14/26 Medically unexplained symptoms (MUS): primary care intervention.

PROJECT TITLE

14/26 Medically unexplained symptoms (MUS): primary care intervention.

PLANNED INVESTIGATION

Study Design An evidence synthesis with decision analytic modelling following a systematic review of available quantitative and qualitative studies evaluating the clinical and cost-effectiveness and acceptability of primary care or community-based behaviour modification interventions for medically unexplained symptoms.

Research Aim

This project will evaluate the clinical, cost-effectiveness and acceptability of behavioural modification interventions for Medically Unexplained Symptoms in primary care or community-based settings. The purpose of the project is to provide a comprehensive systematic review of both quantitative and qualitative studies, using rigorous methods for reviewing, evidence synthesis and cost-effectiveness modelling to evaluate the clinical effectiveness and cost-effectiveness of these interventions.

Research objectives

1. To determine the clinical effectiveness of behavioural modification interventions for MUS in primary care and community-based settings, by undertaking a full systematic review of quantitative literature.
2. To evaluate the barriers and facilitators to effectiveness and acceptability of behavioural modification interventions for MUS from the perspective of both patients and service providers, by undertaking realist synthesis following a systematic review of the available qualitative research literature.
3. To undertake meta-analysis of available evidence on clinical effectiveness, including a network meta-analysis where appropriate.
4. To identify and synthesise evidence on health economic outcomes such as healthcare resource use (e.g GP appointments), and health related quality of life (HRQoL) data from the studies included in the clinical-effectiveness review.
5. To provide new evidence on the cost-effectiveness of behavioural modification interventions for MUS conducted in a primary care or community setting, by conducting a systematic review of existing economic analyses and undertaking a *de novo* model based evaluation where there is an absence of high quality published analyses which are directly applicable to our research question
6. To explain which interventions are appropriate for which MUS patients under which circumstances (via realist synthesis)

Background

Definition of MUS

The term ‘MUS’ is used to cover a wide range of symptoms which cannot be clearly explained by a general medical condition, even after a thorough examination and any relevant investigations. Henningsen (Henningsen et al. 2005) et al (2005) describe three main types of MUS: pain in different locations, for example headache, back pain, non-cardiac chest pain (NCCP); functional disturbance of organ systems; and complaints of fatigue or exhaustion. The term MUS may be applied to patients presenting with single symptoms, multiple symptoms, or clusters of symptoms that are related to one another and are specific to a certain organ system or medical specialty, for example chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), or fibromyalgia. The latter are usually referred to as functional somatic syndromes (FSS) (Wessely et al., 1999). Patients presenting with MUS may vary in terms of reported severity i.e. number of symptoms, functional disability or quality of life, and duration of symptoms.

Diagnosis of MUS may be made either by use of a validated instrument such as the PHQ-15 (Kroenke et al 2002), Screener for somatoform disorders (SOMS, Rief 1997), the Bradford Somatic Inventory (BSI, Mumford 1991), or by clinical judgement, usually by a general practitioner. Hoedeman et al 2010 describe a continuum of severity for MUS, ranging from short-term or incidental to persisting and

recurrent. Most of the functional somatic syndromes are diagnosed according to published diagnostic criteria which include specified symptom criteria alongside the exclusion of medical and or psychiatric conditions which may mimic similar symptoms (e.g. CFS may be diagnosed by the Fukuda Diagnostic Criteria, Fukuda et al 1994; Functional Gastrointestinal Disorders may be diagnosed by the Rome 111 Diagnostic Criteria; Fibromyalgia may be diagnosed by the American College of Rheumatology 2010 Diagnostic Criteria, ACD 2010).

The presence of MUS is also a key feature of a range of somatoform disorders. These include somatisation disorder, pain disorder, undifferentiated somatoform disorder and unspecified somatisation disorder. Diagnosis of any of the somatoform disorders is made by clinical structured interview, with patients meeting diagnostic criteria according to the DSM IV, or V or the ICD-9 or 10. Other acknowledged somatoform disorders that have their own diagnostic criteria include bodily distress syndrome, bodily distress disorder, and complex somatic symptom disorder.

The proposed review will use a broad definition of MUS, which encompasses all of the above definitions, so that the term MUS will be used to refer to any of the following definitions: i) the occurrence of physical symptoms in the absence of clear physical pathology, ii) to functional somatic syndromes such as CFS, IBS or fibromyalgia, iii) the DSM-IV (and more recently V) somatoform disorders, and iv) somatoform disorders that have their own diagnostic criteria e.g. bodily distress syndrome. The reason for this broad definition is that there is clear overlap between these groups and as yet no consensus as to the validity of one syndrome (i.e. MUS) versus many (i.e. the various FSS). Whether patients are diagnosed with MUS as opposed to a more specific diagnosis can be an artefact of clinician or researcher preference rather a defining feature of the included patients (Fink & Schröder, 2010, Wessley et al., 1999, Shorter et al, 1995).

Prevalence and costs of MUS

A range of prevalence rates of MUS have been estimated. Edwards et al. (2010) report worldwide prevalence rates of primary care patients presenting with MUS of 25-50%. In the UK, Taylor et al report a MUS prevalence rate of 18% of consecutive attenders to UK GP practices (2012). It is estimated that this creates an annual cost to the UK National Health Service (NHS) in excess of £3.1 billion (Bermingham et al. 2010, Barksy et al 2005). Taking into account quality of life and sickness absence, wider costs to the economy were estimated at over £14 billion (Bermingham et al. 2010). The inappropriate management of MUS may result in patients undergoing invasive and potentially harmful tests and treatments. A recent pilot study of GP practices in London found that MUS patients averaged 8 investigations per month (Commissioning Support for London 2011). Many patients with MUS have co-morbid depression/anxiety (Li et al 2009). A systematic review of the course and prognosis of MUS and somatoform disorders (Olde Hartman 2009) suggested that the prognosis for patients with MUS is influenced by the severity of the condition at baseline and by the number of symptoms. The review estimates that between 50-75% of patients with MUS will improve, whilst between 10% and 30% will see their condition deteriorate (Olde Hartman 2009).

Interventions for MUS

A wide range of interventions have been implemented in the treatment of MUS. Pharmacological interventions, for example antidepressants, are sometimes used. Reviews of pharmacological interventions have shown these to produce some improvement in responsive patients in terms of symptom severity and functioning (Kroenke 2007, Hoedeman 2010, Ford 2009).

Several types of psychological therapies have been implicated. Cognitive Behavioural Therapy (CBT) for treatment of MUS is based on the model of CBT proposed by Beck (1976), and is one of the most common interventions used for this group of patients. CBT for MUS focuses on the perpetuating cycle that maintains symptoms, distress, and disability. This type of therapy targets the relationship between cognitive, behavioural and physiological responses that are proposed to maintain symptoms (Deary 2007). Reattribution Therapy for MUS is often delivered by General Practitioners (GPs), and is based on providing a psychological explanation for somatised mental disorders. Patients are encouraged to reattribute their symptoms, and relate them to psychosocial problems. The three stages of therapy are; feeling understood; changing the agenda; and making the link (Goldberg et al 1989). Behaviour therapy,

may be delivered to MUS patients. In these cases, therapy aims to modify behaviours such as increased vigilance in detecting physical symptoms, or reducing coping behaviours such as reassurance-seeking or inactivity (Nezu et al. 2001). Relaxation therapies may be used as treatments for MUS - these include biofeedback (Buckelew et al 1998, Keefer and Blanchard), meditation-based stress reduction (Creamer et al 2000), and Qigong (Creamer et al 2000). Third-wave cognitive behavioural therapies include mindfulness for MUS, which focuses on self-regulation of attention and acceptance (van Reijvenstein 2014). Traditional psychological therapies such psychodynamic therapy have also been adopted for the treatment of MUS (Abbass et al 2009). A further category of interventions for MUS are physical therapies. Such physical therapies include Graded Exercise Therapy (GET), whereby exercise is started gradually and increased over time, and may incorporate a range of aerobic or non-aerobic exercise such as walking, pool exercise or strength training (Mannerkorpi and Iversen 2003). Physical activity interventions such as yoga or specific exercises targeting areas of pain may also be delivered. Our review will distinguish between graded and other physical activity interventions. Other therapies that have been adopted for the treatment of MUS include alternative therapies such as hypnotherapy (Witthoft and Hiller 2010) or acupuncture (Paterson et al 2011). Not all of these treatments are available on the NHS, and therefore some patients with MUS may resort to paying to access treatments that they perceive to improve their own symptoms, and where they feel they have more time to express their concerns without the pressure of a time-limited GP consultation.

Evidence for effectiveness of interventions for MUS

Reviews of evidence for the effectiveness of interventions for MUS in general are less common than reviews of individual FSS. A recent review of psychological interventions for MUS (Kleinstauber et al 2011) found that short-term psychotherapy demonstrates small effects for improvement of physical symptoms in patients with MUPS, with type and mode of therapy and profession of the therapist moderating the results (e.g. inpatient therapy was more effective, as was therapy delivered by mental health professionals. However GP delivered interventions were found to be more effective at reducing health care utilisation. Reviews of the FSS have shown that for CFS: CBT and GET improve symptom severity and functioning following treatment and are acceptable to patients (Bagnall et al 2007, Clark et al. 2011, Price (Price et al. 2008) 2008, Chambers (Chambers et al. 2006) 2006). Morriss (Morriss et al. 2010)et al (2010) found limited effectiveness for reattribution therapy. Edmonds (2004) found no significant improvement in depression following exercise therapy. For fibromyalgia, CBT has been shown to improve physical symptoms and functioning (Arnold (Arnold et al. 2012) 2012, Schneider 2009), as have exercise therapies (Schneider 2009, Marcus 2009, Busch 2007) and multicomponent therapy (Hauser (Hauser et al. 2009)2009). For IBS, psychological therapies have been shown to reduce symptoms as effectively as pharmacological therapies (Ford (Ford et al. 2009)2009), whilst Zijenbos (2009) found psychological interventions to be slightly superior to usual care or wait list controls. For other conditions, Aggarwal et al 2011 found only weak evidence of effectiveness of psychosocial interventions including CBT and biofeedback for patients with chronic orofacial pain. Champaneria (Champaneria et al. 2012)et al 2012 found psychological interventions improved pain scores for patients with chronic pelvic pain compared to no psychological intervention.

Behavioural modification interventions.

As evidenced by the existing literature, interventions for MUS are in general based around pharmacological, psychological, or physical therapeutic models. Our review will focus specifically on interventions which aim to promote behavioural change. Whilst there are a number of theoretical models of behavioural change, attempting to assign interventions designed for patients with MUS to any of these theoretical frameworks presents difficulties. For example for psychological therapies, there may be little behaviour modification theory or practice in 'pure' cognitive therapies which has been shown empirically, (e.g Castonguay et al, 1995) but in practice not many therapists will practice pure cognitive therapy - most will incorporate behavioural elements. Similarly, for physical therapies, if an intervention is based around a model of physical fitness rather than behaviour re-engagement then it could be argued that this no longer meets the criteria of a behavioural modification intervention. Many physical fitness methods involve pre-determined goals based on a patient's physiology which are set by the physiologist or sport scientist, and may not be considered as 'therapy'. We will therefore adopt a liberal definition of 'behavioural modification interventions' as 'interventions aimed to achieve behavioural change'. Interventions will include 'named' behavioural interventions such as CBT, behavioural therapy and

Graded Exercise Therapy (GET), (which incorporates principles of systematic desensitisation and behaviour modification with the aim of gradually increasing physical activity, e.g. see Bagnall et al 2002). However, we will also include any intervention where behavioural change is a stated aim of the intervention, or is listed as a primary outcome measure.

Modifying effects

Results of existing reviews suggest that the effectiveness of treatments for MUS may be modified by a number of factors. Treatment may depend on how MUS is defined. There is currently no consensus on whether to use a generic intervention protocol, where all patients with MUS receive the same treatment protocol regardless of key presenting symptoms and/or level of disability versus the use of a very specific protocol, developed for patients with a defined functional somatic or DSM syndrome. There is some suggestion from previous reviews that more specific protocols may get larger treatment effects but this has yet to be investigated systematically (Kleinstäuber et al., 2011). This is an important question as it may contribute towards the debate as to whether or not providing specific diagnoses to patients with MUS has an advantage or not.

Furthermore, the type of control condition used in RCTs may influence an intervention's effectiveness, Some studies have shown that patients with IBS respond well to placebo (Zijenbos 2009), whilst patients with CFS do not respond well (Cho et al 2005). This highlights the importance of recognising differences in the design and conduct of control conditions. Where the control condition is inactive e.g. wait list or treatment as usual, good effect sizes for the experimental intervention have been found, whilst trials with active control interventions have shown small effect sizes (Williams (Williams et al. 2012) 2012). Our review will take account of these issues by analysing differences in outcomes between a number of potential modifiers, including mode of delivery of the intervention and type of diagnosis e.g. different FSS or DSM/ICD, as described in the evidence synthesis section. We will also categorise by broad type of behavioural modification intervention, e.g. CBT, GET, behaviour therapy and will synthesise details of the experimental controls of all included trials.

Primary care interventions for patients with MUS

Interventions for MUS may be delivered in primary care settings, or after referral to secondary care e.g. to one or more specialists such as general physicians, immunologists, neurologists, haematologists, or psychiatrists (Bagnall et al 2002). In primary care, GPs may deliver behavioural modification interventions to MUS patients as part of enhanced care (encompassing techniques including CBT, reattribution or reframing). Alternatively patients with MUS may receive collaborative care, where for example a psychologist may deliver CBT within the primary care setting.

Few of the existing reviews of interventions for MUS have focused specifically on the effectiveness of interventions delivered in primary care. Edwards et al. (2010) review the literature on the treatment of MUS in primary care. Their narrative review provides a summary of current research in this area, and outlines some of the issues related to delivery of interventions in a primary care setting for example the importance of the doctor-patient relationship, involving family members in interventions and the importance of cultural considerations. They conclude that no single approach will effectively treat all MUS patients in primary care, and that care must be taken to investigate which intervention is appropriate for individual patients. Our review will seek to provide more clarity on the factors that may increase or reduce the likelihood that a primary care intervention will be effective, for example type of FSS or mode of delivery. In addition, our qualitative review and realist synthesis will add depth to these results. Other reviews suggest that delivery of an intervention within the primary care setting may provide some benefits, e.g. reduction in healthcare utilisation (Kleinstauber et al 2011), or that they may be no less effective than when conducted in secondary care settings (Garcia-Campayo (Garcia-Campayo et al. 2008)2008).

Delivering interventions in a primary care setting may also offer additional benefits, for example patients with MUS may refuse referral to services outside the primary care setting (Morriss and Gask 2009). However, the success of interventions may depend on who delivers it – CBT when delivered by a GP has been shown to be no more effective than care as usual (Arnold (Arnold et al. 2009) et al. 2009). Our review focuses only on interventions that are delivered in a primary care or community-based setting, but

we will distinguish between who delivers the intervention, e.g. GP or other therapist in order to identify differences in effectiveness or acceptability.

Acceptability of primary care interventions for MUS
Several authors suggest that the relationship between service users and service providers is key to the success of primary care interventions (Smith et al 2003, Heijmans (Heijmans et al. 2011) et al 2011, Morriss and Gask 2009). This point is emphasised by the patient representatives advising us on this application. Poor communication between GP and patient, and lack of emotional and practical support are suggested to be barriers to effective treatment of MUS, whilst creating a safe, therapeutic environment, and the importance of offering effective reassurance are highlighted as important enabling factors. (Heijmans 2011 (Heijmans, olde Hartman, van Weel-Baumgarten, Dowrick, Lucassen, & van 2011)). Therefore this review aims to add greater depth to the clinical effectiveness data by retrieving qualitative data relating to potential barriers to and facilitators of effectiveness and conducting realist synthesis of these data. This is of particular importance as a good proportion of these patients hold strong views about the biological nature of their condition and view the suggestion of a more psychological approach to treatment as invalidating their symptoms (Broom & Woodward, 1996). Refusal of behavioural treatment may ultimately affect the economics of MUS through repeated health care seeking for a more favourable solution. Understanding ways in which to make behavioural approaches more acceptable is likely to increase uptake.

In summary, this review will evaluate the quantitative evidence on the clinical and cost-effectiveness of behavioural modification interventions in primary care settings. A review of the qualitative evidence will provide a richer perspective on their acceptability.

Research methods

Search strategy for identification of intervention studies
A comprehensive search of bibliographic databases will be conducted, combining terms for MUS and related synonyms and primary care setting. Search terms for setting will be identified from a recent Cochrane review on functional somatic symptoms and disorders in primary care (Rosendal 2013). Searches will not be limited by intervention, as we anticipate overlap between interventions and inconsistencies in labels and definitions of behavioural modification interventions. Search strategies will include free-text and thesaurus terms (where available). Terms will be combined using Boolean Operators and database-specific syntax. Searches will be limited to studies conducted with Adults (18 plus years) only. We will review non-English language studies that meet our inclusion criteria if they are conducted in high income countries, i.e. with analogous health systems to the UK. Methodological search filters to identify, systematic reviews, RCTs, and qualitative research, will be utilised where appropriate.

The following databases will be searched:

- MEDLINE & MEDLINE-In-Process
- EMBASE
- CINAHL
- PsycINFO
- The Cochrane Library
- Science & Social Sciences Citation Indexes via Web of Science

All databases will be searched from inception.

Additional Search Methods

Reference lists of identified reviews and any included studies will be checked for further relevant references and, if appropriate, use the citation search facility in Web of Science to identify relevant cited references and additional studies by key authors.

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Search strategy for identification of qualitative studies

1. Qualitative research reporting the perspectives and attitudes of patients with MUS who have received behavioural interventions in UK primary care or community based settings. These may present data relating to issues that may affect the acceptability or effectiveness of interventions.
2. Qualitative research reporting the perspectives of health care providers who have delivered behavioural modification interventions to patients with MUS within UK primary care or community based settings. These may present data relating to issues that may affect the acceptability or effectiveness of interventions.
3. Qualitative research associated with (i.e. conducted alongside or supplementary to) trials of behavioural modification interventions within any primary care or community based setting.
4. In addition we will also seek to identify: Qualitative research that explains patient or provider attitudes to MUS. This research will be purposively sampled specifically to inform aspects of the realist synthesis models.

Review strategy

1. Intervention: *Behavioural modification interventions.* We will include interventions that aim to modify behaviour. These include CBT, behaviour therapy, and GET. Where the intervention is not explicitly named as a behavioural modification intervention i.e. one of the above, we will adopt a broad definition of behavioural change interventions, and will include any intervention where i) at least one primary outcome is a functional or behavioural change measure or ii) the stated explicit aim of the intervention is to change behaviour. Interventions may therefore include but will not be exclusive to a range of psychotherapies, for example CBT, behavioural therapy, psychodynamic therapy, mindfulness, reattribution therapy. Interventions may also include other physical therapies, but only where behaviour change is a specified primary outcome or treatment mechanism. Interventions with multiple components will be included where one of the components can be considered a behavioural modification technique as defined by the above criteria. Individual and group interventions will be treated as separate interventions.

2. Population: Studies of populations meeting the diagnostic criteria for MUS, MUPS, and somatoform disorders will be included. Diagnosis of MUS or MUPS may be either by validated instrument (e.g PHQ-15, SOMS, BSI) or clinician judgement. Diagnosis will not be restricted by duration, (apart from chronic pain where duration should be > 3 months), or severity e.g. number of symptoms. Patients with single symptoms will be included. Populations with FSS will be included, e.g. IBS, CFS, fibromyalgia. For somatoform disorders, diagnosis should be made by formal clinical interview and should meet criteria according to DSM IV or V, or ICD 9 or 10. Somatoform disorders will include somatisation disorder, somatoform disorders, pain disorders, persistent physical symptoms, bodily distress syndrome, bodily distress disorder, functional somatic syndrome, medically unexplained syndrome. Populations should include adults aged 18 years or over.

3. Setting: Studies in primary care or community-based settings will be included. Whilst interventions must be conducted within a primary care or community-based setting (e.g. general practice, occupational health), they may be delivered by any health care discipline within that setting. Interventions may be face-to-face or delivered at a distance e.g. by internet or telephone, and may include computer-assisted interventions. Where interventions are physiotherapy-based, these may be delivered by a community physiotherapist but not by a hospital physiotherapist. With psychological interventions, these may be delivered by a psychologist or therapist within a primary care setting, but not by a psychologist or therapist following referral to secondary or tertiary care. IAPT interventions will be included if delivered in a primary care or community-based setting.

4. Design: Relevant systematic reviews, RCTs and economic evaluations will be extracted in the first instance and assessed for quality. In addition, qualitative research concerning barriers/facilitators of the effectiveness of behavioural modification interventions from the perspective of both patients and service providers will be retrieved. In the absence of RCT data, data from non-randomised comparative studies, pseudo-experimental studies, quasi-experiments and case report/series will be considered.

5. Comparator: Studies where 'usual care' is the comparator will be included. Due to variation in terminology, studies where the comparator is 'treatment as usual', or 'wait list' will also be included. Trials with a 'placebo' control, e.g. which control for time and attention, will be included. As a number of high-quality head-to-head trials of two or more experimental interventions have been identified, head-to-head trials will also be included, where at least one arm meets the definitions outlined above.

6. Outcomes:

Primary outcomes

Patient level: Improvement in symptoms, functioning and/or health related quality of life. Measures of symptom improvement may be through assessment of severity or frequency and must be assessed using a generic or symptom specific validated instrument, for example EQ-5D/SF-36 for HRQL; Symptom Checklist (SCL) for symptom severity; Patient Health Questionnaire (PHQ-15).

Health care level: Use of healthcare resources (e.g. frequency of GP visits, diagnostic outpatient procedures, hospital admission, Emergency Department attendances).

Secondary outcomes

Depression and anxiety as diagnosed by a validated instrument e.g. Beck Depression Inventory (BDI) or Beck Anxiety Inventory (BAI), satisfaction with care, attrition (persistence and adherence).

Quality assessment and examination of bias: We will assess the quality of quantitative studies using the Cochrane Risk of Bias tool (Higgins et al, 2011) (or adapted/Cochrane psychological risk of bias tool; Lackner et al, 2004). Economic evaluations will be assessed using the Drummond quality check-list and the CHEERS statement on reporting standard.

Qualitative studies will be evaluated using the CerQual approach. CerQual (certainty of the qualitative evidence) (Glenton et al., 2013) aims to assess how much certainty can be placed in the qualitative evidence for the review finding, or in other words, how reliable the review finding is. This approach relies on assessing both the methodological quality of the individual included studies and the coherence of the review finding as defined by the extent to which a clear pattern across the individual study data is identifiable. To assess methodological quality individual studies will be appraised using an abbreviated version of the Critical Appraisal Skills Programme (CASP) quality-assessment tool for qualitative studies (CASP, 2011). The coherence of each review finding will then be assessed by looking at the extent to which a clear pattern across the data is identified and is contributed to by each individual study. This is assessed by examining whether the review finding is consistent across multiple contexts and whether it has incorporated explanations for any variation cross individual studies. Coherence is further strengthened where the individual studies contributing to the finding are drawn from a wide range of settings. Using the assessment of methodological quality and assessment of coherence together, the certainty of each review finding can be rated as high, moderate, or low.

Study selection

A two-stage sifting process for inclusion of studies, (title/abstract then full paper sift) will be undertaken. Titles and abstracts of both the quantitative and qualitative studies will be scrutinised by one assessor according to the inclusion and exclusion criteria. There will be no exclusion on the basis of quality at this stage. All studies identified for inclusion using the abstract, together with any in which a decision on inclusion was not possible from these brief details, will be obtained for more detailed appraisal. Agreement on inclusion at title/abstract sift will checked by a second reviewer for 20% of the total search results. Agreement will be calculated using the kappa statistic. If the kappa statistic is below acceptable levels (0.7) then double-sifting will be undertaken. In the event of disagreement regarding the inclusion of a study, the opinion of the MUS experts in the project team will be sought.

Study types:

Include:

*Quantitative studies***:** RCTs.
Qualitative studies: (1) Studies reporting qualitative research or qualitative data elicited via a survey or a mixed-methods study to include qualitative data on the perspectives and attitudes of patients who have received behaviour modification interventions in a primary care or community based setting. (2) Qualitative data, embedded in trial reports or in accompanying process evaluations, which can inform an understanding of how issues of acceptability are likely to affect the clinical effectiveness of interventions; (3) Qualitative data, either from separately conceived research or embedded within quantitative study reports, reporting the acceptability of interventions to health care practitioners.

Data extraction strategy for Qualitative Research Studies

Data extraction from included qualitative studies will be undertaken using a data extraction tool adapted and tailored for the precise purpose of the qualitative review. A framework for extraction will be developed to elicit data extraction elements related directly to the review question. Selective extraction of qualitative findings (Noyes and Lewin, 2011) will be undertaken on the basis that they are data pertaining to characteristics of the interventions of interest.

8. Data extraction: Identification of studies will be conducted by one reviewer and checked by another. Disagreements will be resolved between the two reviewers by discussion, with consultation with a third reviewer where agreement cannot be made. All studies fulfilling the inclusion criteria will be retrieved. Data will be extracted by one reviewer and checked by a second reviewer using a form developed specifically for the current review.
Study identification and data extraction for the cost-effectiveness review will be done by a single reviewer.

Evidence synthesis

Quantitative evidence synthesis

Published guidelines for meta-analyses produced by the Cochrane Collaboration (Ghersi et al 2011) will be adhered to when synthesising the evidence, ensuring the production of a rigorous review. Given that the intention is to compare all behavioural modification interventions, a random effects network meta-analysis will be used, providing that the relevant RCTs form a network of evidence. The random effects model will allow heterogeneity in treatment effects across studies. Random effects pairwise meta-analysis will be performed when data do not form a network of evidence.

For primary outcomes, meta-regression analysis will be used to explain any heterogeneity in treatment effects between studies where compatible data allow. The analysis will be conducted for the following potential treatment effect modifiers if data allows: i) recognised FSS, for example fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome, and 'somatoform disorders' ii) who delivers the therapy, for example GP; specialist iii) number of sessions of intervention; iv) number of symptoms; v) duration of MUS

In the case that no evidence can be synthesised, we will use narrative synthesis to summarise the results of these studies.

Qualitative synthesis

Data synthesis for Qualitative Research Studies

Qualitative meta-synthesis will be undertaken to provide added value to the quantitative analysis by indicating patient and service provider issues around the acceptability of interventions. Specifically, thematic synthesis will be used to aggregate the findings (Thomas and Harden, 2008).

Realist synthesis

Realist synthesis, adapted from the methods described by Pawson, et al. in 2002, will be used to harness the greater explanatory potential of this mixed methods review. The interaction between health service user and those delivering the service requires recognition that any intervention may alter context which,

in turn, triggers mechanisms which produce outcomes. We will therefore use realist synthesis approaches, as used in our previous NIHR projects, to extend a consideration of what works? to 'what about this set of behavioural interventions works for whom in what circumstances?"[1] We will explore intervention theory while recognising that the group of medically unexplained symptoms is heterogeneous and therefore the mechanisms of achieving outcomes may differ significantly. To handle this methodological challenge we will follow recent good practice in realist synthesis which suggests working back from common outcomes in order to identify patterns of variation. It can be argued that the range of outcomes is potentially more finite than the range of intervention components and so an outcome led approach will give structure to the review and allow the integration of quantitative and qualitative data from the preceding stages of the review. We will also use existing behavioural modification taxonomies to inform our data extraction and subsequent analysis.

Through the realist synthesis approach we hope to identify those contextual factors that are associated with an increased likelihood of triggering mechanisms that would produce the desired behavioural change, for example perceived warmth and understanding of the GP. The intention is not to generate generalisable effect sizes as will be the case for the quantitative aspects of the review but rather to inform those commissioning and specifying services by generating statements about situations in which behavioural interventions may be more likely to be effective. We will endeavour to combine the interpretative strengths of realist synthesis with the systematic review-driven requirements to generate a comprehensive audit trail to ensure transparency.

Realist synthesis methods will be used to:

1. Identify from the quantitative and qualitative literature the widest possible range of outcomes of relevance to behavioural modification of medically unexplained symptoms.
2. Work backwards from these outcomes to generate a potential causal chain with explanatory mechanisms of effect
3. Use the resultant causal chains to act as a framework for populating with data from the quantitative and qualitative review components.
4. Explore general mechanisms for effects which work across conditions while faithfully documenting variance associated with particular symptoms or other aspects of context.
5. Generate overarching programme theories for the group of behavioural modification interventions
6. Produce generic and symptom-specific pathways for evaluation of existing interventions and specification of future interventions requiring further exploration.

Realist synthesis will be particularly valuable in exploring the effect (or lack of effect) of multicomponent interventions. Potentially competing explanations will be explored in relation to clinical and patient-focused perspectives. Graphical means of presenting findings, and for integrating quantitative and qualitative data, such as flow diagrams and logic models will be used formatively with stakeholders i.e, our PPI representatives in order to elicit their observations. Systematic approaches will be used to identify and analyse theory as a means of explaining the configuration of causal pathways.

Cost-effectiveness modelling

The aim of the economic evaluation will be to examine the cost-effectiveness of interventions to improve health outcomes in patients with medically unexplained symptoms. Costs will be evaluated from an NHS and personal social services (PSS) perspective. Health benefits will be estimated using quality-adjusted-life years (QALYs) gained. Future costs and benefits will be discounted at 3.5% in line with NICE's current guidance on the methods of technology appraisal [cite NICE methods guide].

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Given that the term 'medically unexplained symptoms' may be used to cover a broad range of health conditions, it is expected that the clinical effectiveness review will identify studies covering a range of populations. As different interventions may work differently depending on the type of symptoms, separate models will be developed for each population identified within the clinical effectiveness review. The population covered by each model will be based on clinical advice regarding the differences and similarities between the populations included within the identified clinical effectiveness studies. If it becomes clear that it is not feasible to conduct a de novo economic evaluation for each separate population then de novo modelling with be prioritised based on the current extent of uncertainty over cost-effectiveness, the likelihood that further economic modelling would reduce that uncertainty and the size of the population likely to receive the intervention. This decision will take into account the evidence identified during the review of published cost-effectiveness analyses, the estimates of effectiveness, and uncertainty surrounding those estimates, based on the clinical effectiveness review, and information from the clinical advisers on the likely impact of the intervention on costs and benefits across the population likely to receive the intervention.

Where data allows we will estimate cost-effectiveness compared to the current standard of NHS care in that population (usual care). Where there is evidence for more than one type of intervention within a particular population then incremental cost-effectiveness will be estimated to determine the most cost-effective intervention for that population across a range of willingness to pay thresholds.

A systematic review of published cost-effectiveness studies will be undertaken and used to inform the structure and choice of data inputs for a *de novo* cost-effectiveness model. The methodology most appropriate for this project will be decided in the context of the data found within the literature review and the advice from our team of clinical and subject experts. The health economics lead (SD) has published cost-effectiveness analyses using Markov [cite AMD model] and decision tree methodologies [cite TLoC model] and a Decision Support Unit technical guide on the use of patient-level simulation techniques including discrete event simulation [cite PLS TSD].

Parameter estimates for the model will be obtained from a combination of sources, including the published literature. Uncertainty about parameters that are subjected to formal evidence will be characterised by drawing samples from their appropriate joint posterior distributions. For parameters where the studies yield no or minimal relevant information with which to populate the model, elicitation sessions with experts (O'Hagan et al, 2006), and scenario analyses will be considered. These sources of evidence will be combined to produce estimates of model parameters and define the associated probability distributions.

To calculate the QALY gain associated with the clinical outcomes (symptoms, functioning and HRQoL) reported in trials we will look for literature based estimates of the health-utility value associated with the clinical outcomes reported. Where they exist, generic preference based estimates of utility from instruments such as the EuroQol-5 Dimension (EQ-5D) will be used as per NICE guidance on the methods of technology appraisal. Where included studies report QALY gains measured directly within the trial, these will be reported and compared against model based estimates.

Differences in resource use between intervention(s) and usual care will be valued by applying Department of Health reference costs or PSSRU unit costs [Curtis et al] Non-pharmacological interventions such as psychological therapy, CBT or other talking therapies, will be costed based on the time and personnel required to deliver the intervention. Changes in the number or type of NHS contacts e.g GP appointments, Emergency Department attendances will be costed using NHS reference costs. Drug based interventions and changes in medication usage following intervention will be costed based on BNF list prices.

Analyses will be undertaken to identify the key parameters determining the cost-effectiveness of the intervention with the objective of identifying how secure the conclusions of the economic analyses are, given the available evidence. In addition, uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA). The information derived from PSA will be summarised graphically (within a cost-effectiveness acceptability curve). The probability that the cost-effectiveness

of the intervention is within the £20,000-£30,000 per QALY range, reflecting the thresholds typically used by NICE (NICE, 2008) in appraising health technologies will be explicitly reported.

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