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Conservative interventions for urinary or faecal incontinence, or both, in adults with multiple sclerosis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Conservative interventions for urinary or faecal incontinence, or both, in adults with multiple sclerosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of conservative interventions for urinary or faecal incontinence (or both) in adults with multiple sclerosis, compared to no treatment, sham and usual care, any other active treatment, or another conservative treatment.

To critically appraise and summarise the current evidence on resource use, costs and cost effectiveness of conservative interventions for adults with urinary or faecal incontinence (or both) and MS.

We will make the following comparisons.

- Conservative treatment versus no treatment
- Conservative treatment versus sham treatment
- Conservative treatment versus usual care
- Conservative treatment versus pharmacological treatment
- Conservative treatment versus surgical treatment
- Conservative treatment versus any other conservative treatment

BACKGROUND

Description of the condition

Diminished control of bladder and bowel function is prevalent among individuals with multiple sclerosis (MS), although accurate estimates of incontinence are hampered by a lack of standardised definitions in epidemiology studies (Apostolidis 2017; Krogh 2009; Milsom 2017). Urinary incontinence (UI), defined as the "complaint of any involuntary loss of urine"(Abrams 2017), is reported to affect between 19% and 80% of individuals with MS, according to the definition used (Apostolidis 2017; Forbes 2006). Less is known about faecal incontinence (FI), defined broadly as "any involuntary loss of faecal material"(Abrams 2017), with a further definition of anal incontinence (AI) that includes the involuntary passing of flatus. Epidemiology studies to date have lacked specificity to draw robust conclusions, however, the more conservative studies estimate that up to 30% of the MS population is affected by FI at least monthly (Hennessey 1999; Koldewijn 1995). Reported prevalence is higher in more recent studies: 50% and over (DasGupta 2003; Norton 2010). Duration of disease and the severity of deficiencies caused by MS are important factors in the occurrence of bladder dysfunction (de Sèze 2007), while only the latter has been reported as a correlate with digestive disorders (Munteis 2008). UI and FI often occur together - which is understandable given the shared musculature, shared innervation, and the propensity of MS to cause spinal cord dysfunction - however they are often treated and evaluated separately. Thus less is known about the prevalence, treatment and outcomes for UI and FI in combination (Donzé 2009). The additional consideration of reduced mobility that may occur with MS can cause further difficulties with the occurrence of incontinence and such associated factors should not be overlooked.

There are few studies which evaluate the impact of incontinence on the quality of life of people with MS, but these studies have reported similar issues to those conducted in a non-MS population. Factors reported to be associated with incontincence and MS are shame (Koch 2001), embarrassment (Wollin 2005), and interference with sex life (Borello-France 2004; Hennessey 1999). More generically, effects such as social isolation, reduced self-esteem, restriction of activities and toilet mapping are common, with individuals' lives being controlled by their bladder and bowel (Cotterill 2008; Donovan 2005; Norton 2010). Incontinence has been identified as having a significant impact on emotional health, ability to perform household chores, and physical recreation, all of which are central to functioning in society (Khan 2009; Wollin 2005).

Studies to evaluate the costs of incontinence often focus on the expenditure associated with the use of continence pads, other products, laundry and dry cleaning (Fader 2008). Studies on costs have largely focused on females in the general population, rather than those with MS specifically. Findings suggest that costs for incontinence management increase with leakage severity and are higher for mixed urinary incontinence by comparison with stress urinary incontinence (SUI) (Subak 2007). Substantial economic burden has also been associated with urinary incontinence due to neurogenic detrusor overactivity (Tapia 2013). Effective conservative treatment intervention has been associated with decreased costs of incontinence management at the personal level in a trial of weight loss for women with urinary incontinence (Subak 2012). With regard to faecal incontinence, a similar association between severity of symptoms and personal costs was reported in a study of men and women presenting to a tertiary referral centre. When costs for medical care were included the association with severity was not evident (Parkin 2011).

The lower urinary tract (LUT) and the anorectum (AR) are interrelated structures under neural control that require reservoir function and effective closure of the urethral and anal sphincters to achieve continence. The diffuse neurodegeneration and particularly involvement of the spinal cord, such as found in MS, affect function of the LUT and AR (Apostolidis 2017).

Lower urinary tract dysfunction (LUTD) occurs in 50% to 92% of patients with MS (DasGupta 2002; Giannantoni 1999; Hinson 1996; Khalaf 2015; Litwiller 1999). The most common urodynamic findings among individuals referred for urodynamic evaluation are detrusor overactivity (involuntary contraction of the detrusor muscle; mean 65%), detrusor sphincter dyssynergia (uncoordinated activity between the detrusor and urethral sphincter; mean 35%) and detrusor underactivity (weak contraction of the detrusor; mean 25%) (de Sèze 2007). UI can be associated with these conditions or occur in isolation, and presents in different forms as defined below (Abrams 2017).

- **Stress urinary incontinence:** the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
- **Urodynamic stress incontinence:** a urodynamic observation characterised by the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction.
- **Urgency urinary incontinence:** the complaint of involuntary leakage accompanied by or immediately preceded by urgency.
- **Detrusor overactivity:** a urodynamic observation characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. This is further defined as neurogenic detrusor overactivity if the overactivity is due to a relevant neurological condition.
- **Mixed urinary incontinence:** the complaint of involuntary leakage associated with urgency and also with effort, exertion, sneezing and coughing.

Bowel dysfunction is less studied, but similar mechanisms for this type of incontinence exist. Interruption of the afferent nerves may alter awareness of the need to open the bowels, and compromise of the efferent nerves may affect innervation of the intestines and voluntary control of the pelvic floor, in addition to reduced anorectal

sensation. About one-third of individuals with MS experience constipation and one-quarter are incontinent of faeces at least once per week (Bakke 1996; Hinds 1990). The main distinction between descriptions of incontinence regarding the bowel is the inclusion or exclusion of flatus as defined below (Abrams 2017).

- **Anal incontinence (AI):** any involuntary loss of faecal material, flatus, or mucus (alone or in combination).
- **Faecal incontinence:** any involuntary loss of faecal material.
- **Flatus incontinence:** any involuntary loss of gas (flatus).

For the purposes of this review, we will use AI unless the exclusion of flatus incontinence is specified.

It is noted that there is currently no accepted definition of mixed urinary and anal or faecal incontinence. In order to include studies that have studied this population, for the purposes of this review we propose the definition below, as a combination of the published definitions.

- **Mixed urinary and faecal incontinence:** the complaint of any involuntary loss of urine and involuntary loss of faecal material.
- **Mixed urinary and anal incontinence:** as above with the addition of involuntary loss of flatus.

Description of the intervention

Treatments for UI and AI - both associated with MS and in the wider population - include conservative treatments (physical therapies, lifestyle and behavioural adaptations and symptom management), drug therapy or surgical treatments (Cotterill 2018; Drake 2016). The focus of this review is conservative treatments, which excludes pharmacological and surgical interventions. We will include the conservative interventions outlined in the sixth International Consultation on Incontinence (Abrams 2017). Physical therapies include pelvic floor muscle training (PFMT), weighted vaginal cones, electrical stimulation, posterior tibial nerve stimulation (PTNS), magnetic stimulation and biofeedback. Lifestyle and behavioural adaptations include education regarding diet and behaviour choices and scheduled voiding and bowel management regimens. Symptom management includes rectal irrigation and intermittent catheter use.

How the intervention might work

Conservative management plays an important role in the treatment of UI and AI as these interventions are the recommended first line of treatment and offer alternative modalities to pharmacological and surgical interventions. Each strategy is detailed below to explore the mechanism of action to improve incontinence symptoms.

Pelvic floor muscle training (PFMT)

PFMT was popularised by Arnold Kegel (Kegel 1948) for the management of UI and is defined as repetitive selective voluntary contraction and relaxation of specific pelvic floor muscles (Abrams 2002). Although initially used for the management of UI, in particular SUI, as the integrity of the pelvic floor appears key to the entire continence mechanism (Salvatore 2017), its potential benefits have been proposed for other types of UI and AI (Bliss 2017; Dumoulin 2017). The aims of PFMT are to promote increased strength in the pelvic floor to provide more automatic protection and more effective voluntary recruitment of these muscles under times of increased abdominal pressure (Bø 2004). Patients are instructed to contract the pelvic floor muscles, including the external anal sphincter and puborectalis, while keeping the abdominal wall muscles relaxed, repeating these exercises several times per day.

Weighted vaginal cones

For use in women only, weighted vaginal cones were originally used to test pelvic floor muscle function and are anticipated to improve continence through strengthening, as with PFMT. Cones vary in weight and size and are inserted into the vagina with the aim of retaining the cone over increasing periods of time and activity, thereby increasing the strength of the muscles required to retain the cone (Peattie 1988; Plevnik 1985).

Electrical stimulation

Electrical stimulation is the application of electrodes on the perineum or probes in the vagina or anal canal to apply mechanical stimulation to the pelvic floor muscles. Underpinning theories suggest the mechanical contraction of the muscles enables patients to identify the relevant muscles in order to support and implement their own contractions, and that the additional stimulation may promote synaptic growth or the size of receptive fields for these nerves in the brain (Hosker 2007). In addition, there is a suggested effect on sensation and the perception of filling by stimulating awareness (Berghmans 2013).

Posterior tibial nerve stimulation (PTNS)

PTNS involves the stimulation of the tibial nerves in order to modify the action of the sacral nerve plexus, which is responsible for regulation of bladder and bowel function. A mild electric current is delivered by a needle or surface electrode to the tibial nerve above the ankle, which is carried to the sacral nerves. The mechanism underlying the effect is poorly understood but is described as the modulation and stimulation of efferent and afferent nerves, and associations with increased rectal capacity and lower sensitivity to distension have been reported (Marti 2017).

Magnetic stimulation

Magnetic stimulation is a non-invasive method of stimulating the central and peripheral nervous systems without the need for probes or electrodes (Galloway 1999; Goldberg 2000). A magnetic field is generated and directed toward the pelvic floor muscles and sacral nerve roots, allowing all tissues of the perineum to be targeted. The mechanism of action is not fully understood but magnetic stimulation is thought to cause sphincter contraction, act as passive pelvic floor muscle exercise, increase urethral closure pressures and affect neural activity to reduce detrusor overactivity (But 2003; Bycroft 2004; Kralj 1999; Lindström 1983).

Biofeedback

Biofeedback is used in addition to the interventions described above and uses the principle of conveying information about a normally unconscious physiological process to the patient or therapist as a visual, auditory or tactile signal. Communicating this information can be used to teach patients to recognise and increase or decrease their voluntary muscle activity (Doggweiler-Wiygul 2002), and aims to improve the accuracy, effectiveness, or duration of pelvic floor muscle contractions. In addition, sensory training can be incorporated into biofeedback training protocols to improve recognition of sensation associated with stool moving into the rectum which can be reduced with neurological disorders such as MS (Bliss 2017). A balloon-tipped catheter is inserted into the rectum and inflated with varying volumes of air to help the patient recognise varying distensions and perform balloon expulsion in order to better co-ordinate pelvic floor muscle activity.

Lifestyle interventions

A number of lifestyle factors may have an influence on the symptoms of UI and AI, for example: excessive weight, lack of physical activity, smoking, diet, caffeine, fluid and dietary intake (including content and patterns), constipation, medication side effects, toilet facilities and access, and patient or carer education. Often patients have a lack of understanding of the effect of these factors on bladder and bowel habits and therefore education and advice, in addition to specific supportive interventions such as peer support and motivational strategies, are crucial to addressing these modifiable factors. Reducing the effects or improving strategies associated with these factors is proposed to reduce the symptoms of incontinence by limiting the irritative or physical effects on the bladder and bowel, and increasing knowledge in order to optimise healthy habits (Dumoulin 2017).

Scheduled voiding and bowel management regimens

These are broad terms to describe toileting interventions intended to improve bladder and bowel patterns in order to avoid or manage symptoms. With regard to UI, these interventions can be divided into three main strategies, as follows.

- Bladder training: a scheduled voiding regimen with progressively increasing voiding intervals, which aims to correct frequent urination habits.
- Timed voiding: a fixed voiding schedule that does not alter, which aims to avoid UI by providing fixed opportunities for bladder emptying prior to exceeding bladder capacity.
- Habit training: a voiding schedule that matches the patterns of the individual but pre-empts episodes of incontinence, therefore, variability in the regimen may be evident throughout the day (Dumoulin 2017).

Bowel management regimens focus on keeping the rectum empty and the avoidance of constipation and diarrhoea through the establishment of a regular, predictable pattern of bowel evacuation. Loose stools and constipation are risk factors for faecal incontinence and the main conservative strategies to avoid these are detailed below.

- Bowel habit and toileting: establishing a pattern for bowel evacuation is promoted, with the period following breakfast being encouraged when peristaltic contractions of the colon are increased.
- Urgency resistance training: teaching strategies to resist the urge to defecate.
- Evacuation training: education and advice to avoid straining and promote appropriate toilet positioning in order to achieve positive evacuation habits.
- Digital stimulation and manual evacuation: strategies to facilitate emptying of the bowel to facilitate a bowel evacuation pattern (Bliss 2017).

Rectal irrigation

Rectal irrigation is the process of water being passed into the anus to reach beyond the rectum to stimulate colonic reflex activity and mechanically wash out the bowel (Coggrave 2014). This method of management enables the timing of bowel opening to be controlled and scheduled for convenience, thereby reducing the risk of an unpredictable occurrence of faecal incontinence.

Intermittent catheter use

Urinary catheters provide a physical method for removing urine from the bladder as a strategy to reduce incontinence. Intermittent catheters can be passed into the bladder via the urethra at a convenient time and are immediately removed. They provide a method for removing urine that is controlled, and to reduce the amount of urine in the bladder that may otherwise leak. Catheters must always be carefully considered due to their associated risks of infection (Cottenden 2017).

Why it is important to do this review

Incontinence symptoms are amenable to conservative treatment interventions in other disease states and a limited number of trials have indicated benefits for individuals with MS. However, there has not been a comparison of the studies to assimilate what can be concluded about its effect in this population. In addition, studies have focused on certain aspects of incontinence or certain sections of the population so it is unclear if there are consensus findings that can be used to inform practice. The economic impact of incontinence - in terms of financial burden to the individuals with MS due to resource use and loss of earnings, and for the healthcare provider - are unknown. Our review is one of several Cochrane Reviews which address conservative management of these symptoms and the associated costs, which include the following.

- Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women (Ayeleke 2015)
- Lifestyle interventions for the treatment of urinary incontinence in adults (Imamura 2015)
- Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women (Dumoulin 2014)
- Management of faecal incontinence and constipation in adults with central neurological diseases (Coggrave 2014)
- Weighted vaginal cones for urinary incontinence (Herbison 2013)
- Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults (Norton 2012)
- Combined conservative interventions for urge, stress or mixed incontinence in adults (French 2010)

OBJECTIVES

To assess the effects of conservative interventions for urinary or faecal incontinence (or both) in adults with multiple sclerosis, compared to no treatment, sham and usual care, any other active treatment, or another conservative treatment.

To critically appraise and summarise the current evidence on resource use, costs and cost effectiveness of conservative interventions for adults with urinary or faecal incontinence (or both) and MS.

We will make the following comparisons.

- Conservative treatment versus no treatment
- Conservative treatment versus sham treatment
- Conservative treatment versus usual care
- Conservative treatment versus pharmacological treatment
- Conservative treatment versus surgical treatment
- Conservative treatment versus any other conservative treatment

METHODS

Criteria for considering studies for this review

Types of studies

We will consider parallel group randomised controlled trials (RCTs) and quasi-randomised studies. We will also include the first phase of crossover RCTs (to avoid carry over effects from the initial intervention phase). We will also search for economic evaluations of the different interventions.

Types of participants

All male and female adults aged over 18 years with existing urinary, faecal or anal incontinence (or a combination of these), with a clinical diagnosis of relapsing/remitting, primary or secondary progressive multiple sclerosis (MS). Incontinence will be established on the basis of symptoms, signs or urodynamic or anorectal physiology studies.

Types of interventions

One arm of all eligible trials must use a conservative intervention to treat urinary or faecal incontinence, or both, which includes:

- pelvic floor muscle training programme (PFMT);
- weighted vaginal cones;
- electrical stimulation;
- posterior tibial nerve stimulation (PTNS);
- magnetic stimulation;
- biofeedback;
- lifestyle interventions such as diet and behaviour choices;
- scheduled voiding and bowel management regimens;
- rectal irrigation;
- intermittent catheter use.

It is recognised that there will not be standardisation between the treatment protocols and therefore variability between programmes will be accepted. We will exclude studies of conservative strategies for prevention of incontinence.
Comparator arms will include no treatment, usual care, sham, pharmacological and surgical interventions, and any of the above interventions.

Types of outcome measures

Primary outcomes

- Number of participants with self-reported 'improved' urinary incontinence (UI) according to validated symptom score, for example, ICIQ-UI Short Form (Avery 2004), Incontinence Severity Index (Sandvik 1993)
- Number of participants with self-reported 'improved' faecal incontinence (FI) according to validated symptom score, for example ICIQ-B (Cotterill 2008), FISI (Rockwood 1999), BBUSQ (Hiller 2002)
- Validated quality-of-life scores, for example, ICIQ-LUTSqol (Abrams 2006; Kelleher 1997), ICIQ-UI Short Form 'Overall bother' item (Avery 2004), ICIQ-B 'Quality of life' domain (Cotterill 2008), FIQL (Rockwood 2000)

Secondary outcomes

Participant observations

- Degree of improvement in incontinence symptoms (validated scores, as measured for primary outcomes)
- Number of participants with alleviation of other urinary or bowel symptoms (validated scores, as measured for primary outcomes)
- Number of participants with improvement in sexual function (validated sexual function self-report measures)
- Satisfaction with treatment
- Compliance with treatment

Quantification of symptoms

- Frequency of incontinence episodes (bladder/bowel diaries)
- Pad tests (weight)
- Number of pad changes (diaries)

Clinician's observations

- We will not include clinician observations, in order to retain a focus on subjective outcomes rather than clinical parameters

Adverse effects

- Number of adverse events reported in the trials
- Number of participants with worsening of other urinary or bowel symptoms (validated scores as measured for primary outcomes)
- Number of participants with deterioration in sexual function (validated sexual function measures)

Economic outcomes

- Resource (type and number) used to deliver the conservative management treatment
- Cost of the intervention to health service provider, such as cost of staff, cost of treatment and care
- Costs of the resources for the patient, such as conservative management equipment, lost wages and lost productivity
- Cost effectiveness (incremental cost effectiveness ratios (ICERs), increment cost per quality adjusted life years (QALYs), incremental cost per disability adjusted life year (DALY), incremental cost benefit ratios, net benefit)

Other outcomes

- Unspecified outcomes judged to be important by the review authors when performing the review

Timing of outcome measures

We will divide outcome time points into short-term (up to three months), medium-term (between three and six months), and long-term (greater than six months), from the start of the intervention.

Search methods for identification of studies

Electronic searches

The Information Specialist will search the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Trials Register which, among other sources, contains trials from the following.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue)
- MEDLINE (PubMed) (1966 to date)
- Embase (1974 to date)
- CINAHL (EBSCO host) (1981 to date)
- LILACS (Bireme) (1982 to date)
- PEDro (1990 to date)
- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's module. The keywords used to search for trials for this review are listed in Appendix 1.

Searching other resources

We will search for conference proceedings to identify studies potentially missed through the database searches and articles from 'grey literature'. This will include the following since 2002.

- We will check the reference lists from published reviews to identified RCTs.
- We will check for conference proceedings for the annual meetings of the United Kingdom Continence Society, European Committee for Treatment and Research in Multiple Sclerosis, Americas Committee for Treatment and Research in Multiple Sclerosis and European Multiple Sclerosis Platform.
- We will check for reviews from the International Consultation on Incontinence 2016 (Abrams 2017).
- We will contact authors and trialists of included studies.

Data collection and analysis

Selection of studies

We will enter all trials identified from the search into Review Manager 5 software (RevMan 2014). Two review authors (NC and AS) will evaluate all studies' titles and abstracts according to the inclusion criteria. We will then access full papers of potentially relevant studies for further assessment of eligibility. Any discrepancies at either stage of screening will be resolved by discussion, and where disagreements remain unresolved a third author (MD) will make the final decision. All excluded studies will be listed with reasons for exclusion.

Data extraction and management

Two review authors (NC and AS) will independently extract data using a data extraction form, and they will cross-reference the information. Extracted data will include:

- date and location of study;
- study design, including methodological quality;
- characteristics of participants (number, setting, age, type of MS, nature of UI/FI diagnosis);
- inclusion and exclusion criteria;
- details of the experimental intervention, including duration;
- details of the comparator arm;
- description of outcomes.

Any discrepancies will be resolved by discussion and, if required, a third review author (MD). Where study data are unclear or not reported in a form that may be useful for formal comparison, further clarification will be sought from the trial authors. We will process all included trial data as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

Two review authors (NC and AS) will undertake critical appraisal of the included studies using Cochrane's 'Risk of bias' tool (Higgins 2011) to assess the risk of bias. It is recognised that given the nature of the interventions, allocation blinding may be difficult, but areas of evaluation will include the following.

- Was there adequate random sequence generation for treatment allocation (selection bias)?
- Was there adequate concealment of allocation to intervention arm prior to allocation (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (performance bias)?Were
- Were outcome assessors blinded (detection bias)?
- Were incomplete outcome data adequately addressed (attrition bias)?
- Was the study free of the suggestion of selective reporting (reporting bias)?
- Was the study free of other issues that could put it as risk of bias?

For each domain we will categorise each study as being at low/unclear or high risk of bias (Higgins 2011). Any discrepancies will be resolved by discussion and, if required, by involving a third review author (MD). The global risk of bias for all the included studies will be displayed in a 'Risk of bias' graph to aid clarity for each included study. We will also summarise the risk of bias across domains to provide an overview of strengths and limitations in the body of research.

Measures of treatment effect

We will use risk ratios (RRs) with 95% confidence intervals (CIs) to express the effect size for categorical data. We will use means and standard deviations to derive mean differences (MDs) with 95% CIs for continuous variables. We plan to undertake meta-analysis where appropriate.

Unit of analysis issues

Trials containing two active treatment comparisons in combination will be included where identified (e.g. bladder training + PFMT versus both a bladder training arm and a PFMT arm). Where combined active treatments are compared with each treatment individually (e.g. bladder training + PFMT versus bladder training only versus PFMT only), we will choose one comparison arm to include in the review to avoid double counting the intervention arm. The comparator anticipated to be least effective to the combined intervention will be selected initially, to identify a treatment effect of any magnitude. We will then undertake a post-hoc sensitivity analysis, replacing the chosen comparator (anticipated to be least effective) with the alternative comparator (anticipated to be most effective). This is proposed to avoid over-estimation in the estimation of treatment effect but to provide outcome

data for each treatment intervention. We will include cross-over trials, but only the first phase will be used to avoid problems with carry-over effects.

Dealing with missing data

If required, we will request further information from the original trial author by written correspondence (e.g. emailing corresponding author/s), and we will include any relevant information obtained in this manner in the review. All missing data will be assumed 'missing at random' but only observed data will be included, without imputation.

Assessment of heterogeneity

We will examine clinical heterogeneity between the trials considering the similarities between the characteristics of the populations, types of interventions and outcomes. We will explore statistical heterogeneity using the I^2 statistic and by visual inspection of the forest plots, according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will define an I^2 of more than 50% as representing substantial heterogeneity, beneath which a fixed-effect model will be used for meta-analysis. Where there is substantial heterogeneity, we will use both fixed- and random-effects models, and will report the most conservative method if the results differ. If it is considered inappropriate to combine data from the included studies, we intend to present a narrative synthesis of the results.

Assessment of reporting biases

To estimate the influence of unpublished studies on the overall effects, we will produce a funnel plot if there are ten or more studies included in the analysis.

Data synthesis

We will synthesise data according to the outcomes through meta-analysis, narrative/descriptive analysis, or both, depending on the availability and appropriateness of data from the included studies, using the fixed-effect model if appropriate. We will analyse the data using Review Manager 2014.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will analyse treatment effects in the following subgroups:

- participant gender;
- type and duration of incontinence (stress urinary incontinence, urgency urinary incontinence, mixed urinary incontinence, faecal incontinence, mixed urinary and anal or faecal incontinence);
- MS diagnosis and duration (relapsing remitting, primary progressive, secondary progressive).

Sensitivity analysis

We will perform sensitivity analysis to evaluate the methodological quality of trials by including or excluding studies with moderate or high risk of bias. Overall risk of bias will be judged based on domain-level judgements with 'low risk' of overall bias indicated where a study is judged to be at low risk of bias for all domains, 'some concerns' indicated where a study has evidence of some concerns in at least one domain, and 'high risk' where a study is at high risk in one domain or displays evidence of some concerns across multiple domains, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

'Summary of findings' table

We will use the GRADE approach to evaluate the quality of the body of evidence collected (GRADE Working Group 2004). Two review authors (NS and AS) will rate the quality of evidence for each outcome, from 'high', which indicates that further research is unlikely to alter the estimate of effect, through to 'very low', where an estimate of effect is very uncertain. Any discrepancies will be resolved by consensus and a third review author (MD). We will produce 'Summary of findings' tables, which will include detail regarding the quality of the evidence, magnitude of treatment effect and summary of the main outcomes according to the published criteria. Gradings will be reduced to reflect the influence of study limitations and inconsistencies. Additional outcomes regarding degree of improvement, alleviation or exacerbation of other symptoms and economic outcomes will be presented. We will produce separate 'Summary of findings' tables for UI and FI, and will include the following outcomes across all time points (short-, medium- and long-term).

- Number of participants with self-reported 'improved' urinary incontinence
- Number of participants with self-reported 'improved' faecal incontinence
- Quality-of-life scores
- Magnitude of improvement
- Degree of improvement in incontinence symptoms (validated scores as measured for primary outcomes)
- Number of participants with alleviation of other urinary or bowel symptoms (validated scores as measured for primary outcomes)
- Number of participants with worsening of other urinary or bowel symptoms (validated scores as measured for primary outcomes)

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Detailed search strategy

(((((((((“Urinary Incontinence”[Mesh]) OR “Fecal Incontinence”[Mesh])) OR (“urinary incontinence”[Title/Abstract]) OR “faecal incontinence”[Title/Abstract])) OR ((“involuntary leakage” OR “involuntary loss” OR “involuntary loss of faecal” OR “flatus incontinence” OR “involuntary flatus” OR “involuntary loss of gas” OR “lower urinary tract dysfunction” OR “lower bowel tract dysfunction”))))) OR (“urinary incontinence”[Title/Abstract] OR “faecal incontinence”[Title/Abstract])))
AND
((((((((((“Multiple Sclerosis”[Mesh:noexp] OR “Multiple Sclerosis, Chronic Progressive”[Mesh]) OR “Multiple Sclerosis, Relapsing-Remitting”[Mesh]) OR “Demyelinating Diseases”[Mesh:noexp]) OR “Optic Neuritis”[Mesh]) OR “Demyelinating Autoimmune Diseases, CNS”[Mesh:noexp]) OR “Encephalomyelitis, Acute Disseminated”[Mesh]) OR “Myelitis, Transverse”[Mesh]) OR ((((((((((((((“multiple sclerosis”[Title/Abstract]) OR “chronic progressive multiple sclerosis”[Title/Abstract]) OR “progressive relapsing multiple sclerosis”[Title/Abstract]) OR “secondary progressive multiple sclerosis”[Title/Abstract]) OR “primary progressive multiple sclerosis”[Title/Abstract]) OR “relapsing remitting multiple sclerosis”[Title/Abstract]) OR “remitting-relapsing multiple sclerosis”[Title/Abstract]) OR “acute relapsing multiple sclerosis”[Title/Abstract]) OR “neuromyelitis optica”[Title/Abstract]) OR “optic neuritis”[Title/Abstract]) OR “devic disease”[Title/Abstract]) OR “demyelinating disease”[Title/Abstract]) OR adem[Title/Abstract]) OR “demyelinating disorder”[Title/Abstract]) OR “clinically isolated syndrome”[Title/Abstract]) OR “transverse myelitis”[Title/Abstract]) OR “acute disseminated encephalomyelitis”[Title/Abstract] OR (“encephalomyelitis”[Title/Abstract])))))))
AND
(((((((“Electric Stimulation Therapy”[Mesh]) OR “Magnetic Field Therapy”[Mesh:NoExp])))) OR “Urinary Catheters”[Mesh]) OR (“pelvic floor muscle training” OR “weighted vaginal cones” OR “electrical stimulation” OR “magnetic stimulation” OR “biofeedback” OR “rectal irrigation” OR “sacral neuromodulation” OR “urinary catheters” OR “intermittent catheters”)) OR (“scheduled voiding” OR “timed voiding” OR “prompted voiding” OR “bowel management regimens”)) OR (“lifestyle” OR “lifestyle modification” OR “weight reduction” OR “physical activity” OR “exercise” OR “smoking cessation” OR “smoking reduction” OR “diet” OR “caffeine” OR “fluid manipulation” OR “constipation” OR “stress reduction”))

CONTRIBUTIONS OF AUTHORS

All authors have contributed to the design, development and refinement of the Cochrane protocol.

DECLARATIONS OF INTEREST

NC: none

AS: none

CN: is a speaker for Abbvie, Ferring and Takdeda and is an investigator on trials that may be included within the review.

AW: none

IW: none

MK: is the economics editor for the Cochrane Incontinence Group.

MD: is involved in research, speaker bureau and advisory boards for Allergan, Astellas and Ferring, and a speaker for Hikma and Pfizer.

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External sources

- MS Society, UK.

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