one aspect was foregrounded. It appeared that skilled practitioners are able to move between explanation components as we observed in MSS3. In contrast a recent pilot study provided information explaining symptoms after a consultation and found that the additional explanatory information – when removed from the context of the consultation – had little added value.<sup>59</sup>

Systematic reviews have found relatively few studies of interventions for persistent physical symptoms or functional disorders that included economic evaluations. Konnopka *et al.*<sup>72</sup> identified eight economic evaluations of which only two were cost-effectiveness analyses. Wortman *et al.*<sup>73</sup> included studies of interventions for specific syndromes in addition to heterogeneous persistent physical symptoms. They identified five studies involving patients with ‘medically unexplained symptoms’ of which four were group interventions and one was an individual treatment randomised controlled trial of brief interpersonal therapy.<sup>74</sup> While clinically effective this was not cost-effective with an estimated ICER of €41,840 per QALY. More recently, primary care-based studies from the Netherlands examined CBT delivered by mental health nurse practitioners for non-specific persistent physical symptoms.<sup>69</sup> The intervention was associated with small change in QALYs, mean difference 0.01 (95% CI –0.01 to 0.04), but lower healthcare costs, mean difference –€2300 (95% CI –3257 to –134). Finally, a third review<sup>24</sup> focused on interventions relevant to the UK setting but found only two economic evaluations, neither of which included a heterogeneous group of patients with persistent physical symptoms.

A number of studies have reported healthcare use after interventions as an outcome without formal economic analysis. These were reviewed by Jones and de C Williams<sup>75</sup> who concluded that CBT showed weak benefits in reducing healthcare use in people with medically unexplained symptoms, and that this was limited to healthcare contacts and medication use, and did not affect medical investigations or healthcare costs.

We are aware of few new qualitative approaches in recent literature. A recent qualitative evidence synthesis of patients’ experience of medically unexplained symptoms identified common themes of uncertainty and threatened sense of self which the Symptoms Clinic addresses.<sup>76</sup> When studies look for what patients value, validation and a coherence between experience and medical explanation are commonly found<sup>77</sup> and there has been increasing

interest in integrating the psychosocial with the body<sup>78,79</sup> which is in keeping with our multilayered approach to explanation that can switch between different levels. Finally a Dutch study of explanations in ordinary GP consultations found that while present, they were short, superficial and non-personalised.<sup>80</sup> Thus our published work on the REAL model and what happens when it is used<sup>28</sup> and on biographical repair<sup>43</sup> along with planned papers on the generation of new possibilities and the Symptoms Clinic as a liminal space, represent substantial contributions to this field.

### Take-home messages

There are four take-home messages:

1. The Symptoms Clinic model is an effective and cost-effective treatment for people with persistent physical symptoms – a large but heterogeneous group in the population – with a teachable consultation model.
2. The intervention appears to work through the hypothesised mechanism: coproduced explanation provides a critical bridge between patient experience and action to manage symptoms. This simultaneously helps the patient to make sense of their condition, regain a stronger sense of self and take on new self-management strategies.
3. Effective explanations are complex, multilayered and personal: including elements of biomedical and neuroscience, psychosocial factors and personal biography. General practitioners, with authority and skills to operate in all of these fields may be particularly well placed to co-construct explanations and management plans that flow from that if suitably resourced.
4. People with persistent physical symptoms – using the criteria in this study – have a low risk of being diagnosed over the next 12 months with a serious disease causing their symptoms.

### Reflections on the project and what could have been done differently

The evaluation provided learning points for future training, in particular about the importance of role-play in training. If running this again, we would include more of it and the use of either actual or simulated (actor) patients. While the study was designed to test the REAL model in a tightly defined clinical trial, the knowledge and skills used appear to be transferrable to shorter ‘ordinary’ GP consultations. Hence several of the GPs described ways in which ways of thinking about symptoms and explanations for them had diffused into their everyday clinical practice.

A major question running through this study was whether GPs were the right people to be delivering this intervention. Reflecting on the study, we believe that they are. Patients with persistent physical symptoms experience fragmented care<sup>77</sup> and as many areas of medicine become more partitioned and fragmented, this is only going to increase. Despite the substantial training overhead, the GPs in the study were able to provide a short and effective period of treatment that reversed the fragmentation. Furthermore, the GPs were, despite initial misgivings about the intensity of the training, highly satisfied with the skills they gained and opportunity to put them into practice. All would take up Symptoms Clinic sessions if commissioned and all reported taking things away from the clinic to use in their routine practice, in discussion with peers and in their training of future clinicians.

### **Challenges faced and changes made**

The study was originally designed as a face-to-face intervention albeit without physical examination. During the COVID-19 pandemic it was necessary to switch to remote online delivery of the intervention. Subgroup analysis showed this had little effect on outcomes. This unplanned alteration suggests that the intervention is suitable for delivery either face to face or remotely. Changes in access to both primary and secondary health care due to the pandemic are also likely to have led to reduced rates of consultation, referral and testing for at least some symptoms. While in normal circumstances up to half of referrals result in no diagnosis,<sup>2</sup> this proportion may have been lower during much of this study. Finally, the original plan was to extract healthcare resource use from GP records, with participant self-report as a backup. However, this became extremely difficult due to access to GP surgeries during the pandemic and so self-report data has been used in all analyses.

### **Engagement with partners and stakeholders**

While MSS3 was adopted by the NIHR Clinical Research Network for the entire duration of the study, we received exceptional support from two primary care non-profit organisations: Primary Care Sheffield and CBC Health Federation in Gateshead. Both signed up to the research vision and both supported us in finding appropriate premises for the face-to-face consultations and in recruiting member practices to take part. As the study restarted after the pandemic, we were well supported by the NIHR CRN which was able to attract practices to take part from a larger area of Yorkshire and the Humber than was possible with face-to-face clinics and then with Northwest London.

### **Individual training and capacity-strengthening activities**

We developed a model for training and supervising extended-role GPs to deliver a Symptoms Clinic. This was developed for the study and therefore was not promoted elsewhere until the results were known. The training manual will need only minor revisions before it can be used again and we are now looking for opportunities to implement the Symptoms Clinic model.

### **Institutional capacity strengthening**

MSS3 provided development opportunities for both the trials unit lead (DW), and the trial manager (CM) under the supervision of the trials unit director (CC). This has increased the capacity of the Sheffield Clinical Trials Research Unit to support more investigators and provide greater capacity to support clinical investigators in developing and submitting NIHR grants. Two of the investigators were promoted to personal chairs during the study (VD and TS).

## **Patient and public involvement**

### **Aim**

The aim of the patient and public involvement (PPI) activity for this trial was to ensure that the views and lived experience of people with persistent physical symptoms fed into all aspects of our research, ultimately helping to ensure that any findings could benefit them.

### **Methods and outcomes**

We included the views and voices of people with persistent physical symptoms in our research throughout the process, from proposal development, protocol writing and ethics application, through adaptations made due to COVID-19 and into dissemination of results.

We worked with one PPI representative on our Trial Management Group and initially one PPI representative on our Trial Steering Committee (TSC), which we increased, to two during the COVID-19 pandemic. We increased the PPI representation on our TSC as this is considered best practice and to provide additional peer support where meetings were unable to take place face to face.

During the proposal development stage of the study, PPI members advised on trial design and our proposed processes including recruitment methods.

During set up of the study and throughout delivery, our PPI members guided decisions around our approach to potential participants, specifically PPI members shared



their views on our decision to send reminder letters to participants who did not provide a response to our initial invitation letter and follow-up questionnaires. Additionally, PPI representatives had the opportunity to contribute to and approve the content of all participant-facing documents and outcome measures.

PPI input was critical in our decision to move to remote delivery in response to the COVID-19 pandemic. Our PPI representatives' guidance on the acceptability of remote delivery of the intervention and consent processes allowed us to feel confident that remote delivery was acceptable to people with persistent physical symptoms.

As all outcome data were collected through the post, our PPI representatives provided essential guidance on the content of the cover letters which aimed to encourage the completion of outcome measures over the 52-week follow-up period and our proposed methods for follow-up of these measures including sending reminder packs and phone calls.

At the end of the study, PPI members have reviewed our interpretation and conclusion of the results and provided input to participant dissemination activity.

### **Reflections and critical perspective**

The inclusion of PPI input has been essential for the successful delivery of MSS3, particularly in navigating the immense challenges presented to research due to COVID-19. As noted above they provided us with reassurance that our proposal to move to remote delivery was acceptable and this crucially enabled us to restart recruitment while the pandemic was at its height and other healthcare contacts were restricted. Their input into our questionnaire cover letters and follow-up processes may also have contributed to our successful follow-up rate allowing us to achieve a primary outcome completion rate of 78% at 52 weeks post randomisation.

## **Equality, diversity and inclusion**

We address this from four perspectives: participant gender, ethnicity and language, socioeconomic status and health literacy.

### **Gender**

Three hundred and fifty-four participants were randomised in this study. Participants were identified and invited to participate by 108 GP practices across England. Sixty-three (17.8%) participants were male and 291 (82.2%) participants were female. Common persistent

symptom syndromes such as fibromyalgia<sup>81</sup> and irritable bowel syndrome<sup>82</sup> are more common in women based on population surveys. However, the gender imbalance is greater in clinic samples<sup>83</sup> and women are also more likely to be coded with these syndrome diagnoses.<sup>84</sup> As the diagnoses were used in the search criteria for MSS3, this is likely to have led to more invitations being sent to women. The best estimate of the expected proportion of people with multiple symptoms and high healthcare use that are male comes from a case series based on hospital referrals which was 37%.<sup>4</sup>

### **Ethnicity and language**

Three hundred and twenty-nine (92.9%) participants reported their ethnicity as white. Three hundred and thirty (93.2%) participants reported their first language as English, 7 (2.0%) as other European language, 6 (1.7%) as an Asian language and 11 (3.1%) as 'Other'. As persistent physical symptoms have broadly similar prevalence across ethnicity and cultures,<sup>85</sup> this indicates an under-representation of black and Asian members of the population in MSS3. This may be partly because one of the exclusion criteria for the trial was difficulty in taking part in consultations in English without a professional or family interpreter or other assistance. This decision was taken due to the nature of the communication intervention being tested. The Symptoms Clinic intervention relied on creating understanding and explanation and so for the current trial we decided that it should be conducted in English and without an interpreter. However, during training one of the ER-GPs conducted a demonstration consultation with one of her patients in Urdu and reported back that the techniques and explanations were transferrable and culturally appropriate. This suggests that the Symptoms Clinic has the potential to be rolled out in languages other than English. Future work will be required to find culturally appropriate ways to implement the Symptoms Clinic, in terms of language and culture.

### **Socioeconomic status**

Our recruiting practices were initially located across the north of England, centred primarily around Sheffield and Yorkshire, Gateshead and Manchester. We expanded our recruitment to sites in North London, which served to improve the diversity and geographical reach of our participant population.

To reach underserved populations, we targeted GP practices in socioeconomically disadvantaged areas. This is a group that has been identified in the NIHR INCLUDE project as underserved in research.<sup>86</sup> More than half (58%) of our recruiting practices are located in the 40% most deprived areas in the country as measured by the

Index of Multiple Deprivation (IMD). Fifty-three per cent of the participants in the study were recruited from these practices, with just over a third (34%) recruited from the 20% most deprived areas as measured by IMD.

### Health literacy

In addition to socioeconomic status, we included a measure of health literacy (HLS-EU-6).<sup>40</sup> Health literacy is an important factor in healthcare use, especially in interventions such as the Symptoms Clinic which uses oral explanations of health information with two of the components of the Symptoms Clinic model being Explanation and Learning. To our knowledge we are the first UK-based trial to collect the HLS-EU-6 measure. The HLS-EU-6 groups individuals into three categories in terms of their health literacy; these are inadequate, problematic or sufficient.

Fifty participants (14.7%) were categorised as having inadequate health literacy, 167 (49.3%) problematic and only 122 (36.0%) sufficient,<sup>41</sup> indicating that 64% of our population had a low health literacy score. A systematic review and meta-analysis found that estimates of low health literacy across Europe were 27% to 48%<sup>87</sup> and an observational study conducted in 2015 found that 43% of working-age adults in England are unable to understand or use everyday health information.<sup>88</sup> With 64% of our study population meeting the criterion for low health literacy on the HLS-EU-6, we are confident that participants were at least as limited in terms of health literacy as UK and European populations with poor health and therefore that this research is generalisable in this regard.

### Summary

In summary, MSS3 was evaluating an innovative clinical communication intervention. By restricting participants to people able to receive health care in English (in order to maximise the fidelity checking and process evaluation), we limited diversity and inclusion by ethnicity and language. However, we achieved our aim of maximising diversity and inclusion in terms of education and socioeconomic status by over-recruiting from areas with high levels of socioeconomic deprivation and including large numbers of participants with low health literacy.

### Impact and learning

In this section we discuss learning during the study, consider pathways to impact from the study and recent/current dissemination of the findings.

### Learning during the study

During the study, we learned how to deliver a clinical communication model within a trial using online remote consultation. The MSS3 trial started in 2018 and was impacted by the COVID-19 pandemic. Recruitment was paused between March 2020 and August 2020. During this time, the trial was redesigned to allow for remote delivery, and this included remote screening and consent procedures as well as intervention delivery. Lessons have been learnt in terms of remote methodologies and processes as well as future proofing the intervention, allowing for multiple delivery methods.

### Pathways to impact

We have identified four pathways to impact from this trial: knowledge and skills of extended-role GPs; new services for patients with persistent physical symptoms; opportunities in medical education and postgraduate medical training; and wider collaborative working. These are all at an early stage, as it would have been inappropriate to begin this until the results of the trial were known.

### Extended-role GPs, knowledge and skills

The ER-GPs who underwent training and delivered the Symptoms Clinic as part of the trial were, and remain, extremely positive about the knowledge and skills they gained. They report adopting elements of their training into their routine consultations with patients. All have described ways of using explanations that are different from before their participation. They also report that possessing a language of explanation also makes them better listeners – because they are looking for cues to which they now have tools to respond. While the MSS3 trial was essential to determine the clinical-effectiveness and mechanisms of the intervention, this adoption of some of the techniques into shorter standard consultations suggests that elements are scalable and have the potential to inform usual clinical care for patients with persistent physical symptoms.

Informally, most of the ER-GPs would willingly take up the opportunity to do a weekly session of the Symptoms Clinic if a new service was commissioned. If that were to happen, they would be well placed to do that and could be supported to be the next series of teachers/supervisors. Furthermore, it is possible that if some more GPs had the opportunity to provide a weekly Symptoms Clinic session [at Primary Care Network (PCN) or Integrated Care Board (ICB)] that is explicitly based on using an enhanced version of their generalist skills, it would provide a high-skill high-value change from the routine of daily GP consultations.

As such, it could offer an opportunity to add to a career portfolio, increase professional satisfaction and possibly promote career longevity.

### New symptoms clinic services

We have spoken with service planners in a small number of areas of the UK about the trial and have a sense that once the trial is published, and with favourable cost-effectiveness data, there is interest in investing in Symptoms Clinic services. We fully intend to step this up after publication and are committed to providing support to at least a first wave of new sites as part of our impact work. One of us (VD) has already been actively involved in plans to set up a new service in one ICB, however as of August 2023 this initiative appears to have been paused.

### Impact pathway: medical education, postgraduate training

Persistent physical symptoms remain largely a Cinderella topic in both undergraduate and postgraduate medical training. Key reasons for this include a sense that there is no science behind symptoms,<sup>89</sup> that consultations are too complex<sup>90</sup> and that conventional communications skills such as generic demonstration of empathy may be sufficient. The results of MSS3 suggest that these pervasive ideas could be overturned.

As a first step, CB is supervising an NIHR In Practice Fellow, Dr Catie Nagel, on a scoping review and framework synthesis of problems with teaching persistent physical symptoms and helping plan a subsequent doctoral fellowship application. We have also made initial contact with the UK Council for Clinical Communication which coordinates teaching in communication skills across medical schools. We are working towards taking part in one of their regular meetings to look at how the REAL model and/or some of the skills may be introduced into the curriculum. In addition to this, CB has provided webinars for the Royal College of GPs on the subject of persistent physical symptoms and we will take this up again, once the results of the trial are public.

### Collaborative working

The CI has extensive links with other European groups with an interest in persistent physical symptoms. This includes the Marie Skłodowska-Curie Innovation Training Network ETUDE,<sup>91</sup> the Euronet Soma network<sup>92</sup> and the European Association for Psychosomatic Medicine. This means that lessons from the study are more likely to be translated into practice and/or evaluated in other settings.

### Dissemination

Prior to 2023 there was limited dissemination activity as the trial was still active/in follow-up. We specifically did not embark on publicity about the trial because of the contested nature of some persistent physical symptoms.

In 2023 we have presented the REAL model and biographical repair at the annual conference of the European Society for Psychosomatic Medicine and the main trial results at the Society for Academic Primary Care Annual Scientific Meeting. Further presentations of both the trial data and qualitative work will be given at the 4th European Conference on Symptoms in Primary Care in the autumn.

Five papers have already been submitted for publication<sup>28,29,41-43</sup> and we have plans for several more, each examining different aspects of the trial.

### Implications for decision-makers

Approximately 2% of adults experience multiple persistent physical symptoms and this is associated with impaired quality of life and fragmented care. Specialist psychological therapies have moderate effects but there is limited availability and some patients do not see them as appropriate.<sup>93</sup> Prior to this study, there were no effective primary care-based interventions.

The Symptoms Clinic is a brief but intensive intervention (2 hours total input) by an extended-role GP who is not involved in the patient's routine care thereafter. It uses an extended medical consultation model of REAL to coproduce explanations for the patient that form a bridge between validation of the person and action to manage their symptoms.

The outcome of the trial was positive in terms of physical symptoms and improved quality of life at 1 year. The benefit may extend beyond that (differences between groups were greater after 12 months than 6) but there is currently no long-term data. The intervention is likely to be cost-effective at a cost threshold of £20,000 per QALY.

In addition to benefits to patients, the practitioners who are trained to deliver the Symptoms Clinic, reported the skills they developed as adding to their daily practice and saw their clinic sessions as a positive opportunity to practice high-quality medicine that they aspired to.

This intervention represents a new and effective approach to a common problem which causes much distress and substantial demand to existing health services.

## Research recommendations

We have four recommendations for further research: translation across language and culture; shortening the intervention to get elements into routine care; maximising the value of negative tests; and adapting the REAL model to other clinical settings.

### *Translation across language and culture*

Persistent physical symptoms are ubiquitous across cultures and ethnicity although their forms in different cultures differ. This study excluded non-English speakers in order to preserve experimental power to demonstrate an effect if present. Furthermore, some of the explanatory language may have been less appropriate in some cultures. A relatively focused observational study should examine the REAL consultation model when applied in different language or cultural settings. Measures of fidelity and qualitative observation of consultation content should be sufficient to demonstrate that the intervention is being delivered and received in the way intended in the original specification.

### *Shortening the intervention to make it deliverable in routine care*

The Symptoms Clinic intervention was deliberately developed to be intensive in order to maximise the 'dose' of intervention delivered to the patient. However, it is likely that elements of REAL can be shortened to be incorporated into more routine consultations. This may be particularly relevant when some personal continuity of care is possible or the consultation is building on a previous therapeutic partnership. This is likely to involve a mixture of co-design with GPs and qualitative evaluation and possibly the use of simulated or analogue patients. An additional benefit of this may be that it leads to a reduction in low-value healthcare referrals.

### *Maximising the value of negative diagnostic tests*

In MSS3 we did not observe a reduction in GP consultation or referrals for diagnostic tests or specialist opinion. This may have been partly due to changes to access and thresholds for referral following the COVID-19 pandemic. However, from the literature it appears that interventions which have had an impact on symptoms have not led to a reduction in healthcare costs.<sup>75</sup> Previous research has shown that while GPs claim that they make

low-value referrals to satisfy patients, they overestimate what patients expect.<sup>94</sup> We suggest that while reduction of medical investigations sounds like a laudable aim, it reduces the opportunity to pick up serious illnesses such as cancer at an earlier stage. An alternative approach would be to use the explanatory models developed in the Symptoms Clinic as part of a strategy – which all referrers could use – for maximising the reassurance that comes from negative tests.

### *Adapting the REAL model for delivery by other professionals or in other clinical settings*

While the Symptoms Clinic model requires the healthcare professional to be able to operate in multiple 'layers' of explanation and across a wide range of symptoms/syndromes, it may be that this can be delivered by other specially trained professionals such as nurses. It should also be possible to develop and test more problem-specific models using the REAL framework: for example fibromyalgia or functional voice problems. While this would still require the practitioner to have the skills and resources to operate across the multiple layers of explanation, it would narrow the breadth of explanations needed. Here, the model could be adapted for use by existing professionals, for instance an allied health professional or a clinical nurse specialist. Because MSS3 took a very heterogeneous population of people with symptoms, it could be reasonable to assume that if the intervention can be shown to be delivered consistently in a new setting, one could expect comparable outcomes (i.e. we are not advocating a suite of fully powered trials, one for each setting).

## Conclusions

The Symptoms Clinic intervention is a series of long semistructured consultations with a specially trained 'extended-role' GP, for patients with multiple persistent physical symptoms. We examined its effectiveness in a large well-conducted randomised controlled trial and found that it can be taught and delivered with a high level of fidelity. Despite this, it requires substantial time and supervised rehearsal before it can be used even by experienced GPs.

The intervention was effective in terms of the primary outcome measure. The adjusted between-group difference was a significant reduction of 1.8 points (95% CI -2.67 to -0.97) in PHQ-15 at 1 year after enrolment and at least 9 months after completion of the intervention. The number needed to treat to produce a substantial

improvement of 4.6 points (twice the clinically important difference) was five.

While the clinic increased costs, the gain in quality of life was such that the incremental cost-effectiveness ratio (ICER) was less than £16,000/QALY with a 69% probability of being cost-effective at a threshold value of £20,000 per QALY. The in-depth process analysis indicated that the hypothesised mechanism underpinning the intervention – that a coproduced clinical explanation acts as a bridge between validation of the individual and action to manage symptoms – occurred and is a plausible explanation for the observed benefits.

This is the first study to provide strong evidence for the effectiveness of a primary care-based consultation intervention for people with persistent physical symptoms.

## Additional information

### CRediT contribution statement

**Christopher Burton** (<https://orcid.org/0000-0003-0233-2431>): Conceptualisation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualisation, Writing – original draft, Writing – reviewing and editing.

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**Vincent Deary** (<https://orcid.org/0000-0001-6115-9259>): Conceptualisation, Funding acquisition, Methodology, Supervision, Writing – reviewing and editing.

### Other contributions

Patient and public involvement: Ellen Mallender.



## Acknowledgements

We thank the patients who participated in this trial, the extended-role GPs who delivered the trial intervention, and staff at the National Institute for Health and Care Research (NIHR) Clinical Research Network.

We thank the independent Trial Steering Committee, Professor Richard Morriss (Chair), Professor Catherine Hewitt, Professor Carolyn Chew-Graham, Professor Laura Bojke, Mr Neal Fitzgerald and Ms Liza Barnett-Tweedie, and the independent Data Monitoring and Ethics Committee, Professor David Kessler, Professor Stefan Priebe and Miss Daisy Gaunt.

## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

## Ethics statement

The trial was approved by the Greater Manchester Central Research Ethics Committee (Reference 18/NW/0422) on 25 June 2018.

## Information governance statement

The University of Sheffield is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679 under the Data Protection legislation. The University of Sheffield is the Data Processor; NHS South Yorkshire Integrated Care Board (previously NHS Sheffield Clinical Commissioning Group) is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for NHS South Yorkshire Integrated Care Board's Data Protection Officer here: <https://southyorkshire.icb.nhs.uk/contact-us>.

## Disclosure of interests

**Full disclosure of interests:** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/KWGX2382>.

**Primary conflicts of interest:** Christopher Burton has received publisher royalties and speaker honoraria in relation to persistent physical symptoms. He was a member of the following NIHR panels HSDR – Commissioned – Associate Board Members end date (01/03/2016). HTA MPOH Panel from January 2015 to May 2018. HTA Prioritisation Committee A (Out of hospital) from January 2015 to March 2018. Jeremy Dawson was a member of the following NIHR committees: HS&DR Commissioned – Board Members July 2013 to March 2016. HS&DR Commissioned R&R (Bird) Sub Board July 2013 to May 2016. HS&DR Evidence

Synthesis Sub Board from May 2016 to November 2016. HS&DR Funding Committee Members from July 2013 to July 2018. In his capacity as a member of the HS&DR Board, he attended the meeting in September 2016 at which the study was first considered. This was before the CI and study had relocated from the University of Aberdeen to The University of Sheffield (January 2017). Jeremy Dawson was absent from subsequent discussion of the study at the Board meeting in May 2017. Cindy Cooper leads the Sheffield Clinical Trials Unit which was funded by NIHR to end date August 2021 and was a member of the NIHR CTU Standing Advisory Committee from July 2016 to September 2023.

None of the other authors have any competing interests to declare.

## Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health and Social Care Delivery Research programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

## Publications

Mooney C, White DA, Dawson J, Deary V, Fryer K, Greco M, *et al.* Study protocol for the Multiple Symptoms Study 3: a pragmatic, randomised controlled trial of a clinic for patients with persistent (medically unexplained) physical symptoms. *BMJ Open* 2022;**12**:e066511. <https://doi.org/10.1136/bmjopen-2022-066511>

Fryer K, Sanders T, Greco M, Mooney C, Deary V, Burton C. Recognition, explanation, action, learning: Teaching and delivery of a consultation model for persistent physical symptoms. *Patient Educ Counselling* 2023;**115**:107870. <https://doi.org/10.1016/j.pec.2023.107870>

Burton C, Mooney C, Sutton L, White D, Dawson J, Neilson AR, *et al.* Effectiveness of a symptom-clinic intervention delivered by general practitioners with an extended role for people with multiple and persistent physical symptoms in England: the Multiple Symptoms Study 3 pragmatic, multicentre, parallel-group, individually randomised controlled trial. *Lancet* 2024;**403**:2619–29. [https://doi.org/10.1016/S0140-6736\(24\)00700-1](https://doi.org/10.1016/S0140-6736(24)00700-1)

Sanders T, Fryer K, Greco M, Mooney C, Deary V, Burton C. Explanation for symptoms and biographical repair in a clinic for persistent physical symptoms. *SSM – Qualitative Res Health* 2024;5:100438. <https://doi.org/10.1016/j.ssmqr.2024.100438>

Neilson AR, Mooney C, Sutton L, White D, Dawson J, Rowlands G, *et al*. Cost-effectiveness of an extended-role general practitioner clinic for persistent physical symptoms: results from the Multiple Symptoms Study 3 pragmatic randomized controlled trial. *Value Health* 2024;27:1710–21. <https://doi.org/10.1016/j.jval.2024.09.015>

Conference papers

Burton C. Reassurance and explanation in primary care management of somatic symptoms. (Keynote), European Association for Psychosomatic Medicine, Rotterdam 2018.

Fryer K. Choosing analytical approaches for a process evaluation for a complex intervention, SAPC Trent Regional Conference 2019.

Greco M. Making sense of symptoms: the role of metaphor and narrative construction (Keynote). European Conference on Symptoms in Primary Care, Sheffield 2019.

Fryer K. Persistent physical symptoms and the self: qualitative analysis of consultations and patient interviews. UK Primary Care Mental Health Conference, York 2020.

Fryer K. Assessing fidelity of delivery of a complex intervention to help people live well with persistent symptoms. SAPC Annual Scientific Meeting Online 2021.

Burton C. Recognition, Explanation, Action, Learning: a teachable framework for consultations. European Association for Psychosomatic Medicine Wroclaw 2023.

Sanders, T. Biographical repair in a clinic for persistent physical symptoms. SAPC Annual Scientific Meeting, Brighton 2023.

Burton, C. What is the effectiveness and safety of an extended-role GP ‘Symptoms Clinic’? Results of Multiple Symptoms Study 3. SAPC Annual Scientific Meeting, Brighton 2023.

Sanders, T. Biographical repair in a clinic for persistent physical symptoms. European Conference on Symptoms in Primary Care, Tromso 2023.

Greco Awakening the sense of the possible: the Symptoms Clinic as a liminal space. 4th European Conference on Symptoms in Primary Care, Tromso 2023.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN57050216.

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health and Social Care Delivery Research programme as award number 15/136/07.

This synopsis provided an overview of the research award Multiple Symptoms Study 3: pragmatic trial of a community based clinic for patients with persistent (medically unexplained) physical symptoms. For more information about this research please view the award page (<https://www.fundingawards.nihr.ac.uk/award/15/136/07>)

About this synopsis

The contractual start date for this research was in February 2018. This article began editorial review in August 2023 and was accepted for publication in August 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health and Social Care Delivery Research editors and publisher have tried to ensure the accuracy of the authors’ article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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List of abbreviations

CBT	cognitive–behavioural therapy
CEAC	cost-effectiveness acceptability curves
CID	clinically important difference
CTRU	Clinical Trials Research Unit
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ER-GP	extended-role GP

GAD-7	Generalised Anxiety Disorder-7
HLS-EU	European Health Literacy Survey
ICB	Integrated Care Board
ICECAP-A	ICEpop CAPability measure for Adults
ICERs	incremental cost-effectiveness ratios
IMD	Index of Multiple Deprivation
PCN	Primary Care Network
PGIC	Patient-reported Global Indicator of Change
PHQ	Patient Health Questionnaire
PPI	patient and public involvement
PROMIS-APS	Patient-reported Outcomes Measurement Information System-Ability to Participate in Social Roles and Activities
PSSRU	Personal Social Service Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REAL	Recognition, Explanation, Action and Learning
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
SOPs	standard operating procedures
SSD-12	Somatic Symptoms Disorder – B criteria scale
TSC	Trial Steering Group

## References

- Steinbrecher N, Koerber S, Frieser D, Hiller W. The prevalence of medically unexplained symptoms in primary care. *Psychosomatics* 2011;**52**:263–71. <https://doi.org/10.1016/j.psym.2011.01.007>
- Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *J Psychosom Res* 2001;**51**:361–7.
- Verhaak PF, Meijer SA, Visser AP, Wolters G. Persistent presentation of medically unexplained symptoms in general practice. *Fam Pract* 2006;**23**:414–20.
- McGorm K, Burton C, Weller D, Murray G, Sharpe M. Patients repeatedly referred to secondary care with symptoms unexplained by organic disease: prevalence, characteristics and referral pattern. *Fam Pract* 2010;**27**:479–86.
- Burton C, McGorm K, Richardson G, Weller D, Sharpe M. Health care costs incurred by patients repeatedly referred to secondary care with medically unexplained symptoms: a case control study. *J Psychosom Res* 2012;**72**:242–7.
- Birmingham SL, Cohen A, Hague J, Parsonage M. The cost of somatisation among the working-age population in England for the year 2008–2009. *Ment Health Fam Med* 2010;**7**:71–84.
- Rosendal M, Olde Hartman TC, Aamland A, van der Horst H, Lucassen P, Budtz-Lilly A, Burton C. 'Medically unexplained' symptoms and symptom disorders in primary care: prognosis-based recognition and classification. *BMC Fam Pract* 2017;**18**:18. <https://doi.org/10.1186/s12875-017-0592-6>
- Chen WG, Schloesser D, Arensdorf AM, Simmons JM, Cui C, Valentino R, et al. The emerging science of interoception: sensing, integrating, interpreting, and regulating signals within the self. *Trends Neurosci* 2021;**44**:3–16. <https://doi.org/10.1016/j.tins.2020.10.007>
- Henningsen P, Gundel H, Kop WJ, Löwe B, Martin A, Rief W, et al.; EURONET-SOMA Group. Persistent physical symptoms as perceptual dysregulation: a neuropsychobehavioral model and its clinical implications. *Psychosom Med* 2018;**80**:422–31.
- Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clin Psychol Rev* 2007;**27**:781–97.
- Van Den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. *Neurosci Biobehavioral Rev* 2017;**74**:185–203.
- Wardrope A, Reuber M. The hermeneutics of symptoms. *Med Health Care Philos* 2022;**25**:395–412.
- Fitzcharles M-A, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociceptive pain: towards an understanding of prevalent pain conditions. *Lancet (London, England)* 2021;**397**:2098–110.
- Creed F, Guthrie E, Fink P, Henningsen P, Rief W, Sharpe M, White P. Is there a better term than 'medically unexplained symptoms'? *J Psychosom Res* 2010;**68**:5–8.
- Stone J, Carson A. 'Organic' and 'non-organic': a tale of two turnips. *Pract Neurol* 2017;**17**:417–8. <https://doi.org/10.1136/practneurol-2017-001660>
- Picariello F, Ali S, Moss-Morris R, Chalder T. The most popular terms for medically unexplained

- symptoms: the views of CFS patients. *J Psychosom Res* 2015;**78**:420–6.
17. Rolfe A, Burton C. Reassurance after diagnostic testing with a low pretest probability of serious disease: systematic review and meta-analysis. *JAMA Internal Med* 2013;**173**:407–16.
  18. Johansen M-L, Risor MB. What is the problem with medically unexplained symptoms for GPs? A meta-synthesis of qualitative studies. *Patient Educ Couns* 2016;**100**:647–54.
  19. Nettleton S, Watt I, O'Malley L, Duffey P. Understanding the narratives of people who live with medically unexplained illness. *Patient Educ Couns* 2005;**56**:205–10.
  20. Burton C, Lucassen P, Aamland A, Hartman TO. Explaining symptoms after negative tests: towards a rational explanation. *J R Soc Med* 2015;**108**:84–8. <https://doi.org/10.1177/0141076814559082>
  21. Morton L, Elliott A, Cleland J, Deary V, Burton C. A taxonomy of explanations in a general practitioner clinic for patients with persistent 'medically unexplained' physical symptoms. *Patient Educ Couns* 2017;**100**:224–30.
  22. Aiarzaguena JM, Grandes G, Gaminde I, Salazar A, Sánchez A, Ariño J. A randomized controlled clinical trial of a psychosocial and communication intervention carried out by GPs for patients with medically unexplained symptoms. *Psychological Med* 2007;**37**:283–94.
  23. Burton C, Weller D, Marsden W, Worth A, Sharpe M. A primary care symptoms clinic for patients with medically unexplained symptoms: pilot randomised trial. *BMJ Open* 2012;**2**:000513.
  24. Leaviss J, Davis S, Ren S, Hamilton J, Scope A, Booth A, et al. Behavioural modification interventions for medically unexplained symptoms in primary care: systematic reviews and economic evaluation. *Health Technol Assess* 2020;**24**:1–490.
  25. Byrne AK, Scantlebury A, Jones K, Doherty L, Torgerson DJ. Communication interventions for medically unexplained symptom conditions in general practice: a systematic review and meta-analysis of randomised controlled trials. *PLOS ONE* 2022;**17**:e0277538.
  26. Morton L, Elliott A, Thomas R, Cleland J, Deary V, Burton C. Developmental study of treatment fidelity, safety and acceptability of a Symptoms Clinic intervention delivered by General Practitioners to patients with multiple medically unexplained symptoms. *J Psychosom Res* 2016;**84**:37–43.
  27. den Boeft M, Huisman D, Morton L, Lucassen P, van der Wouden JC, Westerman MJ, et al. Negotiating explanations: doctor–patient communication with patients with medically unexplained symptoms—a qualitative analysis. *Fam Pract* 2017;**34**:107–13.
  28. Fryer K, Sanders T, Greco M, Mooney C, Deary V, Burton C. Recognition, explanation, action, learning: teaching and delivery of a consultation model for persistent physical symptoms. *Patient Educ Couns* 2023;**115**:107870. <https://doi.org/10.1016/j.pec.2023.107870>
  29. Mooney C, White DA, Dawson J, Deary V, Fryer K, Greco M, et al. Study protocol for the Multiple Symptoms Study 3: a pragmatic, randomised controlled trial of a clinic for patients with persistent (medically unexplained) physical symptoms. *BMJ Open* 2022;**12**:e066511.
  30. Royal College of General Practitioners. *RCGP guide to GP Clinical Extended Roles*. London: Royal College of General Practitioners; 2021.
  31. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36.
  32. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92.
  33. Simon J, Anand P, Gray A, Rugkåsa J, Yeeles K, Burns T. Operationalising the capability approach for outcome measurement in mental health research. *Soc Sci Med* 2013;**98**:187–96.
  34. Al-Janabi H, N Flynn T, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Qual Life Res* 2012;**21**:167–76.
  35. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;**16**:606–13.
  36. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;**166**:1092–7.
  37. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007;**146**:317–25.
  38. Hahn EA, DeWalt DA, Bode RK, Garcia SF, DeVellis RF, Correia H, Cella D; PROMIS Cooperative Group. New English and Spanish social health measures will facilitate evaluating health determinants. *Health Psychol* 2014;**33**:490–9.
  39. Toussaint A, Lowe B, Brahler E, Jordan P. The Somatic Symptom Disorder – B Criteria Scale (SSD-12): factorial structure, validity and population-based norms. *J Psychosom Res* 2017;**97**:9–17.



40. Pelikan JM, Ganahl K. Measuring health literacy in general populations: primary findings from the HLS-EU Consortium's health literacy assessment effort. *Stud Health Technol Inform* 2017;**240**:34–59.
41. Burton C, Mooney C, Sutton L, White D, Dawson J, Neilson A, *et al*. Effectiveness of a symptom-clinic intervention delivered by general practitioners with an extended role for people with multiple and persistent physical symptoms in England: the Multiple Symptoms Study 3 pragmatic, multicentre, parallel-group, individually randomised controlled trial. *Lancet* 2024;**403**:2619–29. [https://doi.org/10.1016/s0140-6736\(24\)00700-1](https://doi.org/10.1016/s0140-6736(24)00700-1)
42. Neilson AR, Mooney C, Sutton L, White D, Dawson J, Rowlands G, *et al*. Cost-effectiveness of an extended-role general practitioner clinic for persistent physical symptoms: results from the Multiple Symptoms Study 3 pragmatic randomized controlled trial. *Value Health* 2024;**27**:1710–21. <https://doi.org/10.1016/j.jval.2024.09.015>
43. Sanders T, Fryer K, Greco M, Burton C. Explanation for symptoms and biographical repair in a clinic for persistent physical symptoms. *SSM Qual Res Health* 2024;**5**:100438. <https://doi.org/10.1016/j.ssmqr.2024.100438>
44. Toussaint A, Kroenke K, Baye F, Lourens S. Comparing the Patient Health Questionnaire – 15 and the Somatic Symptom Scale – 8 as measures of somatic symptom burden. *J Psychosom Res* 2017;**101**:44–50. <https://doi.org/10.1016/j.jpsychores.2017.08.002>
45. Charmaz K. Loss of self: a fundamental form of suffering in the chronically ill. *Sociol Health Illn* 1983;**5**:168–95. <https://doi.org/10.1111/1467-9566.ep10491512>
46. Bury M. Chronic illness as biographical disruption. *Sociol Health Illn* 1982;**4**:167–82.
47. Lawton J. Lay experiences of health and illness: past research and future agendas. *Sociol Health Illn* 2003;**25**:23–40. <https://doi.org/10.1111/1467-9566.00338>
48. Williams G. The genesis of chronic illness: narrative reconstruction. *Sociol Health Illn* 1984;**6**:175–200. <https://doi.org/10.1111/1467-9566.ep10778250>
49. Kuluski K, Dow C, Locock L, Lyons RF, Lasserson D. Life interrupted and life regained? Coping with stroke at a young age. *Int J Qual Stud Health Well-being* 2014;**9**:22252. <https://doi.org/10.3402/qhw.v9.22252>
50. Locock L, Ziebland S, Dumelow C. Biographical disruption, abruption and repair in the context of motor neurone disease. *Sociol Health Illn* 2009;**31**:1043–58. <https://doi.org/10.1111/j.1467-9566.2009.01176.x>
51. Burton C. Beyond somatisation: a review of the understanding and management of medically unexplained physical symptoms (MUPS). *Br J General Practice* 2003;**53**:233–41.
52. Salmon P. Conflict, collusion or collaboration in consultations about medically unexplained symptoms: the need for a curriculum of medical explanation. *Patient Educ Couns* 2007;**67**:246–54.
53. Salmon P, Humphris GM, Ring A, Davies JC, Dowrick CF. Why do primary care physicians propose medical care to patients with medically unexplained symptoms? A new method of sequence analysis to test theories of patient pressure. *Psychosomatic Med* 2006;**68**:570–7.
54. Dowrick CF, Ring A, Humphris GM, Salmon P. Normalisation of unexplained symptoms by general practitioners: a functional typology. *Br J General Practice* 2004;**54**:165–70.
55. Morriss R, Dowrick C, Salmon P, Peters S, Dunn G, Rogers A, *et al*. Cluster randomised controlled trial of training practices in reattribution for medically unexplained symptoms. *Br J Psychiatry* 2007;**191**:536–42.
56. Rosendal M, Blankenstein A, Morriss R, Fink P, Sharpe M, Burton C. Enhanced care by generalists for functional somatic symptoms and disorders in primary care. *Cochrane Database Systematic Rev* 2013;**10**:CD008142. <https://doi.org/10.1002/14651858.CD008142.pub2>
57. Burbaum C, Stresing AM, Fritzsche K, Auer P, Wirsching M, Lucius-Hoene G. Medically unexplained symptoms as a threat to patients' identity? A conversation analysis of patients' reactions to psychosomatic attributions. *Patient Educ Couns* 2010;**79**:207–17. <https://doi.org/10.1016/j.pec.2009.09.043>
58. Burton C, Fink P, Henningsen P, Löwe B, Rief W; EURONET-SOMA Group. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. *BMC Med* 2020;**18**:34. <https://doi.org/10.1186/s12916-020-1505-4>
59. Weigel A, Hüsing P, Junge M, Löwe B. Helpful explanatory models for persistent somatic symptoms (HERMES): results of a three-arm randomized-controlled pilot trial. *J Psychosom Res* 2023;**172**:111419. <https://doi.org/10.1016/j.jpsychores.2023.111419>
60. Reeve J, Byng R. Realising the full potential of primary care: uniting the 'two faces' of generalism. *Br J Gen Pract* 2017;**67**:292–3. <https://doi.org/10.3399/bjgp17X691589>
61. Sattel H, Lahmann C, Gundel H, Guthrie E, Kruse J, Noll-Hussong M, *et al*. Brief psychodynamic interpersonal psychotherapy for patients with multisomatoform disorder: randomised controlled trial.



- Br J Psychiatry* 2012;**200**:60–7. <https://doi.org/10.1192/bjp.bp.111.093526>
62. Chalder T, Patel M, Hotopf M, Moss-Morris R, Ashworth M, Watts K, et al. Efficacy of therapist-delivered transdiagnostic CBT for patients with persistent physical symptoms in secondary care: a randomised controlled trial. *Psychol Med* 2021;**53**:1–11. <https://doi.org/10.1017/s0033291721001793>
  63. Hammarström P, Rosendahl S, Gruber M, Nordin S. Somatic symptoms in burnout in a general adult population. *J Psychosom Res* 2023;**168**:111217.
  64. Hinz A, Ernst J, Glaesmer H, Brähler E, Rauscher FG, Petrowski K, Kocalevent R-D. Frequency of somatic symptoms in the general population: normative values for the Patient Health Questionnaire-15 (PHQ-15). *J Psychosom Res* 2017;**96**:27–31. <https://doi.org/10.1016/j.jpsychores.2016.12.017>
  65. Larisch A, Schweickhardt A, Wirsching M, Fritzsche K. Psychosocial interventions for somatizing patients by the general practitioner: a randomized controlled trial. *J Psychosom Res* 2004;**57**:507–14.
  66. Blankenstein AH, Van H, Schilte AF, de Vries D, Zaat JO, Knottnerus JA, et al. Development and feasibility of a modified reattribution model for somatising patients, applied by their own general practitioners. *Patient Educ Couns* 2002;**47**:229–35.
  67. Patel M, James K, Moss-Morris R, Ashworth M, Husain M, Hotopf M, et al. Integrated GP care for patients with persistent physical symptoms: feasibility cluster randomised trial. *BMC Fam Pract* 2020;**21**:226. <https://doi.org/10.1186/s12875-020-01269-9>
  68. van Westrienen PE, de Wit N, Toonders S, Veenhof C, Gerrits M, Pisters M. Effectiveness of a blended multidisciplinary intervention for patients with moderate medically unexplained physical symptoms (PARASOL): a cluster randomized clinical trial. *PLOS ONE* 2023;**18**:e0283162. <https://doi.org/10.1371/journal.pone.0283162>
  69. Sitnikova K, Finch AP, Leone SS, Bosmans JE, van Marwijk HWJ, van der Horst HE, van der Wouden JC. A brief cognitive behavioural intervention is cost-effective for primary care patients with medically unexplained physical symptoms compared to usual care. *J Psychosom Res* 2020;**138**:110217. <https://doi.org/10.1016/j.jpsychores.2020.110217>
  70. Wortman MSH, van der Wouden JC, Twisk JWR, Visser B, Assendelft WJJ, van der Horst HE, Olde Hartman TC. Effectiveness of psychosomatic therapy for patients with persistent somatic symptoms: results from the CORPUS randomised controlled trial in primary care. *J Psychosom Res* 2023;**167**:111178. <https://doi.org/10.1016/j.jpsychores.2023.111178>
  71. Saunders C, Treufeldt H, Rask MT, Pedersen HF, Rask C, Burton C, Frostholm L. Explanations for functional somatic symptoms across European treatment settings: a mixed methods study. *J Psychosom Res* 2023;**166**:111155.
  72. Konnopka A, Schaefer R, Heinrich S, Kaufmann C, Lupp M, Herzog W, König H-H. Economics of medically unexplained symptoms: a systematic review of the literature. *Psychother Psychosom* 2012;**81**:265–75. <https://doi.org/10.1159/000337349>
  73. Wortman MSH, Lokkerbol J, van der Wouden JC, Visser B, van der Horst HE, Olde Hartman TC. Cost-effectiveness of interventions for medically unexplained symptoms: a systematic review. *PLOS ONE* 2018;**13**:e0205278. <https://doi.org/10.1371/journal.pone.0205278>
  74. Chernyak N, Sattel H, Scheer M, Baechle C, Kruse J, Henningsen P, Icks A. Economic evaluation of brief psychodynamic interpersonal therapy in patients with multisomatoform disorder. *PLOS ONE* 2014;**9**:e83894. <https://doi.org/10.1371/journal.pone.0083894>
  75. Jones B, de C Williams AC. CBT to reduce healthcare use for medically unexplained symptoms: systematic review and meta-analysis. *Br J General Practice* 2019;**69**:e262–9.
  76. Polakovská L, Řiháček T. What is it like to live with medically unexplained physical symptoms? A qualitative meta-summary. *Psychol Health* 2022;**37**:580–96. <https://doi.org/10.1080/08870446.2021.1901900>
  77. Barends H, Botman F, Walstock E, Dessel NC, van der Wouden JC, Olde Hartman T, et al. Lost in fragmentation – care coordination when somatic symptoms persist: a qualitative study of patients' experiences. *Br J Gen Pract* 2022;**72**:e790–8. <https://doi.org/10.3399/bjgp.2021.0566>
  78. Wortman MSH, Olde Hartman TC, van der Wouden JC, Dankers S, Visser B, Assendelft WJJ, van der Horst HE. Perceived working mechanisms of psychosomatic therapy in patients with persistent somatic symptoms in primary care: a qualitative study. *BMJ Open* 2022;**12**:e057145.
  79. Slatman J. Reclaiming embodiment in medically unexplained physical symptoms (MUPS). In: Aho K, editor, *Existential Medicine: Essays on Health and Illness*. Lanham: Rowman & Littlefield International; 2018. pp. 101–14.
  80. Terpstra T, Gol JM, Lucassen P, Houwen J, van Dulmen S, Berger MY, et al. Explanations for medically unexplained symptoms: a qualitative study on GPs in daily practice consultations. *Fam Pract* 2020;**37**:124–30. <https://doi.org/10.1093/fampra/cmz032>

81. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, *et al.* The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010;**62**:600–10. <https://doi.org/10.1002/acr.20140>
82. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol* 2014;**6**:71–80. <https://doi.org/10.2147/clep.S40245>
83. Yunus MB. The role of gender in fibromyalgia syndrome. *Curr Rheumatol Rep* 2001;**3**:128–34. <https://doi.org/10.1007/s11926-001-0008-3>
84. Harkness EF, Grant L, O'Brien SJ, Chew-Graham CA, Thompson DG. Using read codes to identify patients with irritable bowel syndrome in general practice: a database study. *BMC Fam Pract* 2013;**14**:183. <https://doi.org/10.1186/1471-2296-14-183>
85. Simon G, Gater R, Kisely S, Piccinelli M. Somatic symptoms of distress: an international primary care study. *Psychosom Med* 1996;**58**:481–8.
86. NIHR. *Improving Inclusion of Under-Served Groups in Clinical Research: Guidance from the NIHR-INCLUDE Project*. UK: NIHR, 2020.
87. Baccolini V, Rosso A, Di Paolo C, Isonne C, Salerno C, Migliara G, *et al.* What is the prevalence of low health literacy in European Union member states? A systematic review and meta-analysis. *J Gen Intern Med* 2021;**36**:753–61. <https://doi.org/10.1007/s11606-020-06407-8>
88. Rowlands G, Protheroe J, Winkley J, Richardson M, Seed PT, Rudd R. A mismatch between population health literacy and the complexity of health information: an observational study. *Br J General Practice* 2015;**65**:e379–86. <https://doi.org/10.3399/bjgp15X685285>
89. Shattock L, Williamson H, Caldwell K, Anderson K, Peters S. 'They've just got symptoms without science': medical trainees' acquisition of negative attitudes towards patients with medically unexplained symptoms. *Patient Educ Couns* 2013;**91**:249–54.
90. Joyce E, Cowing J, Lazarus C, Smith C, Zenzuck V, Peters S. Training tomorrow's doctors to explain 'medically unexplained' physical symptoms: an examination of UK medical educators' views of barriers and solutions. *Patient Educ Couns* 2018;**101**:878–84.
91. Rosmalen JGM, Burton C, Carson A, Cosci F, Frostholt L, Lehnen N, *et al.* The European Training Network ETUDE (Encompassing Training in fUnc-tional Disorders across Europe): a new research and training program of the EURONET-SOMA network recruiting 15 early stage researchers. *J Psychosom Res* 2021;**141**:110345. <https://doi.org/10.1016/j.jpsychores.2020.110345>
92. Weigel A, Husing P, Kohlmann S, Lehmann M, Shedden-Mora M, Toussaint A, Löwe B; EURONET-SOMA Group. A European research network to improve diagnosis, treatment and care for patients with persistent somatic symptoms: work report of the EURONET-SOMA conference series. *J Psychosom Res* 2017;**97**:136–8.
93. Scope A, Leaviss J, Booth A, Sutton A, Parry G, Buszewicz M, Moss-Morris R. The acceptability of primary care or community-based behavioural interventions for persistent physical symptoms: qualitative systematic review. *Br J Health Psychol* 2021;**26**:1069–94.
94. Salmon P, Humphris GM, Ring A, Davies JC, Dowrick CF. Primary care consultations about medically unexplained symptoms: patient presentations and doctor responses that influence the probability of somatic intervention. *Psychosomatic Med* 2007;**69**:571–7.