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[1]Nursing, Midwifery and Allied Health Professionals Research Unit, Glasgow Caledonian University, Glasgow, UK
[2]Nursing, Midwifery and Allied Health Professionals Research Unit, University of Stirling, Stirling, UK
[3]Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[4]Adult Nursing, King's College London, London, UK
[5]Edinburgh Clinical Trials Unit, The University of Edinburgh, Edinburgh, UK
[6]Tayside Clinical Trials Unit, University of Dundee, Dundee, UK
[7]National Hospital for Neurology and Neurosurgery, University College London, London, UK
[8]Yunus Centre for Social Business and Health, Glasgow Caledonian University, Glasgow, UK

*Corresponding author

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Abstract

Abdominal massage plus advice, compared with advice only, for neurogenic bowel dysfunction in MS: a RCT

Doreen McClurg,[1]* Fiona Harris,[2] Kirsteen Goodman,[1] Selina Doran,[1] Suzanne Hagen,[1] Shaun Treweek,[3] Christine Norton,[4] Maureen Coggrave,[4] John Norrie,[5] Petra Rauchhaus,[6] Peter Donnan,[6] Anton Emmanuel,[7] Sarkis Manoukian[8] and Helen Mason[8]

[1]Nursing, Midwifery and Allied Health Professionals Research Unit, Glasgow Caledonian University, Glasgow, UK
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[3]Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[4]Adult Nursing, King's College London, London, UK
[5]Edinburgh Clinical Trials Unit, The University of Edinburgh, Edinburgh, UK
[6]Tayside Clinical Trials Unit, University of Dundee, Dundee, UK
[7]National Hospital for Neurology and Neurosurgery, University College London, London, UK
[8]Yunus Centre for Social Business and Health, Glasgow Caledonian University, Glasgow, UK

*Corresponding author Doreen.mcclurg@gcu.ac.uk

Background: Between 50% and 80% of people with multiple sclerosis (PwMS) experience neurogenic bowel dysfunction (NBD) (i.e. constipation and faecal incontinence) that affects quality of life and can lead to hospitalisation.

Objectives: To determine the clinical effectiveness and cost-effectiveness of abdominal massage plus advice on bowel symptoms on PwMS compared with advice only. A process evaluation investigated the factors that affected the clinical effectiveness and possible implementation of the different treatments.

Design: A randomised controlled trial with process evaluation and health economic components. Outcome analysis was undertaken blind.

Setting: The trial took place in 12 UK hospitals.

Participants: PwMS who had 'bothersome' NBD.

Intervention: Following individualised training, abdominal massage was undertaken daily for 6 weeks (intervention group). Advice on good bowel management as per the Multiple Sclerosis Society advice booklet was provided to both groups. All participants received weekly telephone calls from the research nurse.

Main outcome measures: The primary outcome was the difference between the intervention and control groups in change in the NBD score from baseline to week 24. Secondary outcomes were measured via a bowel diary, adherence diary, the Constipation Scoring System, patient resource questionnaire and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).

Results: A total of 191 participants were finalised, 189 of whom were randomised (two participants were finalised in error) (control group, $n = 99$; intervention group, $n = 90$) and an intention-to-treat analysis was performed. The mean age was 52 years (standard deviation 10.83 years), 81% ($n = 154$) were female and 11% ($n = 21$) were wheelchair dependent. Fifteen participants from the intervention group and five from the control group were lost to follow-up. The change in NBD score by week 24 demonstrated no significant difference between groups [mean difference total score –1.64, 95% confidence interval (CI) –3.32 to 0.04; $p = 0.0558$]; there was a significant difference between groups in the change in the frequency of stool evacuation per week (mean difference 0.62, 95% CI 0.03 to 1.21; $p = 0.039$) and in the number of times per week that participants felt that they emptied their bowels completely (mean difference 1.08, 95% CI 0.41 to 1.76; $p = 0.002$), in favour of the intervention group. Of participant interviewees, 75% reported benefits, for example less difficulty passing stool, more complete evacuations, less bloated, improved appetite, and 85% continued with the massage. A cost–utility analysis conducted from a NHS and patient cost perspective found in the imputed sample with bootstrapping a mean incremental outcome effect of the intervention relative to usual care of –0.002 quality-adjusted life-years (QALYs) (95% CI –0.029 to 0.027 QALYs). In the same imputed sample with bootstrapping, the mean incremental cost effect of the intervention relative to usual care was £56.50 (95% CI –£372.62 to £415.68). No adverse events were reported. Limitations include unequal randomisation, dropout and the possibility of ineffective massage technique.

Conclusion: The increment in the primary outcome favoured the intervention group, but it was small and not statistically significant. The economic analysis identified that the intervention was dominated by the control group. Given the small improvement in the primary outcome, but not in terms of QALYs, a low-cost version of the intervention might be considered worthwhile by some patients.

Future work: Research is required to establish possible mechanisms of action and modes of massage delivery.

Trial registration: Current Controlled Trials ISRCTN85007023 and NCT03166007.

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Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 The AMBER study: abdominal massage for NBD in PwMS

Supplementary material can be found on the NIHR Journals Library report project page (www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/documentation).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
AMBER	Abdominal Massage for Bowel Dysfunction Effectiveness Research
BMI	body mass index
CI	confidence interval
CMO	context–mechanism–outcome
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSS	Constipation Scoring System
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DMT	disease-modifying treatment
DVD	digital versatile disc
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EQ-VAS	EuroQol-5 Dimensions Visual Analogue Scale
FI	faecal incontinence
GCU	Glasgow Caledonian University
HCP	health-care professional
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
MCID	minimum clinically important difference
MI	multiple imputation
MS	multiple sclerosis
NBD	neurogenic bowel dysfunction
NBDS	Neurogenic Bowel Dysfunction Score
NBIS	neurogenic bowel impact score
NHIS	National Health Interview Survey
NMAHP RU	Nursing, Midwifery and Allied Health Professions Research Unit
OR	odds ratio
PIL	patient information leaflet
PMG	Project Management Group
PT	preferred term
PwMS	people with multiple sclerosis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TCTU	Tayside Clinical Trials Unit
TSC	Trial Steering Committee
UCH	University College Hospital
UKCRC	UK Clinical Research Collaboration
UTI	urinary tract infection
WTP	willingness to pay

Plain English summary

The symptoms of neurogenic bowel dysfunction (NBD) are constipation and/or faecal incontinence; NBD is common in people with multiple sclerosis (PwMS) and affects their quality of life. The Abdominal Massage for Bowel Dysfunction Effectiveness Research (AMBER) study aimed to find out whether or not abdominal massage improved the symptoms of NBD in PwMS.

In total, 191 eligible participants who felt that their constipation was 'bothersome' were allocated randomly to either:

- advice on the management of NBD (control group, $n = 100$ participants)
- advice and abdominal massage (intervention group, $n = 91$ participants).

Quality-of-life questionnaires and a bowel diary were completed by all participants at the start of the trial, at the end of 6 weeks of intervention and again at 24 weeks. To further assess the intervention, 20 participants had telephone interviews at the beginning and end of the trial.

Researchers wanted to know if participants in the intervention group had an improvement in their bowel symptoms compared with the control group at week 24.

At the end of the study, the main symptom questionnaires showed a slight, but not statistically significant, improvement in the intervention group (i.e. not much difference between groups) and the economic analysis showed it was more expensive. However, at the end of the study, participants in the intervention group did register some important findings, they:

- passed stools more frequently
- felt that they emptied their bowel more completely
- generally took fewer laxatives
- felt better.

The interviews also identified that participants liked that:

- drugs were not involved
- they could do the massage themselves
- there was a lack of adverse side effects.

Given the small improvement in the primary outcome but not in terms of cost-effectiveness, a low-cost version of the intervention, for example as part of a self-management pathway, might be considered by some patients.

Scientific summary

Background

Multiple sclerosis (MS) has an increasing prevalence in the UK and is the most common neurological condition in young adults, affecting > 100,000 people at present. It is estimated that 60% of people with multiple sclerosis (PwMS) have problematic neurogenic bowel dysfunction (NBD). NBD is rated as one of the most devastating scenarios affecting these people and includes symptoms of constipation, faecal incontinence (FI), bowel evacuation difficulties or a combination of these. Constipation can lead to the individual becoming housebound, spending hours trying to empty their bowels and limiting their ability to work, whereas FI is often described as the most devastating event imaginable, leading to social and emotional issues. Management of NBD in PwMS has been underexplored and lacks supporting evidence. It is costly both in terms of carer and patient time and to the NHS. PwMS have two or three times more admissions to hospital for bowel complications than people without MS. PwMS use laxatives, suppositories, prolonged digital rectal stimulation and/or rectal irrigation but often these interventions have inconsistent results. Abdominal massage is a minimally invasive modality potentially stimulating gut motility. A Cochrane review (McClurg D, Hagen S, Dickinson L and Campbell P, Glasgow Caledonian University, 2018) reported significant benefits in the reduction of the symptoms of constipation in several small trials with heterogeneous populations. Abdominal massage may offer a new option in the pathway to treat NBD.

Objectives

The aim of this study was to assess the clinical effectiveness and cost-effectiveness of adding abdominal massage to the provision of advice calls compared with advice only, with both groups being supported by weekly telephone calls. We also aimed to identify and investigate, via a process evaluation substudy, pilot transit and anorectal physiological substudy, the mediating factors that affected the clinical effectiveness and possible implementation to identify possible mechanisms of action.

All outcomes were undertaken at baseline, weeks 6 and 24.

Primary outcome

The primary outcome was the difference in change between the intervention and control groups in the Neurogenic Bowel Dysfunction Score (NBDS) from baseline to week 24.

Secondary outcomes

- Change in the Constipation Scoring System (CSS) from baseline to weeks 6 and 24.
- Information from the study trial-specific 7-day bowel diary (recorded at baseline, weekly during the 6 weeks of intervention, and during week 23).
- Bladder dysfunction, as measured by the Short Form (SF)-Qualiveen.
- Quality of life as measured by the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and by a novel NBD questionnaire.
- Resource use as collected by a patient resource questionnaire.
- Bowel transit and anorectal physiological tests (one centre only) undertaken pre intervention and at week 24.

Other outcomes recorded at each telephone conversation

- Change in medication.
- Adverse events.

Process evaluation outcomes

- Qualitative interviews with 20 participants were conducted before and after undertaking the intervention ($n = 40$).
- Interviews with health-care professionals (HCPs) ($n = 25$) involved in the delivery of the trial were conducted shortly after starting the study and/or at the end of the study ($n = 42$).
- Interviews with six key stakeholders involved with incontinence policy or services for PwMS were conducted at only one stage of the study ($n = 6$).

Methods

The study was a UK-based, multicentre, pragmatic, parallel-group randomised controlled trial (RCT). There was 1 : 1 allocation between the groups, with stratification by site and minimisation on level of disability.

Eligibility was being 'bothered' by bowel symptoms.

Inclusion criteria

- Males or females aged ≥ 18 years.
- A diagnosis of MS (no MS relapse in the previous 3 months).
- No major change of medication in the previous 1 month.
- Not used abdominal massage in the previous 2 months.

Exclusion criteria

- Being unable to undertake the massage themselves and did not have a carer willing to do it.
- Being unable to understand the study processes in order to give informed consent.
- Contraindications to abdominal massage, for example abdominal/pelvic cancer, hiatus, inguinal or umbilical hernia, rectal prolapse, inflammatory bowel disease or abdominal scars, abdominal wounds or skin disorders.
- Being pregnant.

After assessment for eligibility and completion of informed consent, each participant was scheduled for one study visit for collection of baseline data. Details were entered into a bespoke database held at Dundee Clinical Trials Unit, which facilitated immediate on-screen randomisation with allocation concealment. All participants were provided with the MS Society Booklet on bowel management. Those in the intervention group additionally received instruction in undertaking the massage (to be given by self or carer), had the massage demonstrated on them and they or their carer were given the opportunity to ask questions and undertake supervised practice. A digital versatile disc (DVD) showing the massage and two leaflets outlining it were also provided. Participants were recommended to undertake the massage daily for ≈10 minutes.

Sample size for the RCT was based on the NBD score using data from a pilot study. To detect a difference between groups of 4.21 [standard deviation (SD) 7.02] at a 5% level of significance with 90% power, 60 participants per group were needed. Thus, for a fully powered study the total sample size, allowing for a 20% dropout rate, was 150 participants. However, in response to suggestions from the funding body, the sample size was increased to 200 participants (100 per group), which allowed for greater attrition.

Ethics approval for the study was granted by the West of Scotland Research Ethics Committee 4, on 11 June 2014 (reference number 14/WS/0111). A total of 11 NHS trusts/health boards granted 12 local NHS site recruitment approvals (two different hospitals belonged to one trust). The study sponsor was Glasgow Caledonian University (GCU) and the Abdominal Massage for Bowel Dysfunction Effectiveness Research (AMBER) trial office was based in the Nursing, Midwifery and Allied Health Professions Research Unit (NMAHP RU) at GCU.

Statistical analysis

Categorical data are presented using counts and percentages; continuous variables are presented using mean (SD) and absolute differences are presented with 95% confidence intervals (CIs). Data for continuous outcome measures (both primary and secondary) were assessed for normality before analysis. Transformations of the outcome variables were used when necessary, if these were not normally distributed.

If data were normally distributed, outcome measures were assessed by multiple linear regression. The primary analysis consisted of comparisons between treatment groups (bowel massage vs. no massage) at the final visit (week 24), adjusted for site, minimisation on level of mobility (walking unaided, aided or wheelchair bound) as well as baseline measure of the outcome and sex.

In a secondary analysis of the primary outcome, the baseline variables of age, sex, body mass index (BMI), type of MS, number of years since diagnosis, cognitive symptoms of MS and minimisation variable on level of mobility (walking unaided, aided or wheelchair bound) were included in the model.

When data were not normally distributed and could not be transformed into a normal distribution, data were analysed using non-parametric methods in addition to multiple linear regression.

In addition to the comparison of baseline data with week 24 outcomes, a repeated measures analysis was performed on the outcomes using all available visits.

Data for categorical outcome measures were assessed by logistic regression in the same way as described for continuous outcome measures.

Statistical significance was taken as two-sided p-value of ≤ 0.05.

Results

Information about the study was given to 389 patients; of these, 273 (60.9%) patients were screened and 191 (48.1%) were randomised: 90 (47.1%) were allocated to the intervention group and 100 (51.8%) to the control group. The number of participants per site ranged from 9 to 26 (median 16 participants). Of the randomised participants, 22 did not complete the study. Two of these were post-randomisation exclusions (essentially randomised in error) from whom data were not collected, leaving 189 for analysis. Fifteen participants in the intervention group and five in the control group withdrew or were lost to follow-up. The missingness of any data appeared to be at random with no obvious bias.

Baseline

Women constituted 81% (154/189) of participants and the mean age of all participants was 53 years (range 26–79 years). The mean time since diagnosis of MS was 14.3 years (range 0–51 years). Demographics and clinical symptom profiles of the two groups were evenly matched. Bowel symptoms had commenced > 10 years previously in 37% of participants and < 1 year previously in 4% of participants. The main bowel

symptoms reported by participants at baseline were feelings of incomplete emptying, straining to pass stool and bloating.

Primary outcome

At baseline, for the intervention group, the mean total NBDS was 7.6 points (SD 5.31 points) and for the control group it was 8.6 points (SD 5.08 points). At week 24, the mean total NBDS was 7.4 points (SD 5.23 points) for the intervention group and 8.7 points (SD 5.70 points) for the control group. The mean difference in change of NBDS between groups was not statistically significantly different for the total score in our primary outcome measure at 24 weeks (–1.61 points, 95% CI –3.32 to 0.04 points; $p = 0.0558$).

Secondary outcomes (primary analysis)

At baseline, the intervention group had a total mean CSS score of 11.7 points (SD 4.05 points) and the control group had a total mean CSS score of 11.5 points (SD 3.77 points). At week 24, the intervention group had a mean CSS score of 10.1 points (SD 4.10 points) and control group had a mean CSS score of 11.1 points (SD 3.91 points). There was no significant mean difference in change of CSS score between groups at week 24 (–0.88 points, 95% CI –2.03 to 0.27 points; $p = 0.1308$).

There were virtually no differences between the two groups, either at baseline or at post treatment, in the SF-Qualiveen or in the EQ-5D-5L.

In our feasibility study on mechanistic evaluation, the low number of participants (11/23) that completed the transit study and anorectal physiology tests make it impossible to undertake meaningful analysis on differences between groups. However, just over 60% of all participants demonstrated slow colonic transit at baseline.

Bowel diary

The mean frequency of stools passed per week at baseline in the intervention group was 3.9 (SD 1.68), and for the control group it was 4.0 (SD 1.74) stools passed per week. At week 24, the frequency of stools passed per week for the intervention group was 4.3 (SD 1.88) and for the control group it was 3.9 (SD 1.89). This was a significant mean difference in change between the groups of 0.62 stools per week (95% CI 0.03 to 1.21 stools per week; $p = 0.039$).

There was no significant difference in the mean change between groups in time spent on the toilet or the number of attempts to pass stool at week 24: –3.35 minutes (95% CI –23.1 to 16.4 minutes; $p = 0.7377$) and 1.14 attempts (95% CI 0.92 to 3.19 attempts; $p = 0.2770$).

There was a significant difference in the mean change between groups in the number of times the participants felt that they had successfully emptied their bowel at week 24 (1.08 times, 95% CI 0.41 to 1.76 times; $p = 0.002$), with the intervention group showing greater effect.

Using repeated measures analysis, statistically significant results were also found at week 6 for the number of stools passed per week [odds ratio (OR) 0.98, 95% CI 0.36 to 1.61; $p = 0.039$] and the number of times participants felt that their bowels were emptied (OR 0.56, 95% CI 0.03 to 1.10; $p = 0.039$), with the intervention group showing greater effect. However, this effect decreased for both outcomes at week 24.

There is also some evidence that the laxative use at week 24 was twice as likely to be lower in the intervention group than the control group (OR 2.37, 95% CI 0.87 to 6.46; $p = 0.092$).

Other outcomes

Regression analysis indicated a greater response in the intervention group for participants walking unaided or aided than for those using a wheelchair. Older participants and those with a higher BMI also did slightly better. The time since diagnosis of MS did not seem to be important, but those with relapsing–remitting MS responded better than those with primary or secondary progressive MS. Cognition severity indicated that those with mild cognitive impairment did better than those with more severe impairment. Consistent with other findings, the outcomes for males were significantly better than the outcomes for women (OR –2.789, 95 % CI –5.179 to –0.399; $p = 0.0226$).

Serious adverse events

There were nine serious adverse events (SAEs); none was related to the trial and all were resolved.

Process evaluation

From the intervention group, 20 participants were interviewed twice: at baseline and at the end of the intervention period. The recordings were transcribed and then supported by NVivo, version 10 (QSR International, Warrington, UK). All 20 completed the study, with 15 reporting benefits such as increased frequency of stools and feeling complete evacuation more often. Other benefits not recorded by trial measures represented important improvements in quality of life for participants, including increased appetite, greater energy, better sleep and greater control over bowel function. Participants shared their experiences of administering the massage, including solutions that they had devised to manage any difficulties. Comparison with change in our primary outcome measure identified inconsistencies in what a participant was saying in the interviews and change in total score. For the five interviewees who felt that there was no change in their bowel habits, analysis of their bowel diaries and interviews gave some indication as to why the treatment may not have worked for them – they had an ideal stool type at baseline and they struggled to administer the massage because of poor dexterity, fatigue and weakness. Eighteen interview participants reported that they would continue with the massage beyond 24 weeks. The HCP interviewees ($n = 25$) were involved with recruitment and had been trained in delivering the massage intervention. Most reported that recruitment of study participants was aided by the fact that this was a non-pharmacy intervention and could be performed by the participant themselves. The six stakeholders identified that there was a lack of evidence-based interventions for patients with NBD and, potentially, abdominal massage could offer a safe, non-expensive additional option for managing bowel problems.

Economic evaluation

A cost–utility analysis was conducted from a NHS and patient cost perspective. The mean incremental cost for the intervention group compared with the control group was £56.50 (95% CI –£372.62 to £415.68). The incremental gain in quality-adjusted life-years (QALYs) was –0.002 QALYs (95% CI –0.029 to 0.027 QALYs). Given these results, the intervention appears to be dominated by the control group.

Conclusions

Abdominal massage is a non-invasive, non-pharmacological intervention. Although the increment in the primary outcome favoured the intervention group, it was small and not statistically significant, and the economic analysis identified that the intervention was dominated by the control group. Given the small improvement in the primary outcome, but not in terms of QALYs, a low-cost version of the intervention, for example as part of a self-management pathway, might be considered worthwhile by some patients. Some secondary outcomes were in favour of the intervention and reached statistical significance with 15 out of 20 interviewees reporting improvements.

Additional research is required to further establish validated outcome measures in this population, as well as further mechanistic investigations.

Trial registration

The trial is registered as ISRCTN85007023, and on ClinicalTrials.gov as NCT03166007.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Scientific background

The prevalence of multiple sclerosis (MS) is increasing in the UK, and MS is the most common neurological condition in young adults (the average age at onset is 34 years), affecting > 100,000 people at present.[1] It is estimated that 60% of people with multiple sclerosis (PwMS) have problematic neurogenic bowel dysfunction (NBD);[2] increased life-expectancy rates, as a result of advances in health care, present additional challenges of the ageing bowel.[3] NBD is rated as one of the most distressing scenarios affecting these patients and includes the symptoms of constipation and faecal incontinence (FI).[4] Constipation can lead to the individual becoming housebound, spending hours trying to empty their bowels and limiting their ability to work; whereas FI is often described as the most devastating event imaginable, leading to social and emotional issues.[5] A MS Trust report[6] published in April 2017 revealed that emergency admissions (many of which are thought to be preventable) to hospital for PwMS have increased by 12.7% over the 2 years 2015/16, with overall admissions for bladder- and bowel-related issues, for example impaction, costing £10.4M in 2015/16.

Aetiology of neurogenic bowel dysfunction

Aetiology of NBD in PwMS is multifactorial; reduced mobility and polypharmacy may have a contributory causative role. Coincidental pelvic nerve lesion, occurring during childbirth, could also contribute to FI in women with MS.[7] Spinal cord lesions appear to be most important in the pathogenesis of NBD symptoms in MS.[8] The pathways of neural control of defecation are not fully defined; however, cortical and pontine centres may play a pivotal role in the regulation of sacral segments.[8,9]

Conduction times of central motor pathways to sphincteric sacral neurons and pelvic floor striated muscle have been shown to be prolonged in MS.[10] Impaired anorectal sensation may also contribute to the symptoms; somatosensory-evoked potentials were delayed in PwMS compared with controls in one study.[11] Loss of central modulation on spinal cord segments may lead to sympathovagal imbalance, which, in turn, can lead to constipation, characterised by lengthened colon transit time.[12] Constipation has thus been attributed to rectal outlet obstruction, absent or incomplete puborectalis, anal canal and sphincter musculature relaxation, and prolonged colonic transit time.[10,13] Regarding FI, studies have described reduced sensation of rectal filling, reduced rectal compliance, low anal sphincter pressures and hyper-reactivity of the rectal wall. The coexistence of FI and constipation can be explained by inco-ordinated action of the external/internal anal sphincter during expulsion; poor pelvic musculature relaxation may cause incomplete emptying of the rectum, which precipitates FI when anal sphincter weakness and anorectal hyposensitivity are present.[14,15]

Current treatment/management options

Management of NBD in PwMS has been little explored and lacks supporting evidence.[16] It is costly both in terms of patient time and to the NHS (e.g. PwMS have two to three times more admissions to hospital for bowel complications than non-MS patients).[17] It also has an impact on the families and carers of PwMS.[18] PwMS use laxatives, suppositories, prolonged digital rectal stimulation and/or rectal irrigation, but often these interventions have inconsistent results. For example, one patient in our previous study would take laxatives two evenings per week, but then could not leave the house the next day as he had no control over when he would pass stool.[5]

Evidence for the clinical effectiveness of abdominal massage for constipation

A Cochrane systematic review[19] has been undertaken to determine the effects of abdominal massage for the relief of symptoms of chronic constipation in comparison with no treatment or other treatment options. Nine randomised controlled trials (RCTs) (12 randomised comparisons) involving 427 participants were included in the review.[19] The study populations were small (with a maximum of 32 participants per group), heterogeneous and all were rated as having a moderate or high risk of bias. Findings from two trials suggested that abdominal massage compared with advice from a physician provided significant additional relief of symptoms from constipation in the short term. Two trials found no significant differences between groups. One trial, which had the three groups (aroma massage, plain massage and control), reported that both the aroma massage group and the plain massage group had an improved quality of life. The review concluded that there were insufficient data to allow reliable conclusions to be drawn on the effects of abdominal massage in the management of constipation. There was some evidence to suggest that there might be a therapeutic effect; however, larger, more rigorous trials are required to provide evidence of both the clinical effectiveness and the cost-effectiveness of abdominal massage.

How the intervention might work

There is some evidence to suggest that abdominal massage will reduce colonic transit time and enable predictable complete evacuation; however, the possible mechanism of action is not yet fully understood.[20,21] The function of the gastrointestinal tract is influenced by, among other things, activity in the parasympathetic division in the autonomic nervous system. Stimulation of the parasympathetic division increases the motility of the muscles, increases the digestive secretions and relaxes sphincters in the gastrointestinal canal.[22–24] Massage is thought to stimulate peristalsis in the gut by producing rectal muscular waves that stimulate the somatoautomatic reflex and initiate bowel sensation, thereby reducing colonic transit time.[25] Furthermore, the active massaging action may result in a softening of stool consistency, allowing the stool to be passed more easily.[26]

Development of the intervention

The abdominal massage intervention used within this trial was based on massage as formally taught in physiotherapy training within the UK and used by an expert in the area in earlier studies.[27–29] This expert was involved in the development of the training materials and in the training of the clinicians undertaking the massage. All clinicians involved with teaching the massage to participants underwent 1 half day of training in the massage technique, as well as presentations on NBD and good bowel care. Information provided to participants on bowel care was based on the MS Society's handbook on bowel management. A description of the intervention has previously been published.[30] A copy of the training materials is available in *Appendix 1*.

Who delivers the intervention

In previous studies, the massage was delivered by a health-care professional (HCP) with experience in massage, a family carer or by the patient themselves. It was discovered, however, that the amount of training and support received by participants is poorly described. In this trial, the massage was designed and taught to be either self-massage or undertaken by a 'carer'. Likewise, the training of the 'trainers' (HCPs involved in seeing the patient and teaching the massage) was such that it was delivered in one half-day session, but also required individuals to undertake further practice, to consolidate their training. If this limited training plus support materials for HCPs and patients were to prove effective, then the abdominal massage could potentially be implemented in many settings to patient populations who experience constipation.

Hypothesis

A 6-week intervention of abdominal massage and bowel management advice (intervention group) will improve symptoms and quality of life in PwMS who have NBD compared with advice alone (control group).

Chapter 2 Trial design and methods design

The Abdominal Massage for Bowel Dysfunction Effectiveness Research (AMBER) trial was designed to evaluate whether or not abdominal massage is an effective treatment in reducing the symptoms of NBD, particularly constipation, in PwMS. This trial was a multicentre, patient-randomised, superiority trial comparing the following in PwMS who have stated that their constipation is 'bothersome': an intervention of optimised bowel care with once-daily abdominal massage for 6 weeks with the control of optimised bowel care without massage. A description of the trial protocol has already been published.[30]

The main trial was supported by a process evaluation to explore the possible mediating factors that may affect the clinical effectiveness of the intervention, how these mediating factors influence clinical effectiveness, and whether or not the factors differ between the randomised groups. Trial processes were evaluated to provide evidence of potential importance in the future implementation of the intervention (see *Chapter 5*).

The main study objectives were to:

- establish if an optimised bowel care programme (i.e. provision of advice/information on bowel management) with abdominal massage, compared with an optimised bowel care programme alone, is more clinically effective and cost-effective in reducing the symptoms of NBD at week 24 in PwMS
- identify and investigate, via a process evaluation, the possible mediating factors that affect the clinical effectiveness of the intervention (including intervention fidelity), how these mediating factors influence clinical effectiveness and whether or not the factors differ between the randomised groups (see *Chapter 5*)
- undertake a formal economic evaluation of the interventions from a NHS and a patient perspective (see *Chapter 4*)
- undertake a feasibility study relating to the mechanisms of action using anal manometry and colonic transit tests at one tertiary bowel centre where these tests are routinely undertaken
- record data to validate the responsiveness of a questionnaire to change in quality of life following an intervention.

Ethics approval and research governance

Ethics approval for the trial was granted by the West of Scotland Research Ethics Committee (REC) 4 on 11 June 2014 (reference number 14/WS/0111). NHS approval was granted for 10 different trusts/foundation trusts in England, and two local health boards granted approval for the two sites in Scotland. The trial sponsor was Glasgow Caledonian University (GCU) and the AMBER trial office was based in the Nursing, Midwifery and Allied Health Professions Research Unit (NMAHP RU) at GCU. The AMBER trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN85007023) and on ClinicalTrials.gov (NCT03166007).

Participants

The trial recruited PwMS who reported that they were 'bothered' (in their own judgement) by their NBD symptoms at 12 sites across UK ($n = 2$ in Scotland and $n = 10$ in England).

Inclusion criteria

People were eligible for the trial if they met the following inclusion criteria:

- bothered by their NBD
- aged ≥ 18 years
- diagnosis of MS (in a stable phase, i.e. no MS relapse in the previous 3 months)
- no major change of medication in the previous 1 month [e.g. introduction of disease-modifying treatments (DMTs)]
- not used abdominal massage in the previous 2 months.

Exclusion criteria

- Being unable to undertake the massage themselves and did not have a carer willing to do it.
- Being unable to understand the trial processes in order to give informed consent.
- Contraindications to abdominal massage, which included the following: history of abdominal/pelvic cancer, hiatus, inguinal or umbilical hernia, rectal prolapse, inflammatory bowel disease, volvulus and pregnancy.
- Abdominal scars, abdominal wounds or skin disorders that may make abdominal massage uncomfortable.

If a potential participant reported recent sudden and severe changes in bowel habits or rectal bleeding, these symptoms were first discussed with the consultant at the relevant site to determine suitability.

Recruitment procedure

The research team at each trial site were responsible for identifying potential participants. Following identification of potentially eligible individuals, a letter of introduction and an 'expression of interest' form was either posted or given to patients at their routine clinic appointment. Each patient approached about the trial was allocated a unique participant identifier number. This consisted of six characters: three letters that were an abbreviation of the site name followed by three numbers that were allocated on a consecutive basis (e.g. 001 for first participant). This unique identifier was used throughout the trial and was added to all participant paperwork. Once a completed 'expression of interest' form was returned, a member of the research team telephoned the individual to provide further information and assess eligibility. If eligible and willing to take part, the individual was sent a baseline appointment letter along with a 7-day bowel diary for completion. The participant completed the bowel diary the week before the baseline appointment. Participants were also asked to bring someone who was willing to do the massage to this appointment, if required.

Informed consent

Informed, written consent was obtained for all participants at the baseline appointment and included consent to any site-specific tests. The REC agreed to the completion of bowel diaries before the baseline appointment, as the participants' consent was implied by them willingly completing the diary. There was no use of these data until participants had provided written informed consent; this method aided recruitment to the trial because it meant that there was only one clinic visit required. Participants were made aware that the treatment was allocated at random, regardless of any personal preference they had. They had the right to withdraw from the trial at any time and for any reason; all participants were also made aware that withdrawal would not affect their routine care.

The consent form also had the option for the participant to be contacted if they were interested in taking part in the process evaluation interviews. *Chapter 5* explains the consent method followed for this part of the study. The general practitioners (GPs) of all those who took part in the trial were informed of their involvement.

Randomisation, concealment and blinding

Participants who provided written informed consent were randomly allocated to one of two treatment groups during their baseline appointment: (1) advice to optimise bowel care (control group) or (2) advice to optimise bowel care and abdominal massage (intervention group). The web-based randomisation service was provided by the Tayside Clinical Trials Unit (CTU), a UK Clinical Research Collaboration (UKCRC)-registered trials unit, and research staff at sites carried out the randomisation. In a few instances, the AMBER trial central office would assist with the randomisation remotely. This took place when there may have been issues for the staff when connecting to the web-based randomisation system (room allocation with no computer or web connectivity issues). Group allocation was relayed by telephone to the site and copies of the relevant randomisation paperwork were sent to all of those involved. Owing to the nature of the intervention, it was not possible to blind the participants or site staff to the allocation. Participant group allocation was unknown to the data analysis team. Randomisation was stratified by site and minimised on level of disability (walking unaided, aided or wheelchair bound).

Treatment group allocation

Both trial groups

Participants in both the intervention and the control group received a 6-week intervention consisting of one face-to-face consultation (baseline appointment) followed by weekly telephone calls to review adherence and any changes/difficulties with their bowel management. This meant that both groups had the same number of contacts with a HCP. Both groups received advice to optimise bowel care, as described in the following section.

Control group (advice to optimise bowel care)

During the baseline appointment, the participants' existing routine bowel care was reviewed and discussed with them by a member of the site research team. Dietary and fluid advice was provided, and participants were encouraged to be more active and to use a correct defaecation position, which was described to them. Participants were given a copy of the bowel care advice leaflet of the MS Society that reinforced this advice [see project web page URL: www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/ (accessed 30 October 2017)].

Intervention group (abdominal massage and advice to optimise bowel care)

In addition to optimised bowel care as described for the control group, staff delivering the intervention (local HCPs all fully trained in the massage technique) taught the participant and/or his or her carer how to deliver the abdominal massage. This teaching included the following:

- Viewing a short trial-specific digital versatile disc (DVD) that demonstrated the massage techniques for carer and self-massage (*Figure 1* shows a picture captured from the training DVD).
- Provision of a study-specific abdominal massage training booklet.
- A demonstration of the massage technique on the participant.
- Practice of the various strokes by the carer or participant.
- An opportunity for the participant and carer to ask questions. Possible adaptations to accommodate a participant's disability were also discussed. A daily massage of 10 minutes duration was recommended.

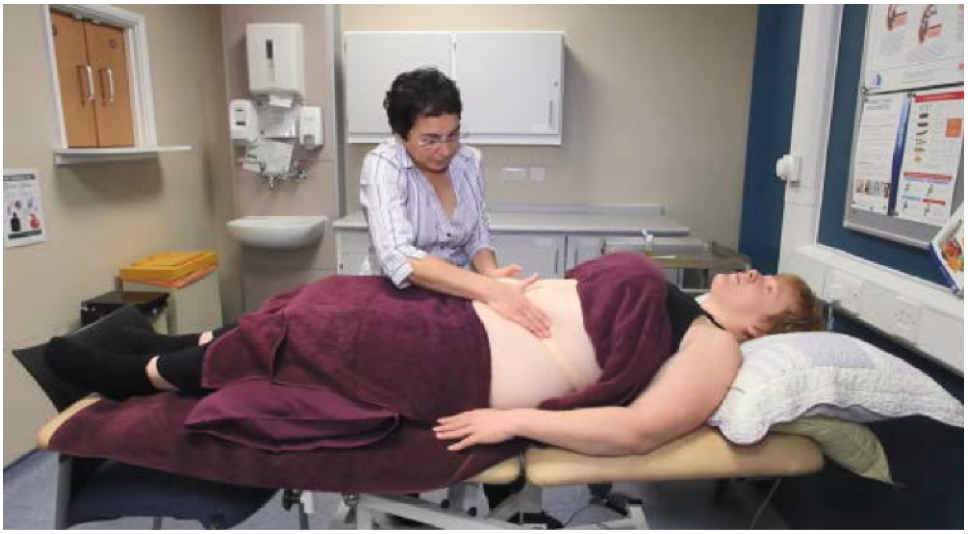

FIGURE 1 A picture from the AMBER trial training DVD, which demonstrates the massage strokes to be used.

Participants in this group were given an information pack that consisted of the following:

- the MS Society's bowel care advice booklet
- the massage DVD
- patient abdominal massage training information leaflets.

In order to standardise the intervention delivery across all sites, training for all site staff delivering the intervention was provided by one individual with clinical expertise in the area. Staff attended a trial training day and/or they were trained during the site initiation visits. Each staff member had to perform practical demonstrations and be deemed proficient in the technique before being signed off as fully competent. Sites were contacted after the baseline appointment of their first participant from the intervention group to discuss how staff found delivering the massage and to answer any questions. Further training was available at this point, but all sites felt confident in the delivery of the intervention. Any questions/feedback from the individual sites were shared with all research site staff via monthly update teleconferences. The weekly telephone calls to participants were done either by the staff member who delivered the massage training, or by another member of staff on the delegation log.

Participants randomised to the control group were informed that they would be given access to the massage training materials at the end of their follow-up (week 24). In addition, some of the sites offered to hold training sessions with the control group participants after they had completed the study.

A description of how to perform the massage technique can be found in *Appendix 1*, along with the training material given to participants as an aide memoire.

Mechanistic evaluation

One of the sites in the AMBER trial [University College Hospital (UCH), London] is a regional NBD centre where standard anorectal physiology and colonic transit tests are routinely undertaken. AMBER trial participants recruited at this site underwent the following tests before the intervention, and then again at 24 weeks:

- Anorectal pressure test – this test involves the insertion of a small probe into the rectum to measure the strength of the anal muscles.

- Anal and rectal sensation and capacity was measured by using a tiny amount of current and inflating a small balloon within the rectum (a balloon was inserted via a tube, and sensory thresholds to progressive distension were established. The initial tube was then removed and a different catheter with a bipolar electrode inserted; the sensory threshold to 1 mA of current was then determined).
- Transit tests – three sets of radiopaque capsules were posted to the participant, who ingested them in the order specified in the instructions on 3 consecutive days. Participants then attended for an abdominal radiography 2 days after the last capsule to determine total colonic transit time (not segmental transit).

This was a small substudy in the AMBER trial to look at possible mechanisms involved in NBD in PwMS and to look at the feasibility of undertaking such tests within this population and their compliance with attending the repeat tests.

Data collection and management

Data were collected and recorded on study-specific paper-based case report forms (CRFs) by either site staff or the participants (bowel diaries and patient-reported outcomes during weeks 1–6 and week 24). Sites were trained on completion of all the paperwork before recruitment commenced and a monthly teleconference, with all sites jointly, allowed any data issues/inconsistencies to be discussed and resolved. The AMBER trial central office entered all data into the OpenClinica database (OpenClinica, LLC, Waltham, MA, USA). This was set up and managed by Tayside CTU. A range of data validation checks was used to minimise erroneous and missing data.

Baseline assessment

Demographic data and information on participants' MS, medical history and bowel symptoms were collected at the baseline assessment. Participants also completed a questionnaire booklet which contained five different questionnaires (including the primary and secondary outcome measures – see *Outcome measures* and *Appendices 2* and *3*). Information on current medication was recorded, including any laxative use. Participants were given the bowel diaries and questionnaires, which were to be completed during the 6-week intervention phase, at the baseline assessment, with an instruction sheet detailing how they should be completed. Baseline anorectal physiology and colonic transit time data were collected from the London participants using an anorectal physiology CRF.

Baseline assessments were conducted between 22 January 2015 and 19 July 2016.

Participant follow-up

The duration of follow-up was 24 weeks from the date of randomisation.

Outcomes were collected through the following documents, which were completed by participants:

- a questionnaire booklet at weeks 6 and 24 (the same as the baseline questionnaire)
- a 7-day bowel diary (control group) or bowel and massage diary (intervention group) at weeks 1 to 6 and during week 23
- patient resource-use questionnaires at weeks 1–6, and weeks 12, 18 and 24.

All information completed by the participants was returned to the AMBER trial central office by reply-paid envelopes that were provided.

Anorectal physiology and colonic transit time data were collected at week 24 in UCH participants only.

Site research staff telephoned all participants weekly during weeks 1 to 6 and again at week 24 to collect additional information on any potential issues, changes in diet/exercise/fluid, adverse events (AEs) and any changes in medication. Any potential issues with bowel management or the massage were discussed and fed back to the AMBER trial central office if deemed necessary.

All AMBER trial follow-ups were completed by 19 January 2017.

Table 1 shows the AMBER trial matrix and data collected at each time point.

Outcome measures

Primary outcome: Neurogenic Bowel Dysfunction Score

The Neurogenic Bowel Dysfunction Score (NBDS)[31] is a 10-item questionnaire covering frequency of bowel movements (0–6 points); headache, perspiration or discomfort during defaecation (0–2 points); medication for constipation or faecal incontinence (0–4 points each); time spent on defaecation (0–7 points); frequency of digital stimulation or evacuation (0–6 points); frequency of faecal incontinence (0–13 points); flatus (0–2 points); and perianal skin problems (0–3 points). The maximum score is 47 points; the higher the score, the more severe the symptoms, with a score of $\geq$ 14 points rated as severe. In the AMBER trial, the primary outcome measure was the change in the NBDS from baseline to week 24.

Secondary outcomes

Bowel symptoms

The Constipation Scoring System (CSS)[32] was completed at baseline and at weeks 6 and 24 to assess constipation symptoms. The CSS is an eight-item questionnaire with items on frequency of bowel movement, difficulty with evacuation, feeling of incomplete evacuation, pain, length of time for evacuation, assistance with evacuation, number of failed attempts and the duration of constipation. The maximum score is 30 points, with higher scores indicating greater severity. A 7-day bowel diary (designed for use in the AMBER trial) was used to record information on bowel symptoms, such as frequency of bowel movement, time spent defaecating, stool type (Bristol stool chart[33]), laxative use, additional interventions (such as digital stimulation) and if there were any episodes of bowel incontinence. The diary was completed prior to baseline, during weeks 1–6 and at week 23. In the intervention group, a 7-day massage diary was used to record daily information on massage compliance and duration and was completed prior to baseline, during weeks 1–6 and at week 23.

Bladder dysfunction

Bladder function was measured using the SF-Qualiveen, consisting of an eight-item questionnaire assessing bladder dysfunction, such as leakage and signs of incomplete voiding.[34] Often, if patients with MS are suffering from constipation, they report that their bladder symptoms are worse, especially urgency and frequency, which can lead to an increase in urinary incontinence. This outcome measure allowed the effect of the change in bowel function on the bladder to be assessed at baseline and at weeks 6 and 24. A higher score indicates a poorer quality of life.

Quality-of-life outcomes

To determine health status, the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), generic questionnaire was used.[35] Participants completed the EQ-5D 5L at baseline and at weeks 6 and 24.

A neurogenic bowel impact score (NBIS) questionnaire was completed at baseline and at weeks 6 and 24. This score was developed by one of the collaborators on the AMBER trial as part of a National Institute for Health Research (NIHR)-funded postdoctoral fellowship. The questionnaire has three subscores [(1) quality

TABLE 1 The AMBER trial matrix

Item	Time point													
				Telephone call						Post		Telephone call and post		
	Screen	Week –1	Baseline appointment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12	Week 18	Week 24	Withdrawal of data collection	
Informed consent			7											
Inclusion/exclusion	7													
Medical history			7											
Current medications			7	7	7	7	7	7	7			7	7	
Randomisation			7											
7-day bowel diary		7	7	7	7	7	7	7	7			7	7	
Process evaluation/ interviews[a]							7					7		
7-day bowel and massage diary[a]			7	7	7	7	7	7	7			7	7	
Trial questionnaires[b]			7						7			7	7	
Physiology forms[c]			7						7			Visit	7	
Patient resource questionnaire				7	7	7	7	7	7	7	7	7		
AEs				7	7	7	7	7	7			7	7	

a Only participants in the intervention group.
b Trial questionnaires included Neurogenic Bowel Dysfunction Score; SF-Qualiveen; EuroQol-5 Dimensions, five-level version; Constipation Scoring System; and the neurogenic bowel dysfunction patient-reported outcome measure questionnaire.
c Only participants in UCH substudy.

of life, (2) faecal incontinence and (3) symptoms] and includes four stand-alone items. It is intended for use with individuals with a range of conditions that result in NBD. The measure's reliability and criterion validity were to be evaluated.

Economic outcomes

The cost and use of NHS services were collected via a patient resource questionnaire [see project web page URL: www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/ (accessed 30 October 2017)] during weeks 1–6 and at weeks 12, 18 and 24. From this information (along with the EQ-5D-5L data) the costs and quality-adjusted life-years (QALYs) were calculated for each group. A cost–utility analysis was conducted to calculate the incremental cost per QALY of abdominal massage compared with optimised bowel care; this is described in detail in *Chapter 4*.

Change of medication

Changes of medication were recorded using a current medication form. Any changes to a participant's medications during their involvement in the trial were recorded. Also recorded were any reductions or stoppage of laxatives between baseline and week 24.

Radiopaque marker transit tests

Different parameters were collected on an anorectal CRF (see *Report Supplementary Material 1*) for the physiology and transit tests. The total number of markers remaining in the gut at abdominal radiography was analysed to determine any differences between baseline and week 24, and all other data were summarised.

Adverse events

Expected AEs arising from the treatments in the AMBER trial are noted below. These are common in individuals with constipation and thus were not collected as AEs but noted in the weekly follow-up data collection:

- increased flatulence
- abdominal cramps
- stomach rumblings/noises
- loose stool, which in some instances may lead to faecal incontinence.

All AEs (for which a participant sought intervention from a HCP) and SAEs (including death, life-threatening conditions, inpatient hospitalisation or prolongation of existing hospitalisation and persistent or significant disability or incapacity) were assessed for causality, severity and expectedness, and were reported to the relevant regulatory bodies. If a site was in doubt about whether or not an event was an AE, this was reported and discussed before data lock. Any AE that was deemed as ongoing at the end of the trial was reviewed and further clarification from the site was sought. If the AE was still ongoing after this (owing to the nature of the event, but not related to the intervention), this was when the follow-up ended.

Adverse events (including SAEs) were coded with the Medical Dictionary for Regulatory Activities (MedDRA)[36] 16.1 and reported by primary System Organ Class (SOC) and preferred term (PT). Participants were counted only once when calculating the incidence of AEs. An overview table was created counting the number of AEs by SOC and PT.

Sample size

The sample size for the RCT was based on the NBDS, using data from a pilot study[37] that provided the only published data available on abdominal massage in this group of patients. That study[37] found a difference of 4.21 points in the NBDS between those receiving the intervention {mean score of 6.86 points [standard deviation (SD) 3.8 points] at 8 weeks} and the comparison group [mean score of 11.07 points (SD 7.02 points) at 8 weeks]. Other outcomes in that study changed in favour of the intervention and participants anecdotally reported that the massage was relaxing and that they were keen to do it themselves. Using these data, we selected a minimum clinically important difference (MCID) of 4.21 points and selected the higher SD of 7.02 points, found in the comparison group, as the basis for our sample size calculation.

Using these data, 60 participants per group was calculated as the necessary number of participants to detect a difference between groups of 4.21 points (SD 7.02 points) at a 5% level of significance with 90% power. Thus, for a fully powered study, the total sample size, allowing for a 20% dropout rate, was 150. However, in response to suggestions from the funding body, the sample size was increased to 200 participants (100 per group), which allowed for greater attrition.

Statistical analyses

Statistical methods for analysis of the main primary and secondary outcomes are detailed in the following sections. This document was drawn up by the trial statisticians, reviewed by the Project Management Group and formally signed off by the chief investigator and trial statistician before analysis commenced.

Analysis populations

Analysis was performed for the intention-to-treat population and is reported in accordance with Consolidated Standards of Reporting Trials (CONSORT).[38]

Subgroups

Subgroup analyses were carried out by first testing for a subgroup factor by intervention interaction. If this was significant at the 5% level, results were estimated separately by the different subgroups. This included a secondary analysis comparing those who undertook the massage themselves with those who had a carer massage them.

Missing data

The extent of missing data was explored in the outcomes, especially the primary outcome. Patterns of missing data were explored and predictors of missingness examined, especially if these varied by intervention. A table was constructed to assess differences in characteristics of those with complete data and those with missing data for the primary analysis. Multiple imputation (MI) was implemented for the primary outcome, assuming data were missing at random.

Summary of trial data

All continuous variables were summarised using the following descriptive statistics: non-missing sample size, number of missing records, mean, SD, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels were reported for all categorical

measures. In general, all data were listed, sorted by subject and treatment and, when appropriate, by visit number within subject.

All summary tables were structured with a column for each treatment group and an additional column for the total population relevant to that table/treatment, including any missing observations.

Demographic and baseline variables

The baseline characteristics of participants that were recorded comprised age, sex, body mass index (BMI), type of MS, site, number of years since diagnosis, cognitive symptoms of MS and level of mobility (walking unaided, aided or wheelchair bound).

Prior and current medications

Prior medications were all medications that were being taken by a participant before the trial started. Concomitant medications were all medications commenced during the trial and all changes to the dosing of prior medications. Prior medications were listed but not analysed. Concomitant medications were analysed by number of medications taken.

Treatment adherence

Treatment adherence was calculated from the weekly bowel diaries. The number of times the bowel massage was done per week was used in the main analysis. For the control group, this number was set to 0.

Efficacy analyses

Data for continuous outcome measures (both primary and secondary) were assessed for normality before analysis. Transformations of the outcome variables were used when necessary, if these were not normally distributed.

If data were normally distributed, outcome measures were assessed by multiple linear mixed-model regression. The primary analysis consisted of comparisons between treatment groups (bowel massage vs. no massage) at the final visit (week 24), adjusted for site, minimisation variable level of mobility (walking unaided, aided or wheelchair bound), as well as baseline measure of the outcome and sex.

In a secondary analysis of the primary outcome, additional baseline variables (age, sex, BMI, type of MS, number of years since diagnosis and cognitive symptoms of MS) were included in the model.

When data were not normally distributed and could not be transformed into a normal distribution, they were analysed using non-parametric methods in addition to multiple linear regression.

In addition to the comparison of baseline with week 24, a repeated measures mixed-model analysis was performed on the outcomes using all available visits.

Data for categorical outcome measures were assessed by logistic regression in the same way as described for continuous outcome measures.

Primary efficacy analysis

The primary outcome measure was the between-group difference in the change of NBDS at week 24 with the analysis adjusted, as described above.

Secondary efficacy analyses

Bowel outcomes

- Between-group difference in change in constipation symptoms. Analysis variable is the total constipation score.
- Bowel symptoms (7-day bowel diary). The percentage of normal stools per week was calculated and used for analysis. In addition, the number of days that a stool was passed and time spent passing stools was analysed.
- Radiopaque marker transit tests. The number of total markers was used for the analysis.
- Adherence to massage schedule (massage diary). As this is only available for the intervention treatment group, data are summarised in the descriptive statistics. No formal testing was done.

Urinary outcomes

- Between-group difference in change in total score of bladder function (SF-Qualiveen).

Quality-of-life outcomes

- Between-group difference in change in health-related quality of life, measured by the EQ- 5D-5L using both the EuroQol Visual Analogue Scale (EQ-VAS) and the index score.
- Between-group difference in change of patient-reported quality of life. This consists of four scores derived from the NBD patient-reported outcomes tool.
- Between-group difference in change in medication, analysed as all patients who stopped using laxatives at week 24. This was determined from the concomitant medication page.
- Between-group difference in change in medication, analysed as the number of changes in usual laxative use at week 24. This was taken from the bowel diary as the number of changes from usual laxative use to use of fewer laxatives at week 24.
- Between-group changes in the regular use of medications to counter constipation were assessed at weeks 6 and 24.

Reporting conventions

Values of ≥ 0.001 are reported to three decimal places; *p*-values of < 0.001 are reported as < 0.001. The mean, SD and any other statistics, other than quantiles, are reported to one decimal place greater than the original data. Quantiles, such as median or minimum and maximum, use the same number of decimal places as the original data. Estimated parameters not on the same scale as raw observations (e.g. regression coefficients) are reported to three significant figures.

All analyses were performed using SAS® 9.3 (SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.) All data, analysis programs and output were kept on the Mackenzie Server and backed up according to the internal Tayside Clinical Trials Unit (TCTU) information technology standard operating procedures.

Analysis programs were required to run without errors or warnings. The analysis programs for outcomes were reviewed by a second statistician and any irregularities in the programs were investigated and fixed, and the date of finalised analysis programs was signed and recorded.

Economic analysis

The cost of abdominal massage and optimised bowel care relative to optimised bowel care alone in PwMS who have NBD was considered from NHS and patient perspectives. Health-care resource use by patients in both trial groups was collected at each of the follow-up time periods (weeks 1–6, 12, 18 and 24). This included contact with health professionals and medications prescribed. These were costed using NHS pay and prices or, when appropriate, other (e.g. market-based) sources. The economic analysis (including the methods used) is detailed in *Chapter 4*.

Important changes to protocol after trial commencement

All sites used protocol version 2, dated 18 November 2014, throughout the trial duration. The London site used an additional patient information leaflet (PIL) to describe the additional tests carried out at this site. After original approval of the PIL, one of the tests was no longer completed routinely at the London site, so this information was removed and the amended PIL was approved by all relevant regulatory bodies. This change was carried out before any patients were recruited at the site.

Another substantial amendment was to incorporate a substudy, entitled SWAT (study within a trial) 24, in the AMBER trial. Participants were randomised to receive either the original cover letter or an enhanced cover letter (sent with the questionnaire at week 24) to evaluate whether or not the wording used would increase return rates of the questionnaires.

Data from the substudy will contribute to the Trial Forge[39] initiative to improve trial efficiency and to the Cochrane review of strategies to improve trial retention.[40]

The results of the Trial Forge[39] project will help to increase the evidence base on the retention of participants to trials. The only change to the AMBER trial was the way that the cover letter sent with questionnaires was written (no protocol change).

Other non-substantial changes included the:

- addition of new sites as the trial progressed (original target was 10 sites but final total was 12 sites)
- set-up of two patient-identifying centres to assist two sites with recruitment
- sites collecting the NBDS during the telephone call with participants at week 24 to maximise the primary outcome data in the study.

Trial oversight

The trial was led by the chief investigator who, along with the trial management team members (consisting of a trial manager, a data co-ordinator and a process evaluation researcher), were employed by NMAHP RU.

The trial was overseen by a Project Management Group (PMG), a Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC).

The PMG had a teleconference approximately every 4–6 weeks during the recruitment period and then bimonthly after this. The group's role was to support any decision-making that the trial management team needed further advice on.

The TSC had both an independent chairperson and members but also consisted of the trial collaborators. The TSC had four meetings over the course of the trial, with additional updates on recruitment when requested. The TSC commended the team on recruiting to target and on time.

An independent DMEC, chaired by a statistician, had three meetings over the course of the study, and additional updates were provided when requested. All statistical reports to the DMEC were prepared by a statistician from the TCTU. The DMEC had no issues with the trial continuing at any time point and commended the team on the recruitment and management of the study. The DMEC charter can be reviewed in *Appendix 2*.

Patient and public involvement

The AMBER trial has had active participation with a group of PwMS (hereafter referred to as the MS focus group). Some of the MS focus group were involved with the development of the grant application, providing feedback on the lay summary, trial design and appropriate outcome measures and questionnaires. Several additional PwMS became involved during the very early stages of the trial and throughout implementation and dissemination of results. The MS focus group included males and females, with various levels of disability and of various ages, some with and some without NBD. Approximately 10 members of the MS focus group attended each of the meetings. Material to review was sent electronically before the meetings and was available in hard copy at the meetings; very helpful feedback and discussions took place. One of the members of the MS focus group has also attended each TSC meeting as a lay representative and has actively engaged in the conversations and discussions at each meeting. Before recruiting any participants to the trial, the MS focus group reviewed the massage training DVD and the massage training material that would be given to the participant to take home with them, and their input to this was extremely influential. The group's opinion of the initial version of the training DVD was that the visual was excellent but the language used was 'too clinical'. This was overcome by the chief investigator of the trial doing a voice-over on the DVD; the group reviewed this again and it was deemed much more acceptable and user friendly. Many of the trial participants subsequently commented that they thought the video was extremely useful and easy to follow.

We initially had two different training documents and we asked the group which would be better used as an aide memoire. The MS focus group had very mixed opinions on their preferences, and discussed the style, language and diagrams used. It was therefore concluded that both of these additional training materials would be provided to all participants in the intervention arm and they could decide which material they felt was better for them. However, there is the possibility of combining the information into one single training document if the intervention is rolled out to clinical care.

Participants in the AMBER trial were given quite a lot of information to take away with them at the baseline appointment, in the form of a 'follow-up pack'. This pack included all the questionnaires and bowel diaries and study instructions on what they had to complete over the 6-week intervention period, and also the massage training DVD and reading materials (only if the participant was in the intervention group). The MS focus group reviewed this pack and thought that it was logical and clear and some further feedback from site staff implied that the participants 'liked' having this pack to take away with them.

We kept in touch with the MS focus group throughout the study, giving updates on recruitment, and there were discussions on dissemination plans. A dissemination day was held on 23 January 2018 in Glasgow Caledonian University, to which all the research staff involved in the study, and local participants, were invited. Representatives of the MS focus group also attended.

Throughout the active recruitment of the study, local and national MS charities were aware of our research and promoted the study where regulations allowed.

Chapter 3 Results

Trial recruitment

Recruitment overall was considered very successful; *Figure 2* shows how well the actual recruitment met the expected monthly targets over the 18 months of active recruitment. The trial oversight committees agreed to stop recruitment on time at 191 participants after reviewing attrition information. Twelve sites recruited participants from 22 January 2015 to 19 July 2016 and each site recruited between 9 and 26 participants (see *Appendix 3*).

The CONSORT flow diagram (*Figure 3*) shows the movement of participants through the AMBER trial. There were 237 PwMS and possible bowel problems screened (≈61% of the 389 PwMS approached by the research staff) and 191 PwMS (81% of those screened; 49% of those approached) were randomised. The near 50% uptake on those approached versus those randomised was in accordance with the estimate of uptake stated in the protocol.

Of the randomised participants, 22 did not complete the study. Two of these were post-randomisation exclusions (essentially randomised in error) and data were not collected from these two participants. Thus, the analysis was based on 189 participants: 90 in the intervention group (abdominal massage plus advice on optimised bowel care) and 99 in the control group (only advice on optimised bowel care). The inequality in the number of participants per group was attributable to minimisation at site level.

For the 20 correctly randomised participants (intervention group, $n = 15$; control group, $n = 5$) who did not complete the study, baseline data were successfully collected and all participants agreed that their existing data could be used. Participants either withdrew (intervention group, $n = 11$; control group, $n = 3$) or were lost to follow-up (intervention group, $n = 4$; control group, $n = 2$). In some instances, if the data were not returned, then the week-6 and week-24 follow-up data collection was completed by the researcher during a telephone call. This explains the differing numbers for the NBDS in the CONSORT flow diagram at weeks 6 and 24 in relation to reported withdrawals or loss to follow-up.

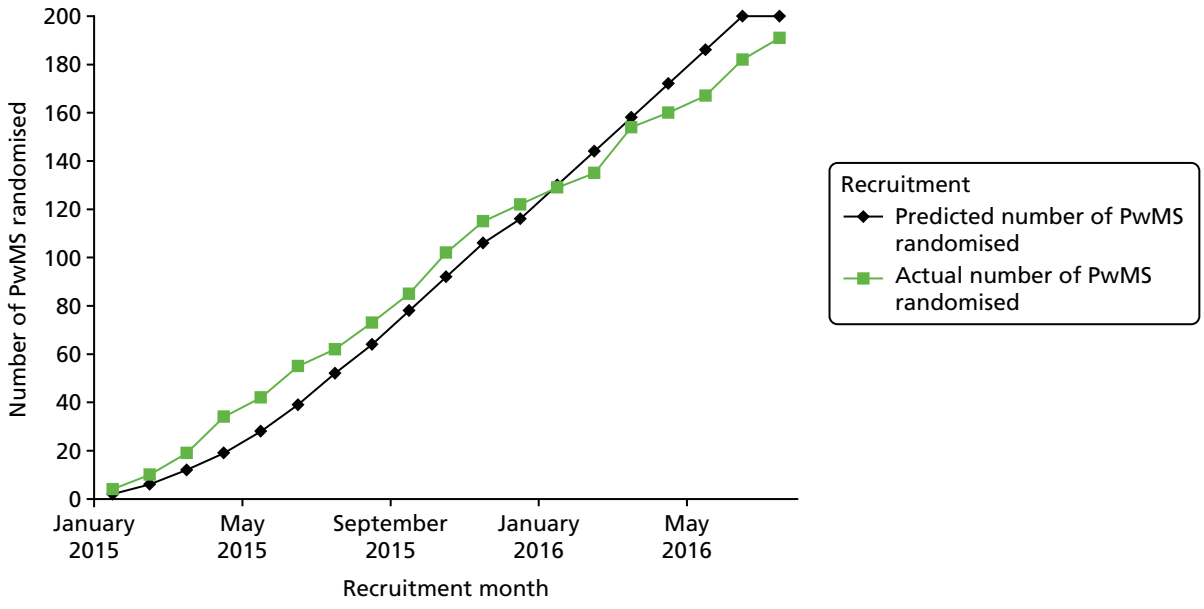

FIGURE 2 Predicted recruitment vs. actual recruitment.

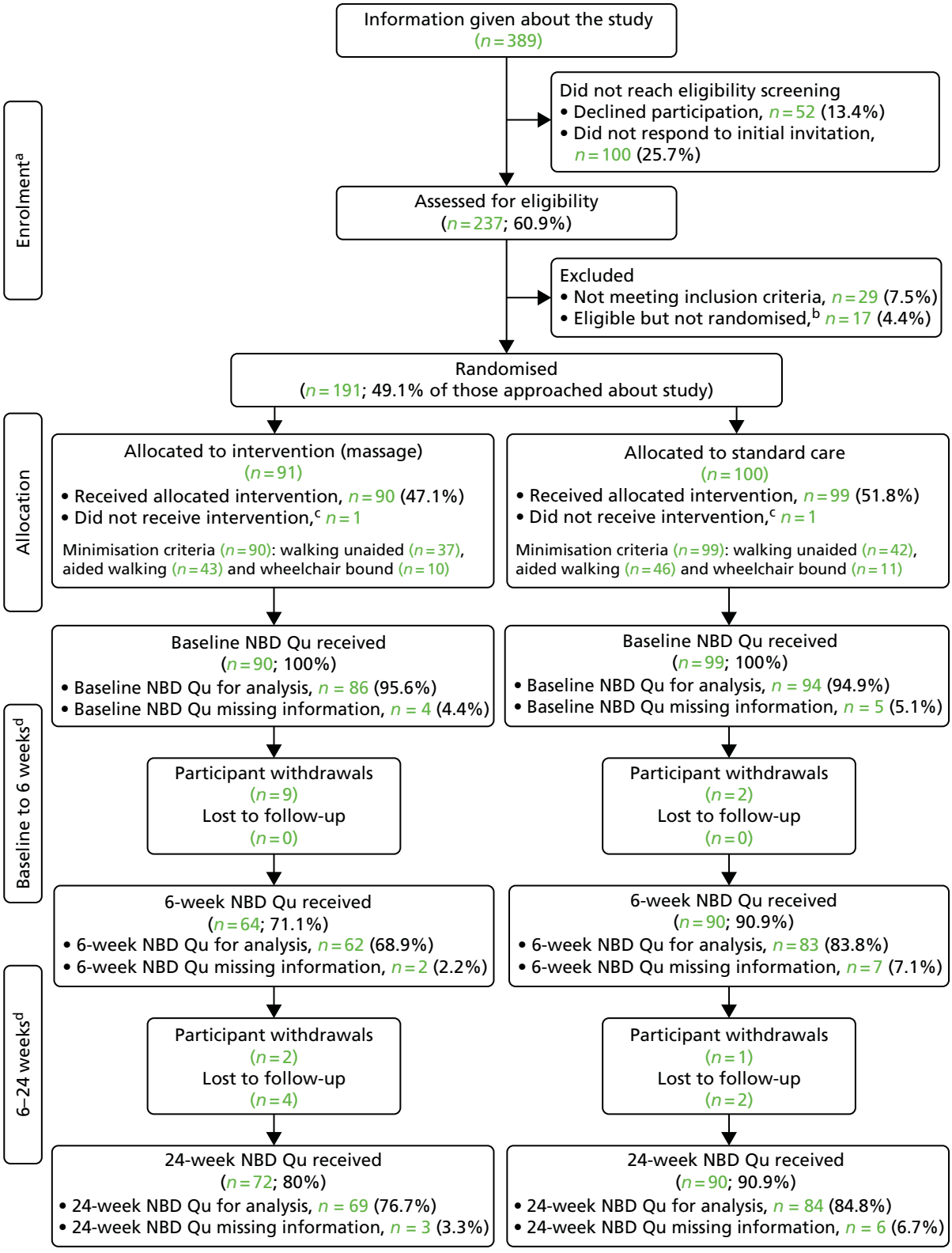

FIGURE 3 The CONSORT flow diagram. Qu, questionnaire. a, In the enrolment and screening information, all percentages are calculated from the number of people approached about the study ($n = 389$); b, reasons for those who were eligible but did not take part vary from a patient's personal circumstances changing to baseline appointments being made for a patient but he/she not attending; c, in each group, one participant was randomised and subsequently deemed ineligible for the trial when eligibility was reassessed. No data were collected for these two participants; and d, these sections show the breakdown for the primary outcome measure (NBDS) at each stage of data collection: baseline, week 6 and week 24. All percentages calculated are from $n = 90$ (intervention group) and $n = 99$ (control group).

Quality of participant-completed outcome data

Participant-completed outcomes were returned by post at weeks 6 and 24. Questionnaire and bowel diary data were checked for completeness and every effort was made to collect any missing information when acceptable to do so.

The CONSORT flow diagram (see *Figure 3*) shows the numbers available for the primary outcome analysis at baseline and weeks 6 and 24 (NBDS). During monitoring of the study attrition rates and primary and secondary outcome data received, it was evident that some participants were stating that they had returned their outcome measures by post but these were not received in the AMBER trial office. Thus, in order to maximise our available primary outcome data for analysis, from 22 March 2016 onwards, the research staff at each site completed the NBDS (10 questions) during the telephone call at week 24. This increased our available data for primary outcome analyses at 24 weeks, compared with 6 weeks, in both study groups (intervention group, 76.7%; control group, 84.8%).

There was a greater number of withdrawals/losses to follow-up in the intervention group (15/90) than in the control group (5/99).

For all outcome data, the numbers available for analysis and any reasons for missing data will be reported when discussing each outcome below.

Reasons for withdrawal/losses to follow-up

There were two randomisation failures and 20 participants who withdrew and were lost to follow-up ($n = 14$ intervention group, $n = 16$ control group; none withdrew consent for use of existing data). We have undertaken an analysis of the missing data (see *Appendix 4*) and it would seem that they do not suggest any major biases in the primary analysis. The reasons for withdrawal in the intervention group were varied and included change in diagnosis of MS, family circumstances, worsening of condition and too much paperwork. There is also the possibility that those in the control group remained in the study so that they would receive the training in the abdominal massage and had not yet experienced the potential disappointment of the intervention not working for them, which might increase the likelihood of withdrawing from the study. Interestingly, of those who took part in the interview study, none withdrew or were lost to follow-up, which may indicate that this was a more motivated group or that taking part in the interviews facilitated retention.

Missing primary outcome data

The missingness of the primary outcome data appeared to be relatively unrelated to baseline characteristics, apart from the following: trial group (more missing data in the intervention group), more missing data in those not wheelchair bound, slightly more missing data for women and for younger participants, and more missing data in some centres (see *Appendix 4* and *Chapter 6* for possible reasons for all of the above). However, using the characteristics at baseline to impute missing data, MI was carried out for the primary outcome and the primary analysis was repeated as a sensitivity analysis. This approach assumes that data are missing at random; this is discussed further in *Chapter 6*.

Baseline data

The mean age of participants was 53 years (SD 10.4 years) and 81% (154/189) were female. Mean time since diagnosis of MS was 14.3 years (SD 9.1 years). Baseline demographics and clinical data are summarised in *Table 2*. Demographics and symptom characteristics of the two groups were comparable at baseline.

TABLE 2 Characteristics of participants at study entry

Characteristic	Trial group	
	Intervention ($N = 90$)	Control ($N = 99$)
Clinical characteristics		
Minimisation variable: walking aids, *n* (%)		
Walking unaided	37 (41.1)	42 (42.4)
Aided walking	43 (47.8)	46 (46.5)
Wheelchair bound	10 (11.1)	11 (11.1)
Age (years), mean (SD)	53.5 (11.32)	51.3 (10.32)
Sex, *n* (%)		
Male	14 (15.6)	21 (21.2)
Female	76 (84.4)	78 (78.8)
BMI (kg/m^2), mean (SD)	27.4 (6.207)	26.22 (5.525)
Time since diagnosis of MS (years), mean (SD)	14.8 (9.76)	13.9 (8.64)
Type of MS, *n* (%)		
Benign	0 (0.0)	2 (2.0)
Relapsing–remitting	45 (50.0)	61 (61.6)
Secondary progressive	36 (40.0)	23 (23.2)
Primary progressive	9 (10.0)	13 (13.1)
Severity of symptoms,* n *(%)		
Cognitive		
None	39 (43.3)	35 (35.4)
Moderate	50 (55.5)	61 (62.6)
Severe	1 (1.1)	3 (3.0)
Pain		
None	41 (46.6)	46 (46.5)
Moderate	43 (47.8)	52 (52.5)
Severe	6 (7.6)	1 (1.0)
Spasm		
None	33 (36.7)	31 (31.3)
Moderate	58 (64.4)	63 (64.7)
Severe	17 (12.2)	11 (11.1)

TABLE 2 Characteristics of participants at study entry (*continued*)

Characteristic	Trial group	
	Intervention ($N = 90$)	Control ($N = 99$)
Depression		
None	41 (45.6)	52 (52.5)
Moderate	45 (50.0)	42 (43.5)
Severe	4 (4.4)	4 (4.0)
Fatigue		
None	8 (8.9)	5 (5.1)
Moderate	58 (64.5)	68 (68.7)
Severe	24 (26.7)	26 (26.3)
Bladder		
None	12 (13.3)	15 (15.2)
Moderate	57 (63.4)	59 (59.6)
Severe	29 (32.2)	29 (29.3)

Bowel symptoms

To be eligible to participate in the trial, participants had to be 'bothered' by their constipation. Bowel symptoms had commenced > 10 years ago in 37% of participants and < 1 year ago in 4% of participants. The main bowel symptoms reported by participants at baseline were a feeling of incomplete emptying, straining to pass stool and bloating (*Table 3*).

TABLE 3 Bowel symptoms reported in CRF

Bowel symptoms	Trial group	
	Intervention ($N = 90$)	Control ($N = 99$)
Pain: yes, *n* (%)	59 (65.6)	60 (60.6)
Bloating: yes, *n* (%)	76 (84.4)	86 (86.9)
Faecal incontinence: yes, *n* (%)	39 (43.0)	60 (60.6)
Successful opening of bowels 2–4 times a week, *n* (%)	59 (65.6)	53 (53.5)
Type of stool (Bristol stool chart) over the last week (%)		
Types 1 and 2	21.8	19.4
Types 3 and 4	20.2	23.6
Types 5, 6 and 7	16.1	14.6
No stool	39.8	38.8
Missing	2.3	2.4
Constipated (no stool + types 1 and 2)	61.6	58.2
Straining to pass stool: yes, ≥ 25% of the time, *n* (%)	80 (88.9)	74 (74.8)
Digital stimulation: yes, ≥ 25% of the time, *n* (%)	28 (31.1)	29 (29.3)
Feeling of incomplete emptying: yes, ≥ 25% of the time, *n* (%)	83 (92.8)	94 (94.9)

Primary analyses

The primary analysis is the comparison between treatment groups (bowel massage vs. no massage) at the final visit (24 weeks), adjusted for site and minimisation variable level of mobility (walking unaided, walking aided, or wheelchair bound), as well as baseline measure of the outcome and sex.

Primary outcome measure

Neurogenic Bowel Dysfunction Score

At baseline, the mean score for the intervention group was 7.6 points (SD 5.31 points) and the median was 6.0 points (range 0–21 points). For the control group at baseline, the mean NBDS was 8.6 points (SD 5.08 points) and the median was 9.0 points (range 0–22 points) (*Table 4*). These scores indicate that the NBD symptoms were having a minor impact on most participants. Scores of 7–11 points indicate minor impact and scores of ≥ 14 points indicate severe impact. The mean NBDS at week 24 was 7.4 points (SD 5.23 points) and the median was 7.0 points (range 0–24 points) for the intervention group; the mean NBDS was 8.7 points (SD 5.70 points) and the median was 7.5 points (range 0–24 points) for the control group at week 24. The mean adjusted difference in change between randomised groups from baseline to week 24 was not statistically significantly different [mean difference between groups (intervention – control): –1.6, 95% confidence interval (CI) –3.32 to 0.04; $p = 0.0558$; *Table 5*]. *Figures 4* and *5* visually show the change over time within the two groups.

TABLE 4 Summary of primary and secondary outcomes at baseline, week 6 and week 24

	Trial group					
	Intervention ($N = 90$)			Control ($N = 99$)		
Score	Mean (SD)	*n*	Median (range)	Mean (SD)	*n*	Median (range)
Primary outcome measure – symptom severity						
NBD score (points)[a]						
Baseline	7.6 (5.3)	86	6 (0–21)	8.6 (5.1)	94	9 (0–22)
Week 6	8.4 (6.2)	62	7 (0–25)	9.1 (5.7)	83	8 (0–34)
Week 24	7.4 (5.2)	69	7 (0–24)	8.7 (5.7)	84	7.5 (0–24)
Secondary outcome measure – symptom severity						
Constipation score (points)[b]						
Baseline	11.7 (4.1)	88	12 (1–25)	11.5 (3.8)	97	11 (3–21)
Week 6	10.6 (4.3)	58	11 (1–22)	10.8 (4.0)	83	11 (1–22)
Week 24	10.1 (4.1)	57	10 (2–22)	11.1 (3.9)	81	11 (3–27)
Bowel diary data						
Time spent on toilet (minutes per week)						
Baseline	75.6 (69.6)	80	57.5 (3–330)	75.8 (74.4)	87	55.0 (3–370)
Week 6	77.9 (73.3)	66	55.0 (5–315)	85.0 (88.5)	85	50.0 (2–400)
Week 24	78.2 (92.4)	53	45.0 (3–550)	77.0 (68.5)	78	56.5 (1–295)

TABLE 4 Summary of primary and secondary outcomes at baseline, week 6 and week 24 (*continued*)

	Trial group					
	Intervention ($N = 90$)			Control ($N = 99$)		
Score	Mean (SD)	*n*	Median (range)	Mean (SD)	*n*	Median (range)
Number of attempts per week to empty the bowels						
Baseline	10.4 (6.7)	86	9 (0–35)	8.6 (5.2)	91	8 (0–32)
Week 6	11.3 (7.1)	65	9 (2–32)	8.9 (6.0)	88	8 (1–32)
Week 24	10.7 (7.2)	53	10 (1–43)	8.3 (5.1)	77	7 (1–23)
Number of stools passed per week						
Baseline	3.9 (1.7)	88	4.0 (0–7)	4.0 (1.7)	98	4 (0–7)
Week 6	4.3 (1.9)	68	4.5 (1–7)	3.9 (1.8)	89	3 (0–7)
Week 24	4.3 (1.9)	57	4.0 (0–7)	3.9 (1.9)	81	4 (0–7)
Bladder symptom severity						
SF-Qualiveen total bladder score[c]						
Baseline	1.8 (1.10)	90	1.8 (0–4)	2.0 (1.20)	99	1.8 (0–4)
Week 6	1.7 (1.13)	61	1.6 (0–4)	2.1 (1.15)	85	2.1 (0–4)
Week 24	1.7 (1.10)	57	1.8 (0–4)	2.1 (1.12)	81	2.0 (0–4)
QoL						
EQ-5D-5L VAS score[d] (maximum score of 100)						
Baseline	60.6 (21.1)	89	60 (3–100)	55.7 (20.6)	98	60 (3–100)
Week 6	59.4 (24.0)	59	65 (5–97)	55.4 (20.8)	86	60 (5–100)
Week 24	59.8 (22.6)	58	62.5 (10–95)	51.3 (20.3)	83	50 (10–90)
EQ-5D-5L health index score[e] (maximum score of 1)						
Baseline	0.50 (0.25)	95	0.6 (–0–1)	0.50 (0.28)	99	0.6 (–0–1)
Week 6	0.50 (0.29)	60	0.6 (–0–1)	0.50 (0.27)	84	0.5 (–0–1)
Week 24	0.50 (0.28)	58	0.6 (–0–1)	0.50 (0.28)	83	0.5 (–0–1)
New QoL measure for validation (NBIS)						
NBIS[f] (total score maximum of 52)						
Baseline	20.2 (8.5)	86	20 (6–41)	20.8 (7.4)	98	21 (5–38)
Week 6	19.9 (8.2)	56	19 (5–42)	21.4 (7.0)	82	21 (3–42)
Week 24	19.0 (8.4)	56	18 (5–50)	20.9 (7.4)	77	21 (1–40)
NBIS QoL (maximum score of 24)						
Baseline	9.6 (5.1)	88	9 (0–22)	10.7 (4.7)	99	11 (1–22)
Week 6	9.9 (4.9)	56	10 (0–21)	10.7 (4.3)	83	11 (1–23)
Week 24	9.2 (4.8)	58	8.5 (2–23)	10.7 (4.7)	80	11 (0–24)
NBIS faecal incontinence score (maximum score of 12)						
Baseline	3.7 (2.4)	90	3 (0–10)	3.7 (2.0)	99	3 (0–9)
Week 6	3.6 (2.3)	61	3 (0–9)	4.1 (2.1)	87	4 (0–11)
Week 24	3.8 (2.5)	57	4 (0–12)	4.1 (1.8)	82	4 (0–9)

continued

TABLE 4 Summary of primary and secondary outcomes at baseline, week 6 and week 24 (*continued*)

	Trial group					
	Intervention ($N = 90$)			Control ($N = 99$)		
Score	Mean (SD)	*n*	Median (range)	Mean (SD)	*n*	Median (range)
NBIS symptom score (maximum score of 16)						
Baseline	6.9 (2.9)	88	7 (0–16)	6.4 (3.1)	98	6 (1–13)
Week 6	6.4 (3.2)	60	6 (1–14)	6.6 (2.5)	84	6 (1–14)
Week 24	6.0 (2.8)	57	6 (1–15)	6.2 (2.8)	80	6 (0–14)

QoL, quality of life; VAS, visual analogue scale.
a NBDS range: 0–47 points; a score of ≥ 14 points indicates severe NBD.
b Constipation Scoring Symptom range: 0–30 points; a score of 30 points indicates severe constipation symptoms.
c SF-Qualiveen total bladder score range: 0–4; a higher score indicates worse bladder dysfunction.
d EQ-5D-5L VAS: maximum score of 100. A higher score indicates better QoL.
e EQ-5D-5L health index: maximum score of 1, which indicates best health.
f NBIS: higher scores for all subscales indicate greater improvement in NBD.

TABLE 5 Analysis of change from baseline of the NBDS

	Trial group				Mean difference in change between groups (intervention–control), mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change (95% CI)	*n*	Mean change (95% CI)	Adjusted[a] (95% CI)	*p*-value
Baseline to week 6	61	0.6 (–0.73 to 1.98)	80	0.9 (–0.5 to 2.22)	–0.58 (–2.38 to 1.22)	0.5236
Baseline to week 24	66	–0.6 (–2.11 to 0.93)	80	0.5 (–0.78 to 1.83)	–1.64 (–3.32 to 0.04)	0.0558

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was entered as a random factor.

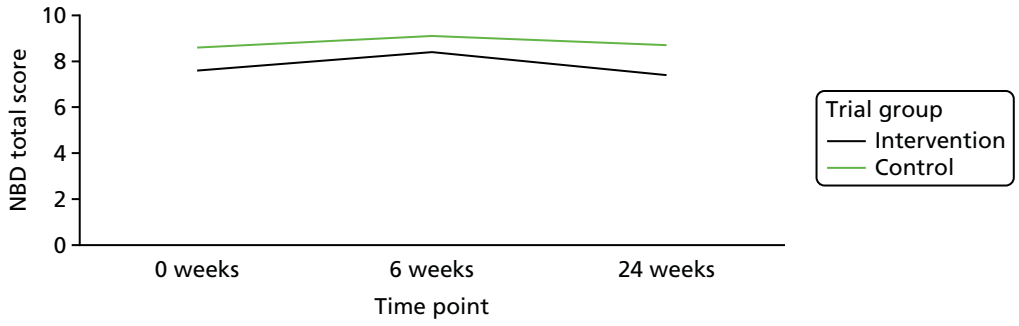

FIGURE 4 Change in NBDS over time.

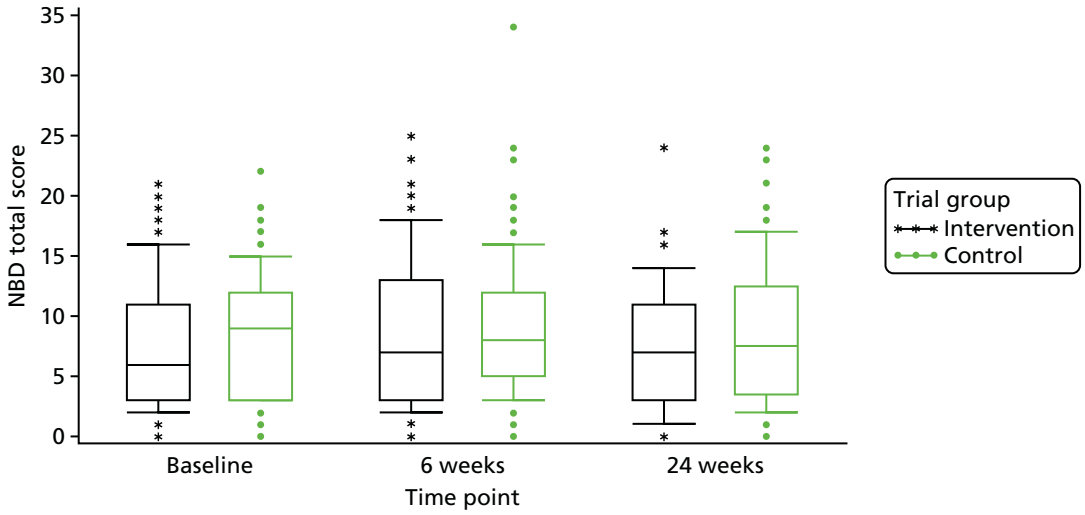

FIGURE 5 Box-and-whisker plot for NBDS.

Secondary outcomes

Constipation Scoring System

At baseline, the intervention group had a mean CSS score of 11.7 points (SD 4.05 points), and the control group had a mean CSS score of 11.5 points (SD 3.77 points). At week 24, the intervention group had a mean CSS score of 10.1 points (SD 4.10 points), and the control group had a mean CSS score of 11.1 points (SD 3.91 points). *Figure 6* is a line graph showing the change over time in the two groups. There was no significant mean difference between the groups in change in the total CSS score between baseline and either time point (*Table 6*).

Short Form Qualiveen Bladder Questionnaire

At baseline, both groups demonstrated moderate effects of bladder dysfunction on their overall quality of life with a total SF-Qualiveen score in the intervention group of 1.8 points (SD 1.10 points) and the control group of 2.0 points (SD 1.20 points). The results in all four domains of the SF-Qualiveen, that is (1) bother with limitations, (2) frequency of limitations, (3) fears and (4) feelings related to urinary problems, were also similar in both groups There were no significant differences between groups in the change from baseline to weeks 6 or 24 in the SF-Qualiveen score (*Table 7*).

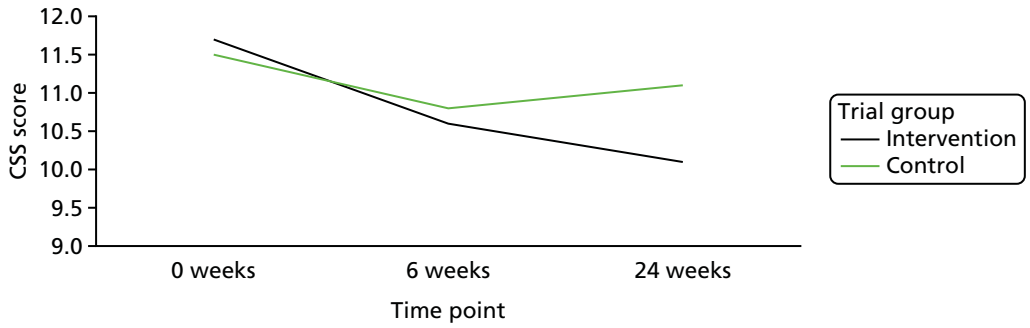

FIGURE 6 Change in total CSS score over time.

TABLE 6 Analysis of change in CSS score from baseline

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change (95% CI)	*n*	Mean change (95% CI)	Adjusted[a] (95% CI)	*p*-value
Baseline to week 6	57	–1.2 (–2.11 to –0.33)	82	–0.3 (–1.05 to 0.48)	–0.89 (–2.03 to 0.26)	0.1273
Baseline to week 24	56	–1.1 (–2.15 to –0.1)	81	–0.3 (–1.08 to 0.45)	–0.88 (–2.03 to 0.27)	0.1308

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

TABLE 7 Analysis of change from baseline in SF-Qualiveen score

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change (95% CI)	*n*	Mean change (95% CI)	Adjusted[a] (95% CI)	*p*-value
Baseline to week 6	61	0.8 (–0.74 to 2.38)	85	1.4 (0.26 to 2.48)	–1.09 (–2.89 to 0.70)	0.2306
Baseline to week 24	57	0.6 (–1.2 to 2.43)	81	0.5 (–0.89 to 1.96)	–0.58 (–2.74 to 1.58)	0.5968

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

EuroQol-5 Dimensions, five-level version: quality-of-life outcomes

All the results of the EQ-5D-5L are summarised in *Chapter 4*.

Neurogenic bowel dysfunction patient-reported outcome measure

There were no significant changes in any of the outcomes from the NBIS. All results are summarised in *Table 8*.

Bowel diary data

Within the statistical analysis plan (SAP), we identified the most important data to be analysed in the bowel diary. These were the number of days passing stools, time spent on the toilet and percentage of normal stools.

Each participant was required to complete 8 weeks of bowel diaries (at baseline, weeks 1–6 and week 24). Overall, these were well completed and compliance was high. For example, frequency of passing of stool was completed by 88 out of 90 (97.7%) participants and 98 out of 99 (98.9%) participants at baseline; by 68 out of 90 (75.5%) and 89 out of 99 (89.8%) participants at 6 weeks; and by 57 out of 90 (63%) and 81 out of 99 (81%) participants at week 24 for the intervention and control groups, respectively.

TABLE 8 Summary of NBIS data

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
NBIS	*n*	Mean change (95% CI)	*n*	Mean change (95% CI)	Adjusted[a] (95% CI)	*p*-value
Total score						
Week 6	53	0.3 (–1.34 to 1.9)	82	1.0 (–0.8 to 2.01)	–1.04 (–2.72 to 0.64)	0.2216
Week 24	53	–0.8 (–2.62 to 1.04)	77	0.3 (–0.85 to 1.47)	–1.46 (–3.43 to 0.52)	0.1468
Quality-of-life score						
Week 6	54	0.6 (–0.21 to 1.47)	83	0.4 (–0.22 to 1.01)	0.04 (–0.93 to 1.01)	0.9387
Week 24	56	–0.2 (–1.17 to 0.81)	80	0.3 (–0.45 to 0.97)	–0.70 (–1.82 to 0.43)	0.2239
Faecal incontinence score						
Week 6	61	0.0 (–0.51 to 0.48)	87	0.3 (–0.03 to 0.68)	–0.49 (–1.03 to 0.05)	0.0768
Week 24	57	–0.1 (–0.69 to 0.52)	82	0.4 (–0.05 to 0.78)	–0.39 (–1.01 to 0.23)	0.2117
Symptom score						
Week 6	59	–0.2 (–0.89 to 0.45)	84	0.2 (–0.2 to 0.68)	–0.42 (–1.12 to 0.29)	0.2469
Week 24	56	–0.4 (–1.04 to 0.22)	80	–0.2 (–0.66 to 0.31)	–0.26 (–0.97 to 0.46)	0.4779

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

Stools passed per week

The mean frequency of stools passed per week at baseline was 3.9 (SD 1.68 stools passed per week) in the intervention group and 4.0 (SD 1.74 stools passed per week) in the control group. At week 6, this increased to 4.3 stools passed per week (SD 1.87) in the intervention group and decreased to 3.9 stools passed per week (SD 1.81) in the control group; at week 24, there was no change from week 6 in either group [i.e. mean frequency of stools passed per week was 4.3 (SD 1.88) in the intervention group and 3.9 (SD 1.89) in the control group]. *Figure 7* is a line graph visually showing the change over time within the two groups.

There was a statistically significant difference between trial groups in the change in number of stools passed from baseline to week 24 (*Table 9*). The difference between the trial groups was 0.62 (95% CI 0.03 to 1.21; $p = 0.039$). As there was some inconsistency in completion of the diaries, the analyses of change values were derived from a combination of two questions [(1) how often did you pass a stool? and (2) type of stool] to give one answer on frequency. If one or the other question was answered, this was taken as having passed a stool; if neither question was answered, this was taken as no stool passed. *Figure 8* highlights very little change in the first 5 weeks.

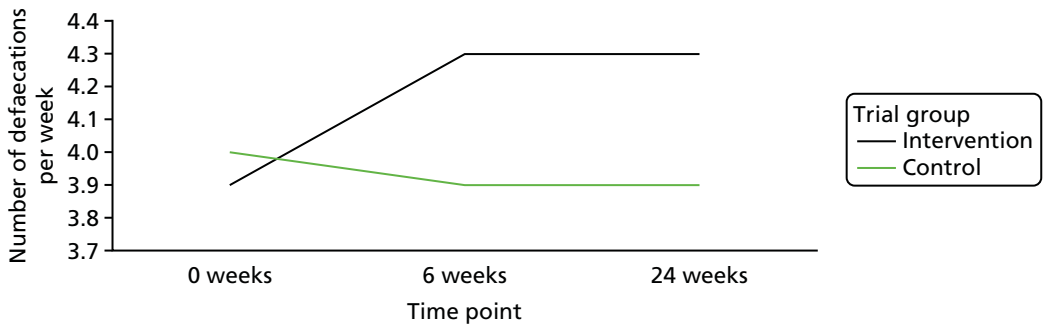

FIGURE 7 Change in the mean number of stools passed per week.

TABLE 9 Analysis of change from baseline in the number of stools passed per week

Time point	Trial group: Intervention ($N = 90$) *n*	Intervention Mean change (95% CI)	Control ($N = 99$) *n*	Control Mean change (95% CI)	Mean difference in change between groups, mixed models: Adjusted[a] (95% CI)	*p*-value
Stools passed per week (adjusted to combine number and type of stool if data inconsistent)						
Baseline to week 6	67	0.4 (0.07 to 0.68)	88	0.0 (–0.34 to 0.39)	0.38 (–0.08 to 0.85)	0.1036
Baseline to week 24	56	0.1 (–0.34 to 0.51)	80	–0.5 (–0.88 to 0.02)	0.62 (0.03 to 1.21)	0.039

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

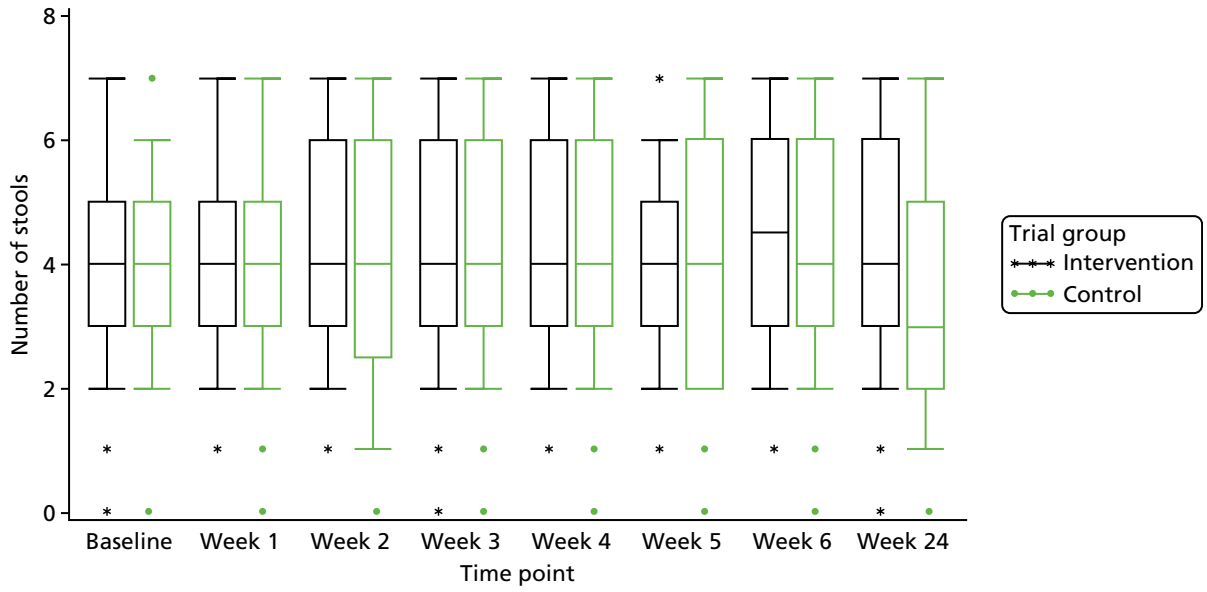

FIGURE 8 Box-and-whisker plot of number of stools passed per week.

Time spent on the toilet

At baseline, those in the intervention group spent a mean of 75.6 minutes (SD 69.60 minutes) per week on the toilet and those in the control group spent a mean of 75.8 minutes (SD 74.36 minutes) per week on the toilet. At week 6, this time was 77.9 minutes (SD 73.26 minutes) per week for the intervention group and 85.0 minutes (SD 88.52 minutes) per week for the control group. At week 24, these times were 78.2 minutes (SD 92.43 minutes) and 77.0 minutes (SD 68.51 minutes) per week for the intervention and control groups, respectively. There was no statistically significant difference between groups in the mean change in time spent going to the toilet between baseline and either time point (*Table 10*).

TABLE 10 Analysis of change in time spent on the toilet from baseline

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change from baseline (95% CI)	*n*	Mean change from baseline (95% CI)	Adjusted[a] (95% CI)	*p*-value
Time spent on the toilet (minutes per week)						
Baseline to week 6	60	–0.7 (–15.7 to 14.39)	80	9.8 (–5.28 to 24.95)	–7.92 (–29.0 to 13.17)	0.4588
Baseline to week 24	50	–6.5 (–21.86 to 8.78)	71	–3.8 (–19.71 to 12.17)	–3.35 (–23.1 to 16.4)	0.7377

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

Type of stool

For each stool passed, participants were asked to indicate the type of the stool, as per the Bristol stool chart.[33] Using types 3 and 4 as normal, and types 1 and 2 and no stool per week as constipated, there was a reduction in the percentage of participants who were constipated in the intervention group (from 61.6% at baseline to 55.4% at week 24) and in the control group (from 59.0% to 58.9% at week 24). The percentage passing normal stools (types 3 and 4) was 20.2% in the intervention group and 17.5% in the control group at baseline; at week 24 this percentage was 23.9% in the intervention group and 22.8% in the control group (see *Appendix 5*).

Medications used in the AMBER trial for bowel management (information from medication form)

At baseline, 67 (74%) participants in the intervention group and 80 (80%) participants in the control group were on at least one medication, with numbers of medications ranging from 1 to 35. The number of participants on medication for management of their bowel symptoms was 44 (i.e. 44/67; 66%) in the intervention group and 54 (i.e. 54/80; 68%) in the control group. Laxido Orange (Almac Pharma Services Ltd, Craigavon, UK), Movicol (Norgrine Ltd, Hengoed, UK) and docusate sodium appeared to be the most popular medications used in both groups, with suppositories being used by approximately only 9% of participants in each group.

At the start of the trial, 44 participants were on zero medications (24 participants in the intervention group and 20 in the control group).

During the course of the study, 32 participants in the intervention group and 44 participants in the control group started new medications, with nearly twice as many new medication entries recorded in the control group compared with the intervention group (69 vs. 135). Thirteen participants in the intervention group had taken at least one additional medication for bowel management, with 19 different entries recorded in total (e.g. one participant had five entries for four different laxatives). In the control group, 12 participants started new medications for their bowels, with 33 different entries (several participants reported three or four additional bowel medications; one had 12 entries, eight for different bowel medications and four for glycerine suppositories).

At the end of the study, 15 participants in the intervention group (18 entries in total) and 13 participants in the control group (35 entries) had stopped taking some of their bowel management medications. There were still 38 participants who were not on any form of medication (intervention group, $n = 20$; control group, $n = 18$) at the end of the study.

Anorectal physiology and transit test results

University College Hospital, London, was the only site in the AMBER trial to recruit participants to a pilot substudy, to determine if any information about the mechanism of action of abdominal massage could be gleaned through anorectal physiology and colonic transit tests, which are routinely undertaken at this site. Participants had a test at baseline and a repeat test at week 24. All participants from UCH took part in the substudy.

A total of 26 participants were randomised at UCH; however, two post-randomisation exclusions occurred. All baseline outcomes for the main study were completed by 24 participants. Of these, 23 participants underwent baseline transit tests; the 23 participants comprised two male (8.7%) and 21 female (91.3%) participants, 11 from the intervention group and 12 from the control group, with a mean age of 53.5 years (SD 12.59 years). There were no baseline transit test data for one of the 24 participants. Three participants withdrew from the study during the 6 weeks of intervention and a further participant was lost to follow-up (could not be contacted for the week-24 follow-up and did not return any patient-reported outcomes). A further eight participants withdrew from having the repeat tests at week 24, leaving 12 participants with week-24 transit and physiology results. One of these participants had no baseline transit data; thus, 11 sets of baseline and week 24 transit test data were available for analysis.

There was no difference between the groups with respect to changes in the duration of bowel symptoms, faecal incontinence, infrequent emptying, pain or bloating (see *Report Supplementary Material 1*). The baseline data indicated that 65.2% (15/23) of the participants who underwent the transit test had slow transit, six (54.5%) in the intervention group and nine (75%) in the control group.

Table 11 shows that there was no significant difference in the change in the number of total markers between the groups; although there was a possibility that the groups were not well matched at baseline with a median number of markers of 17 (range 0–54) in the intervention group, while in the control group the median number of markers was 47 (range 0–60). The CI is wide because of the small number of participants. The markers in the rectosigmoid were relatively well matched at baseline, median 10 (range 0–46) in the intervention group and a median 12.5 (range 0–35) in the control group.

Notwithstanding the substantial number of participants who failed to complete the test at week 24 (five in the intervention group and six in the control group), the change between pre treatment and week 24 was 16 (range –6 to 32) in the intervention group and –5.0 (range –13 to 17) in the control group. This may be explained by the fact that, in the intervention group, the massage was moving content to the distal colon, if not necessarily triggering evacuation.

The difference at baseline for the total markers and markers in the left and right colon, that is, groups not matched at baseline for these outcomes, as well as the numbers not completing the test at week 24, make it impossible to differentiate between changes as a result of regression to the mean and actual changes.

TABLE 11 Radiopaque marker transit test, total number of markers data summary

	Trial group				Mean difference in change between groups, mixed models	
	Intervention		Control			
Time point	*n*	Mean change from baseline in the number of markers (95% CI)	*n*	Mean change from baseline in the number of markers (95% CI)	Adjusted[a] (95% CI)	*p*-value
24 weeks	5	13.2 (–20.04 to 46.44)	6	–7.8 (–20.29 to 4.63)	15.7 (–37.69 to 69.01)	0.4846

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided, wheelchair bound) and sex. Centre was used as a random factor.

Anorectal pressure tests and anal and rectal sensation and capacity

The small number of participants who completed the tests at week 24 mean that the sample size is too small to draw conclusions.

Adverse events

A total of 84 AEs were noted in the trial: 28 in the intervention group and 56 in the control group. *Table 12* summarises this information, along with the numbers of participants affected in each group.

Appendix 6 is a summary of all the AEs. Five AEs were reported as being possibly related to the intervention; however, two of these were reported in the control group [urinary tract infection (UTI) and diarrhoea]; as they had no intervention, the fact that there were two AEs in this group that were classed as possibly related to the intervention is deemed as an error on the part of the site reporting the AE. For the three possibly related AEs reported in the intervention group, two were for one participant who had two UTIs, both of which resolved within 1 week, and one participant had reflux and went to accident and emergency (A&E) but was not admitted. Both of these participants were still continuing with the massage at 24 weeks despite these reported AEs.

Additional information on all AEs (reported by primary SOC and PT) can be found in *Report Supplementary Material 1*.

Summary of serious adverse events

From the 84 reported AEs, nine were classified as a SAE. A summary of the SAEs reported is in *Appendix 6*. Two of these SAEs were a hospitalisation as a result of a MS relapse (one in each study group) and one was a fall, but, considering the study cohort, these are not surprising events. None was related to the trial and all were resolved.

Secondary analysis

In a secondary analysis of the primary outcome, using MI for the missing data, the following baseline variables were included in the model: age, sex, BMI, type of MS, number of years since diagnosis, cognitive symptoms of MS and minimisation variable level of mobility (walking unaided, walking aided or wheelchair bound). *Table 13* shows the results adjusted for all variables; this indicated a similar result as found in the primary analysis, with no significant difference between the intervention and control groups. For assessing if changes in symptoms were dependent on site, with Edinburgh taken as the reference site, there was no statistically significant difference between the sites ($p = 0.8326$), although slightly better results were reported at sites in Sheffield, Salford, Lincoln, Leeds and the John Radcliffe Hospital than in Edinburgh.

TABLE 12 Adverse events reported

Category	Trial group (*n*)		Total (*n*)
	Intervention	Control group	
All participants	91	100	191
Participants with AEs	19	30	49
AEs	28	56	84
Of which, SAEs	3	6	9

TABLE 13 Secondary analysis: primary outcome NBDS adjusted for all baseline variables

Variable	Estimate	95% CI	*p*-value
Intervention vs. control	–1.060	–2.976 to 0.855	0.2751
Centre vs. Edinburgh			0.8326
Southern General Hospital, Glasgow	0.135	–4.334 to 4.604	
Royal Victoria Hospital, Newcastle upon Tyne	2.411	–2.397 to 7.218	
UCH, London	0.997	–3.614 to 5.608	
Royal Preston Hospital, Preston	1.868	–2.996 to 6.732	
The Walton Centre, Liverpool	1.411	–3.704 to 6.526	
John Radcliffe Hospital, Oxford	–0.257	–4.901 to 4.387	
Leeds Community Healthcare NHS Trust	–0.326	–5.321 to 4.668	
United Lincolnshire Hospitals NHS Trust	–0.034	–4.845 to 4.778	
Salford Royal Hospital NHS Trust	–0.687	–5.481 to 4.107	
Sheffield Teaching Hospitals NHS Trust	–1.594	–6.223 to 3.034	
Northampton General Hospital, Northampton	1.893	–3.560 to 7.347	
Baseline NBDS (+ 1 unit)	0.327	0.137 to 0.516	0.0009
Minimisation variable: mobility vs. wheelchair bound			0.9560
Walking unaided	–0.218	–3.476 to 3.040	
Walking aided	–0.425	–3.525 to 2.674	
Age (+ 1 year)	–0.097	–0.211 to 0.018	0.0972
BMI (+ 1 kg/m^2)	–0.042	–0.207 to 0.124	0.6171
Male vs. female	–2.789	–5.179 to –0.399	0.0226
Time since diagnosis of MS (+ 1 years since diagnosis)	0.046	–0.069 to 0.160	0.4309
Cognitive status vs. severe			0.7719
None	–0.754	–6.832 to 5.323	
Mild	–1.720	–7.722 to 4.282	
Moderate	–0.709	–6.833 to 5.415	
Type of MS vs. primary progressive			0.5537
Type of MS: benign	–1.515	–10.071 to 7.041	
Type of MS: relapsing–remitting	–2.525	–6.031 to 0.980	
Type of MS: secondary progressive	–1.749	–5.325 to 1.826	

Regression analysis also indicated that there is more likely to be a benefit in the intervention group for those walking unaided or aided, as they responded better than wheelchair-bound participants, while those of greater age and higher BMI also did slightly better. The time since diagnosis of MS did not seem to be important, but those with relapsing–remitting MS responded more positively than those with primary progressive MS. Cognition severity indicated that those with mild or no impairment did better than those with severe impairment. Consistent with other findings, males responded significantly better (mean difference –2.789, 95% CI –5.179 to –0.399; $p = 0.0226$).

Sensitivity analysis

A sensitivity analysis was carried out using MI of the primary outcome NBDS, and a similar result to the primary analysis was found (difference in change between the intervention and control group: –1.266, 95% CI –2.936 to 0.403; $p = 0.1371$) (*Table 14*). Males, however, again demonstrated a greater beneficial effect (males vs. females: –2.280, 95% CI –4.478 to –0.083; $p = 0.0419$).

The repeated-measures analysis (*Table 15*) was not significant for the primary outcome or all other outcomes, except for the increased number of times that participants felt that their bowel was emptied and the number of stools passed per week, which were in favour of the intervention. Between baseline and week 6, the mean difference in the number of stools for the intervention group was 0.98 (95% CI 0.36 to 1.61; $p = 0.03902$) and for the control group it was 0.56 (95% CI 0.03 to 1.10; $p = 0.039$). This effect was decreased for both outcomes at week 24, but was still statistically significant over all time periods.

Change in laxative use

At week 6, the outcome for the regular use of laxatives or drops at week 6 compared with no use of laxatives or drops had an odds ratio (OR) of 2.37 (95% CI 0.87 to 6.46; $p = 0.092$), using ordinal regression adjusted for all baseline variables (baseline use, centre, age, sex, mobility, BMI, time since diagnosis of MS, type of MS and cognitive status). At week 24, the OR for the same outcome was 1.62 (95% CI 0.74 to 3.55; $p = 0.229$) using ordinal regression adjusted for all the same baseline variables. Although the ORs were not significant, there is some evidence that the intervention group were twice as likely to achieve a lower level of laxative use than the control group (*Table 16*).

TABLE 14 Sensitivity analysis of the primary analysis with MI of primary outcome NBDS

Parameter	Estimate	SE	95% CI	*p*-value
Intervention group vs. control group	–1.266	0.852	–2.936 to 0.403	0.1371
Centre				
John Radcliffe Hospital, Oxford	–0.084	2.289	–4.570 to 4.402	0.9708
Leeds Community Healthcare NHS Trust	–0.012	2.434	–4.784 to 4.759	0.9959
Northampton General Hospital, Northampton	0.847	2.368	–3.794 to 5.488	0.7206
Royal Preston Hospital, Preston	1.062	2.233	–3.315 to 5.438	0.6345
Royal Victoria Hospital, Newcastle upon Tyne	1.225	2.290	–3.263 to 5.712	0.5927
Salford Royal Hospital NHS Trust	0.090	2.254	–4.328 to 4.508	0.9682
Sheffield Teaching Hospitals NHS Trust	–1.622	2.247	–6.026 to 2.783	0.4706
Southern General Hospital, Glasgow	–0.083	2.159	–4.313 to 4.148	0.9694
The Walton Centre, Liverpool	1.039	2.487	–3.835 to 5.914	0.6760
United Lincolnshire Hospitals NHS Trust	–0.468	2.304	–4.984 to 4.048	0.8391
UCH, London	0.168	2.148	–4.042 to 4.378	0.9377
NBD total score at baseline	0.356	0.090	0.181 to 0.532	< 0.0001
Minimisation variable: mobility vs. wheelchair bound				
Walking unaided	0.320	1.449	–2.521 to 3.161	0.8251
Walking aided	–0.192	1.420	–2.975 to 2.591	0.8924
Male vs. female	–2.280	1.121	–4.478 to –0.083	0.0419

SE, standard error.

TABLE 15 Summary of repeated-measures analysis of primary and secondary outcomes

Outcome	Intervention – control				Overall *p*-value[a]
	Week 6		Week 24		
	LS mean (95% CI)[a]	*p*-value[a]	LS mean (95% CI)[a]	*p*-value[a]	
NBDS	–1.16 (–2.84 to 0.53)	0.179	–0.54 (–2.26 to 1.17)	0.535	0.254
Constipation score	–0.88 (–1.99 to 0.23)	0.121	–0.53 (–1.64 to 0.58)	0.349	0.157
Time spent on toilet	–0.42 (–21.5 to 20.6)	0.969	–9.70 (–29.3 to 9.9)	0.331	0.545
No attempts per week	1.31 (–0.66 to 3.29)	0.192	1.01 (–0.83 to 2.86)	0.281	0.138
Did not empty bowels	0.98 (0.36 to 1.61)	0.002	0.48 (–0.11 to 1.07)	0.108	0.007
No stools per week	0.56 (0.03 to 1.10)	0.039	0.32 (–0.18 to 0.82)	0.215	0.026
SF-Qualiveen score	–0.24 (–2.17 to 1.69)	0.809	–0.87 (–2.76 to 1.01)	0.363	0.498
EQ-5D-5L VAS score	4.30 (–2.05 to 10.65)	0.184	0.67 (–5.59 to 6.92)	0.834	0.374
EQ-5D-5L UK Health Index score	0.003 (–0.05 to 0.065)	0.916	0.004 (–0.056 to 0.065)	0.885	0.888
NBIS					
Faecal score	–0.37 (–0.95 to 0.20)	0.203	–0.43 (–0.99 to 0.13)	0.136	0.107
QoL	–0.67 (–1.68 to 0.34)	0.192	–0.06 (–1.07 to 0.95)	0.907	0.403
Symptom score	–0.29 (–0.99 to 0.41)	0.415	–0.43 (–1.12 to 0.25)	0.214	0.226
Total score	–1.40 (–3.15 to 0.35)	0.117	–1.05 (–2.79 to 0.68)	0.234	0.106

LS, least squares; QoL, quality of life; VAS, visual analogue scale.
a Mixed-model, repeated-measures, least squares estimates.

TABLE 16 Secondary analysis of NBDS for regular use of laxative drops or tablets at all time points

Variable	Trial group, *n* (%)		Total, *n* (%)
	Intervention	Control	
Pre intervention			
Missing	0 (0.0)	0 (0.0)	0 (0.0)
No regular use	41 (45.6)	48 (48.5)	89 (47.1)
Regular use of laxative drops or tablets	43 (47.8)	47 (47.5)	90 (47.6)
Regular use of both laxative drops and tablets	6 (6.7)	4 (4.0)	10 (5.3)
Total	90 (100.0)	99 (100.0)	189 (100.0)
Week 6			
Missing	0 (0.0)	1 (1.1)	1 (0.6)
No regular use	34 (53.1)	48 (53.3)	82 (53.2)
Regular use of laxative drops or tablets	27 (42.2)	37 (41.1)	64 (41.6)
Regular use of both laxative drops and tablets	3 (4.7)	4 (4.4)	7 (4.5)
Total	64 (100.0)	90 (100.0)	154 (100.0)
Week 24			
Missing	0 (0.0)	0 (0.0)	0 (0.0)
No regular use	43 (59.7)	51 (56.7)	94 (58.0)
Regular use of laxative drops or tablets	26 (36.1)	35 (38.9)	61 (37.7)
Regular use of both laxative drops and tablets	3 (4.2)	4 (4.4)	7 (4.3)
Total	72 (100.0)	90 (100.0)	162 (100.0)

Post hoc analysis

The following descriptive analysis (and, when indicated, further statistical analysis) focuses on questions within questionnaires and on further bowel diary data on symptoms that were identified as being important to participants and/or were identified in other analyses as significantly changed between the two groups.

Neurogenic Bowel Dysfunction Score: those with constipation at baseline (i.e. with a score of ≥ 11 points)

As the overall level of constipation at baseline was rated as mild in both groups according to the NBDS [at baseline the total mean score for the intervention group was 7.6 points (SD 5.31 points) and the median was 6.0 points (range 0–21 points), whereas in the control group, the mean was 8.6 points (SD 5.08 points) and the median was 9.0 points (range 0–22 points)], the analysis was repeated for only those participants with a NBDS at baseline of ≥ 11 points. The results are presented in *Table 17*.

The univariate analysis and linear regression analysis can be reviewed in *Report Supplementary Material 1*. The numbers in both groups were reduced and the only evidence of any effect was at week 6 for those with a longer time since diagnosis of MS ($F_{4,30}$, $p = 0.043$, estimate 0.153, *t*-test value 2.07, $p = 0.0437$, 95% CI 0.004 to 0.302).

Frequency of defaecation as per question 1 in the Neurogenic Bowel Dysfunction Score

There was an increase in the number of participants passing stools daily from baseline to week 24 in the intervention group (12.2% to 23.6%), with a smaller increase in the control group (16.2% to 20.0%). The intervention group had a small decrease in the percentage passing stools fewer times than once per week (6.7% to 5.6%), compared with an increase in the control group (7.1% to 12.2%).

Frequency of defaecation as per the question in the Constipation Scoring System

The percentage of participants in the intervention group who were passing stool two or more times per week by week 6 was 92.1% and in the control group it was 88.6%; at week 6, 6.6% in the intervention group and 10.1% in the control group were passing stool fewer times than once a week. At week 24, the percentage of participants passing stools more than two times per week had increased to 94.9% in the intervention group and had decreased in the control group to 80.7%; 3.4% of the intervention group were now passing stools fewer times than once per week, whereas in the control group this percentage had increased to 16.8%.

Feeling of incomplete evacuation as per the question in the Constipation Scoring System

At baseline, the percentage of participants who ‘never felt incomplete evacuation’ was 6.7% in the intervention group and 9.1% in the control group; at week 24, this increased to 15.5% in the intervention group and decreased to 8.4% in the control group. At baseline, 21.3% of participants in the intervention group and 20.3% in the control group ‘always felt incomplete evacuation’; at week 24 this decreased to 3.4% in the intervention group and 10.8% in the control group.

TABLE 17 The NBDS for patients with a NBDS at baseline of ≥ 11 points

	Trial group											
	Intervention						Control					
Time point	*n*	Mean SD	First quartile	Median	Third quartile	95% CI	*n*	Mean SD	First quartile	Median	Third quartile	95% CI
Intervention	20	12.3	7.0	13.0	18.5	9.3 to 15.2	28	10.7	7.5	10.5	13.5	8.9 to 12.5
6 weeks		6.4						4.7				
Intervention	22	9.0	4.0	9.5	12.0	6.2 to 11.8	28	9.9	6.0	9.5	13.0	7.8 to 12.2
24 weeks		6.3						5.4				

Bowel diary data

Attempts to pass stool

At baseline, the mean number of attempts to pass stool in the intervention group was 10.4 (SD 6.73 attempts), whereas for the control group this mean was 8.6 (SD 5.22 attempts). At week 6, the mean number of attempts was 11.3 (SD 7.31 attempts) for the intervention group and 8.9 (SD 6.00 attempts) for the control group; and at week 24 the mean number of attempts to pass stool was 10.7 (SD 7.16 attempts) and 8.3 (SD 5.09 attempts) for the intervention and control groups, respectively.

As can be seen in *Table 18* and *Figure 9*, the mean changes between baseline and weeks 6 and 24 for attempts to empty the bowel were not statistically significant between groups.

At baseline, the number of times per week that the participants felt that they had a complete evacuation was 1.9 (SD 2.2 times) and 1.8 (SD 1.73 times) for the intervention and control groups, respectively. At week 6, this was 2.6 times (SD 2.2 times) and 2.2 times (SD 2.0 times) for the intervention and control groups, respectively, and at week 24 this number was 3.0 times (SD 2.16) and 2.2 times (SD 2.14 times) for the intervention and control groups, respectively.

There was a statistically significant difference between groups in the change in number of complete evacuations per week from baseline to week 24 ($p = 0.002$) (*Table 19*). The intervention group had, on average, increased the number of complete evacuations per week by 1.08 more than the control group, although this was a post hoc analysis.

TABLE 18 Attempts to pass stool per week

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change from baseline (95% CI)	*n*	Mean change from baseline (95% CI)	Adjusted[a] (95% CI)	*p*-value
6 weeks	62	0.2 (–1.49 to 1.84)	84	0.4 (–0.83 to 1.66)	1.08 (–0.81 to 2.96)	0.2608
24 weeks	52	–0.9 (–2.82 to 1.02)	75	–0.5 (–1.96 to 1.0)	1.14 (–0.92 to 3.19)	0.2770

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

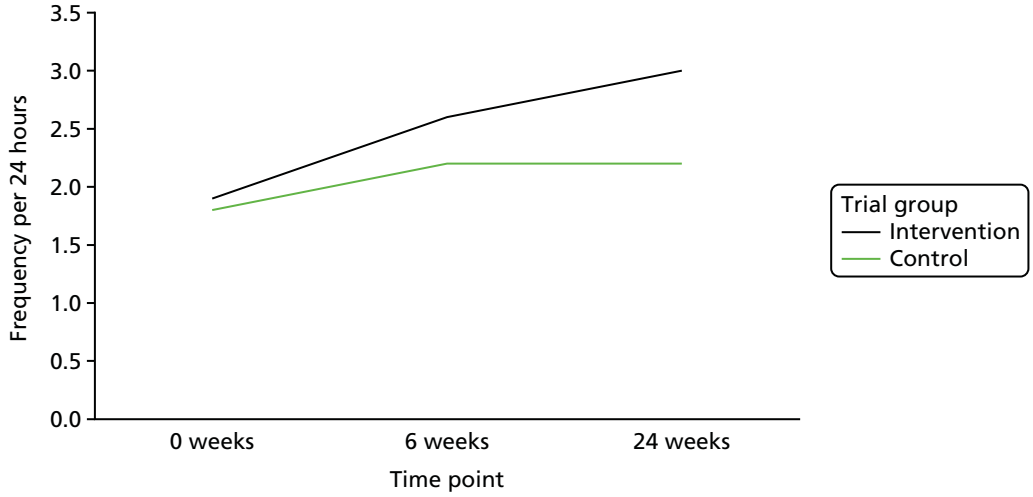

FIGURE 9 Frequency of feeling of successful evacuation.

TABLE 19 Number of times a complete evacuation per week was reported

	Trial group				Mean difference in change between groups, mixed models	
	Intervention ($N = 90$)		Control ($N = 99$)			
Time point	*n*	Mean change from baseline (95% CI)	*n*	Mean change from baseline (95% CI)	Adjusted[a] (95% CI)	*p*-value
6 weeks	62	0.8 (0.4 to 1.2)	84	0.2 (–0.2 to 0.6)	0.48 (–0.10 to 1.06)	0.104
24 weeks	52	1.2 (0.6 to 1.8)	75	0.3 (–0.1 to 0.7)	1.08 (0.41 to 1.76)	0.002

a Adjusted for baseline value, centre, mobility (walking unaided, walking aided or wheelchair bound) and sex. Centre was used as a random factor.

Other diary data

Analysis of other data provided by the self-completed bowel diary was not statistically tested as per the SAP (e.g. frequency of faecal incontinence, use of digital stimulation, type of stool) and no change was identified between groups to warrant post hoc analysis. The bowel diary question on laxative use asked if laxative use was the same, less or more. This was difficult to analyse as it was not being compared with baseline but with the previous week.

Adherence to the intervention (massage diary and nurse weekly telephone calls)

All participants received weekly telephone calls from the research nurse during the 6 weeks of intervention and again at week 24. The aim of the calls was to support fidelity to the trial protocol. There was good response to the follow-up telephone calls made by research staff at sites; 81% of participants in the intervention group and 86% in the control group were reached at week 24 and data were collected during the telephone calls.

According to information collected during the follow-up calls, 72.6% to 83.3% of participants in the intervention group administered the massage themselves throughout the 6 weeks of intervention; for 10.3% to 14.1% of participants, a carer undertook the massage. Some data were missing or massage was not undertaken in 2.6% of cases.

According to the bowel diary records, which also recorded when the massage was undertaken in the intervention group, the mean number of days on which massage was performed per week was 5.2 (SD 1.88). This varied little over the 6 weeks of intervention [at week 6, the mean was 5.4 days (SD 1.75)]. At week 24 those still doing the massage ($n = 57$, 82%) were undertaking it on average 3.2 times per week (SD 2.83 times per week). Mean time spent on the massage during weeks 1–6 was 72.5 minutes (SD 4.0 minutes) and at week 24 it was 55.8 minutes (SD 40.0 minutes).

Participants were shown how to perform the massage lying down, semi-lying down or sitting up. Information on the choice of position utilised, in addition to the time of day the massage was performed, was collected during the 6 weeks of the intervention. During weeks 1–6, 58–64% of participants performed the massage lying down, 16–24% semi-lying down and 1–4% sitting up.

Morning massage administration seemed to be the preferred time (for 46–56% of all participants), then evening (26–31%), with afternoon administration being least common (4–6%).

Information from nurse weekly telephone calls

Reasons for discontinuing the intervention, as reported in the final week 24 telephone call with the research nurse ($n = 77$ interviews; 20 discontinued), included no benefit ($n = 8$; 10%), burden on carer ($n = 1$; 1.3%) and too difficult ($n = 5$; 6.5%); the rest gave no reason or data were missing.

Adherence to lifestyle

In the intervention and control groups, 20% and 30% of participants, respectively, stated that they made at least one change to their lifestyle as part of the optimised bowel care information. More participants in the control group than the intervention group changed their diet during weeks 1–4 but did not seem to continue with this; however, they did continue to alter their fluid intake and do more exercise. The number who changed their position for defaecation was similar in both groups.

Approximately 50% of participants in the intervention group reported a change in their bowel habits compared with 38% in the control group at week 1, and this difference was mirrored at week 24 with approximately 43% in the intervention group versus 31% in the control group reporting a change in bowel habits. Changes reported more frequently in the intervention group were more frequent bowel movements, less time spent on the toilet and softer stools than the control group at weeks 1 and 24.

For the AMBER trial full set of descriptive statistics, see *Report Supplementary Material 1*.

Neurogenic bowel impact score

Analysis of the new NBD symptom score was undertaken for further validation; the analysis carried out is in *Report Supplementary Material 1*.

The new neurogenic bowel patient-reported outcome measure (NBIS) showed only moderate repeatability in the control group for the AMBER trial. However, this was over a longer time period than is usually used for test–retest stability, and it is possible that the MS bowel symptoms had genuinely changed in the control group. It is known that MS bowel symptoms are variable over time. A repeat of this test–retest with a shorter time between the completions, and possibly asking participants if they perceive that their symptoms changed or not, is recommended.

When compared against other bowel symptom scores, such as the NBDS and the Wexner score, a high correlation was found for most items, suggesting good criterion validity for the new questionnaire. It was also highly correlated with the EuroQol-5 Dimensions (EQ-5D) quality-of-life score, but not the EuroQol Visual Analogue Scale (EQ-VAS). NBIS was strongly correlated with the primary outcome measure NBDS. As the new questionnaire was developed after extensive qualitative work with people with NBD, including those with MS, this lends credibility to both scores. However, neither score showed a significant difference between our intervention and control groups, so there is no evidence that one is more responsive to change that the other. Further work is needed to determine which score patients find better reflects what is important to them. As our trial found no significant difference between groups, we are not able to recommend either score as being more or less sensitive to change. We did not find anything to suggest an advantage to either questionnaire and both had similar completion rates.

However, some questions within the NBDS (primary outcome) were difficult for some patients to fully understand (e.g. digital stimulation, use of drops), whereas in the new questionnaire, the language was better but the whole questionnaire was felt to be too long.

Chapter 4 Health economic evaluation

Economic evaluation

The aim of the AMBER trial was to determine the clinical effectiveness and cost-effectiveness of abdominal massage (intervention) as part of an adjunct to the control of optimised bowel care in PwMS who have NBD. This chapter gives the results of a formal economic evaluation of the AMBER trial intervention compared with control from a NHS and patient cost perspective. Health-related quality-of-life (HRQoL) data and health-care resource-use data were used to examine the following:

- the cost of delivery for the patient groups
- the health-care costs for participants in both trial groups
- HRQoL through calculation of utility values using the EQ-5D-5L.

Using the above information, we calculated an incremental cost-effectiveness ratio (ICER) and the probability of the intervention being cost-effective at different thresholds of willingness to pay (WTP) per QALY gained.

Data related to the economic analysis

Abdominal massage costs

The intervention is described in *Chapter 2*. In this chapter, only costs that would be observed if the intervention was delivered in practice will be considered; trial-related costs are not part of the analysis. In terms of the materials used for the training of the patients, it was estimated that the DVD production and the training materials provided would cost approximately £1 per patient. Research staff involved in the AMBER trial confirmed that the training of patients would take approximately 30–45 minutes. If abdominal massage becomes an established intervention in the NHS, it is expected that NHS staff involved in training patients would usually be at a NHS pay grade of 5, 6 or 7 (and could also be non-nursing staff).

For the purpose of this economic evaluation, and based on the above information, an ongoing cost of £90 per patient was calculated for the intervention and £0 costs were assumed for the controls. For the intervention, this is calculated assuming a hospital-based grade-6 nurse would provide this service for 50 minutes, which comes at £89 cost per patient contact, since contact will typically take < 50 minutes and this service can be provided by lower pay-grade staff and non-nursing staff. Duration of contact was not recorded in the trial. Therefore, the exact duration of these appointments could not be determined with certainty, and so the longest possible duration (50 minutes) was chosen for our baseline analysis. It was assumed that standard care involved no additional costs other than resource use; therefore, zero was taken as the baseline cost for the control group, even though, in practice, NBD patients would have access to services, which would involve some costs for the NHS. Moreover, in this trial, the control group did get follow-up calls and they were aware of the potential to be offered abdominal massage in the future. These calls were considered to be trial-only costs and were not included in the cost-effectiveness analysis.

Health-care resource-use data

Resources used by the participants were recorded in the outcome questionnaires at baseline and weeks 6 and 24. Participants were asked to record use of NHS services and all contacts (not just those they directly associated with bowel problems) with HCPs throughout the trial period. These are presented in *Appendix 7*.

Health-care costs

The information on resource use was combined with the unit cost of each resource to estimate the total cost of NHS resources used. Health service unit costs were valued using the most recent Department of Health and Social Care resource cost data, at 2015–16 UK prices.[41] The NHS resources that were included, and their unit costs, are shown in *Appendix 8*, along with the source of cost information. The cost of drugs consumed by participants only includes drugs prescribed by the participant's GP (this is not shown in the *Appendix 8*). The *British National Formulary*[42] was consulted for the unit cost of individual drugs prescribed to participants.

The NHS resource-use costs were calculated using unit costs, as shown in *Appendix 8*. Hospitalisation refers to the cost of an average inpatient stay in a hospital in England and Wales, as estimated in the Personal Social Services Research Unit (PSSRU). Patients did not report length of stay; they only reported if they had been admitted to hospital. Therefore, we assumed that, on average, patients stayed in hospital for the average duration of stay in England and Wales and we applied the cost of £1609 to each reported case of hospitalisation. The total resource-use-related costs for the NHS in each trial group at each time point are also shown in *Appendix 8*.

Between the two groups, NHS resource use and associated costs were not statistically different. Reported resource use suggests that there was little difference between the groups in terms of NHS costs related to resource use. The impact of the costs at weeks 6 and 24 is investigated further in the cost-effectiveness analysis. Costs at week 6 include all resource use from baseline up to the week-6 follow-up point. Costs at week 24 include all resource use from the week-6 follow-up point to the end of the trial at week 24. Baseline costs are not included in the cost-effectiveness analysis because they take place before the trial started, but they are used to show that there is no statistical difference between the two groups at baseline. As standard practice, and as part of the economic evaluation for this trial, we collected information on NHS resource use, prescribed medication costs and out-of-pocket costs. For reasons unknown, completion of prescribed medications and out-of-pocket costs was poor, resulting in many missing observations. Participants did have the option of reporting zero costs in these questions, but most did not respond. Given that the reported medication and out-of-pocket costs were very low, and similar between the two groups, we decided to use only intervention costs and NHS resource-use costs in the economic evaluation that follows, and excluded other costs. In general, few participants reported drug-related costs, resulting in many missing observations. These costs are not taken into account in the cost-effectiveness analysis that follows, because of the low numbers of participants who responded to these questions. Drug prescription costs in the intervention group were driven by one participant who was prescribed very expensive medicinal cannabis-based drugs. For example, if we remove this participant from the calculations below, the mean £187.25 cost per participant decreases to £18 cost per participant. This participant reported a cost of £1372 in the period between 6 and 24 weeks follow-up, vastly inflating the reported mean cost of £187.25 at week 24 in *Table 20*. Testing the equality of means at weeks 6 and 24 using *t*-tests ($t = 1.16$ and $t = 0.79$, respectively) suggests that there is no significant difference between the patients who responded to these questions on drug-related costs.

TABLE 20 Prescribed medication by trial group per-patient spending

	Trial group, per-participant cost (£)	
Time point	Intervention	Control
At baseline	3.20 (0.00)	5.08 (0.19)
At week 6	11.17 (6.00)	22.83 (21.59)
Up to week 24, excluding baseline	187.25 (169.33)	52.48 (52.48)

Notes
Data include all participants who responded to questions on prescribed medication in the trial. One participant in the intervention group and seven participants in the control group reported drug costs at baseline. Five participants in the intervention group and 10 participants in the control group reported drug costs at week 6. Eight participants in the intervention group and 19 in the control group reported drug costs at week 24.

Patient costs

Information on out-of-pocket expenses was collected in the questionnaires. At each follow-up, participants were asked if they had bought medicines or other equipment related to their condition. They reported out-of-pocket expenses for medicines and the majority of participants who responded reported costs related to their NBD needs. The most common items reported were laxatives, suppositories and incontinence pads. The out-of-pocket expenses for incontinence pads and other items are summarised in *Table 21*. In terms of average out-of-pocket cost per participant, there is a very small difference between the two groups; the higher spending costs seen in the control group were driven by one individual only. We report only total costs for the two groups and a mean cost calculated by dividing by the number of participants who reported costs in each group. Overall, out-of-pocket spending reported per participant was very small in both groups and, again, because of the low numbers that responded to these questions, these costs were not taken into account in the cost-effectiveness analysis that follows.

EuroQol-5 Dimensions, five-level version, data

The EQ-5D-5L data were collected via participant-completed questionnaires at baseline, week 6 and week 24. The EQ-5D-5L responses were given in the two sections of the EQ-5D-5L questionnaire: the EQ-VAS and the EQ-5D Descriptive System.[43] The EQ-5D-5L Descriptive System was scored using the UK tariffs.[44] *Table 4* provides a summary of the EQ-VAS and EQ-5D Descriptive System index score. Higher scores represent better quality of life. In the cost-effectiveness analysis that follows, HRQoL, as measured by the EQ-5D-5L index scores in *Table 4*, is combined with resource-use costs as shown in *Appendix 8* and intervention costs (which were described in *Abdominal massage costs* and calculated as £90), and assigned to each participant in the intervention group.

Economic evaluation of abdominal massage (intervention) versus standard care (control)

The raw data indicate that there is little difference between the two groups in this trial both in HRQoL outcomes and costs. However, there were fewer quality-of-life data to analyse than the number of recorded participant withdrawals or losses to follow-up. Missing data occur frequently in RCTs as participants may withdraw, questionnaires may be unreturned and responses to individual questionnaire items may be impossible to use. In the AMBER trial, one reason for the differing numbers was the fact that, in some instances when missing outcome data were chased, participants said that they had already completed the outcomes and returned them by post, but these were never received (previously discussed in *Chapter 3*).

TABLE 21 Total reported patient out-of-pocket costs (£), by trial group

	Trial group, out-of-pocket costs (£)	
Time point	Intervention	Control
Baseline to week 6	244.96	409.98
Week 6 to week 24	148.93	541.10
Total	393.89	951.08
Mean, per patient through to week 24	6.57	11.46

Notes
Data include all participants who responded to these questions. Five participants responded in the intervention group and 11 participants in the control group at baseline. Six participants responded in the intervention group and 4 participants in the control group at week 6. Five participants responded in the intervention group and 19 participants in the control group at week 24. Total costs include all reported out-of-pocket costs.

At the end of the trial, 58 participants in the intervention group and 83 participants in the control group had EQ-5D-5L data to analyse. To account for the missing data, and the highly imbalanced nature of the two groups that resulted in more missing values in the intervention group, the following statistical approaches[45] were used: EQ-5D-5L data were analysed (*Table 22*) and then MI was performed. The imputed data sets were then bootstrapped to perform a cost-effectiveness analysis including NHS resource-use costs and interventions costs. In the economic evaluation that follows, NHS resource use included all costs related to both bowel issues and other health issues as reported in *Appendix 9*.

The results in *Table 22* are not adjusted for missing values. The economic analysis of the AMBER trial data employed methods described in another study to handle missing data by MI (to reduce bias and ensure that missing data are handled appropriately).[46] The economic evaluation, therefore, also included participants with only partial data. For the cost-effectiveness analysis, QALYs and total patient costs were calculated for the 6 months that the trial lasted. The imputation was run 60 times, resulting in 60 different data sets to be used in the cost-effectiveness analysis. The imputation was implemented separately for the intervention and control groups to account for differences in the missing values between the two groups.

Multiple imputation was performed using predictive mean matching.[47] The MI model uses baseline covariates (EQ-5D index scores, age, sex, time since diagnosis of MS and severity of MS symptoms), costs and QALYs at each follow-up to impute unobserved costs and QALYs, so that, for example, missing costs at week 24 are imputed using data on baseline covariates, costs at baseline and week 6 (if available) and QALYs between baseline and week 6 (if available). QALYs were imputed using EQ-5D index scores. One thousand bootstrap samples were drawn from each of the 60 multiply imputed data sets, analysed and the difference in net benefit between the treatment groups in each bootstrap sample was estimated (at a given threshold for cost per QALY). The proportion of bootstrap samples in which the net benefit is positive represents the probability that the treatment is cost-effective for each multiply imputed data set. This probability is then averaged across all multiply imputed data sets.

Tables 23 and *24* show resource-use spending at 24 weeks before and after imputation. As expected, resource use remains not statistically significantly different between the two groups after imputation. *Table 25* shows the estimates of costs and QALYs per patient in the MI models. These costs include intervention costs and resource-use costs as shown in *Table 25*. QALYs were calculated from EQ-5D index score, taking into account the fact that the trial lasted only 6 months.

Table 26 shows the average incremental costs and QALYs for every participant obtained from the multiply imputed sample and the bootstrapping. The ICER based on these data is negative at –£24,149 because the model estimates a negative incremental QALY.

This method accounts for the uncertainty around the mean estimates of both costs and QALYs; to make conclusions about the cost-effectiveness of abdominal massage compared with control, the probability of cost-effectiveness at the WTP threshold of £20,000 per QALY is calculated at 31.3%. That probability increases to 34.2% for a WTP threshold of £30,000 per QALY.

To test if the results were affected by the imputation or the bootstrapping processes, two extra models were estimated. First, it was estimated that a seemingly unrelated regression model was applied on the imputed data sets.[48] Second, a mixed model was employed using maximum likelihood estimation.[44,49] The mixed model did not require an imputation step; this approach is a good check to see if imputation affected the results. The results of the seemingly unrelated regression model and the mixed model are shown in *Appendix 7*.

These results are similar to the bootstrapping model, and all three methods predict a probability of cost-effectiveness that is < 50% at the WTP threshold of £20,000 per QALY gained. Both imputation models predict a negative QALY gain after controlling for baseline HRQoL in these models. For this reason, the ICER of these models is negative, making straightforward comparisons rather difficult. The mixed model also

TABLE 22 The EQ-5D-5L index scores and effect size

EQ-5D-5L index scores	Trial group						Effect size (95% CI)[a]	
	Intervention			Control				
	Baseline ($n = 90$)	Week 6 ($n = 60$)	Week 24 ($n = 58$)	Baseline ($n = 99$)	Week 6 ($n = 84$)	Week 24 ($n = 83$)	Week 6	Week 24
Mean (SD)	0.545 (0.246)	0.520 (0.290)	0.536 (0.276)	0.498 (0.281)	0.481 (0.271)	0.458 (0.277)	0.004 (–0.061 to 0.068)	0.017 (–0.047 to 0.081)
							p-value	
Median (range)	0.615 (–0.183 to 1.000)	0.570 (–0.245 to 1.000)	0.592 (–0.245 to 1.000)	0.555 (–0.467 to 1.000)	0.527 (–0.213 to 1.000)	0.548 (–0.130 to 1.000)	0.916	0.605

a Adjusted for centre, sex, disability and baseline. Bootstrapped 100 times.

TABLE 23 Resource-use NHS costs per participant, by trial group, excluding baseline

	Trial group (£)	
Summary statistics	Intervention	Control
Mean cost per participant	416.40	487.01
Standard error	130.70	83.84
SD	986.79	768.39
95% CI	154.57 to 678.23	320.26 to 653.76
t-test on the equality of means	0.47	

Notes
Data include all patients who participated in the trial. There were 58 participants in the treatment group and 83 in the control group at week 24. Reported contact with NHS services from baseline to 24 weeks.

TABLE 24 Resource-use NHS costs per participant, by trial group, excluding baseline after imputation

	Trial group (£)	
Summary statistics	Intervention	Control
Mean cost per participant	427.49	500.46
Standard error	83.79	71.42
SD	794.87	710.64
95% CI	261.01 to 593.98	358.72 to 642.19
t-test on the equality of means	0.67	

Notes
Data include all patients who participated in the trial. There were 90 participants in the intervention group and 99 in the control group at baseline. Reported contact with NHS services from baseline to 24 weeks after imputation. Average resource-use costs from 60 imputed samples. See *Table 31* for NHS services included in these calculations.

TABLE 25 Multiple imputation estimates

	Trial group (£)	
Summary statistics	Intervention	Control
Mean costs per participant	590.44	540.65
Standard error	127.44	96.28
Mean QALYs per patient	0.230	0.216
Standard error	0.015	0.012

Notes
Data include all patients who participated in the trial. There were 90 participants in the intervention group and 99 in the control group. Costs exclude baseline and include resource-use NHS costs and intervention costs when applicable.

TABLE 26 Mean incremental costs and QALYs per participant

Summary statistics	Estimate	Standard error	95% CI
QALYs	–0.002	0.009	–0.029 to 0.027
Costs	56.50	116.99	–372.62 to 415.68

controlled for baseline HRQoL but the estimate on incremental QALYs and the ICER of this model was positive. In all three estimated models, the impact on quality of life is close to zero, with relatively large standard errors reflecting the uncertainty around patient utility scores. The mixed-model point estimate of the ICER is at £28,722, which is over the £20,000 WTP threshold.

In sensitivity testing, patient characteristics (age, sex, time since diagnosis of MS and severity of MS symptoms) were further controlled for, along with baseline HRQoL, in the three models, but this did not significantly change the results. In another sensitivity test, unit costs were varied by 20%, but this did not have a significant impact on the probability of cost-effectiveness, possibly because of similar resource use between the two groups. In a final sensitivity test, the impact of changing the intervention cost was explored. All three models were ran with the intervention halved and doubled. The results do appear sensitive to the intervention cost, as the probability of cost-effectiveness at the WTP threshold of £20,000 per QALY gained ranges from 21% for high intervention costs of £180 per patient to 55% probability of cost-effectiveness for low costs of £45 per patient. Notably, the point estimate of the ICER drops to between £6000 and £7000, which is in the cost-effective range given a WTP threshold of £20,000 per QALY gained. As described earlier, it is more likely that the intervention costs will be < £90 per patient than > £90, and the results in *Appendix 7* should be considered as conservative. However, it should be noted that given the negative QALY increment, the control was bound to dominate as long as the mean cost was higher in the intervention group.

The economic evaluation results show that abdominal massage is less likely to be a cost-effective alternative to standard care than the other way around. However, all models predicted a probability of cost-effectiveness of > 30% and, in the mixed model, close to 47%. In the sensitivity analysis, this probability was > 55% assuming a low intervention cost per participant. The probability of cost-effectiveness can be seen as the probability that an individual (random) patient will have a positive individual incremental net benefit. It can also be seen as the proportion of all patients in the population who have positive individual incremental net benefits; therefore, it is reasonable to assume that our results suggest that there is a subset of patients who had a positive incremental net benefit from abdominal massage.[50] If there were no patients with a positive net incremental benefit, then the likelihood of cost-effectiveness would have been close to zero. Further research is needed to establish the type of patient that may have benefited from abdominal massage (discussed further in *Chapter 6*).

This economic evaluation has certain limitations. First, excluded drug costs and out-of-pocket costs were excluded because very few participants responded to these questions. The participants who responded reported very low costs per patient and it is not expected that inclusion of these would have a large impact on our results. Second, subgroup analysis, by estimating these models on a subset of participants, was not performed. This was decided against because regression results (available on request) did not show a statistically significant impact of participant characteristics, such as age and sex, on costs and QALYs gained. Finally, the results were not extrapolated over a horizon longer than 6 months. The results suggest that the impact of the intervention on quality of life as measured by the EQ-5D-5L is small and significant differences in the probability of cost-effectiveness are not expected if the trial lasted for a longer period.

Chapter 5 Process evaluation

Introduction

The AMBER trial included a process evaluation, in line with advice from the Medical Research Council guidance for evaluating complex interventions.[51,52] This was informed by realist evaluation methodology, which goes beyond the evaluation question 'What works?' to 'What works, for whom and in what context?'[53] 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 outcomes, and to assess fidelity to implementation processes. Furthermore, results of the process evaluation also provide data to inform the optimisation of the intervention and seek to explore potential routes to sustainable implementation. The process evaluation follows a longitudinal case study design.[54,55]

The objectives of the process evaluation are to explore:

- fidelity to processes of implementation of the trial intervention
- implementation contexts (including settings, demographics and implementation processes, delivery and take up of the intervention, and adherence and non-completion)
- intervention optimisation and sustainability beyond the life of the funded project.

This chapter presents the research methods for the process evaluation, the results of the analysis of data from interviews, bowel diaries and telephone support recordings. The chapter ends with practice recommendations.

Methods

Recruitment and sampling

People with multiple sclerosis

A total of 20 PwMS taking part in the trial, and randomised to the intervention group, were selected via convenience sampling.[56] The small numbers recruited into the trial from each site meant that our intended purposive sampling strategy was not feasible. However, as *Figure 1* illustrates, the sample achieved a variation in terms of geographical location, age, MS type and different stages of the disease progression. This sample variation facilitated the exploration of hypothesised context–mechanism–outcome (CMO) configurations. We did not adhere rigidly to definitions of 'contexts' or 'mechanisms,' since previous experience of using this approach informed us that contexts can become active mechanisms that promote change in some instances and, at other times, mechanisms of action can be better conceptualised as contexts.[57,58] For instance, sampling reflected the following hypotheses: that there could be sex differences in the acceptability of massage, severity of MS might have an impact on ability to do the massage and length of time living with MS may also contribute to attitudes towards self-care. This sample is reflective of the characteristics of trial participants as a whole, with those aged > 50 years and women being the most prominent. The mean age for the intervention group participants was 52.2 years (51.3 years for those in the control group); 84.4% of intervention participants were female (78.8% for the control group). Of the interview participants, 16 lived in the north of England, reflecting the fact that half of the 12 sites involved in the study were located in that part of the UK. *Table 27* provides further details on the characteristics of those interviewed. *Figure 10* shows the flow chart for the process evaluation.

TABLE 27 Characteristics of interviewed participants

Characteristic	Number of participants
Age range (years)	
< 21	0
21–30	0
31–40	1
41–50	4
51–60	7
> 60	8
Sex	
Male	1
Female	19
Employment status	
Unemployed	2
Employed	3
Business owner	1
Retired (on ill-health basis)	12
Retired (reached retirement age)	2
Geographical location	
West Scotland	3
North-west England	10
North-east England	6
South-east England	1
Type of MS	
Benign	0
Relapsing–remitting	11
Secondary progressive	8
Primary progressive	1
Years with MS[a]	
< 5	3
5–10	3
11–20	6
21–30	3
> 30	6

a This is estimated, as a number of participants reported living with MS symptoms for years.

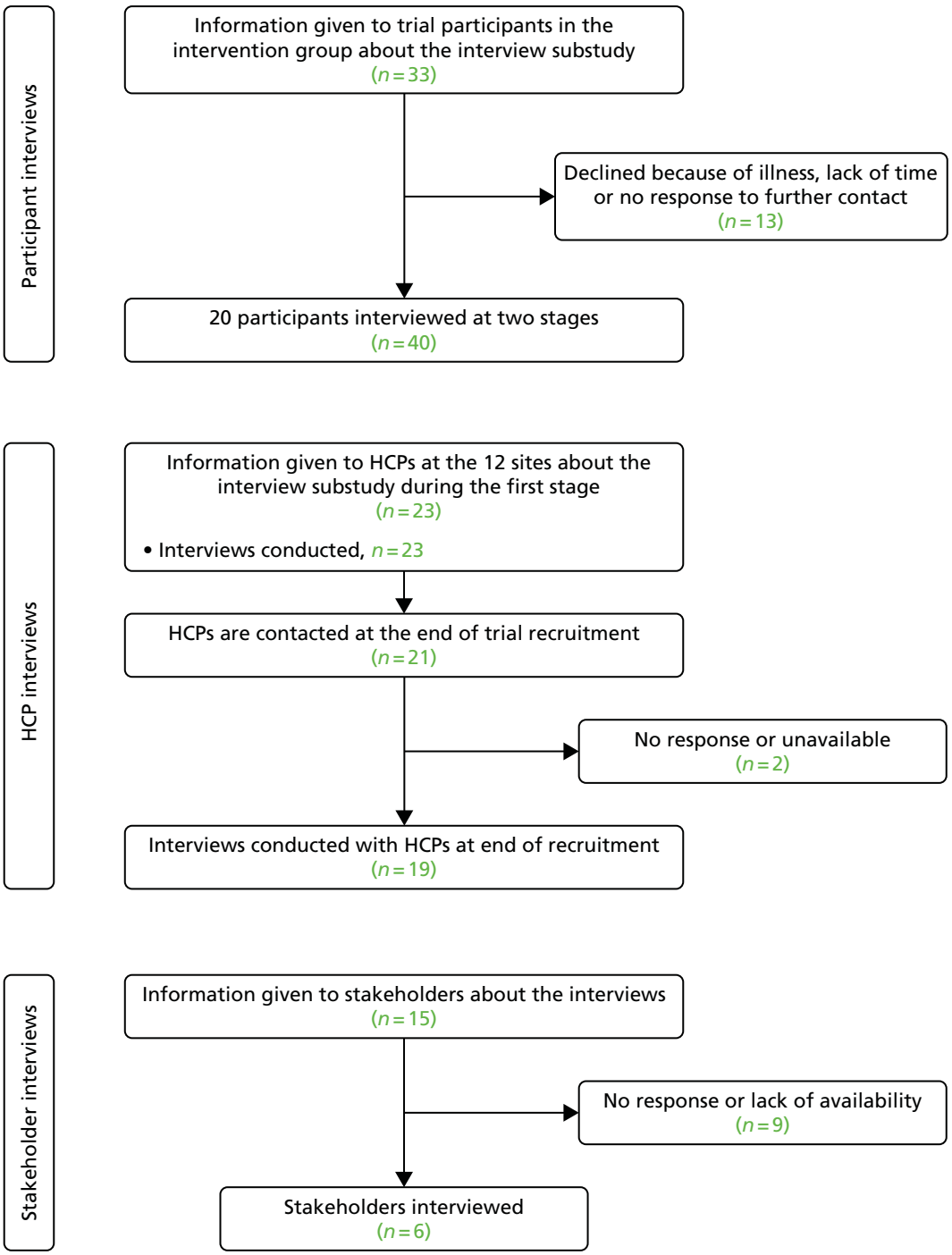

FIGURE 10 Flow chart for the process evaluation.

By the time of the first interview, participants had been enrolled in the trial for ≈4 weeks. All those who took part in a first interview agreed to participate in a second interview. A total of 20 PwMS were interviewed twice, giving a total of 40 interviews.

Health-care professionals

Forty-two interviews were conducted with 25 different HCPs. One or two people involved in delivering the AMBER trial from each of the 12 sites were recruited to interviews. The range of involvement in the trial varied from those who delivered the massage training and/or the participant follow-up to the local principal investigators, whose role centred on identifying suitable patients for the trial. *Appendix 10* documents the roles of the HCPs interviewed and the number of interviews. This sample was also designed to reflect the realist evaluation approach.

Initial interviews with HCPs were usually conducted within a few weeks of recruiting their first intervention participant. Owing to variation in site initiation and trial recruitment, initial interviews took place between January 2015 and March 2016. During this first stage, 23 staff members were interviewed.

Second interviews were sought with staff members who were actively involved in patient training and follow-up, in order to explore any problems that may have arisen since the first stage of interviewing. In a small number of cases, a different staff member who had since become more involved in the trial or delivery of the treatment was selected for interview at the second stage. Nineteen staff members were interviewed in the second stage of interviews.

Stakeholders

Six interviews were carried out with stakeholders purposefully selected for their expertise in neurological and incontinence treatment provision, policy-making and service development. The process of identifying suitable interviewees began with research into neurological and incontinence services throughout the UK. Snowball sampling was also used, meaning those interviewed recommended other potential interviewees. *Appendix 10* illustrates the types of organisations that stakeholders came from and the number of interviews.

Fifteen potential interviewees were contacted and six people were interviewed after giving informed consent. The interviews took place from early to mid-2016, in order to capture their knowledge and insights into recent policy and clinical developments related to the treatment of MS.

Data collection

Interviews

Data collection consisted of qualitative semistructured interviews, allowing the views and 'lived experiences' of participants to be explored.[59] Interviews drew on topic guides (see *Appendix 11*), taking an iterative approach to allow unanticipated themes to be explored in subsequent interviews.[59] All interviews were conducted by telephone to save on travel costs, as interviewees lived in locations throughout the UK.

The purpose of the interviews with trial participants was to explore experiences of living with MS and bowel problems, as well as experiences of taking part in the trial. The second stage of interviews focused on exploring any change in symptoms, any adaptations that they had made to the massage, further thoughts on taking part in the trial and whether or not they intended to continue with abdominal massage at the end of the trial. *Appendix 11* details the main topics covered in each stage of interviews and *Appendix 12* details the interview schedules and site questionnaires.

The aim of the interviews with HCPs was to explore any issues with the training processes (both their own training in massage as well as delivering massage training to trial participants), trial delivery and implementation. The first stage of interviews aimed to detect any problems faced in delivering the trial and anything that worked well. The original interview transcripts were used to write the topic guide for the second stage of HCP interviewing. Second stage interviews gathered an overview of staff members' experiences in participant recruitment, the delivery of massage training and advice and participant follow-up. *Appendix 11* gives an indication of the topics explored during both stages of interviews with HCPs.

Stakeholder interviews explored ways to implement the abdominal massage intervention on a larger scale and any potential challenges to doing so. Background research was conducted into the organisations for which the interviewees worked. Current neurological and incontinence policy developments at local, regional and national levels were also extensively researched to ensure that appropriate, targeted questions were asked during the interviews. Although wider policy developments and trends were acknowledged during interviews, the focus remained on those that may facilitate or hinder the possible implementation of abdominal massage treatment. *Appendix 11* gives an indication of the range of topics covered in stakeholder interviews; although this varied in accordance with the expertise of each organisation and interviewee.

Data analysis

Interview recordings were transcribed verbatim. Data were analysed by drawing on an adapted framework approach.[60] This followed an initial categorising and coding process similar to thematic analysis, using the qualitative data analysis software NVivo version 10 (QSR International, Warrington, UK). Coding and all further stages of analysis were conducted by Selina Doran (SD) and checked for consistency by Fiona Harris (FH). Analysis was conducted continuously with interviewing, contributing to the iterative process, allowing emerging themes of interest to be explored further in future interviews. The initial coding was then transferred into framework matrices for the three categories of interviewees. These summary tables explored within-case issues, in which each trial site was considered as a case, that is, the unit for analysis. During the analysis, attention was paid to any contextual differences that could have an impact on outcomes. Cross-case comparison then identified higher-level themes that explored facilitating contexts and mechanisms, and any barriers to successful implementation. The matrices also tracked the process of change over time, taking account of the longitudinal aspect of interviews. Interviews with PwMS also retained attention to case study sites to ensure that analyses were sensitive to any contextual variations. However, given the small numbers recruited from each site, participants have not been identified by recruitment location. Identifiers in quotes simply read as, for example, PwMS1 or HCP1. When second interviews were conducted with the same person, the identifier illustrates this by the additional number so that, for instance, the second interview with PwMS 1 would be identified as PwMS1_2. Bowel diaries were also analysed for those participants who reported either no improvement or only a temporary improvement in bowel symptoms. To ensure validity and reliability of the analyses, these tables were deliberated within the process evaluation team (SD and FH), and received further clinical input from the wider study team.

Results

This section presents the analysis of interviews with trial participants alongside bowel diary analysis, and analysis of interviews with HCPs and higher-level stakeholders. The within-case descriptive data informed the beginning of *Chapter 5*; here the focus is on presenting experiences of trial participation and a cross-case comparison of implementation issues drawn from interviews with HCPs.

Bowel dysfunction and treatment

We begin this section by exploring the experiences of interviewees, who provided some powerful narratives of how living with NBD affects their everyday lives. This is followed by views from HCPs and stakeholders on current treatments and the delivery of care for constipation.

Living with bowel dysfunction

Trial participants revealed the extent to which quality of life is impeded by severe constipation, which might range from passing a stool four times per week to passing a stool once a fortnight. Bowel problems, coupled with their impact on other symptoms, had a negative impact on the quality of their lives:

> *My whole life is ruled by my bowels – that's all I think about every day, 24/7.*
>
> *PwMS20_1*

One person explained that they felt thus:

> *I can go for days without having to go to the toilet, it can be, like, a week, and of course my stomach ends up bloated away out to here and then you get worried that if you go out somewhere, that you're going to have to make a quick dash to the toilet, and then when you're there you can be there for ages. So if you're out with friends and you disappear to the toilet, you're stressed 'cause you think, 'God, they're going to wonder where I am, what's happened?' and it becomes embarrassing then, and I have, on maybe two occasions, actually had an accident when I've been out and it's just been an absolute nightmare, so you've got to try and plan ahead, you know, to work round it.*
>
> *PwMS11_1*

This sometimes resulted in taking extreme measures to cope with symptoms. For instance, some participants avoided eating at certain times because of the uncertainty of when they would next pass a stool:

> *I can't eat because I'm scared, I can't eat because I don't know when I . . . if we're going on holiday I can't eat because I don't know when I can go to the toilet again or what the toilet facilities are when you go away and things like that. And when I went [on holiday] . . . I only ate [for] 2 of those 6 days and I managed, even though I was really, really hungry.*
>
> *PwMS20_1*

Constipation was linked to laxative usage, which could also result in negative side effects. Interviewees reported that taking laxatives caused pain, sleeplessness, cramps and diarrhoea. The unpredictability of passing a stool when taking laxatives meant that a number of patients became very concerned about their potential for bowel accidents, sometimes not leaving home for days because of the lack of control. For some people, this can lead to social isolation:

> *At the moment it's absolutely disastrous, like today I won't even answer the doorbell if the doorbell rings. . . . That's what happens when I have a day that I know I'm going to spend it hanging around, hovering, trying to go to the toilet, I can't even answer the door, I can't leave the toilet 'cause I'm scared I'll have an accident, . . . I have no control whatsoever.*
>
> *PwMS20_1*

Current delivery of care for constipation

Health-care professional and stakeholder interviews revealed consistent views that abdominal massage could provide a useful addition to current treatments that commonly involve oral therapies. Abdominal massage has a number of positive attributes as a form of treatment: it is cheap, low technology, simple, non-invasive and can be used anywhere.

However, stakeholder interviews revealed that most patients are underinformed about bowel matters. They stated that people do not fully understand constipation; thus, in some cases, they do not report it as an issue until it is quite advanced. Furthermore, HCPs reported that constipation is not discussed enough, and patients may not connect this to their MS. There is also a lack of evidence and education around treatment for bowel problems. In addition, the huge workloads of MS nurses have led to increasing numbers of MS patients being managed by general nurses (Stakeholder 1 and Stakeholder 4). As one stakeholder put it:

> *Excellence in continence care comes from a degree of specialists, who would be able to make better decisions and better treatment plans at a local level.*
>
> *Stakeholder 6*

Ten out of the 12 sites did not currently use abdominal massage as a form of treatment for bowel problems. Although one site had a bowel specialist who offered some form of abdominal massage, MS patients were only referred to her when their bowel problem was at a critical stage. The other site currently using abdominal massage offered specialist bowel clinics as part of a community service. This meant that this site struggled to find PwMS who had not used abdominal massage before to recruit into the trial. One further site had previously used abdominal massage as part of the continence service; however, only one member of staff had been trained in it and had since left, so massage treatment was no longer offered.

Experiencing and delivering the intervention

In this section, we explore how the intervention was experienced by participants, and issues around implementation. Interviews gathered data on various aspects of trial experience and delivery that may inform any future implementation of abdominal massage as a treatment for PwMS. This included experiences of massage training, supporting materials and telephone support. This is briefly reported in the following sections.

Recruitment and retention

By the end of recruitment, four sites had recruited to or exceeded their targets. The main reasons for failing to meet recruitment targets centred on understaffing and time constraints. At one site, recruitment was entirely reliant on one research nurse, who was also working on 15 other trials. This meant that she did not have the time to repeatedly chase patients and was sometimes not available to see them in clinic. The incorporation of the AMBER trial into the existing workloads of staff members also proved troublesome in some cases, with an already limited staff capacity further stretched unexpectedly by sickness absence or resignations.

Sites that did not meet their recruitment targets were, nevertheless, usually successful in retaining those that were enrolled in the trial. Retention was affected by being patient-centred in approach during baseline appointments. In one site, both staff members involved attended every baseline appointment: one demonstrated the massage technique while the other checked the paperwork. These were also all home visits, because that was more convenient for the participants. Another site that conducted home visits reported the unexpected benefit of establishing a better understanding of patients' home contexts:

> *It helped to see them at home because you had an idea about their home set-up – how chaotic their lives were.*
>
> *HCP19_2*

Probably the most important contributor to retention was the relationships established between those delivering the trial and the participants. For some sites, this was facilitated by the fact that participants already knew the staff members involved. One way of enhancing the rapport with participants was to have the same staff member carrying out the weekly calls:

> *I think it's just getting to know me and feeling comfortable with giving me information.*
>
> *HCP21_2*

Being supportive and offering advice during the first appointment and follow-up also appeared to enhance retention.

Massage training

Delivery of massage training by health-care professionals

The massage training delivered to participants during the baseline appointment was a critical component of the trial. Staff members had a variety of techniques: showing participants how to position their hands during the massage, administering the technique on them to give them an idea about pressure, watching participants do the massage themselves and commenting on it. A problem that arose during this initial training was that some people preferred the massage to be administered over their clothes or on body parts other than their stomach. This may have affected how the staff member was able to deliver the training, since the massage should be administered on the abdomen in order to allow them to gauge pressure. As per the AMBER trial protocol, the staff member advised that a carer or spouse could administer or assist with the massage, or that they could use their fist as opposed to a flat hand in order to provide more pressure.

Trial participants

All 20 trial participants agreed that the massage training and follow-up materials were very useful. For most participants the training comprised being given the AMBER trial DVD, having the massage demonstrated on them and then engaging in supervised practice. One-quarter of interviewees had their partner present at the baseline appointment to receive the training:

> *If there's a day where I'm not capable of doing it or can't remember a bit, then I'm covered.*
>
> *PwMS3_1*

Most interviewees were very positive about the massage video:

> *The DVD is brilliant. It is so simple and easy to understand.*
>
> *PwMS12_1*

Engagement with the DVD was enhanced by the woman demonstrating the massage in the video, who appeared to normalise the technique:

> *She's a real person . . . when I saw her I immediately relaxed and felt I could do it.*
>
> *PwMS3_1*

Feedback on the video was positive and, after initial viewings, most people used the quick reference guides as aids during the administration of the massage. The quick reference guides were found to be helpful, clear, portable and ideal to use while administering the massage. The few negative comments about the DVD were related to the format, as some participants found that their copy of the DVD would not work on their DVD players and had to seek alternative copies. Others preferred to use the information leaflet as it was easier to carry around and refer to.

Experiences of doing the massage

The frequency of administering the massage varied, with participants fitting the massage around their daily routines. A number stated a preference for administering the massage last thing at night, as part of their bedtime routine:

> *It's part of my ritual now, before I go to bed.*
>
> *PwMS15_2*

However, all participants adjusted the frequency and timing of their massage routine based on their stamina levels and personal circumstances. Circumstances that interfered with the massage routine included grandchildren visiting, a house refurbishment, family bereavement and festive periods, such as Christmas. Health problems that affected adherence included diarrhoea, vomiting and bladder infections.

Physical weakness and numbness in fingers, hands and arms caused by the MS posed another challenge, which led to several participants adapting the massage technique to suit their abilities or enlisting the help of a partner. Adaptations included administering the massage first thing in the morning (when feeling stronger), using one hand to guide the other and asking a partner to assist with parts or the whole of the massage routine.

As *Table 28* illustrates, these results were drawn on to establish some key CMO configurations that might impede or facilitate positive impacts. Those contextual factors that might facilitate positive outcomes are linked to the adaptability of participants, with those who demonstrate an ability to adapt either the massage techniques or the massage oil to suit their own capabilities and preferences.

Supporting and experiencing the trial

Site staff made weekly calls to participants, in both the intervention and the control groups, for a period of 6 weeks and then again at the 24-week stage. Fourteen of these calls were audio-recorded from 8 out of the 12 sites in order to check fidelity to the AMBER trial support call protocol. Calls were not recorded at the remaining sites because of the timing of patient calls, the site not completing the calls (the AMBER trial office took over this task for one site) or the availability of the recording equipment. In the sample of recorded calls, one was in week 24 and the remainder took place in weeks 1–6. The support calls were structured by a CRF guide of questions and, at the 24-week stage, questions were asked about issues relating to the primary outcome measure. Questions covered the following three areas:

1. participant experience – changes to bowel habits, health condition and personal circumstances; self-administration of the massage (if applicable)
2. managing symptoms – usage of medication and laxatives; any changes to diet, fluid, exercise and positioning on the toilet seat
3. delivery of the trial – more practical aspects, such as time and staffing arrangements for weekly calls and completing and returning paperwork.

However, from the 18 recordings it was identified that, in some instances, these calls were not as supportive in discussing the lifestyle changes and/or the massage as had been anticipated and were more of a tick-box exercise. In an effort to improve the quality of support, the control and intervention participant calls completed by one site, which were deemed by the AMBER trial office to be exemplary, were transcribed, anonymised and circulated to all sites as a good practice guide.

Further review of these transcripts highlighted a number of strategies that may have enhanced participant engagement in the trial. Some HCPs referred to the results from the previous call or information in participants' forms, highlighting the value of providing information about their condition. Callers gave

TABLE 28 Context–mechanism–outcome configuration: adaptability and capability

Context	Mechanism/action	Outcome
Severity of MS	Ability to do massage	Impedes adherence or effective massage technique, unless administered by a carer
Physical weakness/mobility issues/fatigue	Adaptability and commitment to continue	Achieves adherence via adaptations to massage technique or enlisting help
Greasy massage oil leads to increased time involved (e.g. showering after massage); may reduce adherence	Adaptability and commitment to continue: use alternative massage products	Continued adherence; no lubricant being used may lead to poor massage technique and negative outcomes

positive reinforcement to encourage positive lifestyle change, explored diet and fluid intake and advised on massage technique. Some of the callers reminded participants to complete and return paperwork and advised on how to complete the questionnaire.

The weekly telephone calls from sites were positively received by participants. The additional support available from staff members seemed to be the main attraction, as one person stated:

> *It's nice to think there's somebody out there that's listening and helping.*
>
> *PwMS2_1*

Participants found the advice useful and supportive; this may have been one of the reasons that trial retention was high within the control group. The only minor points of criticism came from a few trial participants who became anxious over missed calls and one person was initially given the wrong dates, which led to waiting in for calls that never came:

> *We had a wee bit of a hiccup with the first one, I was sitting waiting because it was written down as the 19th and it was written down as a Monday and I remember her saying about a Monday and I sat for about an hour and nobody phoned.*
>
> *PwMS13_1*

However, this initial mix up with dates was sorted out and subsequent calls were received when expected.

Participants' reactions to the trial paperwork were mixed. Although some participants found the paperwork tiring and burdensome, a number of people felt that completing the bowel diary was invaluable for keeping track of progress and may have encouraged adherence to the massage:

> *You forget and think 'did I go or did I not go?' and then you have a look back and you're like 'oh, yeah, I did'.*
>
> *PwMS9_1*

During the second stage of interviews, some people said that they would have liked to have continued completing the bowel diaries, as this acted as a record.

The consensus from HCPs was that the paperwork was fairly straightforward for participants to complete, with the exception of one person who had severe visual impairment. In this case, a staff member completed the paperwork during the baseline appointment and the participant developed their own bowel diary. This issue may have been mitigated by large print materials for visually impaired participants.

A number of suggestions were made by HCPs to improve the bowel diaries. These included being more explicit about when they should be started and picking up an error in the reporting of stool frequency, which added up to > 100%. It was also reported that bowel diaries did not fully capture bowel habits; for instance, although it recorded the number of attempts to pass a stool, it did not record how many times this led to a bowel movement. Another area of confusion was the options for laxative usage of 'usual,' 'less' and 'more', and the lack of a category for no laxatives.

For whom does abdominal massage work?

Positive improvements related to massage

Three-quarters of those interviewed ($n = 15$) reported improvements in their bowels as a result of the massage. The main benefit seemed to be a feeling of empowerment and control over their bowel habits:

> *I know when I get to the toilet I'm going to have a bowel movement.*
>
> *PwMS17_1*

By the time of the second-stage interviews, one participant said:

> *I have to make myself look back to see how bad things were because there's a terrific improvement.*
>
> *PwMS1_2*

This was the case for many people in the second stage of interviewing, with them passing the 'ideal types' of stools (type 3 or 4) more frequently, and with less pain. For example, one participant who mainly passed stool types 1 or 2 every 3 to 4 days or longer before the trial stated:

> *It was just awful. I'd sit on the toilet for ages and ages and ages just knowing that I had to do something and it was painful.*
>
> *PwMS17_2*

However, by the second interview, she had a bowel movement of stool type 3 or 4 every day. Others reported being able to stop taking laxatives and an increased frequency of bowel movements or, as one person reported, the time spent trying to pass a stool changed from 3 hours to only 5 minutes.

Although improvements were not so dramatic for others, one of the consequences of even small improvements was, for instance, a reduction in anxiety about potential impaction and hospitalisation. Notably, when participants stopped doing the massage because of personal circumstances, any improvements in symptoms were lost:

> *In some ways that was a positive thing because it proves that while I wasn't doing it [the massage] things deteriorated.*
>
> *PwMS3_2*

Other reported benefits from doing the massage included feeling less bloated, clothing becoming looser and a decrease in sluggishness, which reduced fatigue levels. As one person reported:

> *I don't think I've been tired since I've been on this [trial].*
>
> *PwMS14_1*

Some participants were also able to stop or reduce laxative usage, which was reported to disrupt sleep patterns. Improved diet was also noted by some participants, which was particularly important for those who ate very little because of their bowel problems. One person, who had a diminished appetite at the beginning of the trial, stated that by the end:

> *It's weird to say I feel hungry, even saying the word starving.*
>
> *PwMS12_1*

At the second stage of interviews, all 15 people who had reported some improvements agreed that participating in the trial had been worthwhile.

Exploring reasons for no improvement

Five interviewees reported no improvement arising from the massage. A complete set of bowel diaries for these participants was analysed alongside their interview data in order to determine whether or not this captured any changes in bowel habits, and to explore potential explanations for the lack of improvement.

A higher severity of MS and body numbness may well have interfered with the ability to administer the massage effectively. Indeed, one stakeholder interviewee reported that effectiveness of abdominal massage is likely to vary:

> *Some people find it beneficial and some people don't find it that effective. I think it depends on how advanced the MS is.*
>
> *Stakeholder 3*

Furthermore, when delivering the massage training, one HCP expressed doubts as to the likely effectiveness of the massage, attributable to the reduced physical dexterity of some participants:

> *Some of them, when you're watching them doing it and you're thinking 'how effective is that going to be?'*
>
> *HCP19_2*

Another person who found no improvement experienced a worsening of their MS during the course of the trial, perhaps impeding the potential to show improvement. Although bowel diary data support the reported lack of improvement, the interview data reveals that in fact this person, unlike before the massage, now had sensation and was able to feel the urge to pass a stool. This was perceived as a positive change related to the massage that, nevertheless, would not have been captured by trial outcome measures. Unfortunately, this person's condition worsened during the course of the trial and they reported the impact of worsening symptoms thus:

> *I find now I've sort of got quite a bit worse and I find if I get down and do these massages I can't get up again, I have real trouble getting up. So I've had to stop doing them which was a shame really.*
>
> *PwMS5_2*

Two further participants showed no improvement on the main indicators for constipation and consistently responded 'no' to the question 'Do you feel you have emptied your bowel?' However, both of these participants reported 'ideal stool types' at baseline, indicating that the severity of constipation was not significant enough to demonstrate any improvement.

Another participant felt that, although the treatment worked initially, this effect was not sustained:

> *It started to work a little bit, that was really good; unfortunately, it didn't last.*
>
> *PwMS16_2*

The initial benefit was improved control over when bowel movements happened, which in her case meant that she no longer remained at home for 3 days at a time in fear of bowel accidents. Her bowel diaries revealed that she only ever passed type 1 stools and that there was no noticeable improvement in frequency, stool type or amount of time spent passing stool throughout the course of the trial. As this participant was wheelchair bound, mobility issues may well have played a part in her ability to effectively administer the massage.

Despite a perceived lack of impact, these five participants remained in the trial. This may be attributable to their overall trial experience being positive. Indeed, perhaps a 'positive outlook' could explain why three of these participants expressed the intention to continue with the massage after the trial, in case it did eventually work.

A coding matrix was applied to all interview transcripts from trial participants to explore attributes, such as severity of MS, severity of constipation and massage adherence. This revealed contextual factors that affected outcomes, as illustrated in *Table 29*.

TABLE 29 Contextualising participant outcomes

Context	Mechanism/impact	Outcome
High severity of MS: reduced mobility, fatigue, severe constipation, numbness and lack of sensation	Reduced ability to massage effectively or apply correct pressure unless carer administers the massage; high severity of bowel problem means it is difficult to show an improvement	No improvement ($n = 5$)
Bowel diary reports show ideal stool type, reasonable frequency and duration on toilet	Bowel diary cannot demonstrate improvement as baseline recorded as 'ideal' with no capacity to demonstrate benefit	

Further analysis was undertaken to explore whether or not expectations of the trial might have been linked to perceived impact, as a means of exploring whether or not 'hopefulness' might have an association with subsequent outcomes. The majority of those interviewed had no previous knowledge about abdominal massage and were unsure of what to expect. As a result of this, around two-thirds of participants initially felt doubt about whether or not the massage would help them. This was especially true for those for whom other forms of treatment had failed:

> *Because nothing else had worked like the Senna tablets and stuff, I was a bit like 'well, I wonder if it is going to work?'*
>
> *PwMS15_2*

Although frequency data must be approached with extreme caution when reporting on such a small sample, *Table 30* serves to illustrate the likelihood that there was no association between expectations and trial outcomes.

Contextualising the trial primary outcome

One further piece of analysis was conducted in order to explore the discrepancy between the statistical analysis of the NBD total score and self-reported outcomes of the trial. The NBD total scores for all interviewees were matched up with data from interviews. *Table 31* illustrates the discrepancies found by comparing these data. Although 15 interviewees reported some improvements related to the massage, only seven participants recorded an improved NBD score between baseline and week 24, six participants showed no change and seven worsened over the course of the trial. However, of those seven participants who showed improved NBDSs, two of these interviewees self-reported as not having experienced any improvement in their symptoms. There are several potential explanations for these discrepancies. First, both the interview and the NBDS questionnaire captured snapshots of participant experience tied into particular weeks. Although interviews roughly followed the same time point as the trial measures, they were within the same month rather than completed at the same time as the trial measures. Second, and perhaps more importantly, the NBDS questionnaire did not necessarily explore those aspects of participant experience that affected quality of life more generally, hence the discrepancy between self-reported outcomes and those measured by the NBD questionnaire.

TABLE 30 Participant expectations and trial outcomes

Expectation (n)			
Hopeful of improvement		Sceptical/no expectation of improvement	
Positive impact	No impact	Positive impact	No impact
6	2	9	3

TABLE 31 Neurogenic Bowel Dysfunction Scores compared with self-reported outcomes

Identification	Type of MS	NBDS total score	Adherence to massage reported in interviews	Perceived impact
PwMS6	Relapsing–remitting	Baseline, $n = 13$ Week 6, $n = 7$ Week 24, $n = 8$	• Mixed • Some weeks this was daily; other times no massage	No perceived impact. Continuing to take laxatives. Bowel diary shows ideal stool type and frequency of three or four stools per week
PwMS16	Relapsing–remitting	Baseline, $n = 6$ Week 6, $n = 13$ Week 24, $n = 9$	Daily for 18 weeks then stopped	• No perceived impact • It initially worked and then no positive changes. Began taking opiates that affected appetite; has poor mobility and bowel diary shows lack of improvement
PwMS18	Secondary progressive	Baseline, $n = 5$ Week 6, $n = 5$ Week 24, $n = 5$	Sporadic. A few times a week up to week 6	No perceived improvement. On medication for bladder problems; bowel diary shows ideal stool, regular frequency but not feeling full evacuation
PwMS20	Secondary progressive	Baseline, $n = 12$ Week 6, $n = 21$ Week 24, $n = 24$	Daily	No perceived improvement. High severity of MS and body numbness means massage likely not to be effective; does not seek help with massage
PwMS5	Secondary progressive	Baseline, $n = 3$ Week 6, $n =$ NR Week 24, $n = 3$	Sporadic. Had problems with the massage oil and administering the massage	• No perceived improvement but now has urge to pass and feels gas moving after massage • Started taking an oral solution to treat constipation and feels that has worked. MS worsened during trial
PwMS8	Secondary progressive	Baseline, $n = 14$ Week 6, $n = 19$ Week 24, $n = 13$	Two or three times a week	Slight improvement. It still takes a long time to pass a stool but massage seems to help and she has reduced stomach pain
PwMS1	Primary progressive	Baseline, $n = 16$ Week 6, $n = 8$ Week 24, $n = 2$	Daily (carer assistance)	Improved: passing a stool daily. Decreased laxative usage. Better sleep
PwMS2	Secondary progressive	Baseline, $n = 1$ Week 6, $n =$ NR Week 24, $n = 8$	Two or three times a day	• Improved: stools feel more solid. Bowels are ‘functioning better.’ Improved appetite • Longer on toilet, but greater emptying

Identification	Type of MS	NBDS total score	Adherence to massage reported in interviews	Perceived impact
PwMS3	Relapsing–remitting	Baseline, $n = 7$ Week 6, $n = 7$ Week 24, $n = 7$	Five times a week	Improved. Passes a stool every 2 or 3 days with 'less bother.' When stopped massage, improvements disappeared
PwMS4	Relapsing–remitting	Baseline, $n = 1$ Week 6, $n = 6$ Week 24, $n =$ NR	Daily	Improved. Passes a stool every 2 or 3 days and she has managed to stop taking laxatives. Improved appetite
PwMS7	Relapsing–remitting	Baseline, $n = 5$ Week 6, $n = 6$ Week 24, $n = 5$	Daily	Improved. Feels that if she starts to feel constipation, the massage clears it. Managed to stop taking oral constipation solution
PwMS9	Relapsing–remitting	Baseline, $n = 5$ Week 6, $n =$ NR Week 24, $n = 3$	Every second day	Improved. Passes stool three times a week and has stopped taking laxatives. Without massage, there is no movement at all
PwMS10	Secondary progressive	Baseline, $n = 5$ Week 6, $n = 11$ Week 24, $n = 3$	Daily	Improved. Passes stool every second day. Greater sensation of emptying, less bloating, improved appetite and energy levels
PwMS11	Relapsing–remitting	Baseline, $n = 3$ Week 6, $n = 11$ Week 24, $n = 8$	Daily	Improved. Feels it is easier to pass a stool
PwMS12	Relapsing–remitting	Baseline, $n = 11$ Week 6, $n = 13$ Week 24, $n = 11$	Daily	• Improved. Passes a stool daily and it is the ideal type • Improved appetite, less bloating and reduced abdominal pain
PwMS13	Secondary progressive	Baseline, $n = 21$ Week 6, $n = 13$ Week 24, $n = 8$	Five times a week	Improved. Passes a stool once a week with more ease and it takes less time (reduced from 3 hours to 5 minutes). Has lost weight since being on the trial (regarded as positive)

continued

TABLE 31 Neurogenic Bowel Dysfunction Scores compared with self-reported outcomes (*continued*)

Identification	Type of MS	NBDS total score	Adherence to massage reported in interviews	Perceived impact
PwMS14	Relapsing–remitting	Baseline, $n = 11$ Week 6, $n = 7$ Week 24, $n = 14$	Every second day	Improved. Passes a stool three or four times a week. Stopped massage during trial because of bladder infections but plans to resume as felt that it worked
PwMS15	Secondary progressive	Baseline, $n = 3$ Week 6, $n = 11$ Week 24, $n = 7$	Daily	• Improved. Passes a stool four times a week with less pain • Stopping laxatives. Less bloating and feels full evacuation
PwMS17	Relapsing–remitting	Baseline, $n = 7$ Week 6, $n = 0$ Week 24, $n = 4$	Three times a week	Improved. Passes a stool every day with more ease and stopped laxatives. Feels lighter
PwMS19	Relapsing–remitting	Baseline, $n = 7$ Week 6, $n =$ NR Week 24, $n = 14$	Daily (carer-led massage)	Improved. Passes a stool every 6 days and has reduced abdominal pain, less bloating

NR, not reported.

Post-trial intentions

From discussions with participants during second-stage interviews, it appeared that all but two of them intended to continue with the massage. This is either because it worked for them or they hoped that it would work in the future. The massage seemed to have been incorporated seamlessly into their routines.

Views on potential future implementation

This section explores the views of both HCPs and stakeholders regarding the potential to implement the intervention within the NHS. These data are situated within the larger body of work conducted by the process evaluation team, and interviews were done on the premise that the intervention may demonstrate effectiveness and were carried out before the results of the trial were known.

Health-care professionals in the majority of sites reported issues related to staff capacity, which represents a potential barrier to future implementation of abdominal self-massage within the NHS.

Across all services in NHS England and Scotland, there are threats to the specialist nurse role and other positions through despecialisation, redundancy and not replacing staff members when they leave. At one site, there was a problem with staff recruitment and retention, which resulted in a reliance on agency staff to deliver the service.

To successfully implement abdominal massage as a form of treatment, staff members would require reassurance regarding workload and capacity. There was a perception that this would require additional resources, although in many cases this might replace more invasive, time-consuming treatments and could reduce the 'revolving door' of hospital admission or attendance for severe constipation. There were also concerns that if massage training was extended to other patient groups, there could be a resulting marked increase in referrals:

> *We could potentially be inundated with patients.*
>
> *HCP16_2*

There was also some debate about which staff members would be best placed to deliver the massage training. It was suggested that massage training could be offered by the colorectal and continence team in hospitals, or built into existing MS or continence clinics. This could be coupled with the DVD and written training materials to assist people in learning the technique. Furthermore, it was suggested that the massage could possibly benefit patients on bed rest or in nursing homes:

> *That could be something we teach them, to look after more progressive patients.*
>
> *HCP18_2*

It was suggested by some sites that community and district nurses could become involved in training people in massage in their homes. Indeed, there were indications that abdominal massage could be introduced to a wider population in a range of health-care and community settings.

Enthusiasm for abdominal massage was such that a number of sites indicated a willingness to incorporate it into current services. For instance, a HCP from one site who had set up a bowel clinic during the trial said that, since the staff members who delivered the AMBER trial were already trained in the massage, this could be rolled out more widely. Interest was also expressed in distributing training materials and engaging in additional training.

Stakeholders indicated that there are a number of policy and capacity issues affecting the potential for abdominal massage to be successfully implemented within the NHS. Evidence of clinical effectiveness is

required in order to convince commissioners and other services to support this new treatment option. Moreover, in the current NHS environment, health boards and trusts are 'just looking for a short-term gain from cost savings' (Stakeholder 6), thus evidence of cost-effectiveness is also important.

The case for abdominal massage needs to be persuasive to convince Clinical Commissioning Groups, HCPs and other services to adopt this intervention if it was found to be clinically effective. This might highlight, for instance, the potential for abdominal massage to free up capacity within GP, continence and MS services by dealing with bowel problems before they deteriorate (Stakeholder 4 and Stakeholder 5). Training in the massage could be framed as upskilling staff members:

> *It should be career-enhancing rather than career-threatening for those involved.*
>
> *Stakeholder 6*

It could also reduce the costs and capacity issues associated with long-term bowel damage: unplanned hospital admissions, bed occupancy and the prescribing of medications/other forms of treatment (Stakeholder 1, Stakeholder 2 and Stakeholder 6). Secondly, there would be the potential to improve quality of life for patients:

> *It's the cost to the patient of the indignity of having bowel management such as a suppository.*
>
> *Stakeholder 2*

A potential barrier to implementation is the challenge of 'getting something from best practice to common practice' (Stakeholder 4). First, massage treatment would probably be most useful if administered at an early stage in the development of constipation problems, rather than when patients are at crisis point (Stakeholder 3). GPs are integral to this process:

> *They see the whole person and spot potential issues around bowel dysfunction at a much earlier stage.*
>
> *Stakeholder 6*

A health-care assessment for each individual needs to be carried out to determine what is causing the constipation and to ensure that abdominal massage is the right treatment for them (Stakeholder 2). Furthermore, one stakeholder suggested that abdominal massage should be part of an individual's self-management programme, supplemented by advice around fluid intake, changes to diet and exercise suggestions (Stakeholder 5). The use of tracking tools like bowel diaries can help demonstrate how things have progressed (Stakeholder 2 and Stakeholder 3).

Stakeholders felt that abdominal massage could be taught by community nurses or other HCPs, such as general nurses, physiotherapists and continence advisors (Stakeholder 3). They also suggested that consideration should be given as to how this treatment could be taught to those who are severely disabled and unlikely to be able to self-massage (e.g. those in care homes). As reported by HCPs above, this suggests the need for staff members at care homes to be trained in the carer-led massage.

Stakeholder interviewees suggested ways of disseminating the massage training materials to reach the people who matter most: those with NBD and HCPs dealing with these issues. To that end, PwMS would need to be given access to videos and other training resources, and HCPs would need to be trained in the intervention and how to teach it. Stakeholders suggested that a number of key organisations should be included in approaches to dissemination of training and, when appropriate, training materials could be hosted on their websites:

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Royal College of Nursing

- Association for Continence Advice
- MS Society
- MS Trust
- Association of British Neurologists
- UK MS Nurse Association.

Process evaluation discussion

The experiences of PwMS provide powerful illustrations of how constipation can have a wide-ranging, negative effect on their everyday lives. Quality of life is severely impaired, to the extent that some people are afraid to leave their homes and may end up socially isolated, anxious and in pain. Interviews revealed the vicious cycle of symptoms, such as reducing food intake and disturbed sleep as a result of laxative use, and the fatigue commonly associated with MS[17] was exacerbated by constipation. Despite the symptom burden, there are few evidence-based treatments available and the cost to the NHS of dealing with constipation is substantial.[61]

The findings from the process evaluation demonstrate the potential for abdominal massage to be adopted as a bowel management technique more widely within the NHS. Seventy-five per cent of interviewees ($n = 15$) experienced improvements in their symptoms, and we were able to offer possible explanations for the lack of improvement in others. In some instances, it would be more appropriate to report that there were only minor improvements rather than none, but these minor improvements were not detectable via primary and secondary outcome measures in the main trial. It seemed that only the more dramatic improvements were able to be captured. The training focused on supporting patients to administer the massage themselves and, although the AMBER trial protocol did include the option for carer-/partner-administered massage, this option may have been missed by those unaware at the outset that they did not have the physical dexterity to perform the massage effectively.

Most of the sites involved in the trial were not currently using abdominal massage as a form of treatment and the consensus, from both HCPs and stakeholders, was that bowel problems in PwMS had to be better managed. The interviews revealed that most participants intended to continue with the massage, demonstrating the acceptability of this noninvasive treatment.

The process evaluation presents results of an approach that draws on longitudinal interviews. Following both trial participants and trial delivery over time allowed us to track processes of change and offer explanations for trial outcomes. The finer nuance achieved by bringing together interviewee experiences with bowel diary data offered insights that suggest that the outcomes may actually be more positive than the statistical analysis suggests. Furthermore, arguably, the AMBER trial achieved greater value by incorporating insights on trial processes. While being mindful of the need to protect trial equipoise, the process evaluation team worked closely with the trial team to establish a feedback loop to report anything that could be easily addressed without affecting the intervention itself. For instance, the time burden associated with compiling information packs was reported back to the trial team and they subsequently changed the format of recruitment packs to address this. This ensured that HCPs within the sites felt listened to and it encouraged them to reflect on the trial and share their feedback with us.

Capacity issues at sites mainly affected recruitment levels in the trial. Understaffing, part-time contracts and hectic workloads meant that staff members were limited in the amount of time that they could spend on the trial. As some sites were already offering massage, this also meant that there were few eligible participants to recruit. Interestingly, it was reported across all sites that participants randomised to the control group of the trial were disappointed, but the retention rate was higher in this group. This may be because the control group had a greater incentive to remain in the trial until the end, when they would be offered the opportunity to learn the massage technique. Control group retention may also have been positively affected by the telephone support offered by site staff. This may also have contributed to

fewer differences between intervention and control group outcomes, because site staff gave advice on medications as well as lifestyle.

What may be extrapolated from our process evaluation is that there is the potential for massage to improve the symptoms of NBD; this in turn may then lead to reduced hospitalisations, reduced prescriptions, amount of time HCP spend with patients and improved quality of life for PwMS. The main macrolevel changes from the massage are said, by interviewees, to be freeing up staff capacity in the long term and greater quality of life for PwMS. The argument would need to be made that the short-term work and costs associated with implementing massage training would save money in the long term.

Health-care professional and stakeholder interviewees expressed interest in implementing abdominal massage in the longer term. A number of sites were willing to adopt abdominal massage as a form of treatment and many of these interviewees felt that there was potential to roll this out to wider population groups, in a range of health and community settings. Finally, the words of our trial participants are worth repeating:

> *It made a terrific difference, in fact I have to make myself look back to see how bad things were because there's a terrific improvement, yes. It's made an awful lot of difference to me 'cause things were really bad to start with, but they're a lot better now.*
>
> *PwMS1_2*

There are some strengths and limitations to the process evaluation. Strengths include the fact that although we were unable to purposively sample, nevertheless the convenience sample yielded a participant mix that reflected our initial hypotheses regarding time since diagnosis, severity of symptoms and sex. This enabled us to capture robust data from which to explore potential variations in the experiences of trial participation (PwMS), trial delivery (HCPs) and to reflect on issues of potential future implementation and sustainability. The HCP interviews all included at least one staff member involved in delivering the trial at each site. This allowed the researcher to identify any challenges around recruitment or other trial processes that could be fed back to the trial management team. Another strength was the longitudinal nature of the research, thus facilitating scope for follow-up on any problems raised during the original interviews and exploration of the longer-term impact of abdominal massage. This is a methodological innovation rarely accomplished within process evaluations and is a major strength of the AMBER trial. Similarly, interviewing HCPs in two stages provided an opportunity to talk to additional staff members who had become involved in the trial later on, allowing for the exploration of contextual factors, such as change in capacity over time, that might have negatively affected trial delivery and implementation.

There are, however, some limitations to the process evaluation study. Owing to limited resources, only those in the intervention group were recruited for interview; therefore, we could not explore any contexts experienced by control group participants that might also have had an effect on outcomes. Another potential limitation was that those who agreed to be interviewed were likely to have had a higher level of engagement with the trial; thus, they may have been both more likely to fully participate in the intervention and to remain in the trial until its completion. However, our analysis of bowel diaries linked to interview participants revealed that they had variable levels of adherence to the massage. Although all interviewees remained in the trial, interviews with those that did withdraw would have been informative. Finally, participants' expectations of the trial were not associated with positive or negative outcomes, suggesting that our conclusions regarding their trial experiences and outcomes can be used to interpret wider trial outcomes. As only 12 sites (hospitals in Scotland and England) were involved in the trial, and our stakeholder interview numbers were small, the results cannot be seen to be representative of health-care services across the whole of the UK.

Chapter 6 Discussion

Neurogenic bowel dysfunction in PwMS has a significant impact on quality of life as demonstrated by this quotation:

> *My whole life is ruled by my bowels – that's all I think about every day, 24/7.*
>
> *PwMS20*

Despite this, it remains a topic that is often not discussed by patient or clinician and is perceived as an area with few evidence-based treatment options.[16]

This is the first large RCT looking at the short- and long-term effects of a supported programme of advice on lifestyle and training in abdominal massage compared with lifestyle advice only. Moreover, this research adds to the evidence on the impact of NBD on quality of life, and identifies the most frequent symptoms and possible mechanisms; it also facilitates the triangulation of information from the quantitative and process evaluation substudies.

Overall, the study recruited to statistical target sample size; the 20% dropout rate was in alignment with that expected in our sample size calculation. The increment in the primary outcome measure, the NBDS,[31] favoured the intervention group but was small and did not show a statistically significantly different change between groups at any time point, but we believe that findings of trials should not be described as 'negative' on the simplistic metric of whether the *p*-value is strictly < 0.05. There is a small effect (–1.64 units) that is around two-fifths of the specified MCID (4.21, as specified in the power calculation). We estimated with good precision (i.e. we have narrow 95% CIs) a treatment effect on the primary outcome that was around half the magnitude that we declared as being the estimated MCID, and we found a *p*-value of 0.0558 for this difference. The bulk of the 95% CI (–3.32 to 0.04) is in favour of the intervention, making benefit a more likely outcome than harm. Our lower 95% CI, at 3.32, rules out our original suggested MCID of 4.21. It would, therefore, seem appropriate to say that we have weak evidence of a small effect (< 2 units on the NBD measure) and our study has been able to rule out the larger MCID of 4.21. The conclusion could then boil down to a CI that is mostly in favour of benefit, but an effect that is smaller than the one the trial was designed to detect. Frequency of defaecation and feeling of more complete emptying are two secondary outcomes specifically mentioned as being of great importance in our interviews, and in both we did demonstrate statistically significant improvement in those that undertook the massage, with similar benefits being reported by the bowel diary and specific questions within the questionnaires.

As identified in *Chapter 5*, there does, however, appear to be some disparity between the quantitative and qualitative findings. This may be attributable to the questionnaires being insensitive in this population or could perhaps be a result of interviewees wishing to please the interviewer, or a mixture of the two. The NBDS[31] is only validated for NBD in spinal cord-injured patients. We used this as our primary outcome measure because spinal cord-injury and MS patients have relatively similar NBD symptoms, the differences being that only some symptoms in PwMS correspond to the level of the spinal cord lesions, can fluctuate between constipation and faecal incontinence and may involve slow transit and/or pelvic floor dyssynergia. However, there are also some differences in the pathophysiology of the diseases and approaches to treatment.

Once stabilised and rehabilitated, spinal cord-injury patients tend to establish a bowel care routine often established while in hospital. Their 'disease' does not progress and the bowel symptoms relate to the level of injury. PwMS, on the other hand, have an ultimately progressive disease with many symptoms that can fluctuate in nature and severity. In addition, we do not know all the physiological implications of the disease on the bowel itself or on the neural control of the bowel. For this reason, the NBDS may not have

been sensitive enough to detect changes in the symptoms that we have identified as mattering most to the patient, that is, empowerment and control:

> *I know when I get to the toilet I'm going to have a bowel movement.*
>
> *PwMS17*

Our other symptom questionnaire, the CSS,[32] is validated in those with chronic but non-neurological constipation and, like the NBDS, uses terms that have been shown to be unfamiliar to the general public, such as defaecation, use of drops for evacuation, evacuation, digital stimulation, evacuation of the rectum, constipation, FI, flatus incontinence and perianal skin problems. A recent study has suggested that many of these terms are unrecognised by the public[62] and this aligns with some of our incomplete questionnaires in which questions, for example, about digital stimulation were left incomplete, either because the patient did not know what this was or were too embarrassed to answer (information gleaned from nurses' calls). There were also some participants who stated that completing the questionnaires was very tiring, especially the length of the NBIS questionnaire, which we were hoping to validate; this again may have attributed to poor or indeed inaccurate completion. Moreover, the EQ-5D-5L[35] results indicated that, in both groups, MS symptoms worsened over the study period and this may have made it difficult to improve one symptom significantly. Following on from our analyses of the NBIS questionnaires' repeatability and criterion reliability, further work is needed to determine which questions truly reflect what is important to PwMS who have NBD.

Throughout the quantitative results, there is evidence of greater improvement in the intervention group when compared with the control group in the symptoms of incomplete evacuation, infrequency and reduced laxative use (and, therefore, side effects), which were also identified in the interviews. The sensation of incomplete evacuation is a symptom that is rated as very common and causes a lot of distress with > 90% of participants indicating that they were distressed:

> *Sometimes it would get so bad that I could hardly sit down because I was so bagged up and just couldn't go.*
>
> *PwMS13*

Data from the bowel diary indicated a significant benefit in this outcome [incomplete evacuation (mean change 1.08, 95% CI 0.41 to 1.76; $p = 0.002$, see *Table 19*)]. The response to the individual question in the CSS also indicated a benefit in this symptom (the percentage of participants in the intervention group who never felt incomplete evacuation increased from 6.7% at baseline to 15.5% at week 24, and in the control group this percentage decreased from 9.1% at baseline to 8.4% at week 24 (i.e. more participants in the intervention group improved). Those in the intervention group who always felt that there was incomplete evacuation decreased from 21.3% at baseline to 3.4% at week 24; in the control group, this percentage decreased from 20.2% at baseline to 10.8% at week 24. Moreover, the results of the transit study test identified that the markers in the intervention group moved more quickly to the distal colon, and so, if not triggering voiding, could potentially aid evacuation once defaecation was started. Change in stool type could also indicate a possible decrease in transit time with a move towards normal stool types 3 and 4. For example, one participant who mainly passed stool types 1 or 2 before the trial every 3 to 4 days or more stated:

> *It was just awful. I'd sit on the toilet for ages and ages and ages just knowing that I had to do something and it was painful.*
>
> *PwMS17*

By the second stage of interviews, however, she had a bowel movement of stool type 3 or 4 every day:

> *It's back to what it used to be years ago before the MS . . . really, really quite consistent.*
>
> *PwMS17*

The results of stool consistency in the main study as recorded in the bowel diary also indicated a greater percentage in the intervention group passing stool type 3 or 4 at week 6, as well as reporting less total constipation at both weeks 6 and 24 (see *Table 13*).

An increase in stool frequency was evident from the responses in the NBDS, the CSS score and from the bowel diary. This bowel diary outcome was significant ($p = 0.039$) and indicated an increase of 0.7 stools per week [adjusted change from pre treatment versus week 6 was 0.5 stools per week (SD 1.55 stools per week) in the intervention group and –0.2 stools per week (SD 1.64 stools per week) in the control group; pre treatment versus week 24 in the intervention group was 0.4 stools per week (SD 1.79 stools per week) and in the control group it was 0.2 stools per week (SD 1.62 stools per week)]. In addition, within the repeated-measures analysis, the change in frequency of defaecation was significant at week 6 (OR 0.56, 95% CI 0.03 to 1.10; $p = 0.039$); although this effect was decreased at week 24. It is, however, worth noting that at baseline the frequency of defaecation in the bowel diary was not that severe, with a mean of 3.9 times a week (SD 1.71) and the NBD mean score of 8.2 (SD 5.2), indicating low to medium levels of constipation; this was also supported in the CSS.

An episode of FI can have a devastating impact on a person's self-esteem and confidence, creating a reluctance to leave the house, and was described by one participant as an 'absolute nightmare' when it happens, especially if out of the house. FI may be frank and unexpected or may be attributable to the urgency created by the use of laxatives. There was no change in the frequency of FI episodes in the quantitative data, but participants in our qualitative study reported decreased episodes of FI and more confidence in leaving the house. Other reported benefits from doing the massage included feeling less bloated, clothing becoming looser and a decrease in sluggishness with reduced fatigue levels.

Adherence

According to the self-completed diary, which recorded the frequency of undertaking the massage, adherence to the massage intervention was good; 75% of participants administered the massage five times per week, although, interestingly, the vast majority were undertaking self-massage. At week 24, 66% of participants were continuing with the massage at least three times per week. In the qualitative interviews, participants reported that they practised the massage when it fitted into their routine and altered it according to effect, that is they did not necessarily do it every day. In fact, one person felt it to be too effective if undertaken every day.

The adherence to changing lifestyle, such as diet and exercise, was slightly greater in the control group, with 30% (20% in the intervention group) saying that they had made at least one lifestyle change. Such changes may have facilitated the changes reported within the control group. The overall uptake of the suggested modifications, supported and discussed at the weekly telephone calls, was perhaps lower than expected and is in contrast to what was reported in the qualitative interviews in which the participants said that they found the information to be helpful. To that end, discussing it with the nurse should have aided implementation in both groups. However, those in the control group were not interviewed (a limitation of the study), so there is no feedback as to how they felt about the delivery of the advice. It is a recognised feature that for some PwMS, the processing of such information is difficult and requires frequent, spaced reinforcement.

Who benefits and why?

Abdominal massage is thought to work by stimulating the bowel and decreasing the overall transit time; thus facilitating defaecation by the stronger propulsion of stools that are less hard and difficult to evacuate. Within our anorectal substudy, it was identified that 60% of this subgroup demonstrated slow transit; if we could extend this frequency of slow transit to the whole study group then it may, to some extent, explain why

the response was varied and less than expected. Patients may also have anorectal dyssynergia, which can make it difficult to pass stool; if this was the primary reason for their constipation, then abdominal massage would have little effect. However, slow transit and dyssynergia often coexist and, unfortunately, owing to poor uptake of the follow-up anorectal outcomes, we can only speculate and identify this as an area requiring further investigation. Given the small improvement in the primary outcome but not in terms of QALYs, a low-cost version of the intervention might be considered worthwhile by some patients. For example, it could be a part of a supported self-management pathway for NBD in PwMS.

Our data indicate consistently that the male participants reported better outcomes from the intervention. Although only a small group ($n = 14$ in the intervention group and $n = 21$ in the control group), the reasons behind these findings are unclear (see *Tables 18* and *19*). It may be that the male participants were stronger and less fatigued and undertook the massage more effectively. To date, we do not know the amount of force that is needed to be effective in stimulating the bowel. Within our qualitative study, a theme emerged around the adaptations made as a result of fatigue and difficulties actually doing the massage; yet there was also a theme that this was something PwMS wanted to do themselves, so as not to increase care burden, and a way of improving symptoms without taking medications. The amount of pressure and an assistive device to help with self-massage are potentially other avenues that should be explored. There was also some evidence that those with a slightly higher BMI, those who were slightly older, those who were less cognitively impaired and those with relapsing–remitting MS improved with the abdominal massage more than those with a lower BMI, who were younger, more cognitively impaired and did not have relapsing–remitting MS. Potentially, the older participants may be retired and have more time; however, why the slightly heavier people should improve more is difficult to explain.

Medication

Constipation was linked to laxative usage, which could also result in negative side effects. Interviewees reported that taking laxatives caused pain, sleeplessness, cramps and diarrhoea. The unpredictability of passing a stool when taking laxatives meant that a number of patients were afraid to leave the house once they had taken laxatives. From the analysis of laxative use, it would seem that those in the intervention group were more likely to reduce their laxative use. Participants' overall medication change was monitored and the number of medications seemed to change more in the control group; however, this was difficult to analyse as several participants had multiple changes and, in one instance, suppositories were individually mentioned. It was, however, interesting to see the history of the prescribing of laxatives, where it seemed to be the norm to increase the dose as well as prescribing additional laxatives within a short space of time.

This is an intervention for which we found no evidence of harm and which does not require extensive resources or training. There were a small number of AEs, none of which could be directly attributable to the massage. Moreover, this is the first time that the reduced training, to both clinicians and participants, was rolled out. In our earlier studies, those teaching the massage to the participants were experienced continence clinicians and the participants received weekly follow-up visits for support. In this trial, some of the clinicians had no experience of treating either bladder or NBD and only one had pre-trial experience with the massage. Feedback from clinicians was very supportive of the intervention and our recruitment is testimony to this. Some reported that further training may have been helpful and this is understandable if a 'hands-on' concept was new and also the lifestyle information was not within their usual scope (clinicians comprised MS nurses, continence nurses, a research nurse and one research assistant). However, as shown in our secondary and sensitivity analyses (see *Tables 18* and *19*), results were not significantly dependent on sites and the experience of the researchers.

If this intervention was to roll out within the NHS, then we suspect that it would depend on local services to facilitate staff training; yet, where these staff sit (e.g. the continence service or the MS nurse service) is undecided at the moment. Remarkably, there was no feedback from participants that they would have preferred more training or support with the massage. The interviews did highlight that, during the initial

training, some people preferred the massage to be administered over their clothes or on body parts other than their stomach. This may have affected how the staff member was able to deliver training, because the massage should be administered on the abdomen in order to allow the patient to gauge pressure. The clinicians interviewed all remained enthusiastic about the intervention, which influenced the mainly positive feedback participants were giving to them. Those used to treating PwMS recognised that interventions to treat the symptoms of NBD are scarce and that this could be a part of their 'toolkit', as an adjunct or perhaps instead of, for instance, laxatives, rectal irrigation, biofeedback, none of which is evidence based. Stakeholders also recognised that there was a definite need for additional treatment modalities and that this is a relatively cheap intervention if, after appropriate assessment and training, it is undertaken by the patient themselves or a carer. Additional resources may, however, be required should NHS employees be required to administer the massage routinely.

Limitations

There are several limitations in this study. The differential numbers recruited to our two groups (attributable to minimisation by centre) coupled with the additional numbers in the intervention group who failed to complete the study meant that we ended up with a smaller number in the intervention group than we had hoped. The extent of missing data and the reasons behind it have been explored but do not seem to be related to any predictable factors. One site, UCH, London, which undertook the anorectal physiology tests, had a slightly lower retention rate (76.9%); this may have been because of the invasive nature of these tests and the unwillingness of participants to return for follow-up. Royal Preston and the Walton Centre both had a retention rate of 81%, but no specific pattern for loss to follow-up could be identified as reasons were varied and appeared unconnected to the intervention (e.g. family illness, moving location).

It may also have been better to use more stringent inclusion/exclusion criteria, such as Rome III,[63] as some participants were not severely affected (according to the primary outcome measure) by their constipation and, therefore, had limited capacity to improve. These criteria had been used in a previous study by the authors, but were felt to be too stringent, focusing, as they do, on a clinical expert definition rather than a patient-based or a combined clinician–patient definition of constipation. Indeed, the suitability of the Rome III criteria for assessing symptoms of constipation has been challenged, as studies show that many patients who report constipation symptoms do not fulfil the Rome III criteria.[64–66] Patients' perception of 'bothersomeness' seemed to fit better. A large number of participants undertook the massage themselves, but because of their weakness and fatigue the effectiveness may have been reduced. Several participants in our qualitative study stated some difficulty self-massaging because of fatigue, but tried to work out a way around it by, for example, taking rests. However, for some participants, the massage was probably undertaken at a suboptimal level. Within our process evaluation study, owing to financial constraints, the interviews were only conducted with those who were undertaking the abdominal massage, which poses a limitation on our knowledge of the uptake of the advice and perceptions of taking part in the trial as part of the control group. The limitations in the economic evaluation have already been discussed in *Chapter 4*.

Future research

It would seem from the results of the RCT, the qualitative study and the health economic component that, similar to other studies, abdominal massage is effective on some patients. Most likely, these would be patients who have primarily slow transit (potentially 60% in this study). Therefore, future research should focus on identifying those with slow transit, which, as our anorectal substudy showed, is not easy to do using invasive tests. There have been attempts to validate questionnaires (e.g. Kess Questionnaire[66]) that may indicate which type of constipation a person has, that is slow transit and/or dyssynergia, and these should first be validated in a MS population and then used for possible screening of those with predominant slow transit constipation. In addition, the optimum frequency and, importantly, intensity of massage should be explored with use of pressure-sensitive devices and massage devices.

The following is a list of recommendations for future research:

- further mechanistic evaluation of NBD and ways of identifying those with predominantly slow transit
- further validation of the NBIS questionnaire
- development of a treatment algorithm that would aid clinicians in the treatment of NBD
- development and evaluation of a device to aid abdominal self-massage
- development and clinical trials of other interventions that may help with the symptoms of constipation/FI, for example the superfruit baobab, which has recently been developed into a drink, Baotic (Hippo & Hedgehog Ltd, Glasgow, UK).

Chapter 7 Conclusion

The benefits of using abdominal massage for the relief of symptoms in PwMS and NBD are not clearly demonstrated by the results of this methodologically high-quality trial. Moreover, there is uncertainty around cost estimates with domination by the control group. The research identified that, although the increment in the primary outcome favoured the intervention, it was not statistically significant. The analysis of the process evaluation component identified that most (15/20) participants reported benefit and felt it an attractive option as it was non-pharmacological and non-invasive. Feedback from clinicians teaching the massage was also positive, although in a few cases they expressed concern around the capability of the participant to do the massage effectively. Budget holders, albeit before the results of the trial were known, thought that the infrastructure and training required to introduce abdominal massage as an additional treatment option in this group of patients was implementable.

Based on the results of this programme of work, we believe that there are some PwMS and NBD who may benefit from undertaking abdominal massage as a low-cost, self-management intervention; the challenge is to identify these individuals and introduce it as part of a self-management bowel care pathway. Bowel dysfunction is not widely researched; there are fewer than 30 RCTs ($n = 1300$ participants)[16] published relating to all neurogenic bowel conditions.

Work such as this should be used to develop a treatment algorithm to facilitate better management of FI and/or constipation, thus improving the lives of patients and their carers.

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The AMBER trial group

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Contributions of authors

Professor Doreen McClurg (Chief Investigator and lead grant holder and member of the PMG/TSC) conceived the study and led on the protocol development, analysis and interpretation of the data, and drafting and submitting the final report.

Dr Fiona Harris (Associate Professor, grant holder and member of the PMG/TSC) led and supervised the process evaluation component of the trial and contributed to the analysis and drafting of the final report.

Dr Kirsteen Goodman (Trial Manager and member of the PMG/TSC) contributed to the running of the trial, data management, interpretation of results and drafting the final report.

Dr Selina Doran (Qualitative Researcher and member of the PMG/TSC) conducted the process evaluation data collection and analysis and contributed to drafting the final report.

Professor Suzanne Hagen [Interventions Programme Director (NMAHP RU), grant holder and member of the PMG/TSC] contributed to the study design, provided clinical expertise throughout the study and reviewed the final report.

Professor Shaun Treweek (Professor of Health Services Research, grant holder and member of the PMG/TSC) contributed to the study design, provided clinical trial expertise throughout the study and reviewed the final report.

Professor Christine Norton (Professor of Nursing, grant holder and member of the PMG/TSC) contributed to the study design, provided clinical expertise throughout the study and reviewed the final report.

Dr Maureen Coggrave (Research Fellow, grant holder and member of the PMG/TSC) contributed to the study design, provided clinical expertise throughout the study and reviewed the final report.

Professor John Norrie (Chair of Medical Statistics and Trial Methodology, grant holder and member of the PMG/TSC) contributed to the study design, provided clinical trial expertise throughout the study and reviewed the final report.

Miss Petra Rauchhaus (Trial Statistician at TCTU and member of the PMG and TSC) contributed to the trial analysis and reporting of results.

Professor Peter Donnan (Co-Director of TCTU, Senior Trial Statistician, grant holder and member of the PMG/TSC) led on the statistical aspect of the trial design and analysis of data, contributed to the drafting and review of the statistical sections of the final report.

Dr Anton Emmanuel (Senior Lecturer and Consultant Gastroenterologist, grant holder, member of the PMG/TSC and a PI) contributed to the study design and provided clinical expertise throughout the study and reviewed the final report.

Dr Sarkis Manoukian (Health Economist and member of the PMG/TSC) led on the health economic aspects of the trial design, interpretation of the data and drafting the health economic section of the final report.

Dr Helen Mason (Reader in Health Economics, grant holder and member of the PMG/TSC) led on the health economic aspects of the trial design, interpretation of the data and drafting of the health economic section of the final report.

Publication

McClurg D, Goodman K, Hagen S, Harris F, Treweek S, Emmanuel A, *et al.* Abdominal massage for neurogenic bowel dysfunction in people with multiple sclerosis (AMBER – Abdominal Massage for Bowel Dysfunction Effectiveness Research): study protocol for a randomised controlled trial. *Trials* 2017;**18**:150.

Data-sharing statement

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

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Massage training materials

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.

Abdominal Massage Quick reference guide

STEP 1 Stroke upwards to relax the abdominal muscles, in case of hiatus hernia or reflux stroke down.

STEP 2 Stroke from lumbar, to stimulate vagus nerve, which tells the bowel to wake up. Stroke from small of back, round and down inside of iliac crests, finish stroke at groin. Do ten strokes.

STEP 3 Effleurage (toothpaste stoke). Do this in a clockwise direction to stimulate bowel directions to move faecal matter Along. Do this stroke for two minutes.

Heart of Massage, the kneading helps to propel the faecal matter along the colon to load the rectum STEP 4

Palmar Kneading, Descending colon (down pipe) for 2 minutes.

STEP 5 Palmar kneading, up ascending colon (up pipe) for 2 minutes.

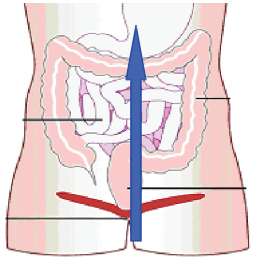
STEP 6 Repeat steps 4 (down pipe) for 2 minutes.

STEP 7 Repeat step 3 for further 2 minutes.

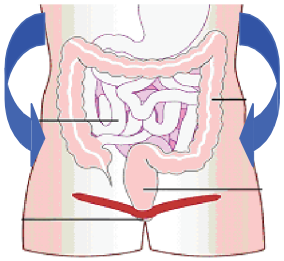
STEP 8 Stroking to relax abdominal muscles and to help body to know the massage is ending. Do this ten times.

STEP 9 Vibrations over umbilicus to relieve flatus (wind). Do this four times.

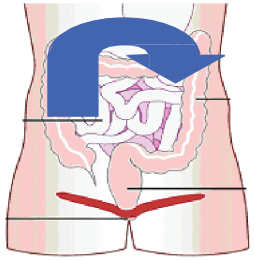
STEP 1 Stroke upwards to relax



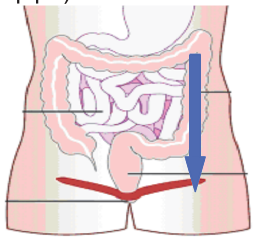
STEP 2 Stroke from lumbar, to stimulate vagus nerve (x10)



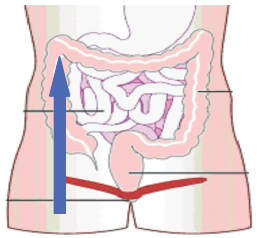
STEP 3 Effleurage (toothpaste stoke) for 2 minutes



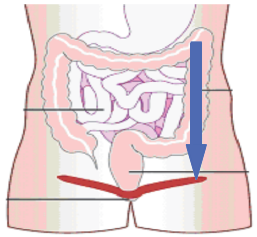
STEP 4 Palmar Kneading, Descending colon (down pipe) for 2 minutes



STEP 5 Palmar kneading, up ascending colon (up pipe) for 2 minutes

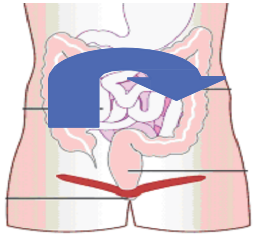


STEP 6 Repeat steps 4 (down pipe) for 2 minutes

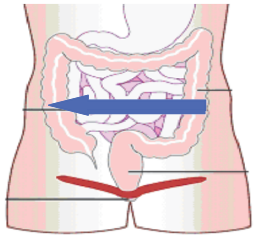


Abdominal Massage Quick reference guide

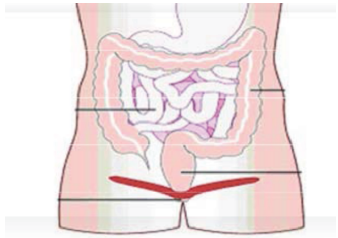
STEP 7 Repeat step 3 for further 2 minutes.



STEP 8 Stroking to relax (x10)



STEP 9 Vibrations over umbilicus (x4)



Appendix 2 Data Monitoring and Ethics Committee charter

AMBER Abdominal Massage for Bowel Dysfunction Effectiveness Research

Abdominal massage for neurogenic bowel dysfunction in people with multiple sclerosis

DATA MONITORING AND ETHICS COMMITTEE CHARTER

Funder number	12/127/12
REC number	14/WS/0111
ISRCTN	**85007023**

Authorised by:

Name: Dr. Chris Sutton Role: DMC Chair

Signature: [redacted] Date: 21st May 2015

Prepared by:

Name: Dr Doreen McClurg Role: Chief Investigator

Signature: [redacted] Date: 21ST MAY 2015

1.Introduction

The AMBER trial is funded by the NIHR HTA. Research Ethics Committee approval has been given by West of Scotland (ref. no. 14/WS/0111). The sponsors of the study are Glasgow Caledonian University. AMBER trial has been registered on Current Controlled Trials (www.controlled-trials.com, ISRCTN). The Trial Office is located in Glasgow at the NMHAP Research Unit, Glasgow Caledonian University, Glasgow.

1.1.*Trial Objectives*

AMBER is a randomised controlled clinical trial to compare intervention versus no intervention in clinical practice.

1.2.*Scope*

The purpose of the document is to describe the roles and responsibilities of the independent DMEC for the AMBER trial, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other committees.

1.3.*Facilitation*

The AMBER trial manager will be nominated as a facilitator for the committee. The Facilitator will be responsible for the organisation of the meetings. A summary of each DMEC meeting will be sent to the trial manager for information.

2.Roles and responsibilities

2.1.*Aims of DMEC*

To safeguard the interests of the trial participants, assess the safety and efficacy of the interventions during the trial and monitor the overall conduct of the clinical trial.

2.2.*Terms of reference*

The role of the DMEC is to receive and review information on the progress of recruitment and accruing data of this trial, and to provide advice to the Trial Steering Committee (TSC).
The DMEC should inform the Chair of the TSC if, in their view:

i) The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.
ii) There are significant concerns about patient safety in either arm of the trial.

2.3.*Specific roles of DMEC*

The DMEC's role will include, but not be restricted to, the following:

- monitor recruitment rate and loss to follow up rate
- assess data quality, including completeness of data collection
- define the timing and nature or interim analyses required
- monitor evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (eg SAEs, deaths, complication rates)
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- suggest additional data analyses
- monitor planned samples size assumptions
- monitor continuing appropriateness of patient information
- assess the impact and relevance of external evidence

6. Organisation of meetings

6.1. ***Frequency***

The DMEC will meet approximately yearly or more often if the DMEC considers it necessary to do so.

6.2. *Attendance*

Effort will be made to ensure that all members can attend. The CI and trial statistician will attend at the request of the Chair. Members who cannot attend in person should be encouraged to participate by teleconference. If, at short notice, any DMEC members cannot attend then the DMEC may still meet if at least two independent members, including the Chair (unless otherwise agreed), will be present. If the DMEC is considering a major action after such a meeting the DMEC Chair should communicate with the absent members, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMEC.

The meeting report will be circulated at least one week before the meeting in order to enable DMEC members who will not be able to attend the meeting to pass comments for consideration during the discussions at the meeting to the DMEC Chair.

6.3. *Independent members who fail to attend meetings*

If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they should be asked if they wish to remain part of the DMEC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member.

6.4. *Resignation and replacement of independent members due to change in circumstances*

If an independent Committee member's circumstances change (e.g. if he/she moves job to the same institution as the CI) he/she would resign from the committee. A replacement independent member would be identified and appointed.

7.Trial documentation and procedures to ensure confidentiality and proper communication

7.1. *Material to be considered during meetings*

The statistician will provide a report to the DMEC including data to be specified by the DMEC and a short report regarding recruitment progress and any management issues will be prepared by the central coordinating office. This will report on accrual against time and target and any matters affecting the trial.

As a minimum the following information will be reviewed:

- Recruitment to time and target
- A list of reported SAEs
- Any new, relevant or possibly relevant publications identified by the Trial Office
- Interim analyses as specified by the DMEC

7.2. *Accumulating data*

The accumulating study data by arm and interim analyses will be confidential. These will be available to the DMEC. The DMEC will make recommendations in writing to the TSC based on the interim data.

7.3. *Retention of papers after the meeting*

The Chair of DMEC will keep a central record of all minutes, reports and correspondence by the DMEC. Summary reports will be sent to the TSC and Trial office, with any appropriate recommendations. DMEC members will be expected to securely and confidentially retain minutes and reports until the end of the trial. After completion of the trial, confidential DMEC

documents will be archived centrally with the other trial documentation. DMEC member will then delete, or destroy copies of the reports to and from the DMEC, agenda and minutes, as well of copies of communications between meetings. All documentation should be considered confidential.

8. Decision making

8.1 *Possible DMEC recommendations*

Based on review of interim analyses by the DMEC, the possible recommendations to the DMEC could include:-

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, or external evidence
- Stopping recruitment within a subgroup
- Requesting an additional interim analysis

The DMEC may recommend unblinding of the TSC to outcome data if a recommendation to stop the trial or recruitment to a subgroup is made.

8.2. *Analysis*

The DMEC should review and agree any interim analysis plan at their first meeting.

8.3. *DMEC decision making methods*

The role of the Chair is to summarise discussions and encourage consensus; therefore, it may be best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical and financial) for the trial be considered before any decision is made.

8.3. *When the DMEC is quorate*

At least two independent members of the DMEC should be present including the Chair, plus a representative of the trials unit and, if major action is to be considered, the CI.

8.4. *Voting rights*

If a vote is required, all independent members will have a full vote. In addition the CI, or appropriate deputy if CI is unable to attend the meeting, may also vote. In the event of a tied vote, the independent DMEC Chair will have the casting vote.

9. Reporting

9.1 *Communication of DMEC recommendations*

Reports of meetings will be sent to the Chair of the Trial Steering Committee within three weeks of each meeting. A copy will be lodged with the trial office, and also sent to the Chief Investigator. Minutes of the meetings will be kept and signed off by the Chair after each meeting.

A meeting of the TSC will be convened within a few weeks of receipt of the report, to discuss recommendations made by the DMEC. A copy of the minutes of that meeting will be sent back to the Chair of the DMEC.

9.2. *Conflict resolution with other study Committees*

If the DMEC has serious problems or concerns with the TSC decision made in response to the DMEC report, a meeting of both committees should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting.

The meeting would be chaired by a senior member of the central Trial Office or an external expert who is not directly involved with the trial.

10. After the trial

10.1 *Publication of results*

At conclusion of the trial, a copy of the final analysis will be proviced to the DMEC chair. He may convene a final meeting of the committee to review this. Names and affiliations of the DMEC members will be included in the trial protocol and the final report. The details of the trial conduct, the results, and the members' involvement in the trial shall remain confidential until 12 months after publication of the final report.

There may be a meeting to allow the DMEC to discuss the final data with the writing committee to give advice about data interpretation.

10.2. *DMEC acknowledgement in publications*

DMEC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.

Annexe 1: Agreement and competing interests form for independent members

AMBER Data Monitoring and Ethics Committee: Agreement to join the AMBER Trial Data Monitoring and Ethics Committee as an independent member and disclosure of potential competing interests.

Please complete the following document and return to the DMEC Facilitator
(Please initial box to agree)

☐ I have read and understood the DMEC Charter version 1.0, 25th August 2014.

☐ I agree to join the Data Monitoring Ethics Committee for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a DMEC may be biased in some fashion is important for the credibility of the decisions made by the DMEC and for the integrity of the trial.

Potential competing interests should be disclosed via the DMEC facilitator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent DMEC member should remove the conflict or stop participating in the DMEC. **Table 1** lists potential competing interests.

☐ **Yes,** I have potential competing interests to declare (please detail below)

☐ **No,** I have no potential competing interests to declare

Please provide details of any potential competing interests:

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for independent members

Stock ownership in any commercial companies involved
Stock transaction in any commercial company involved (if previously holding stock)
Consulting arrangements with the Sponsor/Funder
Ongoing advisory role to a company providing drugs and devices to the trial
Frequent speaking engagements on behalf of the intervention
Career tied up in a product or technique assessed by trial
Hands-on participation in the trial
Involvement in the running of the trial
Emotional involvement in the trial
Intellectual conflict e.g. strong prior belief in the trial's experimental arm
Involvement in regulatory issues relevant to the trial procedures
Investment (financial or intellectual) or career tied up in competing products
Involvement in the writing up of the main trial results in the form of authorship

Note: This DMEC charter was developed using MRC CTU template DMEC Charter version 2.01, 13-Mar-2006

Appendix 3 Site and recruitment information

Site	Type of facility	Governing body	Target, *n*	Participants recruited, *n* (% met)	Retention, *n* (%)	Trial group, *n* (%)		HCPs involved	Current bowel treatments offered
						Abdominal massage	Standard care		
Anne Rowling Clinic, Edinburgh	Neurological research facility	NHS Lothian Health Board	10	9 (90)	9 (100.0)	4 (4.4)	5 (5.1)	Consultant neurologist	None. This site is focused more on advancing MS research
John Radcliffe Hospital, Oxford	Tertiary teaching and research hospital	Oxford University Hospitals NHS Foundation Trust	20	17 (85)	15 (88.2)	9 (10.0)	8 (8.1)	MS specialist nurse and research nurse	Bowel problems are underrecognised and only referred to the bowel specialist nurse when explicitly raised
St Mary's Hospital, Leeds	Community health-care service	Leeds Community Healthcare NHS Trust	10	10 (100)	10 (100.0)	4 (4.4)	6 (6.1)	Bowel specialist nurse and research nurse	Specialised bowel clinics and home visits for those with constipation, FI and irritable bowel dysfunction
Lincoln County Hospital, Lincoln	District general hospital	United Lincolnshire Hospitals NHS Trust	10	13 (exceeded by $n = 3$)	13 (100.0)	7 (7.8)	6 (6.1)	Consultant neurologist and research nurses	Advice from a MS specialist nurse
Northampton General Hospital, Northampton	General, specialist and teaching hospital	Northampton General Hospital NHS Trust	20	14 (70)	12 (85.7)	7 (7.8)	7 (7.1)	Research and Development team, research nurse and MS nurse specialist	Home visits and a bladder and bowel clinic, with bladder specialist nurse and bowel specialist nurse
Royal Hallamshire Hospital, Sheffield	Clinical research facility	Sheffield Teaching Hospitals NHS Trust	10	17 (exceeded by $n = 7$)	16 (94.1)	8 (8.9)	9 (9.1)	Research sister, clinical research nurse and consultant neurologist	Laxatives and diet advice in neurology department
Royal Preston Hospital, Preston	District general hospital	Lancashire Teaching Hospitals NHS Foundation Trust	20	22 (exceeded by $n = 2$)	18 (81.0)	10 (11.1)	12 (12.1)	Senior research nurse and neurologist	Laxatives, digital stimulation, medication and self-administration of enemas
Royal Victoria Infirmary, Newcastle upon Tyne	Tertiary teaching hospital	Newcastle upon Tyne NHS Foundation Trust	20	17 (85)	16 (94.1)	8 (8.9)	9 (9.1)	Consultant (50% neurology, 50% MS) and research nurse	MS patients only get to see the bowel specialist in Newcastle upon Tyne if there is a significant problem
Salford Royal Hospital, Salford	General, specialist and teaching hospital	Salford Royal Hospital NHS Foundation Trust	20	15 (75)	14 (93.3)	7 (7.8)	8 (8.1)	Research officer and senior research nurse	Dietary advice from MS specialist nurses. If bowel problems continue, they refer PwMS to colorectal specialists

Site	Type of facility	Governing body	Target, *n*	Participants recruited, *n* (% met)	Retention, *n* (%)	Trial group, *n* (%)		HCPs involved	Current bowel treatments offered
						Abdominal massage	Standard care		
Southern General Hospital, Glasgow	Tertiary referral centre	NHS Greater Glasgow and Clyde Health Board	20	20 (100)	18 (90.0)	10 (11.1)	10 (10.1)	Health-care support worker, MS nurse and consultant neurologist with specialist interest in MS	MS team can refer to gastroenterology department for them to investigate the problem and offer medication
The Walton Centre, Liverpool	Neuroscience centre	The Walton Centre NHS Foundation Trust	20	11 (55)	9 (81.8)	5 (5.6)	6 (6.1)	Consultant neurologist and research nurse	Bowel issues are discussed in multidisciplinary clinic and bowel management advice is given
UCH, London	National referral and teaching hospital	University College London Hospitals NHS Foundation Trust	30	26 (87)	20 (76.9)	11 (12.2)	13 (13.1)	Bowel management specialist nurse and gastroenterologist consultant	This is a specialist bowel centre. Sustainable provision for those with lower bowel conditions: irrigation feedback, pelvic floor physiotherapy, tailored drug regimes, irrigation therapy, surgery and diet advice

Appendix 4 Differences in characteristics of missing Neurogenic Bowel Dysfunction Score at 24 weeks compared with complete data

Variable	NBDS at week 24, *n* (%)		
	Present	Not present	Total, *n* (%)
Intervention			
Abdominal massage	72 (44.4)	18 (66.7)	90 (47.6)
Standard care	90 (55.6)	9 (33.3)	99 (52.4)
Total	162 (100.0)	27 (100.0)	189 (100.0)
Centre			
Southern General Hospital, Glasgow	18 (11.1)	2 (7.4)	20 (10.6)
Royal Victoria Hospital, Newcastle upon Tyne	15 (9.3)	2 (7.4)	17 (9.0)
UCH, London	18 (11.1)	6 (22.2)	24 (12.7)
Royal Preston Hospital, Preston	14 (8.6)	8 (29.6)	22 (11.6)
The Walton Centre, Liverpool	9 (5.6)	2 (7.4)	11 (5.8)
John Radcliffe Hospital, Oxford	15 (9.3)	2 (7.4)	17 (9.0)
St Mary's Hospital, Leeds	10 (6.2)	0 (0.0)	10 (5.3)
Lincoln Community Hospital, Lincoln	13 (8.0)	0 (0.0)	13 (6.9)
Salford Royal Hospital, Salford	14 (8.6)	1 (3.7)	15 (7.9)
Royal Hallamshire Hospital, Sheffield	16 (9.9)	1 (3.7)	17 (9.0)
Northampton General Hospital	11 (6.8)	3 (11.1)	14 (7.4)
Anne Rowling Centre, Edinburgh	9 (5.6)	0 (0.0)	9 (4.8)
Total	162 (100.0)	27 (100.0)	189 (100.0)
Minimisation criterion			
Walking unaided	66 (40.7)	13 (48.1)	79 (41.8)
Aided walking	76 (46.9)	13 (48.1)	89 (47.1)
Wheelchair bound	20 (12.3)	1 (3.7)	21 (11.1)
Total	162 (100.0)	27 (100.0)	189 (100.0)
Sex			
Male	31 (19.1)	4 (14.8)	35 (18.5)
Female	131 (80.9)	23 (85.2)	154 (81.5)
Total	162 (100.0)	27 (100.0)	189 (100.0)

Differences in continuous characteristics of missing Neurogenic Bowel Dysfunction Score at 24 weeks compared with complete data

Variable	NBDS at week 24		Total
	Present	Not present	
Total NBDS at baseline			
Complete, *n*	155	25	180
Missing, *n*	7	2	9
Mean (SD)	8.1 (5.1)	8.3 (6.0)	8.2 (5.2)
Median (minimum, maximum)	8.0 (0, 22)	6.0 (1, 22)	7.5 (0, 22)
Age (years)			
n	162	27	189
Missing, *n*	0	0	0
Mean (SD)	52.8 (10.7)	49.4 (11.3)	52.3 (10.8)
Median (minimum, maximum)	52.0 (26, 79)	48.0 (32, 70)	51.0 (26, 79)
Time since diagnosis of MS (years)			
n	162	27	189
Missing, *n*	0	0	0
Mean (SD)	14.4 (9.4)	14.1 (8.1)	14.3 (9.2)
Median (minimum, maximum)	13.0 (0, 51)	14.0 (1, 32)	13.0 (0, 51)
BMI			
n	157	25	182
Missing, *n*	5	2	7
Mean (SD)	26.7 (5.9)	27.3 (5.8)	26.8 (5.9)
Median (minimum, maximum)	25.8 (14.7, 48.8)	26.5 (19.8, 43.9)	25.9 (14.7, 48.8)

Appendix 5 Summary of stool type (Bristol stool chart information)

Time point	Trial group (%)	
	Intervention	Control
Baseline		
No stool	39.8	40.1
Types 1 and 2	21.8	18.9
% constipated	61.6	59.0
Types 3 and 4	20.2	17.5
Types 5, 6 and 7	16.0	19.6
Missing	2.3	3.8
Week 6		
No stool	35.0	38.8
Types 1 and 2	22.4	19.0
% constipated	57.4	58.2
Types 3 and 4	29.9	23.6
Types 5, 6 and 7	11.4	14.6
Missing	0.9	2.4
Week 24		
No stool	32.0	41.4
Types 1 and 2	23.4	17.5
% constipated	55.4	58.9
Types 3 and 4	23.9	22.8
Types 5, 6 and 7	15.5	12.0
Missing	5.0	5.7

Appendix 6 Summary of all adverse events

Variable	Trial group, *n* (%)		Total, *n* (%)
	Intervention	Control	
Severity			
Mild	10 (35.7)	26 (46.4)	36 (42.9)
Moderate	14 (50.0)	23 (41.1)	37 (44.0)
Severe (not serious)	4 (14.3)	7 (12.5)	11 (13.1)
Total	28 (100.0)	56 (100.0)	84 (100.0)
Causality			
Unrelated	25 (89.3)	54 (96.4)	79 (94.0)
Possibly related	3 (10.7)	2 (3.6)	5 (6.0)
Total	28 (100.0)	56 (100.0)	84 (100.0)
Action taken			
None	14 (50.0)	22 (39.3)	36 (42.9)
Hospitalisation	2 (7.1)	4 (7.1)	6 (7.1)
Medication(s) commenced	6 (21.4)	23 (41.1)	29 (34.5)
Other	2 (7.1)	2 (3.6)	4 (4.8)
Hospitalisation/medication(s) commenced	1 (3.6)	3 (5.4)	4 (4.8)
Intervention reduced/other	1 (3.6)	0 (0.0)	1 (1.2)
Medication(s) commenced/other	2 (7.1)	0 (0.0)	2 (2.4)
None/other	0 (0.0)	2 (3.6)	2 (2.4)
Total	28 (100.0)	56 (100.0)	84 (100.0)
Outcome			
Recovered	17 (60.7)	37 (66.1)	54 (64.3)
Ongoing	11 (39.3)	19 (33.9)	30 (35.7)
Total	28 (100)	56 (100)	84 (100.0)

Summary of serious adverse events

SAE	Trial group (*n*)		Total (*n*)
	Intervention	Control	
Breast cancer	1	0	1
Cholecystitis	0	1	1
Fall	1	0	1
Femoral neck fracture	0	1	1
Localised infection	0	1	1
MS relapse	1	1	2
Myocardial infarction	0	1	1
UTI	0	1	1

Appendix 7 Cost-effectiveness analysis of abdominal massage versus standard care

Measurement	MI with a seemingly unrelated regression model	Mixed model
Difference in costs (£)		
Mean	50.02	77.54
SE	156.84	143.8
Difference in QALYs		
Mean	–0.002	0.0026
SE	0.012	0.011
ICER (£ per QALY)	–19,392.89	28,722.05
Probability of cost-effectiveness at £20,000 per QALY gained (%)	37	46.6

Appendix 8 Frequency of health-care contacts, by trial group, at baseline

	Trial group (*n*)			
	Intervention group		Control group	
Service used	BR	HR	BR	HR
GP at surgery	0	5	0	6
Nurse at surgery	0	2	0	0
GP on the telephone	0	1	1	4
Nurse on the telephone	0	0	1	2
GP at home	0	0	0	0
Nurse at home	3	0	1	0
Out-of-hours clinic	0	0	0	0
Outpatient department	1	3	2	6
Admitted to hospital	0	0	0	0
A&E visit	0	0	0	0
Allied Health Professionals	0	8	0	9
Continence Service	0	0	1	1

A&E, accident and emergency; BR, resource use for bowel problems; HR, resource use for health problems other than bowel problems.

Note

Data include all participants who participated in the trial at baseline. There are 90 participants in the intervention group and 99 in the control group.

Frequency of health-care contacts, by trial group, recorded at week 6

	Trial group (*n*)			
	Intervention group		Control group	
Service used	BR	HR	BR	HR
GP at surgery	1	15	1	
Nurse at surgery	0	7	0	
GP on the telephone	1	7	1	
Nurse on the telephone	6	7	11	4
GP at home	0	0	0	1
Nurse at home	10	2	5	0
Out-of-hours clinic	0	0	0	2
Outpatient department	4	13	1	
Admitted to hospital	0	2	1	5
A&E visit	0	0	0	1
Allied Health Professionals	2	41	0	
Continence Service	3	2	0	2

A&E, accident and emergency; BR, resource use for bowel problems; HR, resource use for health problems other than bowel problems.

Note

Data include all participants who participated in the trial at week 6. There were 60 participants in the intervention group and 84 in the control group.

Frequency of health-care contacts, by trial group, recorded at week 24

	Trial group (*n*)			
	Intervention group		Control group	
Service used	BR	HR	BR	HR
GP at surgery	7	29	7	42
Nurse at surgery	4	15	1	27
GP on the telephone	7	18	2	20
Nurse on the telephone	12	0	3	9
GP at home	1	2	1	9
Nurse at home	6	7	14	10
Out-of-hours clinic	0	0	0	3
Outpatient department	3	20	4	40
Admitted to hospital	1	6	1	8
A&E visit	1	1	0	4
Allied Health Professionals	8	27	14	73
Continence Service	3	3	5	7

A&E, accident and emergency; BR, resource use for bowel problems; HR, resource use for health problems other than bowel problems.

Note

Data include all participants who participated in the trial at week 24. There were 58 participants in the intervention group and 83 in the control group.

Total frequency of health-care contacts, by trial group, excluding baseline

	Trial group (*n*)			
	Intervention group		Control group	
Service used	BR	HR	BR	HR
GP at surgery	8	44	8	60
Nurse at surgery	4	22	1	42
GP on the telephone	8	25	3	32
Nurse on the telephone	18	7	14	13
GP at home	1	2	1	10
Nurse at home	16	9	19	10
Out-of-hours clinic	0	0	0	5
Outpatient department	7	33	5	67
Admitted to hospital	1	8	2	13
A&E visit	1	1	0	5
Allied Health Professionals	10	68	14	117
Continence Service	6	5	5	9

A&E, accident and emergency; BR, resource use for bowel problems; HR, resource use for health problems other than bowel problems.

Note

Data include all participants who participated in the trial excluding baseline. There were 60 participants in the intervention group and 84 in the control group.

Appendix 9 NHS unit costs

Service	Unit cost (£)	Reference
GP at surgery	44	PSSRU
Nurse at surgery	16	PSSRU
GP on the telephone	27	PSSRU
Nurse on the telephone	5	PSSRU
GP at home	114	PSSRU
Nurse at home	47	PSSRU
Out-of-hours clinic	66	PSSRU
Outpatient department	117	DHSC reference costs[41]
Admitted to hospital	1609	DHSC reference costs[41]
A&E visit	138	DHSC reference costs[41]
Allied Health Professionals	24	PSSRU
Continence (Hospital) Service	108	PSSRU

A&E, accident and emergency; DHSC, Department of Health and Social Care; PSSRU, Personal Social Services Research Unit.
Notes
Admitted to hospital refers to the cost of an average impatient stay as estimated in the PSSRU. The cost of £1609 was applied to each case of hospitalisation assuming an average inpatient stay.

Resource-use NHS costs per participant, by trial group, at baseline

	Trial group (£)	
Summary statistics	Intervention	Control
Mean cost per participant	14.59	17.73
Standard error	4.12	5.12
SD	35.41	48.82
95% CI	6.39 to 22.80	7.56 to 27.89
t-test on the equality of means	0.46	

Notes
Data include all participants who participated in the trial. There were 90 participants in the intervention group and 99 in the control group at baseline. See *Table 31* for NHS services included in these calculations.

Resource-use NHS costs per participant, by trial group, at 6 weeks

	Trial group (£)	
Summary statistics	Intervention	Control
Mean cost per participant	120.65	186.78
Standard error	38.01	52.36
SD	299.29	485.60
95% CI	82.67 to 290.89	82.67 to 290.89
t-test on the equality of means	0.95	

Notes
Data include all participants who participated in the trial. There were 60 participants in the intervention group and 84 in the control group at week 6. Reported contact with NHS services from baseline to 6 weeks. See *Table 31* for NHS services included in these calculations.

Resource-use NHS costs per participant, by trial group, at 24 weeks

	Trial group (£)	
Summary statistics	Intervention	Control
Mean cost per participant	312.14	313.18
Standard error	104.45	65.90
SD	795.49	600.41
95% CI	102.98 to 521.30	182.08 to 444.28
t-test on the equality of means	0.01	

Notes
Data include all participants who participated in the trial. There were 58 participants in the intervention group and 83 in the control group at week 24. Reported contact with NHS services from 6 weeks to 24 weeks. See *Table 31* for NHS services included in these calculations.

Appendix 10 Roles of health-care professionals interviewed

Type of interviewee	Interviewees in total (*n*)	Interviewed in first stage (*n*)	Interviewed in second stage (*n*)
Principal investigator	6	6	2
Research nurse (including those in senior positions)	7	6	6
General nurse	1	1	1
MS specialist nurse	3	3	3
Health-care support worker	1	0	1
Bowel management specialist nurse	2	2	2
Research co-ordinator/officer/assistant	5	5	4

Stakeholders selected for interview

Type of organisation	Aim of organisation	Interviewees (*n*)	Expertise of interviewees
MS charities	Support and resources for PwMS	2	Policy and research
Incontinence foundations	Supporting people with continence problems; developing educational and commissioning guidelines	3	Continence service provision; commissioning
NHS Specialist Commissioner	Commissioning support for neurology services in the NHS	1	Neurology expertise; policy and research

Appendix 11 Topics discussed during interviews

Intervention group

First stage at week 4	Second stage at end of study
Personal experiences with MS and bowel problems	Issues faced during first stage
Recruitment into trial	Trial paperwork
Massage training	Weekly nurse calls
Weekly nurse calls	Any other challenges to lifestyle
Trial paperwork	Impact of massage on bowel problems
Administering massage	Unexpected health benefits of massage
Initial impact of massage on bowel problems	Post-trial intentions with the massage
Any problems	Any problems
Advice for other participants/staff members	Advice for other participants/staff members

Health-care professionals

First stage	Second stage
Training delivered by the AMBER trial team	Issues faced in first stage
Recruiting participants	Participant recruitment (target met or not)
Training participants in massage	Training participants in massage
Dealing with control group participants	Dealing with control group participants
Participant follow-up (weekly calls)	Participant follow-up (weekly calls)
Current treatment options at the site	Any problems faced/advice for other sites
Other policy and clinical developments at the site	Implementing the treatment long term
Any problems faced/advice for other sites	Any problems faced/advice for other sites

Stakeholders

- The organisation's role in neurological and/or incontinence services.
- Current policy developments in this area (local, regional and national).
- Current treatment options for bowel problems, particularly neurogenic ones.
- Whether or not there is a need for an additional treatment option.
- The long-term implementation of abdominal massage and any challenges involved.

Appendix 12 Process evaluation interview schedules and site questionnaire

Includes:

- draft interview schedule – participant interviews (first stage)
- interview schedule – participant interviews (second stage)
- interview schedule – stakeholder interviews
- draft interview schedule – HCP site interviews (first stage)
- draft interview schedule – HCP site interviews (second stage)
- six-month site-tracking questionnaire.

Draft Interview Schedule: Participant Interviews (First Stage)

Introduction to the project

1.I'd like to start by finding out a little bit about you (sets context).

Please could you tell me about your life:

Where do you live? Who do you live with?

Are you employed, unemployed or retired? If unemployed or retired, what was your previous occupation?

2.I would now like to move on to discuss your health.

Could you tell me a little about your health:

How long ago were you first diagnosed with MS? Which type of MS do you have and has this always been the case (i.e. it might have progressed into another type)? What impact does this have on you physically (mobility issues, visual, bowel/bladder, fatigue, numbness) and emotionally (cognitive issues, depression, mood swings)?

How do you manage your symptoms (e.g. gentle exercise, sleep patterns, diet, medication, bladder/bowel strengthening exercises)? Have you ever used any non-abdominal form of massage? If so, did this elevate your symptoms and how was this treatment administered (self, carer, nurse)? If not, why not, and would they consider having any non-abdominal massages post-AMBER?

Do you go to any support groups (charities, community groups, friends) relating to MS?

If any experience with bowel problems: You mentioned earlier that you had problems with your bowel – could you expand on this, explaining the difficulties you face and the impact this has on your life?

3.I would like to explore your previous knowledge of abdominal massage

Before you signed up to the AMBER trial, what did you know about abdominal massage as a form of treatment for bowel problems and have you ever used it before the AMBER trial?

If little knowledge and experience, then what are your thoughts on it as a way of managing bowel problems? Is this preferable over alternative forms of treatment (e.g laxatives)?

If knowledge but no experience, then why did you never use it as a form of treatment – perhaps alternative methods were used?

If knowledge and experience, how has AMBER differed from previous massages? Did you find the other abdominal massages worked and, if so, what encouraged you to sign up for AMBER?

4.Now I would like to find out a bit about your experience of taking part in AMBER.

Let's start from the beginning. How did you find the process of recruitment? How did you feel about the treatment before attending your baseline appointment? Did anyone (e.g. relative, friend) attend the baseline appointment with you? Was everything clearly explained to you at the baseline appointment? Is there any way this could be improved?

How was the AMBER training administered and by whom? How do you feel the training went – was everything clearly explained and did you feel you had a clear understanding by the end of it? Is there any way this could be improved?
Will you be administering the massage yourself at home or will someone else? If yourself, how confident were you after the baseline appointment – has this changed at all? If someone else, did they attend the massage training? If yes, do they feel confident after the training? Did they have any suggestions for improvement?

5.I now would like to look at expectations of AMBER when agreeing to take part in the trial.

Why did you sign up for the AMBER study (i.e. expectations about outcomes)? Was anything different to what you expected? Did these outcomes change at any point during the study (baseline appointment, training, after that)?

6.Could we now discuss how you have been getting on with the abdominal massage.

[Based on response to question 4 about who is administering it]: how often have you/they been do this? Do you/they do this at a set time or whenever is convenient? How long does the massage and setting up/winding down take? Is this similar to your other forms of symptom management (i.e. has it been incorporated into a daily routine or is it burdensome)?
Have you altered the massage at all to suit your needs (e.g. using fists to combat fatigue)? Do you feel you/they have a good grasp of the technique? How motivated are you to carry out the massage? Do you have any support when doing the massage or to chat to people about the massage (e.g. local support groups, carer)?

7.May we now discuss whether you have experienced any benefits of doing the massage?

Have you seen an improvement in your bowel functions? If so, in what way (passing stools more frequently and easily)? If not, why do you think this is the case (.e.g. massage not administered correctly, diet, medication, any other factors)?
Have there been any other unexpected benefits (e.g. decreased use of laxatives, more confidence, other physical symptoms)? What impact has this had on your life (e.g. able to go out more, able to eat more, able to engage in another activity like exercise without feeling bloated)?

8.Have you experienced any problems in doing the massage?

[Based on response to question 7 about their success so far with the massage] Have you/they encountered any problems when carrying out the massage? If so, what was the main issue (e.g. pressure to apply, fatigue (if themselves), timing of steps, confusion about massage)? Did you/they devise any solutions to deal with this?
If not, did you believe there would be any problems (e.g. see those above) before undertaking the treatment and, if so, what were related to? Why do you think this has problem has not arisen (e.g. good grasp/adaption of technique, found the right amount of pressure, etc.)? Would you recommend that intervention staff at other sites adopt this lesson in their training?

9.We hope that if AMBER works well for patients, that we might roll this out more widely to help others. Based on your experience so far, is there anything that we could do better?

You have summarised your experience with AMBER so far, is there anything that could be done differently to improve it (e.g. information leaflets provided, training with intervention team, DVD and other training materials, providing more support during the process – telephone calls with nurses in particular, provisions for visual problems and other disabilities)?
Do you think there is anything in particular that could improve the experience for patients who are of a similar age group, as well as the same gender and employment status, as yourself? [Captures demographic details – perhaps there will be different requirements for younger employed females, for instance, compared to older, retired males]

10.Lastly, is there anything that we could do to encourage more MS patients to take part in AMBER?

Earlier we discussed why you were motivated to sign up for AMBER – do you think those reasons would encourage other people with MS to do the same? If not, why not? Do you think there is a way to tackle this issue (e.g. be clearer about what the study involves, provide more incentives to take part)?
[If they stated they keep in touch with other MS patients in their answer to question two] Did you tell your friends/group members about your participation in AMVBER? If so, what were their thoughts about it? Did you try to encourage them to sign up? If not/they declined, why was this the case (do not meet criteria, not enough support in place, unsure about study)? What about motivation during the study: did you feel engaged and motivated throughout the process? If not, why not (e.g. not enough support, difficulties with massage, etc.)? If this was the case, why did you refrain from dropping out? What would you suggest to encourage completion from other MS patients?

For those interviewed who have 'dropped out'/not completed:
Ask questions 1-5 (modifying as appropriate to their responses) then follow with:
11.I understand that you withdrew early from the study. We would like to learn from you what might have put you off and what we might be able to do better.

Could you please explain why you dropped out the study (e.g. personal reasons, lack of time, problems with study)? If personal/unrelated to study, is there anything AMBER could have done to help you with this? Have you got adequate support in place to deal with this issue? [This is where a recommendation to a support centre for advice might come in]

If directly related to the study, follow up on why they did not feel motivated and engaged with the process: What would have helped with your motivation? How could the level of support provided been improved? What would you recommend to avoid making the same mistakes with future patients of AMBER?

Thank you for your time – we value your input.

Interview Schedule: Participant Interviews (Second Stage)

Pre-amble to the second stage: it will assess what was said in the first stage to see if anything has changed and also to get an overview of their experience with AMBER now they have reached the 24 week stage.

1.I would like to start by looking at your expectations of AMBER when agreeing to take part in the trial.

Why did you sign up for the AMBER study (i.e. expectations about outcomes)? [Add details from first stage about extent of bowel problems.]

Did these outcomes change at any point during the study (baseline appointment, training, 6 weeks, after that)? You said in the first stage of interviewing that you felt the massage was working/not working [delete as appropriate and add details based on perceived impact discussed in first stage of interviewing.] – has this stance changed? How frequently do you visit the toilet now? Did you ever previously have accidents with your bowel, because of urgency in needing to go?

Was anything about the trial different to what you expected?

2.Any problems mentioned last time

[Ask about any problems mentioned during the first stage]. Did any problems occur relating to paperwork or nurse telephone calls or other health problems?

3.In the first stage of interviewing, you shared your experiences of administering the massage:

Did any problems arise that might have impacted upon the effectiveness of the massage [Add details from first stage]

4.Continuing lifestyle changes:

Have you made any lifestyle changes since we first spoke (i.e. more exercise, changes to diet, laxatives, changes to medication)? [Add details from changes made during first stage of interviewing.]

5.Post 6 week AMBER experience?

Last time we spoke, you said you were going to carry on/stop [delete as appropriate] with the massage after the 6 week intervention period – did you do this? If so, please share your experiences on that (i.e. carrying out the massage, but not having to complete bowel diaries and receive weekly telephone calls)? Did this make any difference to your bowel problems? If not, why not and have your bowel problems worsened, improved or stayed the same during this period?

Have you received your 24 week pack? [Due to receive this on the[add date.]] If so, please indicate your thoughts about it. Will you continue to use abdominal massage following your completion of the trial? If so, how often and will you use any measures to track your progress (e.g. keep your own bowel diary)? If not, why and what other form of treatment are you going to use for your bowel problems - would you consider ever using abdominal massage?

Have you got any further questions or comments for the AMBER team?

Thank you for your time – we value your input.

Interview Schedule: Stakeholder Interviews

Introduction

1. I'd like to start by finding out a little bit about you. Please could you tell me about your role as [insert role]?

   I'd like to find out more about the current projects you are involved with [add details based on background research and tailor questions around these.]

2. [Check how much she knows about AMBER beforehand] What do you think the potential might be for self-led abdominal massage to help MS patients with bowel problems? How does this compare to other forms of treatment for bowel problems?

-What kind of savings could be made by patients using self-led abdominal massage (i.e. in terms of not having to see a more expensive staff members like a GP or consultant, reducing nurse contact with patient and chances of hospitalisation)?

Some people with MS are not under the care of an MS service – impact on them?

3. If AMBER proves to be effective for managing bowel problems in MS patients, we would like to take this forward to implement the intervention within NHS contexts. Do you have any thoughts on what might help or hinder that?

Implementing massage

-Could details for the massage be detailed in existing resources, such as guide to bowel problems or 'Making Sense of MS' booklet provided to newly diagnosed patients?

-Which stakeholders/NHS gatekeepers would need to be engaged/involved in the process? [Scottish MS Register, British Neurologists, third sector organsiations?]

-Sustainability: would this be a long-term initative?

-Would it be implemented in MS Trust educational training, e.g. 'MS Nurse Support Programme.'

4. Can you tell us anything about current or forthcoming policies related to the treatment of MS patients that might have a bearing on the rollout of AMBER in the future?

[Add details based on background research pertaining to neurology/continence services based on expertise of interviewee.]

Draft Interview Schedule: Health Care Professional Site Interviews (First Stage)

Introduction to the process evaluation

1.I'd like to start by finding out a little bit your background and your role in the organisation.

Explore their role and involvement with MS: Please could you tell me about your involvement in multiple scleorisis treatment/services? (Amend according to role of interviewee) How long have you been working in this specialist area and at [add name of site]? What does your role entail?

[Add details based on background research.]

Explore the size and location of facility

Could you tell me a bit more about the [add name of site]? Its mission statement is [add from website] – how does this impact your role and the way you treat patients? How is the shift towards consolidating specialist services and working with other specialist centres impacting upon the services offered to patients? Are there any new forms of training being offered to specialist staff?

[Add details about site]

2.How would you describe current difficulties facing the MS patients that come to your centre

Since MS patients can suffer from cognitive and visual difficulties, how does the [add name of site] accommodate patients with speech, visual and hearing problems?

[Add any information available about services.]

3.I'd like to find out about how recruitment of AMBER is going in your area.

Explore how many recruited to Intervention & Control and any barriers or facilitators to recruitment:

First of all, please could you tell me how many have been successfully recruited so far? Could you tell me more about your experience in recruiting these patients (i.e. how did they find out about the study, what convinced them to take part, was the process of sending out recruitment packs, screening and arranging a baseline appointment straightforward, was the information included in the recruitment packs helpful and relevant to the patients)? Did those interested in the study have any questions/concerns before their baseline appointment or wish any additional information to be included in the recruitment packs? Have there been any problems along the way and, if so, what was the cause?

[Patients can be recruited either in clinic or by sending out an **"AMBER Recruitment pack"** to patients who have been screened from notes or a clinic list. The nurse then sends out a recruitment pack to potential patients and, if interested, they return an 'expression of interest' form. The research nurse then telephones the patient to complete the CRF screening; thereafter a baseline appointment is arranged for the patient (either usual time or alternative appointment). The nurse sends out a bowel diary before their baseline appointment.]

4.If we focus now on delivering the intervention itself – what has been your experience of this so far

Explore: how have patients received the information and training; how do staff perceive the intervention:

What have patients reacted to the intervention treatment? Were there any difficulties during the process of administering the massage? Did patients have any questions/concerns about performing the massage themselves? Did patients find the materials provided (DVD, training manual, guide and leaflet) to be helpful and informative or were there any issues? Were there any particular questions about completing the bowel diaries and using the Bristol stool chart?

Now, I want to move onto talk about the experiences of those involved in delivering the intervention. What were your thoughts on the training and materials provided (i.e., was everything clearly explained, were there any problems, any suggestions for ways to improve the training and training materials)? How do you feel about completing the remainder of the intervention (i.e. six weekly telephone calls, 24 week follow-up)?

5.Have you faced any particular challenges in implementing AMBER

Explore challenges and local solutions (changes in staffing; resources; local policy/initiatives):

Does the [add name of site] currently have any treatment options to deal with bowel problems? If so, what does this involve and what challenges arose? If not, why is this the case (lack of funding, specialism in this area, other symptoms take priority)?

Overall, how do you feel about the process of implementing AMBER in the [add name of site] (i.e. challenges involved, what was successful)? With the current financial challenges faced and difficulty in recruiting trained nurses and other forms of clinical staff, are staffing conditions being met?

[Add background research findings.]

6.What do you think has worked particularly well for your centre in terms of implementing AMBER?

Explore local adaptations to the intervention; lessons learned that could be transferred to other teams:

What worked well during the process of implementing AMBER? Did you liaise with any other teams during the process (e.g GPs and community nurses about administering AMBER to those requiring long-term care in their homes)?

Are any additional resources required to successfully implement AMBER? What advice would you give other teams looking to implement AMBER?

7.Are there any other initiatives happening locally for MS patients that might have an impact on our results?

Explore: any local campaigns that might improve recruitment/take-up/completion, or make patients more receptive to self-management etc; other interventions/new treatments being rolled out as part of usual care that might have an impact on bowel problems?

Are there any developments relating to funding, service provision or any local initiatives (such as self-managing symptoms, dealing with bowel conditions) outside the organisation by groups [add names of local and regional groups] that are relevant to the treatment of MS patients? Are there any on-going initiatives, trials and proposed treatments in the [add name of site] or in the local community relating to bowel problems? If so, how would this impact on the administering of AMBER? Are there any charities or other organisations offering support to MS patients?

What kind of psychological and neuropsychological support is provided to patients with MS? Is funding being raised for specific initiatives and, if so, how (private treatment, training levies, fundraising))?

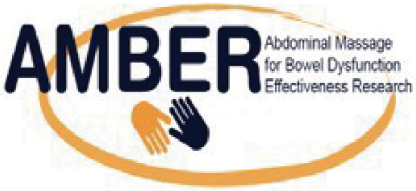
8.To finish, what are the general demographics of MS patients who come to your centre.

Explore: SES range of catchment (deprivation range; urban/rural; ethnicity; age range of patients; if fairly similar to other areas or anything different):

Which groups are most likely to fall into the category of 'did not attend for admission?' Do you think there is a way to change this?

[Add any details found during background research.]

With regards to the catchment area, what are the rates of deprivation, poverty and unemployment? Are these rural or urban places? What is the population of patients with regards to gender, age, ethnicity and unemployment status? Is this fairly similar to other catchment areas within NHS England/Scotland [delete as appropriate]?



Draft Interview Schedule: Health Care Professional Site Interviews (Second Stage)

1. Recruitment

The [add name of site] has currently recruited [add number of participants at time of second stage interview]. Do you think the site will reach its target of [insert number] participants and, if so, do you think it will be able to recruit over this? What advice would you give to other teams in order to recruit successfully?

[Add details of recruitment and any problems faced during first stage of interviewing, including information discovered from interviews with other HCPs at this site.]

There has been [add number] potential withdrawal (check this). Why do you think the site has been so successful/struggled [delete as appropriate] with retention? Have there been any particular problems with patient recruitment and/or retention during the AMBER trial?

[Only ask to those actively involved in recruitment] In the last interview, you were the one been dealing with recruiting patients (e.g. sending out packs, arranging appointments, etc.) – did this continue during the trial or did another member of staff get involved in this?

2. Delivering intervention

Since we spoke last year, were there any difficulties during the process of administering the massage. If so, what impact do you think this would have had on the effectiveness of the massage? If not, did this improve patients' understandings of the pressure required? Did patients have any other questions/concerns about performing the massage themselves? Since you have been carrying out the follow-up calls, how have patients reacted to the intervention treatment?

[Any anecdotes or details mentioned during first stage.]

How has this compared to the reaction of those in the control group? Are you still planning to show the ones in the control group the massage at the end of the trial?

Did patients find the rest of the materials provided (DVD, training manual, guide and leaflet) to be helpful and informative? Have patients had any issues playing the DVD or accessing the videos online?

[Any information provided during first stage.]

Last time we spoke, you said some patients were a bit concerned about completing their bowel diaries properly. Did this continue or what were the reactions of the four other patients you have recruited since then?
How did you get on with the 24 week calls?

I will now move onto any larger changes that may have affected the delivery of the trial. Have there been any changes in staff involved in delivering AMBER in the past six months (e.g. staff leaving or joining the AMBER team)?

What impact, if any, have these changes had on the delivery of the AMBER trial?

Has there been any substantial funding or other changes to your organisation since we last spoke?

3. Problems mentioned during first stage

Mention any problems discussed during the first stage of interviewing – were these resolved?

Are there any other ways to improve the AMBER trial, particularly thinking in terms of an implementation study?

4. Implementing AMBER long-term

Considering your experience with AMBER, do you think it would be possible to implement this as a form of treatment in your centre in the long-term? If not, why not? If so, what additional resources would be needed (staffing, funding, liaisons with external stakeholders)?

Overall, based on your experience of delivering the trial how do you feel about the process of implementing AMBER in the Walton Centre (i.e. challenges involved, what was successful)?

SIX MONTH SITE TRACKING QUESTIONNAIRE

The purpose of this questionnaire is to collect some additional information from the sites involved in delivering the AMBER trial.

It should be completed by the Principal Investigator or their delegate.

Name of Organisation: _____

Name of Staff Member: _____

Date site recruited its first AMBER patient: _____

Date of questionnaire completion: _____

Have there been any new forms of treatment (including treatment for bowel symptoms) introduced to MS patients in your centre/department? YES/NO

If yes, please provide more details e.g. medication, physical therapy, symptom/pain management, any other issues):

How many other trials is your Unit involved in? ☐

How many of these are specifically related to MS? ☐

Are any of these trials related to bowel problems? YES/NO

If yes, please provide more details:

During the last 6 months:

1. *Have there been any substantial funding or other changes to your organisation? YES/NO*

If yes, please provide more details:

What impact, if any, has this has on the delivery of the AMBER trial?

2. *Have there been any changes to care pathways in your organisation and the local area, which could affect MS patients?* YES/NO

If yes, please provide more details (e.g. the primary and secondary services patients can access, social care and community health services, etc.):

3. *Have there been any changes in staff involved in delivering AMBER in the past six months (e.g. staff leaving or joining the AMBER team)?* YES/NO

If yes, please provide more details:

What impact, if any, has this has on the delivery of the AMBER trial?

4. Have there been any particular problems with patient recruitment and/or retention during the AMBER trial? YES/NO

If yes, please provide more details:

Thanks very much for your time. Please return either by email to [redacted] or post to the AMBER Trial Office.

Appendix 13 Summary of 'yes' responses to questions asked during the weekly telephone call (weeks 1 and 24)

	Time point, trial group (% of yes responses)			
	Week 1		Week 24	
Outcome	Intervention	Control	Intervention	Control
Diet changed	13.4	19.1	13.1	18.1
Fluid intake changed	20.4	27.7	15.5	25.1
Defaecation position changed	25.3	27.7	9.1	8.5
More exercise	15.1	18.1	12.9	18.8
Concomitant medication(s) changed	5.7	9.6	15.6	14.9
Use of laxatives changed	13.8	16.0	9.1	15.4
Bowel habits changed	49.4	38.3	42.9	30.9
Bowel habits (more often)	35.6	24.5	29.9	19.1
Bowel habits (less time)	6.9	4.3	18.2	6.4
Bowel habits (less hard stool)	20.7	5.3	20.8	14.9

EME
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