# Abdominal massage for neurogenic bowel dysfunction in people with multiple sclerosis

# PROTOCOL

**A UK Collaborative Study funded by the**
**NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC),**
**Health Technology Assessment (HTA) Programme**

**PROTOCOL APPROVAL**

Abdominal Massage for Neurogenic Bowel Dysfunction in people with Multiple Sclerosis

**Signatures**

| | | |
|---|---|---|
| |  | 18th November 2014 |
| Chief Investigator | Signature | Date |
| Principal Investigator | _____ Signature | _____ Date |

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**PROTOCOL SUMMARY**

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| **QUESTION ADDRESSED** | Is abdominal massage and optimised bowel care more effective and cost effective than optimised bowel care alone for the treatment of neurogenic bowel dysfunction in people with Multiple Sclerosis? |
| **CONSIDERED FOR ENTRY** | Individuals with Multiple Sclerosis seeking treatment for neurogenic bowel dysfunction |
| **POPULATIONS** | Adults with MS experiencing bothersome NBD and have not undertaken abdominal massage for 2 months |
| **TRIAL ENTRY** | Consent will be obtained from eligible patients after written and oral information has been provided. |
| **INTERVENTIONS** | 1. Optimised bowel care<br>2. Optimised bowel care with abdominal massage |
| **OUTCOME ASSESSMENT** | • Participant completed questionnaires at 6 and 24 weeks after the date of their randomisation<br>• Bowel diary at one week prior to intervention, during the 6 weeks of intervention and at week 23 after the date of randomisation |
| **CO-ORDINATION** | Local: by local lead Principal Investigator, an Intervention Nurse and a Recruitment Officer.<br>Central: by Trial Office in Glasgow.<br>Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring and Ethics Committee. |
| **FUNDING** | National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment (NETSCC HTA) Programme |
| **Start date:** | June 2014 |
| **Planned finish date:** | May 2017 |
| **Planned reporting date:** | December 2017 |

## Glossary of abbreviations

| | |
|---|---|
| AMBER | Abdominal Massage for Bowel Dysfunction Effectiveness Research |
| CI | Chief Investigator |
| CSS | Constipation Scoring System |
| DMEC | Data Monitoring and Ethics Committee |
| HTA | Health Technology Assessment |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MS | Multiple Sclerosis |

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|---|---|
| NBD | Neurogenic bowel dysfunction |
| NBDS | Neurogenic Bowel Dysfunction Score |
| NETSCC | NIHR Evaluation, Trials and Studies Coordinating Centre |
| PMG | Project Management Group |
| QALY | Quality Adjusted Life Years |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SOP | Standing Operating Procedure |
| TCTU | Tayside Clinical Trials Unit |
| TSC | Trial Steering Committee |

**Protocol summary in plain English**

Neurogenic bowel dysfunction (NBD: constipation and/or faecal incontinence) is common in people with multiple sclerosis (MS) and is rated as the most severe impact of their disease/injury, above wheelchair dependence. Despite this, current treatment options are limited, poorly evaluated and complex.

This research aims to find out whether abdominal massage can help improve the symptoms of NBD in these patients. A small study has already shown that it is possible for patients or carers to perform abdominal massage and in some cases this helped the patient with their symptoms. A larger study is now required to confirm the results one way or another.

Patients with Multiple Sclerosis who attend one of the participating study centres who are bothered by constipation and or faecal incontinence will be asked to take part if they fit the other requirements for the trial. Those who agree to take part will be allocated at random to one of two groups, one will receive advice on the management of bowel dysfunction (called optimised bowel care), and the other will receive the same advice and will be taught how to do the abdominal massage (called abdominal massage and optimised bowel care). Both groups will visit a specialist nurse for 1 additional hour after their normal clinical appointment, or at an agreed time, to receive optimised bowel care advice. The patients in the intervention group +/or their carers will receive training on abdominal massage and a DVD/copy of demonstration of the massage for home use. All patients will also be called weekly for 6 weeks to discuss their bowel care.

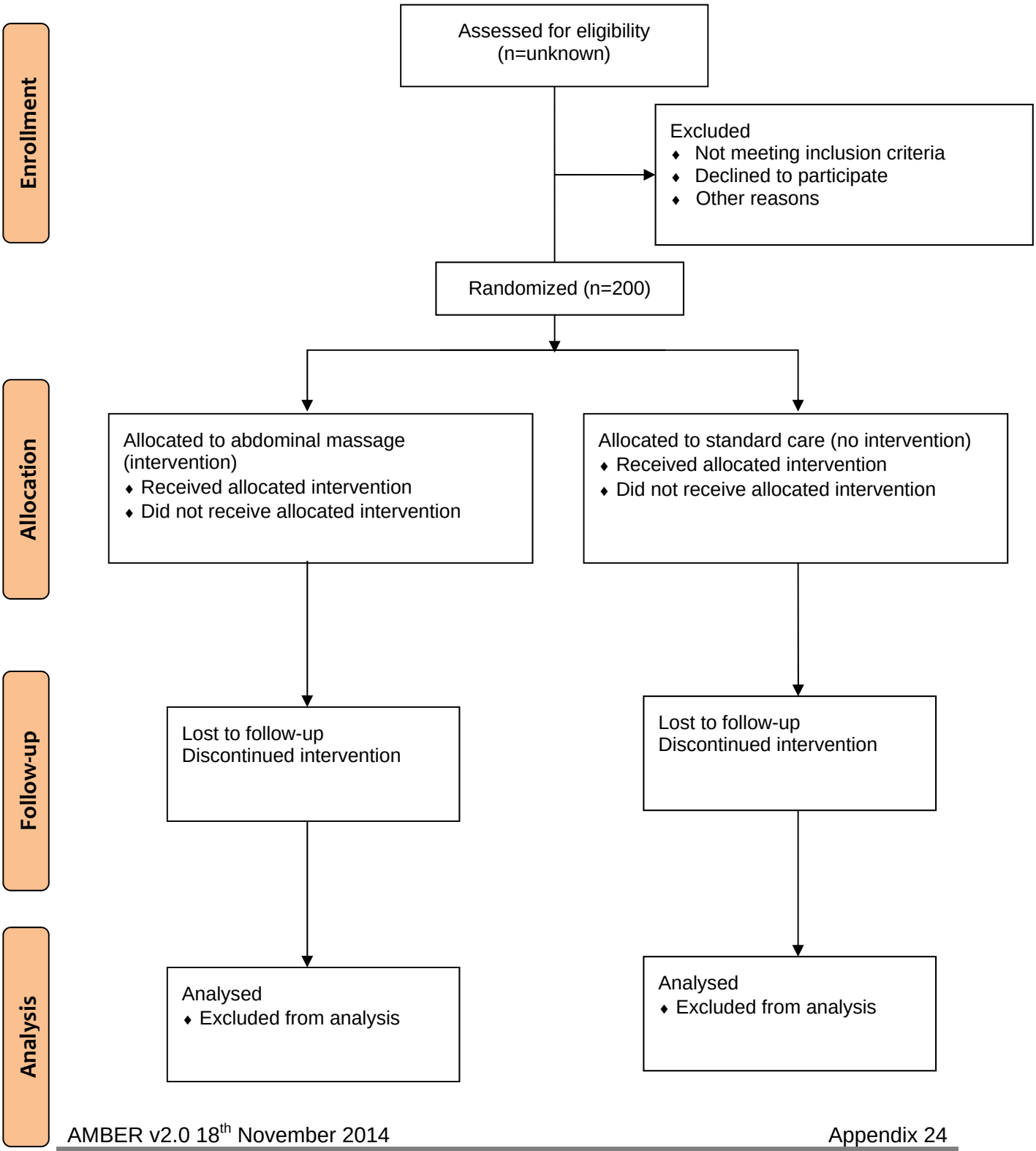
We will measure the results of treatment after 6 and 24 weeks. We are primarily interested in whether patients in the intervention group (receiving optimized bowel care & abdominal massage) have had more of an improvement in their NBD symptoms at 24 weeks after they start the study that the control group (receiving optimized bowel care only). We also want to find out how bad the constipation and bowel symptoms are, how much this affects their life and if they have any problems with their bladder. We will also measure the costs of the treatments and any costs to the patient and their family, and balance these against any benefits of the intervention treatment.

During the trial we will assess how well the optimized bowel care and abdominal massage training was delivered by speaking with nurses and listening to recordings of some of the telephone calls. We will talk to the patients to find how they perceive the treatment they received and how they got on during the treatment period and once the treatment finished. We will explore how the treatment delivery and patient's perceptions impact on the patients NBD symptoms.

We have worked out from previous research that if 200 patients take part and most complete the trial, we will have enough data to successfully compare the treatments to find out if one is better

than the other. Individual participation will be entirely voluntary and we do not believe there are any risks associated with taking part.

**AMBER Study Flow Diagram**



**AMBER Personnel**

**Grant Holders**

| | | | |
|---|---|---|---|
| 1 | Doreen McClurg | 10 | Helen Mason |
| 2 | Suzanne Hagen | 11 | |
| 3 | Fiona Harris | 12 | |
| 4 | Shaun Treweek | 13 | |
| 5 | John Norrie | 14 | |
| 6 | Anton Emmanuel | 15 | |
| 7 | Christine Norton | 16 | |
| 8 | Peter Donnan | 17 | |
| 9 | Maureen Coggrave | | |

**Project Management Group**
This group is comprised of all grant holders along with the AMBER trial researchers.

**AMBER trial researchers based at GCU (site delegation logs will indicate local researchers)**

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|---|---|---|
| 1 | Trial Manager Kirsteen Goodman | |
| 2 | Assistant trial manager | |
| 3 | Process Evaluation position | |

**Trial Steering Committee**
This committee is comprised of independent members along with the Chief Investigator (Doreen McClurg). Representatives from the other AMBER grant-holders and trial researchers (e.g. the trial manager) may be invited to attend meetings to provide information as appropriate. The funders and the sponsor will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate.

**Independent members of TSC**

| | | | |
|---|---|---|---|
| 1 | John Saxton Chair | 3 | |
| 2 | Richard Morris Stats | 4 | |
| 3 | Ashley Pollock MS Nurse | | |

**Data Monitoring and Ethics Committee members:**

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|---|---|---|---|
| 1 | Chris Sutton Statistician and chair | 3 | Lorna Paul |
| 2 | Diane Stark Clinician | | |

**AMBER Trial Office Team:**
This team is comprised of the Glasgow based grant holders and trial research team members.

**Other Information**

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|---|---|
| International Standard Randomised Controlled Trial Number (ISRCTN) | 85007023 |
| REC Reference Number | 14/WS/0111 HTA Project Number HTA 12/127 |
| The NETSCC, HTA Programme website | http://www.nets.nihr.ac.uk/programmes/hta |
| Trial website: | TBC |

## 1 Reasons for the Trial

### 1.1 Scale of the problem and use of NHS resources

Multiple sclerosis (MS) is a life-long condition primarily affecting younger adults. Neurogenic bowel dysfunction (NBD) occurs in 50-80% of these patients and is the term used to describe constipation and faecal incontinence (FI) secondary to neurological disease or trauma, and is caused, in both, by damage to the nerves controlling colonic function and autonomic and voluntary control of defecation. Constipation causes pain and prolonged difficult evacuation of stool, can, if left untreated, lead to impaction which often requires hospital admission. FI has devastating psychosocial consequences. Initial management of NBD includes conservative measures such as modification of diet and fluids, laxatives or constipating medication, rectal interventions such digital rectal stimulation and manual evacuation of stool, suppositories/enemas progressing to more invasive and expensive interventions such as rectal irrigation and surgery (e.g. stoma).

MS has an increasing prevalence in the UK and is the most common neurological condition in young adults (average age of onset 34 years) affecting over 100,000 people at present (1); up to 80% of these patients have problematic NBD (2). Advances in healthcare resulting in increased life expectancy presents additional challenges of the ageing bowel (3) and the issue of longer duration of disease which is associated with reduced function (4). NBD is rated as one of the most devastating scenarios affecting these patients and includes the symptoms of constipation and FI, which are often linked (5). Constipation, primarily caused by slow colonic transit time, can lead to the individual becoming housebound, spending hours trying to empty their bowels (6) limiting their ability to work. FI is often described as the most devastating event imaginable leading to social and emotional issues (6). Management of NBD is costly both in terms of patient time and to the NHS e.g. people with MS have 2-3 times more admissions to hospital for bowel complications than non-MS patients. People with MS use interventions such as suppositories, prolonged digital rectal stimulation and/or rectal irrigation often with inconsistent results. For example, one patient in our previous study would take laxatives two evenings per week but could not leave the house the next day as he had no control of when he would pass stool.

### 1.2 Abdominal Massage

Bowel management plays a significant part in the lives of these patients; abdominal massage is thought to facilitate transit of stool through the colon but the mechanism of action has not been much explored. However a small study in an SCI sample (7) suggested that changes in anorectal physiology parameters could be detected during abdominal massage in individuals with SCI and recommended further exploration using these techniques. In people with MS, there is even less current service provision for training as their bowel care is less formalised, but our pilot RCT in people with MS (n=30) concluded that it was feasible and potentially beneficial (8). This is supported by findings in a small non-neurogenic sample of constipated individuals in whom constipation and abdominal pain were significantly reduced (9). In order to find out if abdominal massage should be made more widely available to patients, especially in the community, robust evidence of health and cost benefit is needed. We aim to study the effectiveness of this simple intervention in a real-world setting of current health care provision by undertaking a pragmatic RCT focusing on the effectiveness of abdominal massage plus optimised bowel care, compared to optimised bowel care alone; for the alleviation of neurogenic bowel dysfunction in people with MS. The applicants have already undertaken a pilot trial of abdominal massage in people with MS, including the development of the abdominal massage training DVD and booklet.

A Cochrane Review on Neurogenic Bowel Dysfunction has recently been updated by two of the co-applicants (10) and a Cochrane review on abdominal massage for the relief of constipation was carried out by PI and a co-applicant (SH) (11). The latter and an earlier review by Sinclair (12), both

conclude that studies on abdominal massage are of poor quality, there is very limited evidence regarding the effect of abdominal massage on bowel function, and there is also limited evidence with which to make judgements around benefit. It is in light of these reviews and findings from our pilot study that we propose this RCT.

### 1.3 Why this research is needed

This research is needed now as the number of people with MS is increasing and, due to better healthcare, life expectancy is improving. As well as the increase in the size of the patient population, the ageing bowel, which is more prone to constipation, is an additional consideration. Management within the community (where the overwhelming majority of individuals with NBD live) is not well developed with remarkably limited research (10) and almost no evaluations of models, methods or guidelines related to delivery of bowel care. Abdominal massage is frequently recommended but is poorly taught, has no robust evidence and wastes a lot of time if it does not work. However, it has the potential to improve care, it can be taught and delivered in any setting, is a person centred and an individualised approach to intervention as is called for in the National Service Framework for Long-term Conditions (13). It may well prevent progression to more expensive and invasive options.

There has been a renewed interest in the use of abdominal massage within various populations but the lack of robust evidence has been highlighted in two recent reviews on abdominal massage (11, 12) and two on the management of bowel dysfunction in neurological conditions (10,14). The review by Sinclair (12) concludes that abdominal massage can have measureable effects upon constipation but further research is required to define those patients who will benefit most and a Cochrane Review, undertaken by 2 of the applicants (11), on 'Abdominal massage for constipation', again confirms possible effect but concluded a large scale definitive trial was required to determine effectiveness. The conclusions of the updated Cochrane Review 'Management of faecal incontinence and constipation in adults with central neurological diseases' undertaken by two of the co-applicants (10) has found only 25 trials worldwide on NBD, across all neurological conditions but with little robust evidence on conservative management such as abdominal massage.

In addition to the overall effectiveness of the intervention the ability of patients and/or their carers to learn and undertake the technique both in the short and long-term needs to be confirmed. Strategies for teaching and support are being tested, and, to meet these needs consumer centred involvement in the development and evaluation of this self-management intervention has been paramount. Abdominal massage has the potential to improve NBD symptoms and quality of life without the requirement for long-term health professional input.

### 1.4 Questions which this trial will address

The aim of the AMBER trial is to determine the effectiveness and cost effectiveness of abdominal massage as part of an adjunct to optimised bowel care in people with Multiple Sclerosis who have NBD.

Specific Objectives are:

1. To establish if an optimised bowel care programme with abdominal massage, compared to an optimised bowel care programme alone is more effective and cost-effective in reducing the symptoms of NBD in people with MS
2. To identify and investigate via a process evaluation the possible mediating factors that impact upon the effectiveness of the intervention (including intervention fidelity), how these mediating factors influence effectiveness, and whether the factors differ between the randomised groups.
3. To undertake a formal economic evaluation of the interventions from a societal perspective with a focus on the NHS and the participants

4. To validate responsiveness of a new quality of life questionnaire on NBD.

## 2 Trial Methods

The research comprises:

1. A parallel, two-arm multicentre randomised controlled trial to compare effectiveness of abdominal massage and optimal bowel care versus optimised bowel care in people with MS who have NBD;
2. A longitudinal mixed-methods, nested process evaluation in three sites selected as case studies;
3. Validation of the responsiveness to change of a new patient reported bowel symptom questionnaire, and;
4. Economic Evaluation of abdominal massage and optimal bowel care compared with optimized bowel care for the multi–centre trial for people with MS

Recruitment will take place in approximately 10 centres within the UK. The trial intervention will be delivered by a trained intervention nurse at each centre.

### 2.1 Planned inclusion/exclusion criteria

We are explicitly designing the study to have high applicability so inclusion criteria are broad and exclusion criteria few in number.

Inclusion criteria:

- Male or female over the age of 18 years;
- Diagnosis of MS (in a stable phase i.e. no MS relapse for 3 months);
- No major change of medication for 1 month e.g. introduction of disease modifying medications;
- Individual is bothered by their Bowel Dysfunction, and;
- Must not have used abdominal massage for at least 2 months

Exclusion criteria

- Individuals who are unable to undertake the massage themselves or do not have a carer willing to do it;
- Individuals who are unable to understand the study processes/give informed consent;
- Individuals who have contraindications to abdominal massage e.g. history of abdominal/pelvic cancer, hiatus, inguinal or umbilical hernia, rectal prolapse, Inflammatory Bowel Disease, pregnancy and past history of volvulus.
- Recent abdominal scars, abdominal wounds or skin disorders that may make abdominal massage uncomfortable.

The following are not exclusion criteria but should be discussed with the PI before recruiting
Recent sudden and severe changes in bowel habits
Rectal bleeding

### 2.2 Practical arrangements for allocating participants to trial groups

Recruitment will take place in 10 centres within the UK. It is hoped that the intervention visit will primarily be scheduled to coincide with the patient's routine clinic appointment thus decreasing the burden of an extra visit on the participant, some of whom have long distances to travel to these centres. If this is not feasible an appointment at a suitable time will be made with re-imbursement of travel expenses. A trial manager based at the trial office in Glasgow will manage the research with

support from Tayside Clinical Trials Unit. A Project Management Group, Trial Steering and Data and Ethical Monitoring Committees will provide governance (see later for more details). Each centre will have a local PI, a person responsible for identifying (via patient notes) and contacting possible participants (Recruiter), and a nurse who will deliver the intervention (Intervention Nurse).

Following identification of potential participants a letter of introduction and an Expression of Interest Form will be posted or given to patients in the routine clinic. All patients are asked to return the Expression of Interest Form even if unwilling to take part (in the stamped addressed envelope provided). If there is no response potential participants will be contacted one more time by the site. .A member of the research team will telephone those patients who express an interest to provide further information and complete a short eligibility screening proforma.

If eligible and willing to take part, a time for them to attend clinic will be arranged. An appointment letter will be posted to the patient along with the 7 day bowel diary which they will have verbally agreed to complete. In some instances sites will also post the consent form (as formally agreed by ethics) but most sites will wait and complete the consent at the first visit. The patients will be asked to complete the bowel diary during the week prior to this appointment.

At this appointment patients will complete the consent form and one copy will be placed in the patient's notes one in the Trial Site File, one to the patient, and one will be sent to the Trial office. The baseline questionnaires will also be completed at this appointment or, if preferred, may be taken home by the participant to be posted to the trial office. Participants will also have been asked to bring someone who is willing to do the massage, if required. The intervention nurse will see all participants to randomise the patient and deliver the allocated intervention. Should a further appointment be required this may be arranged.

### 2.3 Randomisation

Randomisation will utilise the web-based randomisation system at the Tayside Clinical Trials Unit. This randomisation system will be accessed by researchers at the CTU when contacted by the Trial Office (NMAHP Research Unit, Glasgow Caledonian University).

Randomisation will be stratified by site and minimised on level of disability (walking unaided, aided or wheelchair bound).

### 2.4 Methods to protect against other sources of bias

**a) Ensuring standardisation of intervention and outcome measurement (performance bias)**

Standardisation of intervention delivery will be the responsibility of the CI who has clinical expertise in this area (DM). The training required to standardise the use of the intervention protocols will be conducted by her and will be directed towards ensuring standardisation across centres. All Intervention Nurses from each centre will attend a training day where all aspects of research and intervention delivery will be explained e.g. not discussing the massage with the control group. Practical sessions will be incorporated and there will be a forum for discussion with opportunities for questions. Following this training day each intervention nurse will also be observed delivering the massage when the site visit is undertaken.

The recruiters in each centre will ensure completeness and accuracy of local data entry e.g. Screening Log data and Clinical Assessment Form data (including patient contact details). The CTU will monitor site fidelity to study processes.

**b) Attrition bias**

We will take very active measures to minimise loss to follow-up, such as obtaining back-up 'best contact' addresses, sending reminders after 2 weeks, with a telephone call after another 2 weeks if no response and allowing telephone completion of questionnaires at this stage. We will provide a £5 voucher with the final set of questionnaires.
In addition we will obtain consent from the participants to enable us to access routine NHS data for example via the NHS Strategic Tracing Service in England and Wales, and using Community Health Index numbers from the Information Services Division in Scotland.

**c) Detection bias**
Group allocation cannot be concealed from the participant or the Intervention Nurse. Participant group allocation will be unknown to researchers running data analysis and to those undertaking and analysing the transit study tests. All participants will be actively followed up, with analysis based on the intention-to-treat principle. All analyses will be clearly predefined, in agreed statistical and economic analysis plans.
It is thought unlikely that participant contamination will occur at the single, face-to-face clinic visit; contamination in the social context may be a possibility. However, the face-to-face individual training by a professional trainer is essential to undertaking the massage technique and without this we do not believe that the technique will be successful. So, contact between individuals from control and intervention groups but without professional input will not lead to substantive contamination, and certainly nothing at the levels considered necessary for cluster randomization (15). The control group will also be asked if they undertook any sort of abdominal massage during the study period, the intervention group will be asked if they continued using the abdominal massage once the intervention period is over, and if they intend to continue it beyond 6 months

### 2.5 Proposed sample size
The only published data available on the Neurogenic Bowel Dysfunction Score to inform sample size calculations is from our own pilot trial in the MS population. (The difference in the mean change of score between groups from base-line to Week 8 was 7.35, SD 2.4 [t=-2.95, df= 27, p=0.006, 95% Confidence Interval -12.45 -2.25]). Based on data at 8 week (i.e. Week 16) follow-up, a sample size of 60 per group would be indicated to detect a difference between groups of 4.21 (SD 7.02) at the 5% level of significance with 90% power. Thus for a fully powered study the sample size, allowing for a 20% drop out, is 150. However it was suggested by the HTA board that this figure be reviewed and possibly increased. Therefore we have increased our sample size to 200 (100 per group) which would allow for greater than expected attrition.
We are evaluating a technology (abdominal massage) that has promise for MS patients as demonstrated by our pilot and will therefore run a full-scale trial in this population to confirm or refute that promise. The MS population is large and neurogenic bowel dysfunction is the problem they rate as most severe.

### 2.6 Number of centres involved
We will recruit patients from 10 centres which have agreement in principle to participate all of which are research active. These centres each have approximately 200 people with MS, who are reviewed bi-annually or annually with 60% reporting NBD. One centre, UCLHreceives 6 new referrals per week specifically relating to NBD and it is at this centre we will recruit for the additional ano-rectal physiology tests. At the other centres from the 200-300 patients with MS, we estimate that 200 will be eligible and with a conservative estimated consent rate of 50% this will give us a population of 100 per site to recruit 20 patients over a 12 month recruitment period; which is approximately 2 new participants per month. We will continue to gather expressions of interest from additional centres as insurance against unexpected problems or delays at our identified sites. Although at present we have no reason to believe that our sample size will not be achieved from the sites that have already given their agreement in principle.

### 2.7 Process evaluation methods

Advised by MRC guidance for evaluating complex interventions (16, 17), the proposed RCT includes a theory-driven process evaluation. This will be informed by realist evaluation methodology (18), which goes beyond the evaluation question "What works?" to: "What works, for whom and in what context?" The aim of this approach is to situate and explain outcomes within the contexts in which they are achieved in order to explain potential discrepancies between expected and observed outcome and to assess fidelity to the implementation processes. Furthermore, results of the process evaluation will provide data to inform the optimisation of the intervention and seek to explore potential routes to sustainable implementation in the event that effectiveness is demonstrated. The process evaluation will follow a mixed methods, longitudinal, case study design (19, 20).

The objectives of the process evaluation are as follows:

- To explore fidelity to processes of implementation (to be embedded within data collection on implementation contexts);
- To explore implementation contexts (including settings, demographics and implementation processes; delivery and take up of the intervention; adherence and non-completion), and;
- To explore intervention optimisation and sustainability beyond the life of the funded project.

Meso-level and micro-level contextual data on the ten intervention sites will be gathered in order to explore pre-existing background contexts and any changes (e.g. in local capacity) that might have an impact on delivery or take up of the intervention. Micro-level data on the potentially changing landscape of implementation contexts and fidelity to implementation processes will be gathered via process tracking questionnaires for each intervention site and semi-structured interviews with key stakeholders, those delivering the intervention and trial participants. Bowel care/massage diaries initiated through the trial will also be analysed for data on intensity and duration of massage for a sub-sample of interviewees.

#### 2.7.1 Interview study methods

Longitudinal interviews will be conducted with clinicians/implementation teams and trial participants. Interviews will be conducted at two time points in order to track implementation processes (delivery and take-up of the intervention; issues of fidelity to implementation), experiences of receiving the intervention. Five additional (single) interviews will be conducted with high level stakeholders in order to gather data primarily on the policy landscape and clinical developments.

*Sampling and recruitment:*

1. Stakeholder interviews (30-45 minutes): 5 stakeholders will be recruited to include perpectives/views from an MS Charity, a policymaker, senior nurse, consultant neurologist and a continence service.
2. Longitudinal telephone interviews will also be conducted with key staff (n=2) at each of the ten implementation sites at two time points: at inception of implementation, and at the end of the implementation period. The sample will consist of the site lead/PI and one other member of staff involved in intervention delivery. Staff will be selected who have a high degree of involvement in implementation activity. 20 staff will be interviewed two times. As participants will be members of the implementation teams, recruitment will be via site leads who will provide potential interviewees with an information sheet explaining the purpose of the interviews and seeking agreement to pass their contact details to a researcher. Those who are willing to take part will then be contacted by a researcher and a date and convenient time for a telephone interview will be agreed.

3. Trial participants in receipt of the intervention will be recruited from any of the study sites (a maximum of 5 participants per site). different geographical locationsThis will allow the process evaluation to explore any variation in experience related to receiving the intervention from various settings.

   Participants in the control group will not be eligible to take part as the process evaluation as it will focus on experiences of receiving and delivering the intervention and implementation processes. Sampling characteristics will include: geographical location, type of MS; severity of condition (self-care or massage done by carer/family); gender; levels of deprivation; those with home support and those without. 5In total, a maximum of 20 patients will be recruited for interviews. Telephone interviews will be conducted within the first month of enrolment on the trial and on completion/drop-out. On enrolment, trial participants will be asked if they are willing to take part in interviews. If so, they will be given a patient information sheet and asked for permission for their contact details to be given to a researcher. When contacted, the researcher will emphasise that taking part in an interview is voluntary and will not have any bearing on their status as trial participants or other medical treatment. Participants will be given the opportunity to ask questions about the study prior to signing a consent form. Interviews will be conducted by telephone and will last approximately one hour. In total 20 MS patients will be recruited who will be interviewed twice. The researcher will inform patients that their agreement to take part in the first interview does not oblige them to take part in the second one and that they are free to withdraw from the study at any time without giving a reason.

*Data Collection:*

The interviews will be semi-structured, following an iterative approach informed by on-going analysis, to explore some areas in more depth or follow potential new lines of inquiry. This will be supported by input from FH (qualitative expertise) and the CI (Clinical expertise). All interviews will be conducted by telephone by an experienced qualitative researcher. With participants' consent, all interviews will be audio recorded. Participants will be assured that any quotes used in reports or publications will remain anonymous. Transcripts will be anonymised and will only be shared with members of the research team involved in the process evaluation analysis. This will exclude site leads/local PI's in order to ensure that implementation team members' views and those of patients remain confidential. This is because details of a patient's medical condition and experiences of abdominal massage revealed in an interview may well reveal their identity. Furthermore, it is important to allow clinical/implementation staff similar protection in order to encourage open and honest responses to questions regarding implementation. However, it is acknowledged that clinical staff in particular may well be identifiable therefore care will be taken with reporting to ensure that all quotes used are not attributable to individuals. Further information related to each of the three categories of interviewees are addressed separately below.

1. Stakeholder interviews will explore issues related to current and developing policy of relevance to MS patients and self-management; current service delivery and organisation of services for MS patients; new treatments currently being rolled out that may have an impact on variable outcomes for trial participants; issues of sustainability and potential future implementation into practice of the AMBER intervention if effectiveness is demonstrated. These semi-structured interviews will follow an iterative approach in order to draw on the interviewee's expertise and experience. The interviews will last approximately 30-45 minutes and will be conducted by telephone by a researcher experienced in qualitative approaches. Only one interview will be conducted with each stakeholder.

2. Longitudinal interviews with implementation teams. These semi-structured, telephone interviews will explore: barriers, facilitators and contexts of implementation (local capacity, organisational structures and any changes to these); fidelity to implementation processes (recruitment to the trial, information given to patients, training issues) and views of the intervention. Interviews will last 30-40 minutes and will be conducted at two time points: once on inception of the intervention and again at the end of trial recruitment.

3. Patients will also be interviewed at two time points: after one month post-enrolment in the trial and again on completion or drop-out. These interviews will explore: personal circumstances (e.g. time since diagnosis, employment, family/community support issues, mental health & well-being); acceptability of abdominal massage; expectations of participants versus actual experience; barriers and facilitators to adherence; support from health professionals; information provision and training material; fidelity to massage technique versus potential self-adaptations to address-mobility or other issues; implementation processes such as diary completion and so on. Particular attention will be paid to including the views of non-completing participants to explore reasons for non-adherence and their views on how the intervention experience might have been improved. The telephone interviews will last approximately 30-60 minutes and will be informed by the topic. Patients will be given the opportunity to ask questions about the study before signing the consent form, which participants will be asked to return (in an sae provided) on completion of the interview.

*Data Handling*

The process evaluation will fully comply with the terms of the Data Protection Act 1998. When participants have been recruited into the study and given informed consent they will be assigned a non-identifiable code and all data (paper and electronic) will use this code. Identifiable data (e.g. contact details) will be held on a separate database (i.e. will not be linked to any data) and will only be used to contact the participant about the study. Transcribers, if outsourced, will be asked to sign a confidentiality statement. Interviews will be digitally recorded and transcribed verbatim in order to ensure fidelity to the views of interview participants is retained in the analysis.

All data will be held on a secure, password protected University computer. The analysis will be undertaken by the process evaluation researchers and they will be the only members of the team who will have access to interview transcripts. The analysis will take place on University computers at the University of Stirling and Glasgow Caledonian University. The digital voice recordings will be destroyed at the end of the study. The anonymised transcripts will be retained in a secure archive setting for 15 years (as for the rest of the study data) to facilitate future analysis and publication of the study material.

2.7.2. Process tracking questionnaires

Questionnaires will be sent to each of the ten sites at 6 monthly intervals. They will be completed by one member of the implementation team. These will track progress with implementation of the intervention arm of the trial to include the following: numbers recruited by each time point; numbers completed; non-completers; any changes in local capacity that might affect implementation; any new treatments or care pathways being rolled out for MS patients. These questionnaires will not collect any personal data.

*Risks and safe-guards related to the process evaluation:*

Little/no risk is associated with taking part in an interview. There will be no additional discomfort for participants as they will be interviewed in their own homes at a time convenient to themselves.
There is a small possibility that patients may find it upsetting to talk about their health and experience of bowel dysfunction, however interviews will be managed by a trained qualitative researcher with experience of conducting interviews on sensitive topics. In the event that the researcher had any concerns about the well-being of a participant, they would urge the patient to speak to a named clinical contact within the MS centre or else contact their GP.

*Ethical issues related to the process evaluation:*

Informed consent procedures will ensure that participants understand that participation is purely voluntary and that they can withdraw from the study/interviews at any time without this affecting their trial participation or other medical treatment. After participating in one interview, they will be free to decline to take part a second time. Thus consent will remain a continued process.

While every precaution will be taken to preserve patient anonymity and confidentiality there will be limits to this. In the event that the researcher was concerned for the well-being of a participant, action would be taken to disclose concerns to a named clinical contact within the relevant intervention site. If a participant (either intervention team or patient) were to disclose anything indicating unsafe practices or misconduct, they would be urged to follow hospital complaints procedures.

## 3 Trial Interventions

### 3.1 Both trial arms

Both intervention and control groups will receive a 6-week intervention, consisting of one, 1-hour outpatient consultation followed by weekly telephone calls for 6 weeks to review adherence. Thus both groups will have the same amount of health professional contact. The intervention and control group will differ as described below.

Both groups will receive what we have termed 'optimised bowel care'. Often, in people with MS, bowel care is delivered in a haphazard fashion with little standardisation or guidelines for treatment. As detailed in the application our optimised care (delivered to both groups after initial assessment) will focus on a step-wise self-management approach. This will be reinforced in the Bowel Care Advice Leaflet which is part of the Information pack provided to all participants that will be developed jointly by the co-applicants and people with MS. Furthermore, in order to ensure standardisation across both groups we will work with four people with MS and neurogenic bowel dysfunction and expert clinical members of the research team (CN, MC, AE & DM) to update and operationalise "best practice" on bowel assessment and management in MS into a single good practice booklet and checklist for guiding health practitioners in their bowel consultation. We will include information from the current MS Society bowel management advice (written by CN), the NICE guidance on FI (CN & AE were on guideline group) and MASCIP guidance on neurological bowel management (written by MC), including practical advice on bowel habit and timing, diet and fluids, practical coping and products. This will be a training booklet for professionals with a checklist for assessment and suggestions for areas to be 'optimised' and will therefore standardise the advice offered to all participants. This booklet will be discussed and guidance on its use given during the training day for clinicians.

A clinical assessment form will be completed for all participants when they first see the Intervention

Nurse. This will record basic demographic details, medical and surgical history, additional/confirmation of screening for Red Flag symptoms (e.g. rectal bleeding) with a SOP indicating when it is appropriate to refer. This form will also be used by the Intervention Nurse to record what happens during the one hour intervention and the follow-up phone calls, and any additional phone calls made by those in the Intervention group.

A Patient Information Pack is in the process of being developed by the research team and will consist of:

- The Multiple Sclerosis Society's Bowel Care booklet

For those participants in the Intervention Group the Information Pack will also include;

- The massage DVD/or equivalent, demonstrating a carer/clinician undertaking the massage on a patient model and how it can be adapted for self-massage (approx. 15 minutes in total).
- Patient abdominal massage training information leaflet

**3.2 Control Group (optimised bowel care)**

During the 1-hour outpatient appointment the Clinical Assessment form will be completed, the participant's Bowel Diary will be reviewed and the information in the Patient Information Pack discussed. The participants' existing routine bowel care will be reviewed and optimized. For example explaining the necessity of adequate fluid intake is important as sometimes patients who have urinary urgency reduce their fluid intake and make their stool drier and more difficult to pass. No change in medication will be advocated. The participants in this group will also receive one telephone call per week during the following 6 week period to further discuss their bowel management. This group will not be offered routine access to telephone support but will have the contact details of the CI should they have any problems relating to the study.

**3.3 Intervention Group (abdominal massage & optimised bowel care)**

In addition to optimised bowel care as described for the control group, the Intervention Nurse will teach the participant and/or their carer how to deliver the abdominal massage. This will include viewing the massage DVD and the abdominal massage training booklet, as well as the demonstration of the technique on the participant by the Intervention Nurse.

Abdominal massage protocol: The ideal position of the participant is supine with appropriate head and knee support, and in a relaxed atmosphere. Adaptations to this position may be required depending on the patient's disability.

There are 4 basic strokes with the massage lasting about 10 minutes.

1. Stroking commences from the small of the back, over the iliac crests, and down both sides of the pelvis towards the groin.
2. Effleurage follows the direction of the ascending colon across the transverse colon and down the descending colon. This is also repeated several times with increasing pressure
3. Palmar Kneading tracks down the descending colon, up the ascending colon, and down the descending colon once again. Effleurage is repeated and continued with a relaxing transverse stroke over the abdomen.
4. Vibration over the abdominal wall to relieve flatus concludes the massage session.

During the training the carer or participant will try the various strokes and will be able to ask questions. Possible adaptations due to the participant's disability will also be discussed. It is recommended that the abdominal massage is included as part of the participant's usual bowel care regimen. Daily application was recommended in our Pilot Study in people with MS and this was found to be acceptable with 80% adherence reported in the massage diary.

Back up support whereby those in the Intervention group can telephone the Intervention nurse or PI as required will be available and usage monitored as part of the process evaluation.

During week's 1-6 weekly telephone calls (lasting approximately 10 minutes) will be made to discuss frequency of use and any problems in using abdominal massage and any changes/difficulties with bowel management.

No issues with compliance were identified in the MS Pilot Study so it is not anticipated that there will be any serious problems with compliance or attrition in the MS population, although we will ask about compliance to undertaking the massage and or advice (and adverse events) at the weekly calls and attrition will be recorded as part of trial management.

**3.4 Intervention nurse training**

The Intervention Nurses (who sees all participants) will have completed a one day training course which will cover the research processes involved in the study, the physiology of NBD, treatment options including lifestyle advice and the theory and practice of abdominal massage. A Clinician's Handbook will have be developed which will cover this information together with research governance, standard operating procedures for the control and intervention group which will include eventualities such as participants who are disappointed with their group allocation. The Clinical/Nurse Assessment form,the Patient Information Pack, a detailed protocol and protocol checklist, the recently updated MASCIP Guidelines for Management of NBD in Individuals with Central Neurological Conditions (21); (MC chaired the Guideline Development Group) and a copy of the DVD demonstrating the massage will also be in the Clinician's Handbook.

This study day will be organised by the CI who will undertake the training in the massage, and by co-applicants MC and CN both of whom are highly experienced experts in NBD. During this training day there will be facilities for the nurses to watch the massage on the DVD, observe the massage being undertaken by the CI, to practice the massage on each other and to ask questions. Several case studies will be provided which will discuss patients with various levels of disability.

An abdominal massage training DVD was used in our Pilot Study; this is in the process of being further developed by the research team to include possible modifications when undertaking self-massage; similarly a patient's abdominal massage training booklet will be developed.

Following this training day the Intervention nurses will be encouraged to practice the massage either on patients or other volunteers before the site visit by the research team. This intervention is of low risk and is routinely suggested to patients. During the site visit the CI will observe the Intervention Nurse undertaking the massage and assess for competency.

**3.5 Radio Opaque marker transit tests**

Standard anorectal physiology tests and colonic transit studies are routinely undertaken before treatment at the UCLH which see people with MS (which will recruit 30 MS participants), and the outcomes will be recorded as they may have some predictive value. These participants will have a repeat transit study test at 24 weeks. Transit studies have been used in previous trials and have been shown to be sensitive to change (22). Radio-opaque marker transit studies most commonly involve the ingestion of a number of Sitzmarks capsules, each containing different shaped radio-opaque markers, followed by a single plain abdominal x-ray 5 days later (23, 24). These transit studies enable an assessment of total colonic transit time, but not segmental transit (25). The radio opaque markers will be posted to the participant who will ingest them and then attend for abdominal x-ray 5 days later. Out of pocket expenses will be paid to the participant for attending the follow-up transit study.

Furthermore, during the routine anal physiology testing undertaken at this site, abdominal massage will be carried out during a repeat pressure test on those randomised to the Intervention Group. One of the co-applicants (MC) undertook a similar study in over 100 people with SCI and reported that change in pressure was noted in 98% of participants (26). Undertaking the transit study repeat test and recording of changes whilst undertaking the massage, will provide information on the possible mechanisms of action and pilot data for future mechanistic work.

## 4 Data Collection

Data will be collected via participant-completed questionnaires at baseline, 6 and 24 weeks. A one week bowel diary will be completed prior to baseline, during the intervention and at 23 weeks. A massage diary will be completed during weeks 1-6 for those participants in the Intervention Group.
Ano rectal physiology and colonic transit time data will be collected formfrom the UCLH London site only using an Ano Rectal Physiology form.

Outcome measures on which data will be collected are as follows:

### 4.1 Primary Outcome

Neurogenic Bowel Dysfunction Score (NBDS) (27) records changes in NBD. It is a 10 item questionnaire covering frequency of bowel movements, headache, perspiration or discomfort during defecation; medication for constipation or faecal incontinence; time spent on defecation; frequency of digital stimulation or evacuation; frequency of faecal incontinence; flatus incontinence; and perianal skin problems. Maximum score is 47 with over 14 considered severe.

### 4.2 Secondary outcomes

*Bowel Outcomes*

- Constipation symptoms (Constipation Scoring System (CSS) (28)
- Bowel Symptoms (7-day bowel diary)
- Radio Opaque marker transit tests
- Adherence to massage schedule (massage diary)

*Urinary Outcomes*

- Bladder function (Qualiveen Questionnaire Short Form) (29)

*Quality of Life Outcomes*

- Health Status (EQ-5DL) (30)
- Patient reported Quality of Life (patient reported symptom and quality of life questionnaire for NBD)
- Change of medication (This will be collected using a CON Med form which will be completed at base-line during the weekly telephone follow-up calls and at week 24.)

*Economic outcomes*

- *A short patient resource questionnaire has been developed to collect this data and will be completed* during weeks 1-6 and thereafter at 12, 18 and 24 weeks.
- cost and use of NHS services
- cost to the patients and their families/carers
- the incremental costs, QALYs and incremental cost per QALY derived by the economic model.

## 5 Data analysis

### 5.1 Main effectiveness analysis

Analysis will be performed for the intention to treat population and reported in accordance with the CONSORT statement and the ICH E9 'Statistical Principles in Clinical Trials'. All study data will be summarized by treatment group and total. Continuous data will be reported as mean (SD), categorical data as N (%). Primary outcome analysis will be a general linear model comparing the difference in mean NBDS score at 24 weeks between the intervention and control with adjustment for the minimisation covariates and baseline score. Other covariates will be considered for further adjustment and if necessary stated in the statistical analysis plan prior to data lock (31). Secondary analysis will use similar ANCOVA models, correcting for baseline characteristics. A 2 sided p value of 0.05 will be taken as significant for each outcome.

The extent of missing data will be explored in the outcomes especially the primary outcome. Patterns of missing data will be explored and predictors of missingness examined, especially if these vary by intervention. If necessary, multiple imputations will be utilised to impute missing data assuming the missingness mechanism is missing at random (MAR). A detailed statistical analysis plan will be agreed before the end of data entry and before the treatment code is broken.

An independent Data Monitoring and Ethics Committee will review accumulating data annually.

### 5.2 Subgroup analysis

Subgroup analyses will be carried out by first testing for a subgroup factor by intervention interaction (31). If this is significant at the 5% level, results will be estimated separately by the different subgroups. These analyses will also be repeated for all the secondary outcomes. Appropriate transformations of outcomes will be performed where necessary to satisfy modelling assumptions. This will include a secondary analysis comparing those who undertook the massage themselves to carer massage.

### 5.3 Process Evaluation analysis

Interviews will be coded and analysed using techniques of framework analysis (32), using QSR NVivo 10. Framework analysis is an approach that lends itself to exploring process evaluation data as it facilitates analysis that retains an overall view of the data at different time points, while also offering the facility to 'drill down' into recurrent themes across cases. We will pay particular attention to drawing out details related to causal mechanisms that may impact on intervention uptake and have an impact on quantitative outcomes. All transcripts will be summarised, charted and coded for recurrent themes by a researcher experienced in qualitative research, supported by a senior researcher (FH). An NVivo coding frame will be developed informed by discussion with the wider team to ensure that clinical expertise informs the analysis. The analysis will pay particular attention to barriers and facilitators to take up of abdominal massage for MS patients, synthesising staff and patient views into an overall narrative of implementation. Case attributions will be assigned to transcripts related to sampling characteristics (e.g. condition, severity, gender etc.) in order to explore themes within NVivo matrix coding frames. This will ensure that the analysis captures potential differences in experience related to social, physical or environmental differences. Staff interviews will be analysed longitudinally, using a framework matrix to explore developments over the two time periods. While the analysis will explore patterns across the data, we will also seek to explain any disconfirming cases, drawing on individual characteristics as appropriate.

Progress tracking data for trial recruitment and adherence will be synthesised in narrative form with themes from the qualitative data, thus the mixed methods will complement each other rather than

be used to triangulate and verify either data source (33). The process evaluation will also draw on the results of the participant massage diaries, seeking to explain adherence/intensity rates via qualitative interview data. Informed by the realist evaluation approach, the analysis will seek to identify key mechanisms involved in the implementation of the intervention, barriers and facilitators to success and what might impinge on outcomes. Finally, the lessons learned from the process evaluation will provide analytical input into the optimisation of the intervention for future implementation into practice if effectiveness is demonstrated.

### 5.4 Economic Analysis

The trial will include a formal economic evaluation of the interventions from a societal perspective with a focus on the NHS and the participants and their families.
If there is no statistically significant evidence that one treatment strategy is more effective than another, a cost-minimisation framework will be used and the less expensive form of care will be recommended. If one strategy appears to be dominant i.e. to be more effective and less costly than the alternative, the uptake will be recommended. If one form of care appears to be more effective and more expensive than the comparator, estimates of incremental cost-effectiveness (and cost-utility) ratios will be generated.

Incremental cost effectiveness ratios (ICERS) will be computed comparing the cost of the experimental and comparator interventions. The difference in effectiveness will be expressed in terms of the change in score on the NBDS. These data will be retrieved from the participant's questionnaire responses to the NBDS questionnaire. The difference in utility will be expressed in terms of QALYs. Where appropriate the analysis of incremental costs, effectiveness and cost-effectiveness will be based on similar statistical models as those outlined in the statistical analysis section above. This 'within' trial analysis will include both deterministic and stochastic sensitivity analyses to explore statistical and other forms (e.g. around unit costs or the source of utility estimates) of uncertainty.

All study analyses will be according to an economic analysis plan that will be agreed in advance. Similar subgroup analysis will be performed in the economic analysis as defined in the statistical analysis if deemed relevant.

## 6. Milestones and Recruitment Rate

### 6.1 Trial timetable and Milestones

| | |
|---|---|
| **Before Start** | Refine and agree the Intervention protocols and patient documents within the Project Management Group for NRES approval. Once gained sign contracts and advertise and recruit project manager and process evaluation RA |
| **Year One** | |
| By month 3 | Set up office and administrative base<br>Design data management system<br>Define the randomisation system. |
| | Establish first two centres<br>Finalise site recruitment and recruit local investigators<br>Commence REC approvals for all sites |

| | |
|---|---|
| | Finalise the Clinician's Handbook and hold the Intervention training day, Printing of study documentation, questionnaires, Patient Information Pack. Finalise the abdominal massage training DVD<br>CI visits first two sites |
| By month 6 | First Trial Steering Committee meeting<br>First Data Monitoring and Ethics Committee meeting |
| | Start recruitment at first two centres including anal manometry |
| | Continue Site recruitment, R&D approvals and appoint local recruiter and Intervention Nurses<br>On-site visits by CI |
| | 6 month report to HTA (and thereafter at 6 monthly intervals) |
| By month 10 | Collaborators' Meeting |
| | Roll out participant recruitment to the remaining 8 centres |
| By month 12 | First annual report to funders |
| **Year Two** | |
| By month 18 | Second Data Monitoring and Ethics Committee meeting<br>Second Trial Steering Committee meeting |
| By month 24 | MS recruitment complete<br>Second annual report to funders |
| **Year Three** | |
| By month 26 | Third Data Monitoring and Ethics Committee meeting<br>Third Trial Steering Committee meeting |
| | Baseline interviews completed<br>Audio-recordings of consultations completed |
| By month 30 | Questionnaire follow up at 6 months after randomisation completed<br>Interview follow up at 6 months after randomisation completed<br>Interviews with therapists completed |
| By month 36 | Final Trial steering committee meeting<br>Data analysis completed<br>Final collaborators meeting<br>Data archiving arrangements for long-term follow-up |
| **Year Four** | |
| By month 39 | Final report |
| Post funding | Dissemination via main papers describing the trials |

### 6.2 Recruitment rate

It is projected that the first centre will commence recruitment in Month 6 and following this 2 new centres per month will commence recruiting. Each centre will aim to recruit 2-3 patients per month and it is estimated that each centre will need 12 months for recruitment (allowing for holidays etc.). Recruitment will be completed at month 22, follow-up by month 29.

## 7 Organisation

### 7.1 Trial coordination

**The Trial Office team**
A trial manager will be appointed and will be based at the research office - The Nursing Midwifery and Allied Health Professions, Research Unit (NMAHP RU) Glasgow Caledonian University, and will be responsible for the day to day running of the project. A research assistant (80% Fte) will also be recruited to this office and will co-ordinate and undertake many of the interviews, transcriptions for the Process Evaluation component under the supervision of a co-applicant based at Stirling University, the co-host of the NMAHP RU. The trial management team (CI, trial manager, research assistant, Process Evaluation Lead, TCTU deputy director) will initially meet weekly (using teleconferencing as appropriate) and summary notes and action points will be disseminated within a day. Once the trial is established these will change to bi-weekly meetings. A co-applicants meeting will be arranged for every 3 months to monitor overall progress.

**The Centre Team**
All sites will have an initial set up visit from the CI and one other co-applicant to ensure all study processes are in place before recruitment commences. Each site will have an additional one visit per year as part of the Process Evaluation component.

***Local Principal Investigator***
Each collaborating centre will identify a lead clinician who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the trial locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint, train and supervise a local Recruitment Officer; and inform all relevant local staff about the trial)
- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)
- notify the Trial Office of any unexpected clinical events which might be related to trial participation
- provide support, training and supervision for the local Recruitment Officer
- represent the centre at any collaborators' meetings.

***Local Recruitment Officer***
Each collaborating centre will appoint a local Recruitment Officer to organise the day to day recruitment of patients to the trial. The responsibilities of this person will be to:

- keep regular contact with the local lead clinician, with notification of any problem or unexpected development
- maintain regular contact with the Trial Office
- keep local staff informed of progress in the trial

- contact potential participants by: mailing out a letter of introduction and an Expression of Interest Form to individuals who are potentially eligible based on referral letters; explain the trial and the potential for participation in the trial if they are eligible; explain what is intended by research access to their NHS data; discuss the possibility of being invited to take part in the interview study; and describe the possibility of long-term follow up and participation in other research
- ensure therapy data are collected, and send paper copies to the Trial Office
- ensure audio recording of any consultations selected by the Trial Office as part of the Process Evaluation
- file relevant study documentation (e.g. consent forms) in the patient's medical records
- organise and supervise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meetings.

***Intervention Nurse***

Each collaborating centre will appoint a local Intervention Nurse to organise the day to day recruitment of patients to the trial. The responsibilities of this person will be to:

- keep regular contact with the local lead clinician, with notification of any problem or unexpected development
- maintain regular contact with the Trial Office
- keep local staff informed of progress in the trial
- attend training course on research processes involved in the study, the physiology of NBD, treatment options including lifestyle advice and the theory and practice of abdominal massage.
- arrange clinical appointments for each randomised participant and deliver the optimised bowel care advice. Deliver massage training for patient / carer and advice on frequency of massage (intervention group only).
- arrange and deliver follow up telephone call to discuss bowel care and massage
- distribute patient pack information and DVD's as required
- complete the Clinical Assessment Form and return to the Trial Office
- file relevant study documentation (e.g. consent forms) in the patient's medical records
- represent the centre at the collaborators' meetings.

### 7.2 Research Governance, data protection and sponsorship

The trial is supported by the Tayside Clinical Trials Unit (TCTU). This will ensure compliance with the Research Governance Framework and Good Clinical Practice, and provide the data management system, web based randomization system and statistical analyses

The trial will comply with the Data Protection Act 1998 and regular checks and monitoring will be in place to ensure compliance. Data will be stored securely in accordance with the Act and archived to a secure data storage facility. The consent form will state that other researchers may wish to access (anonymised) data in the future. The Senior IT Manager (in collaboration with the trial statistician) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

The trial will be sponsored by Glasgow Caledonian University. It will be overseen by a Trial Steering Committee (TSC) which will include an independent Chairperson, at least 2 other independent

members, representative from Tayside Clinical Trials Unit (TCTU) and our Patient representatives. We anticipate that the TSC will meet on three occasions

### 7.3 Data and safety monitoring

#### 7.3.1 Data Monitoring and Ethics Committee

A separate and independent Data Monitoring and Ethics Committee (DMEC) will be convened. This Committee will be independent of the trial organisers and the TSC. It is anticipated the members will meet once to agree terms of reference and on at least two further occasions to monitor accumulating data and oversee safety issues. During the period of recruitment to the trial, no formal interim analyses are planned; however the DMEC will review a report on accumulating safety data, together with any other analyses that the committee may request, at each meeting, and any serious adverse events reported to the DMEC as detailed in Section 7.3.3. If necessary, the DMEC may request an unblinded analysis of safety data to address any concerns, although it is not anticipated that this will be necessary as no Serious Adverse Events related to the intervention or other trial procedures are anticipated. This report may also include analyses of data from other comparable trials. In the light of this report, the DMEC will advise the Trial Steering Committee if, in its view, the trial should continue as planned, or stop early due to clear harm of a treatment, or external evidence; it may also make recommendations as to other amendments to the trial protocol based on this report.

The TSC can then decide whether or not to modify intake to the trial. Unless this happens, however, the TSC, PMG, clinical collaborators and trial office staff (except those who supply the confidential analyses) will remain ignorant of any unblinded analyses.

The Chair and the other independent members are to be appointed after confirmation by the HTA.

#### 7.3.2 Safety concerns

The AMBER trial involves treatments for individuals with Multiple Sclerosis who have Neurogenic bowel dysfunction which are well established in clinical practice, therefore adverse effects (although these are unlikely) will be those observed in everyday practice associated with optimised bowel care and abdominal massage. Expected events arising from the treatments are noted below and thus will not be collected as adverse events.

- **Increased flatulence**
- **Abdominal cramps**
- **Stomach rumblings/noises**

**Loose Stool, which in some instances may lead to faecal incontinence**

#### 7.3.3 Procedure for reporting AEs and SAEs in this trial

**DEFINITIONS**

**Adverse Event (AE)**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

**Adverse Reaction (AR)**

Any untoward and unintended response that has occurred due to the intervention.

A number of factors affecting the trial population suggest that we would expect to observe a larger than normal incidence of episodes of adverse events (AEs) such as fatigue and ill health due to co-morbidities of the study population. For the purpose of the AMBER study we will record any AEs that require the study participant to seek advice from a health care professional (e.g. common colds dealt with at home will not be reported) and which are NOT expected events of having MS. All **known** disease progression and co-morbidities will be noted but not reported

A **serious adverse event (SAE), or Serious Adverse Reaction (SAR)** is any AE or AR which

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- or is a congenital anomaly or birth defect

Note: Hospitalisations for treatment planned prior to randomisation will not meet SAE criteria. Any hospitalisation post randomisation, will be recorded.

**DETECTING AEs AND SAEs**

All AEs and SAEs must be recorded from the time a participant signs the consent form to take part in the study until the last follow up call (24 weeks).

The research team will ask about the occurrence of AEs/SAEs at every visit or telephone call during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

**RECORDING AEs AND SAEs**

When an AE/SAE occurs, it is the responsibility of the PI to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Principal Investigator (PI) should then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes type of event, onset date, PI assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

**ASSESSMENT OF AEs AND SAEs**

Each AE must be assessed for seriousness, causality, severity and expectedness by the PI or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role.

### 7.3.4 Reporting responsibilities of the PI and CI

Once the PI becomes aware that an SAE has occurred in a study participant, they will report the information to the AMBER trial office immediately office within 24 hours. The SAE form will be completed as thoroughly as possible with all available details of the event, signed by a member of the research team. If the PI does not have all information regarding an SAE, they will not wait for this

additional information before notifying the AMBER trial office. The form will be updated when the additional information is received.

The SAE form should be transmitted by fax to the AMBER trial office on 0141 331 8101.

If, in the opinion of the local PI and the CI, the event is confirmed as being related and unexpected, the CI will submit a report to the main REC, the trial sponsor and the DMEC within 15 days of the CI becoming aware of it.

Collaborators and participants may contact the chairman of the TSC through the AMBER Trial Office about any concerns they may have about the trial. If concerns arise about procedures, participants or clinical or research staff (including risks to staff) these will be relayed to the Chair of the DMEC.

As the trial arm to which participants are allocated cannot be masked from the participants or the therapist after randomisation has occurred, unblinding is not an issue in this trial.

**FOLLOW UP PROCEDURES**

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant's medical progress. Follow up information on an SAE should be reported to the AMBER Trial Office when received.

AEs still present in participants at the last study visit should be monitored until resolution of the event or until no longer medically indicated.

### 7.4 Ethical issues and arrangements

We will submit our research proposal for review and approval to the National Research Ethics Service approval from Greater Glasgow and Clyde before the start date of the project. Application to the NIHR Clinical Research Network will facilitate local R&D approvals. We believe that the proposed research does not pose any specific risks to individual participants nor does it raise any particular ethical issues. Abdominal massage is a low-risk intervention.

Trial participants in the experimental arm will benefit from exposure to a highly specified training in abdominal massage with the addition of a DVD/equivalent demonstrating the massage and a training manual. All participants will benefit from the Information Pack developed by the co-applicants. The wider benefit of the trial for society will be the generation of evidence regarding an intervention which may provide significant benefit for people with NBD, reducing symptoms that are bothersome and improving quality of life, and reducing costs, both personal and to the NHS, of products and other treatment. The cost of the trial will be recouped either by savings to the NHS from avoiding abdominal massage if it is found to be ineffective, or reduction in the uptake of other treatment such as laxatives or surgery if the massage is found to be effective.

Participants will be informed of possible benefits and known risks of participation in the trial by means of a Patient Information Sheet, discussion with the local recruitment teams, the local PI and the Trial Office researchers. Participants will sign a consent form approved by the ethics committee. They will be consented to participating in the trial, being randomised and followed up, including electronic tracing using NHS data, and data linkage with computerised NHS data sources, and being contacted in the future about this and other research. Participants who are not able or not willing to be randomised will not be recruited. Participants will be sent an additional Patient Information Sheet relating to the interview study, with separate consent subsequently sought.

It is intended to follow up the whole cohort of participants for a further year at least and data will be retained as long as necessary for this purpose. Permissions will be sought from the relevant Research Governance bodies and the Ethics Committee. Attention has recently been drawn to the importance of long-term follow up (34).

## 8 Finance

The trial is supported by a grant from the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Health Technology Assessment (HTA) Programme (HTA 12/127).

## 9 Indemnity

The Patient Information Leaflet provides a statement regarding indemnity for negligent and non-negligent harm.

We do not expect any harm to come to patients by taking part in the study. All the materials and techniques are being used to a certain extent in the NHS for conservative management of neurogenic bowel dysfunction. Participation in the study will help evaluate the training procedures and effectiveness. Taking part in this study does not affect normal legal rights. Whether or not patients take part, the same legal rights apply as any other patient in the NHS (which includes professional indemnity insurance for negligence). If a participant wishes to complain about their health care or any aspects of this study, the normal NHS mechanisms will be available.

In addition, the universities involved with the trial hold and maintain a 'no fault' insurance policy. This policy covers all employees of the universities and those working under their direction.

## 10 Publication

The success of the trial depends entirely on the wholehearted collaboration of a large number of participants with multiple sclerosis, as well as the nurses and local PI's involved. For this reason, chief credit for the trial will be given, not to the committees or central organisers, but to all those who have collaborated in the trial. A trial publication policy will be developed. The results of the trial will be reported first to study collaborators. The main report will be drafted by the Project Management Group and circulated to all collaborators for comment. The final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of all the AMBER collaborators.

To safeguard the integrity of the main trial, reports of any explanatory or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the trial by publication of AMBER newsletters at intervals for participants, staff and collaborators. In addition we will advertise the study in appropriate patient and clinically focussed Newsletters and web-sites. Once the main report has been published, a lay summary of the findings will be sent in a final AMBER Newsletter to all involved in the trial and will be disseminated through the Newsletters and web-sites

We will also make available our Patient and Clinician's abdominal massage training handbooks and DVD/equivalent through charities and relevant clinical groups.

**Reference List**


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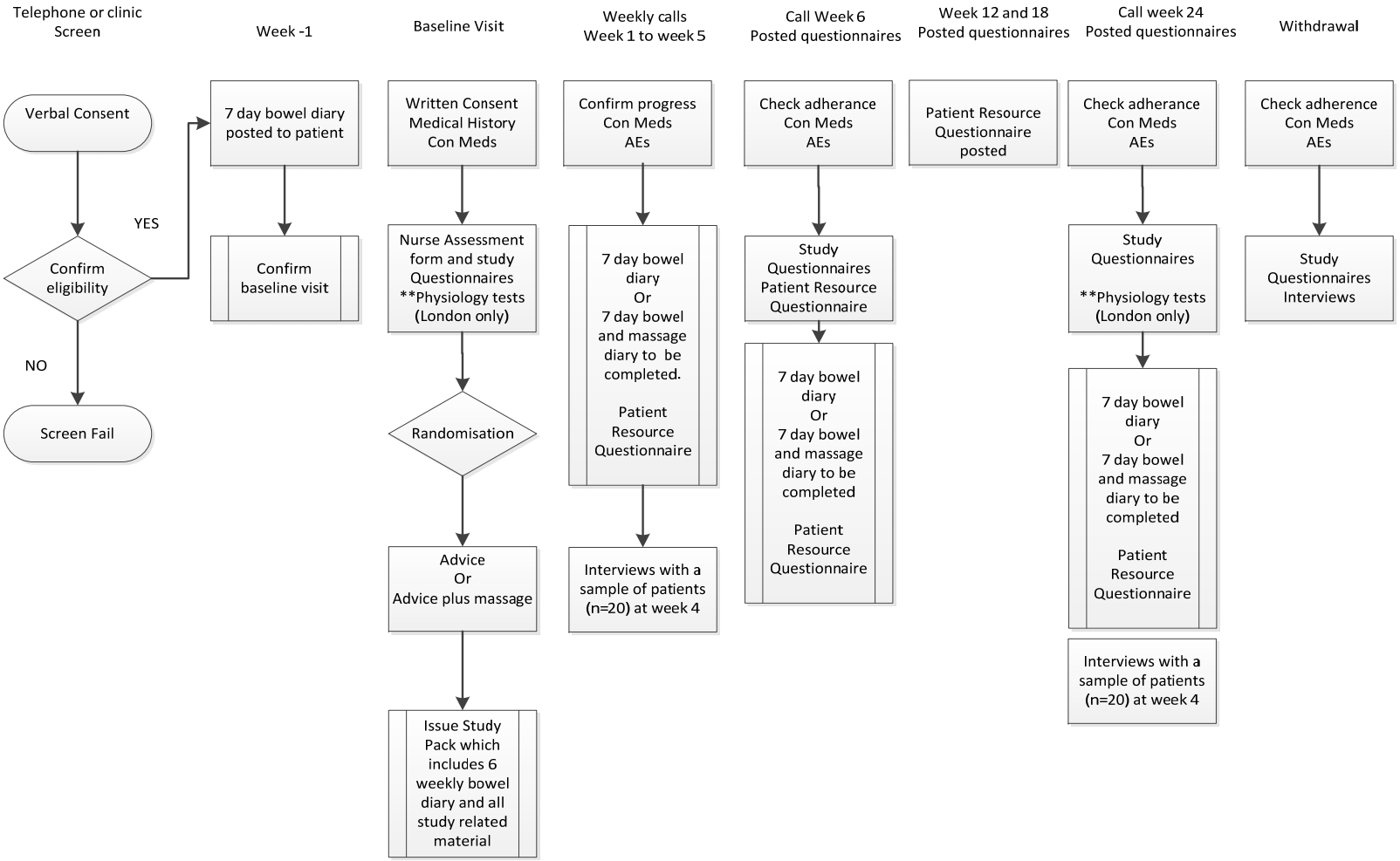
**Appendix 1**

<table>
<tr><th colspan="3">Process Evaluation</th><th>Randomised Controlled Trials</th></tr>
<tr><td>Fidelity Study</td><td>Trial process Implemen-tation evaluation</td><td>Qualitative Interviews</td><td rowspan="2">• 10 centres, n=3000 MS patients,<br>• Screening of notes to potentially identify participants<br>• 50% with NBD (n=1500) minus 50% (n=750) contraindicated<br>• Number of potential participants n=750<br>• Letter of introduction sent to 750 participants<br>• Expression of interest form returned (50% [n=375])<br>• Further information covered by telephone call<br>• Informed written consent obtained ( n=200)<br>• Baseline questionnaires completed (n=200)<br>• Completion of all outcomes plus attrition (70% n=170)</td></tr>
<tr><td rowspan="2">Intervention delivery fidelity<br><br>Protocol adherence checklist<br><br>On-site visit to all centres<br><br>Sample of telephone sessions recorded (n=20)<br><br>Participant Interviews include describing the massage</td><td rowspan="2">Random checks on completion of study documents<br><br>Scrutiny of centre recruitment and retention<br><br>Interviews with key stakeholders (n=3X1)<br><br>Questionnaires to be given to each of the 10 sites at 6 monthly intervals (Process Tracking)<br><br>Additional checks on centres failing to recruit to target</td><td rowspan="2">Purposive sample of MS (n=20 :max 5 per Study Sites interviewed one month after enrollment and 24 weeks<br><br>On study completion, interviews with Intervention Nurses, recruiters or local PIs (2 from each site) (n=20)</td></tr>
<tr><td>Full trial MS (n=200)<br>Randomised<br><table><tr><td>Intervention (n=100)</td><td>Control (n=100)</td></tr></table>All participants<br>Attend one hour clinic appointment with Intervention Nurse and receive Information Pack plus:<br><table><tr><td>Optimised bowel care advice<br>+<br>Massage training delivered by nurse<br>+ DVD/equivalent<br><br>Advised on frequency of massage</td><td>Optimised bowel care advice (e.g. diet, fluid, positioning advice)</td></tr></table></td></tr>
<tr><td>Massage fidelity<br><br>Massage diary completed by participants during intervention period</td><td colspan="2">All participants<br>Receive one telephone call per week for 6 weeks from Intervention Nurse and at week 24. Discuss bowel care (both groups) and massage (intervention groups only)<br>All Participants will complete a Patient Resource Questionnaire during weeks 1-6 and weeks 12,18 and 24.<br><br>Outcome Measure (Baseline, Week6 and 24)<br>Primary OCM - NBD score from self-complete questionnaires at week 24<br>Secondary Outcome Measures - Constipation Scoring System, Qualiveen Questionnaire and EQ-5D, Bowel Diary<br>Patient Resource Data<br><br>Mechanistic measures at 1 centres<br>30 MS patients standard ano-rectal physiology test at baseline and 24 weeks (intervention group have an additional pressure test during massage)</td></tr>
</table>

**Appendix 2**
**AMBER Participant Pathway**



**Appendix 3**

**AMBER Study Matrix**

| **Item** | **Screen** | | **Baseline Visit** | **Call** | **Call** | **Call** | **Call** | **Call** | **Call Posted** | **Posted** | **Posted** | **Posted and call** | **Withdrawal Data collection** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screeni | week -1 | Baseline | week 1 | week 2 | week 3 | week 4 | week 5 | week 6 | Week 12 | Week 18 | week 24 | |
| Informed Consent | | | X | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | |
| Medical History | | | X | | | | | | | | | | |
| Con meds | | | X | X | X | X | X | X | X | | | X | X |
| Randomisation | | | X | | | | | | | | | | |
| | | | | | | | | | | | | | |
| 7 day bowel diary | | X | X | X | X | X | X | X | X | | | X | X |
| Process evaluation/interviews ([a]) | | | | | | | X | | | | | X | |
| 7 day bowel and massage diary[a] | | | X | X | X | X | X | X | X | | | X | X |
| Study Questionnaires[(c)] | | | X | | | | | | X | | | X | X |
| Physiology Forms[b] | | | X | | | | | | X | | | Visit | X |
| Patient Resource Questionnaire | | | | X | X | X | X | X | X | X | X | X | |
| Adverse Events | | | | X | X | X | X | X | X | | | X | X |

a Only participants in intervention arm
b Only participants in London sub study

(c) Study Questionnaires include Neurogenic Bowel Dysfunction Score, SF Qualiveen, EQ-5D, constipation scoring system and the PROM Bowel Questionnaire