Statistical Analysis Plan

Standing Up in Multiple Sclerosis

(SUMS Study)

A multi-centre randomised controlled trial to assess the effectiveness and cost effectiveness of a home-based self-management standing frame programme plus usual care versus usual care in people with progressive multiple sclerosis (MS) who have severely impaired balance and mobility

ISRCTN30081

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Contents

ADMINISTRATIVE INFORMATION

Title of Trial	Standing Up in Multiple Sclerosis (SUMS Study) A multi-centre randomised controlled trial to assess the effectiveness and cost effectiveness of a home-based self-management standing frame programme plus usual care versus usual care in people with progressive multiple sclerosis (MS) who have severely impaired balance and mobility
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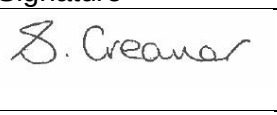
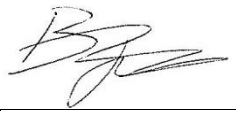
	Name	Signature	Date
Statistical Analysis Plan Authored by:	Trial Statistician: Siobhan Creanor		17/01/2018
	Ben Jones		17/01/2018
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ABBREVIATIONS

AE	Adverse Event
AMCA	Amended Motor Club Assessment
ANCOVA	Analysis of Covariance
BWCS	Bowel Control Scale
BLCS	Bladder Control Scale
CACE	Complier Average Causal Effect
EDSS	Expanded Disability Status Score
ITT	Intention To Treat
MS	Multiple Sclerosis
MSIS	Multiple Sclerosis Impact Scale
SAE	Serious Adverse Event
SD	Standard Deviation
SUMS	Standing Up in Multiple Sclerosis

1. INTRODUCTION

1.1. Background and Rationale for the Trial

The full background and rationale for the SUMS trial is detailed in the SUMS study protocol[1]. In summary, the SUMS study will assess whether the provision of a home-based standing programme using an Oswestry Standing Frame will improve motor function, and thus aid in the alleviation of mobility-related MS symptoms, in patients with progressive MS. All participants will be provided with standard care, and half of the participants will additionally participate in the home-based standing frame programme.

1.2. Purpose of statistical analysis plan

The study protocol includes an outline of the statistical methods to be employed in the analysis of the trial data. The purpose of the Statistical Analysis Plan is to provide full details of the planned statistical methods to be used in the primary report of the trial results, and has been produced in line with the 2017 CONSORT Extension for Non-pharmacological Trials[2] and the ICH E9 Guidelines[3].

2. TRIAL OBJECTIVES AND OUTCOME MEASURES

The objective of the SUMS study is to assess the clinical and cost effectiveness of a home-based standing frame programme for people who are severely impaired by MS. If demonstrated to be effective and cost effective, the evidence can be used to develop recommendations for a health service delivery model which could be implemented across the United Kingdom.

2.1. Primary Objective

To assess in patients with progressive multiple sclerosis, whether the implementation of a standing programme using a standing frame alongside standard care will improve motor function compared to standard care alone.

2.2. Primary Outcome Measure

The primary outcome measure is motor function, measured using the Amended Motor Club Assessment (AMCA)[4]. This rates motor impairment of the lower limb and trunk and key functional movements such as sit-to stand and standing balance. It was developed specifically for people with MS and has demonstrated validity, reliability and responsiveness[4-6].

The primary endpoint will be AMCA scores at week 36; in order to improve the accuracy of the estimated effect size, baseline AMCA measures will be controlled for in the analyses.

2.3. Secondary Objectives

- To understand the experience of the standing programme from the perspective of both the participant and the carer
- To measure the effects of the standing programme on physical impairments
- To measure the effects of the standing programme on key clinical outcomes
- To measure the effects of the standing programme on an individual's quality of life
- To determine adherence to the programme
- To record and monitor adverse events
- To understand the experience of the standing programme from the perspective of both the participant and the carer
- Establish the cost effectiveness of the standing frame programme

2.4. Secondary Outcome Measures

- Knee extensor strength using a portable hand-held dynamometer
- Length of hip flexors, hamstrings and ankle plantar-flexors using manual goniometry
- Spasm frequency using the Penn Spasm Frequency Scale
- Respiratory capacity using a hand-held spirometer to record forced expiratory volume at 1 second
- Bowel and bladder control using the self-report Bladder and Bowel Control Scales
- Sitting balance using the Single Item Modified Functional Reach in sitting
- Falls frequency through a binary yes/no daily response questionnaire
- Self reported, 29-item MS impact scale (MSIS-29)
- EuroQol EQ-5D-5L
- Pre-formatted diary to be completed by the participant or carer to measure compliance with the standing programme and, where appropriate, reasons for non-compliance
- Daily participant diary to record adverse events
- Audio diaries for 10 participants and 10 carers

3. TRIAL DESIGN

3.1. General Design

A blinded outcome, individually-randomised, controlled, multi-centre superiority trial in patients with progressive multiple sclerosis.

Patients diagnosed with either primary or secondary progressive MS according to McDonald's criteria[7] will be drawn from two geographical regions; Devon/Cornwall and East Anglia. Participants will be randomised using random sized permuted blocks, on a 1:1 basis, to either the control group, and receive standard care, or the intervention group where they will receive standard care as well as participating in the standing programme for 20 weeks. Participants will be followed up for a further 16 weeks after completion of the programme, for a total of 36 weeks.

3.2. Blinding

Due to the nature of the intervention, it will not be possible to blind participants. However, the assessment of participants and the primary statistical analysis of the results will be undertaken in a blinded manner.

3.3. Analysis Populations

Primary analysis of the primary outcome will be based on the intention-to-treat (ITT) principle; participants will be analysed as randomised, regardless of their compliance with the trial protocol or lack of participation/completion if allocated to the intervention group. ITT is generally accepted to be the gold standard approach and provides a conservative estimate of the intervention effect. The ITT population will include all participants with associated primary outcome data, excluding only patients who were deemed ineligible following randomisation, those who withdrew from the trial and were unwilling for their previously collected data to be utilised or those who failed to provide baseline and week 36 measurements (i.e. there will be no imputation of missing baseline and/or week 36 scores for the primary analysis).

Due to the home-based nature of the trial, it is possible that there will be a number of deviations from the trial protocol. In this statistical analysis plan, deviations are considered to be either non-compliance with the intervention (see section 4.4.1) or non-adherence to other elements of the protocol, for example assessments completed outside the pre-specified windows. As such, it may be of interest to consider alternative populations for analysis, in order to investigate the robustness of the conclusions of the primary analyses.

One alternative is a per protocol analysis, although this approach could introduce bias into the trial through excluding participants after randomisation and thus jeopardising the group comparability achieved through randomisation. As an alternative, a complier-average causal effect (CACE) analysis may be undertaken, which would provide an unbiased estimate of the intervention effect, based on those who complied with their allocated group's protocol.

The CACE analysis will be used for the purposes of a sensitivity analysis, and as it is a less conservative approach than ITT, will likely result in a larger difference between the groups. Following discussions with the Trial Steering Committee, it is planned to undertake a CACE analysis if ≥20% of intervention participants are categorised as non-compliers (see section 4.4.1 for detailed definition of a complier). It is likely that a one-sided CACE will be appropriate, but if there are any participants in the control group who access a standing frame independently from the trial, a two-sided CACE will be undertaken.

3.4. Inclusion and Exclusion Criteria

The study population will comprise individuals diagnosed with primary or secondary progressive MS according to McDonald's criteria[7], and will be:

- over 18 years of age
- be willing and able to consent and participate
- score 6.5 – 8.0 on the Expanded Disability Status Scale (EDSS)
- be able to get into a standing frame independently or with assistance from a carer, and have agreement from the carer should they be required
- be willing and able to accommodate the Oswestry Standing Frame in their home

- be willing and able to travel to local assessment centres for blinded outcomes assessment

Participants will be excluded if they:

- have had any recent changes in disease modifying therapies. More specifically, they will be excluded if they have ever received Campath, have ceased Nataluzimab within the past six months, or are within 3 months of ceasing any other MS modifying drug
- have relapsed/received steroid treatment within the last month
- are currently, or during the past 6 months have undertaken a regular standing frame programme for longer than a week
- have a history of osteoporotic-related fractures

4. STATISTICAL PRINCIPLES

4.1. Randomisation, Stratification and Allocation Concealment

Randomisation will be achieved using an allocation sequence computer-generated by the Peninsula Clinical Trials Unit. Randomisation will take place after baseline assessment, when the blinded assessor will input participant details directly into the randomisation website. This will generate an e-mail confirming allocation to the regional study co-ordinators, the study administrator and the treating therapist, but not to the blinded assessors.

Participants will be stratified according to their region (South West or East Anglia) and, as their scope for improvement may be affected by their current disability severity, to their baseline Expanded Disability Status Scale (EDSS) category. This stratification will be achieved by categorising participants into two groups; those with an EDSS score of ≤7.0 or ≥7.5 (the eligibility criteria for the trial is a baseline EDSS score of 6.5-8.0). EDSS scores are scaled in steps of 0.5.

The randomisation will occur on a 1:1 basis using random sized permuted blocks.

4.2. Sample Size Calculation

The primary outcome is the AMCA at 36 weeks follow-up. This is based on data from Hendrie's[8] MS standing pilot study where AMCA improved by a mean of 9.6 following use of the standing frame (SDs 10.6 at baseline and 13.3 at follow-up; correlation between baseline and follow-up AMCA scores 0.82).

The primary analysis will utilise analysis of covariance (ANCOVA), comparing AMCA scores at week 36 between allocated groups, adjusting for baseline AMCA score. The target between-group difference to be detected is 9.0 points, which is both plausible and considered clinically relevant. The estimates of final SD and baseline/follow-up correlation for AMCA are subject to uncertainty and thus the sample size calculations used conservative 80% confidence limits for both parameters, namely 20 for the SD and 0.55 for the correlation. To detect a between-group difference of nine points, with 80% power at the 5% significance level, requires 55 participants per group. Allowing for up to 20% loss to follow-up, the target sample size is 69 participants per group, rounded to a total of 140 participants.

4.3. Statistical Significance Levels

All applicable statistical tests will be two-sided and at the 5% significance level, unless otherwise specified, with two-sided 95% confidence intervals presented whenever possible. As there is a single primary endpoint, and the secondary endpoints are to be used only in providing additional supportive exploratory information, there will be no adjustments for multiple testing.

4.4. Compliance and Protocol Violations

4.4.1. Compliance with Allocated Treatment

Each participant will be randomised to either the intervention group or to the control group, and those allocated to the intervention group will be provided with a standing frame and programme. It may, however, be possible that participants allocated to the control group will purchase their own standing frames. In line with the intention to treat principle, in the primary analyses, participants will be analysed in accordance with their randomly allocated group.

The trial protocol specifies that participants allocated to the intervention group should stand three times a week for 30 minutes over 16 weeks of the 20 week intervention period. The intervention period duration of 20 weeks factors in up to four weeks for individuals to become re-accustomed to an upright position and achieve the desired intensity of standing whilst also allowing for time when the participant is unable to use the frame (illness, holidays, etc). Following detailed discussions, it was agreed that compliance should be considered in terms of total standing time over 16 weeks, leading to a minimum standing time of 1440 minutes if the protocol is strictly followed. Based on a minimum 80% compliance level, the minimum total standing time required over the 16 weeks is 1152 minutes. Therefore, in the intervention group, a complier will be defined as a participant who has stood for a mean of at least 72 minutes per week over 16 weeks within the 20 week intervention period. In the control group, a complier will be defined as somebody who does not use a standing frame during the study period.

The number and proportions of participants categorised as non-compliers will be summarised for each group separately and overall, alongside the details of the non-compliance.

Analyses will be undertaken by considering a complier as a participant allocated to the intervention group who (during the 20 week intervention period) (i) stood for at least 1152 minutes over their best 16 weeks; (ii) stood for at least 1152 minutes over their worst 16 weeks; (iii) stood for at least 1152 minutes over weeks 5-20.

Further analyses will similarly explore compliance over the full 36 week trial period, again allowing four weeks for acclimatisation, holiday or illness. Assuming that ideally participants in the intervention group continued to stand for a minimum of 30 minutes, three times per week over 32 weeks, this equates to a total standing time of 2880 minutes. Based on a minimum 80% compliance level, the minimum total standing time over 32 weeks will therefore be 2304 minutes.

A CACE analysis may be undertaken for the purposes of a sensitivity analysis, to allow the estimation of the intervention effect, having accounted for participants categorised as non-compliers as defined above (see sections 3.3 and 6.6.1).

4.4.2. Other Protocol Deviations

As well as non-compliance with the protocol as outlined above, there could be other protocol deviations, for example if follow-up assessments took place outside the pre-specified ±2 week window. The numbers and proportions of participants with protocol deviations will be summarised by allocated group with details of type of deviation provided. No formal statistical testing will be undertaken.

In addition, it is possible that participants may be administered drugs during the trial period which would have excluded them from participating in the trial. Such participants will be analysed as randomised, in line with the principle of intention to treat.

Any reported protocol deviations will be documented and reported to the Chief Investigator and Sponsor.

4.5. Interim Analysis

There is no planned interim analysis for this trial. If, for any reason, the Trial Steering Committee (TSC) requests an interim analysis of the data, they will seek to appoint a statistician independent of the trial team to undertake such work, in order to retain the blinding of the trial statistician.

4.6. Collection of Outcome Measures

Outcome measures will be collected from participants at baseline, at 20 weeks post-baseline (coinciding with the end of the intervention programme for those allocated to the intervention group) and again at 36 weeks during three blinded assessments.

	Pre-intervention	Intervention Period	*Post-intervention*	
	Baseline		**20 weeks**	**36 weeks**
AMCA Score	x		x	x
Knee extensor strength	x		x	x
Length of hip flexors, hamstrings and plantarflexors	x		x	x
Spasms frequency	x		x	x
Respiratory capacity	x		x	x
Bladder function	x		x	x
Bowel Function	x		x	x
Sitting balance	x		x	x
Falls Frequency	*Daily Diary*		*Daily Diary*	
Health related quality of life	x		x	x
Adherence/Compliance	*Throughout*		*Throughout*	
Audio Diary	*Throughout*		*Throughout*	

4.7. Time points of Statistical Analysis

The statistical analysis, with the exception of any interim analysis, will be undertaken after the final data at the 36 week follow-up has been collected for each participant and the database locked.

4.8. Data Sources and Data Quality

The data will come from information entered onto Case Report Forms (CRFs) completed at baseline, 20 weeks and 36 weeks. +/-2 weeks tolerance will be allowed for collection of outcome measures, after which point a protocol deviation will be recorded. In addition, participants will complete a daily dairy with a yes/no response to whether they have fallen each day. A pre-formatted diary will also be completed by participants to collect information on compliance with the intervention and to record adverse events. Ten participants will also be asked to complete audio diaries detailing their experience of the intervention. Data, excluding diary data and interview transcriptions, will be double-entered and discrepancies checked by the SUMS study administrator and the research therapists and stored securely on a PenCTU database.

4.9. Missing Data

4.9.1. Missing Primary Outcome Data

As baseline data will be obtained prior to the commencement of the study it is unlikely that any significant amount of information will be missing. However, if this is the case, it will not be possible to include the participant in the primary analysis. Such participants will be included in both the analysis of secondary outcomes and the secondary analysis of the primary outcome where appropriate.

It is, however, possible that there may be some missing data by the time the trial concludes. This could be because a participant has dropped out of the study, or did not attend the final follow-up assessment. If a participant has dropped out of the study before the end of the trial period and has not provided a week 36 measurement, it will not be possible to include them in the primary analysis. However, if they miss their 20 week assessment but attend the 36 week assessment then they will be analysed as randomised, as they will have provided the data necessary for the primary outcome comparison.

The intention is to use complete case data for the primary analysis, on an intention-to-treat basis, so any participants who do not provide baseline and 36-week AMCA data will be excluded from the primary analysis. As the sample size calculation allowed for up to 20% loss to follow-up, the analysis should be sufficiently powered, although there is a risk of bias if there is differential loss to follow-up between the intervention and control groups. Any imputed datasets will be used for the purpose of sensitivity analyses (see section 6.6.1 below).

4.9.2. Other missing data

Other missing demographic data such as sex and age will be queried following data entry, although it is not expected that there will be a considerable amount of such missing data. Analyses of secondary outcomes will be based on complete case data only.

5. STUDY POPULATION

Data from the screening process through to the completion of the trial will be recorded and presented in a CONSORT-style flow diagram. In particular, the following data will be provided:

- Number of participants screened for eligibility
- Number of participants ineligible*
- Number of participants eligible and asked to participate
- Number of participants who declined to participate*
- Number of participants consented to participate
- Number of participants withdrawn prior to randomisation*
- Number of participants randomised to each allocated group
- Number of participants who did not receive their allocated treatment*
- Number of participants who did receive their allocated treatment
- Number of participants who did not complete their allocated treatment*
- Number of participants who completed their allocated treatment
- Number of participants who completed the 36 week follow-up
- Number of participants lost to follow-up*
- Number of participants analysed

*Reasons will be provided where available

5.1. Participants who discontinue, withdraw or are lost to follow-up

It is possible that participants may withdraw consent part way through the trial, or their treatment may be discontinued due to medical reasons. It is unlikely that a participant will discontinue on medical grounds if allocated to the control group, but for reasons such as extreme fatigue or injury, some may not be able to complete the standing frame programme. Participants who discontinue will be categorised into one of the following:

- Continue to consent for follow-up and data collection
- Consent to use pre-collected data only
- Withdrawn consent to use any data

Reasons for withdrawal or loss to follow-up will be summarised in the CONSORT diagram where possible, at each stage of the process (withdrawal prior to randomisation, participants who did not receive their allocated treatment, non-completion of treatment, lost to follow-up).

Participants who withdraw from the study, or whose treatment is discontinued on medical grounds, will not be replaced although their available data will be used unless they have specifically requested for it to be removed from the database.

5.2. Baseline characteristics and demographics

Baseline characteristics, collected prior to randomisation, will be cross-tabulated according to allocated group to check for balance between groups and provide an overview of the study population. The variables will include age, sex, walking aid use, type of MS, AMCA score, dynamometer of knee extensors, goniometry of passive range of motion, spasms frequency, respiratory capacity, bladder and bowel function, sitting balance, fall frequency and health related quality of life.

Summary statistics for continuous measures will be reported as means, standard deviations and ranges where the distribution appears normal, and as medians, inter-quartile ranges and ranges if the distribution is skewed. Categorical data will be summarised by frequencies and percentages. Formal statistical analysis of randomised groups at baseline is not good practice[9, 10] and thus will not be performed; relative balance between allocated groups is expected. Any considerable imbalance will be noted, assessed for clinical relevance and, where appropriate, additional adjustments will be made in secondary sensitivity analyses[3] [11].

6. STATISTICAL ANALYSES

6.1. Outcome Variables

AMCA Score: (primary outcome) will be measured at baseline, end of intervention period (week 20), and at 36 week follow-up. Week 36 AMCA scores will be compared between allocated groups in order to test for a significant difference between the week 36 AMCA scores, with adjustment made for baseline AMCA scores.

Knee extensor strength, length of hip flexors, hamstrings and ankle plantarflexors, frequency of spasms, respiratory capacity, bladder function, bowel function and sitting balance (secondary outcomes): will be measured at baseline, at the end of treatment (week 20) and at 36 weeks follow-up. 36 week follow-up scores be will compared between allocated groups, with adjustment made for baseline scores.

Fall frequency: will be collected via the use of a daily yes/no questionnaire, recorded in a diary by participants. The proportion of fallers at the end of treatment (week 20) and at 36 weeks follow-up will be compared between allocated groups, where a faller is defined as somebody who has fallen at least twice.

Compliance with the Intervention: A pre-formatted daily diary will be completed by participant (or their carer) to record compliance with the intervention. Data will be summarised to assess whether participants allocated to the intervention group stood for the minimum required time. The data will be used to assess whether a sufficient level of compliance was achieved. Exploratory analysis will be undertaken of the potential effect of total standing time, mean standing time per week and frequency of standing on the primary outcome (see section 6.7.3).

6.2. General Considerations

Wherever possible, analyses will be presented with 95% confidence intervals and all reported p-values will be two-sided, unless otherwise stated. For continuous outcomes, summary information will be presented in the form of means (including mean difference between follow-up and baseline where appropriate) alongside standard deviations and ranges for outcomes that are normally distributed. For ordinal outcomes and non-normally distributed continuous outcomes, summary information will be presented in the form of medians, inter-quartile ranges and ranges.

6.3. Adjustments

Analyses of the outcomes will be adjusted for stratification variables, region (South West or East Anglia) and EDSS category at baseline (≤7.0 or ≥7.5), and baseline measure, where available. Data will be pooled across recruitment centres.

6.4. Primary Analysis of the Primary Outcome

The Amended Motor Club Assessment (AMCA) comprises a series of physical tests designed to assess motor function for participants with MS. The series of examinations to be conducted within this trial includes 14 lower limb activities and 16 functional activities. Each lower limb assessment returns a score based on scale of movement, ranging from 0-2, with a higher value representing better movement. In the case where an exercise was not tested, a score of 0 will be allocated. For the functional activities, a score between 0-3 will be assigned to each examination, with higher values representing better function. As for lower limb movement examinations, if an activity is not tested a score of 0 will be allocated (correspondence with Lorraine De Souza, developer of the AMCA measure - see appendix B). A participant's AMCA score is the total of each of the individual scores and can range from 0-76, with a lower score indicating a higher degree of motor and functional deficit.

Descriptive summary statistics (e.g. means and standard deviations) will be presented for the primary outcome of AMCA scores at each of the three time points by allocated group. The primary analysis will compare the difference between AMCA scores at 36 weeks (the primary endpoint) and baseline between the two allocated groups using ANCOVA, including the stratification variables (region and baseline EDSS category) and baseline AMCA as covariates. Utilising the baseline AMCA levels will increase the precision of the estimated intervention effect at 36 weeks. The assumptions underpinning the ANCOVA model will be visually assessed, with suitable transformation of AMCA scores undertaken as necessary if the ANCOVA model assumptions are not met. If there is a suggestion of violation of the model assumptions and no suitable transformation can be identified, bootstrapped confidence intervals for the between-group differences in change in AMCA scores will be produced.

Unadjusted analyses will also be presented for completeness. Both adjusted and unadjusted between-group comparisons will be presented with 95% confidence intervals.

6.5. Interpretation of primary analysis results

The primary analysis will test the following null and alternative hypotheses:

H_0: There is no difference between the change in AMCA score from baseline to week 36 follow-up assessment between the two treatment groups.

H_1: There is a difference between the change in AMCA score from baseline to week 36 follow-up assessment between the two treatment groups.

If the results of the primary adjusted analyses suggest that there is sufficient evidence to reject the null hypothesis, it will be concluded that the standing frame programme is different to the standard treatment currently available in improving motor function in participants with progressive multiple sclerosis.

6.6. Secondary analyses of the primary outcome

6.6.1. Sensitivity Analysis

As described above, the primary analysis will use complete cases of the data, meaning only participants who have provided both baseline and week 36 data will be included. As outlined in sections 3.3 and 4.4.1 above, a CACE-based sensitivity analysis will be undertaken to allow the estimation of the intervention effect having accounted for participants categorised as non-compliers as defined in section 4.4.1, if more than 20% of participants allocated to the intervention group, and who complete the 36 week follow-up, are categorised as non-compliers.

To assess the robustness of the conclusions of the primary analysis of the primary outcome to missing outcome data, consideration will also be given to undertaking a sensitivity analysis after imputing missing data, if there is evidence of differential loss to follow-up between allocated groups of ≥10% and/or ≥10% of participants followed-up are missing primary outcome data. If either threshold is met, an imputed data set, including participants with missing data, will be used for the purposes of a sensitivity analysis. It is anticipated that multiple imputation will be used to impute the missing AMCA scores, based on the assumption of missing at random, with this assumption assessed by examining reasons for missingness (where available). Both adjusted and unadjusted analyses of the imputed data will be conducted, with mean differences and corresponding 95% confidence intervals presented.

6.6.2. Repeated Measures Modelling

To make further, maximal use, of the repeated measures data structure, a generalised linear model will be then be fitted to the AMCA scores across the three time points, with the model including allocated group and the two stratification variables. This model will also include the interaction between time point and allocated group, to examine for evidence of different between-group differences at the two follow-up time points. The advantage of this approach is that a missing measurement will not result in the participant's remaining data being removed from the analysis (but rather just their data at that time point) and it will allow for exploration of the potential interaction between time point and allocated group.

6.7. Further Exploratory Analysis

6.7.1. Sub-scores

It is of interest to consider the effects of the standing frame programme on the AMCA scores of each of the two sub-domains of the measure: lower limb movement and functional activities. This will be achieved by simply calculating an AMCA total sub-score for each assessment; one comprising the sum of the lower limb scores and the other the sum of the functional activities scores. Analysis of each of these outcomes will be conducted as described above for the AMCA total score; via utilisation of ANCOVA, with adjustment for EDSS score, region of recruitment and the appropriate baseline measurement for the AMCA sub-score of interest.

6.7.2. Interactions

Exploratory analyses of the following possible interactions will be undertaken to assess whether the effect of the intervention on AMCA score at 36 weeks is modified by baseline EDSS score. This subgroup analysis will be performed by adding the interaction term

between allocated group and the subgroup variable into the model. As the study is not powered for this interaction analysis, the results will be treated with caution; given the exploratory nature of these investigations, the emphasis will be on the interpretation of the corresponding confidence intervals for such sub-groups.

6.7.3. Intervention Intensity

Exploratory analysis will be conducted to assess the potential relationship between the intensity of the intervention and the primary outcome in participants in the intervention group. In particular, the relationship between the AMCA score at 36 weeks and (a) the mean number of minutes stood per week and (b) the frequency and/or average number of standing sessions, will be summarised and modelled if appropriate using a general linear model, if normality assumptions are satisfied, both unadjusted and adjusted for the two stratification variables. If the modelling assumptions are not met, non-linear regression models will be explored. Levels of compliance will be explored by considering the average standing time not just over the 20 week intervention period, but over the full 36 week duration of the trial.

6.8. Analysis of Secondary Outcomes

Secondary analyses will involve considering the changes between baseline and (a) week 36 and (b) week 20 for each of the secondary outcome measurements.

6.8.1. Secondary measurements:

Knee Extensors: three repeated measurements taken per knee at each assessment. The mean of the six measurements will be calculated to provide a single measure per participant*.

Manual goniometry of passive range of motion: six individual measurements taken at each assessment; length of each hip flexor, hamstring and ankle plantar-flexor. The mean of each pair of measurements will be calculated and analysed*.

Penn Spasms frequency scale: recorded over one week, either the mode or the median of the seven scores will be computed for each participant at each time point.

Forced Expiratory Volume: three attempts performed at each time point, with the best of the three to be used for analysis, as specified in the SUMS protocol[1] and in line with similar research[12, 13].

Modified functional reach in sitting: three measurements provided per assessment. Average of final two measurements to be used for analysis, as per the Modified functional reach guidelines[14].

Bladder Control Scale: Total score, obtained based on a four item questionnaire, ranging from 0-22 at each time point, with higher scores indicating greater bladder control problems[15].

Bowel Control Scale: Total score, obtained based on a five item questionnaire, ranging from 0-26 at each time point, with higher scores indicating greater bowel control problems[15].

Falls frequency: Measured via the use of a daily yes/no question, self-reported via the daily diaries.

Multiple sclerosis impact scale (MSIS-29): Based on a 29-item questionnaire at each assessment, questions 1-20 inclusive are transformed to a 0-100 scale representing physical impact score; questions 21-29 are transformed in the same manner and represent psychological impact score, with a higher score representing a higher degree of disability [16, 17]. Each of the impact scores will be analysed separately.

*The decision was made to conduct bilateral averaging, in line with other similar work[18] and following correspondence with an author and others in the field.

As with the primary analysis, continuous secondary outcomes will be analysed using ANCOVA with adjustment for the stratification variables (EDSS score and region) as well as baseline measurement where available. The distribution of each of these secondary outcomes and the model assumptions will be examined visually and, where necessary, appropriate transformations will be sought. In any cases where transformations of the outcome are unsuccessful in satisfying the normality assumption, alternative methods of analysis will be considered and explored. This may include non-linear regression modelling if appropriate. Otherwise, a non-parametric approach will be adopted in the form of a Mann-Whitney test used to test for between-group differences.

Analyses will also be undertaken to compare the change in week 20 AMCA score from baseline between the two allocated groups, following the same approach as detailed above.

The adjusted mean difference between the two groups will be presented alongside 95% confidence intervals and p-values. In addition, unadjusted analyses will be presented with 95% confidence intervals for the mean difference and p-values.

To facilitate analysis of the available falls frequency data, participants need to be classified as a “faller” or “non-faller”. A participant will be defined as a faller at the 20 week time point as someone who has self-reported falling on two or more days between time of randomisation and week 20 follow-up. A participant will be defined as a faller at the 36 week time point as someone who has self-reported as a participant who has fallen on two or more days between time of randomisation and the week 36 assessment. The proportions of fallers will be compared between allocated groups through the use of binary logistic regression modelling with adjustment for the two stratification factors, with unadjusted analyses also presented. Participants will also be classified and compared over the post-intervention period between week 20 and week 36. In addition to comparing the proportions of fallers between allocated groups, the falls rates per person-year will also be calculated[19, 20].

6.9. Safety Data

The adverse event risks of taking part in the study have been assessed to be low[1]. However, use of the standing frame can cause fatigue, pain/discomfort, spasms, a hypotensive episode or musculoskeletal injury to the carer. Numbers and percentages of adverse events and serious adverse events will be cross-tabulated for each type, categorised by severity and relatedness to trial treatment. For each participant, only the maximum severity experienced of each type of AE will be displayed. No formal statistical analysis will be conducted, but AEs and SAEs will be closely monitored and assessed for clinical significance throughout the process.

Serious Adverse Events (SAEs) will be recorded and each site will notify the trial co-ordinator and the project Chief Investigator at the University of Plymouth immediately of any

SAEs, who will then notify the project sponsor and local R&D department within one working day.

6.10. Statistical Software

The statistical analyses will be undertaken using StataSE version, supplemented where required by packages such as R.

REFERENCES

1. Freeman, J.A., et al., *Standing up in multiple sclerosis (SUMS): protocol for a multi-centre randomised controlled trial evaluating the clinical and cost effectiveness of a home-based self-management standing frame programme in people with progressive multiple sclerosis.* Bmc Neurology, 2016. **16**.
2. Boutron, I., et al., *CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts.* Annals of internal medicine, 2017. **167**(1): p. 40-47.
3. *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9.* 1998.
4. De Souza, L.H. and A. Ashburn, *Assessment of motor function in people with multiple sclerosis.* Physiotherapy research international : the journal for researchers and clinicians in physical therapy, 1996. **1**(2): p. 98-111.
5. Davis, C., *Physiotherapy or Self-Selected Exercise in Multiple Sclerosis, A Comparative Evaluation of Community-based Interventions.* PhD Thesis, University of Nottingham, 2008.
6. Craig, J., et al., *A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment.* Journal of neurology, neurosurgery, and psychiatry, 2003. **74**(9): p. 1225-30.
7. Polman, C.H., et al., *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Annals of neurology, 2011. **69**(2): p. 292-302.
8. Hendrie, W.A., M.J. Watson, and M.A. McArthur, *A pilot mixed methods investigation of the use of Oswestry standing frames in the homes of nine people with severe multiple sclerosis.* Disability and rehabilitation, 2015. **37**(13): p. 1178-85.
9. Moher, D., et al., *CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials.* Journal of clinical epidemiology, 2010. **63**(8): p. e1-37.
10. Senn, S., *Testing for baseline balance in clinical trials.* Statistics in medicine, 1994. **13**(17): p. 1715-26.
11. *Points to Consider on Adjustment for Baseline Covariates*. 2003, The European Agency for the Evaluation of Medicinal Products.
12. Gosselink, R., et al., *Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients.* Arch Phys Med Rehabil, 2000. **81**(6): p. 747-51.
13. Buyse, B., et al., *Respiratory dysfunction in multiple sclerosis: a prospective analysis of 60 patients.* Eur Respir J, 1997. **10**(1): p. 139-45.
14. *Rehabilitation Measures Database. Functional Reach Test and Modified Functional Reach Instructions.*
15. *National Multiple Sclerosis Society. Multiple Sclerosis Quality of Life Inventory: A User's Manual.*
16. Hobart, J., et al., *The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure.* Brain, 2001. **124**(Pt 5): p. 962-73.
17. Hobart, J. and S. Cano, *Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.* Health Technol Assess, 2009. **13**(12): p. iii, ix-x, 1-177.
18. Broekmans, T., et al., *Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis.* Multiple sclerosis (Houndmills, Basingstoke, England), 2011. **17**(4): p. 468-77.
19. Ibrahim, M., et al., *ERIC Notebook: Calculating Person-Time*, in 2000, Epidemiologic Research & Information Centre: Durham, North Carolina.
20. Gunn, H., et al., *Frequency, characteristics, and consequences of falls in multiple sclerosis: findings from a cohort study.* Archives of physical medicine and rehabilitation, 2014. **95**(3): p. 538-45.

APPENDIX A: Examples of Figures and Tables for the Primary Publication Reporting the Results of SUMS

Figure 1: CONSORT Flow Diagram of participants through SUMS.

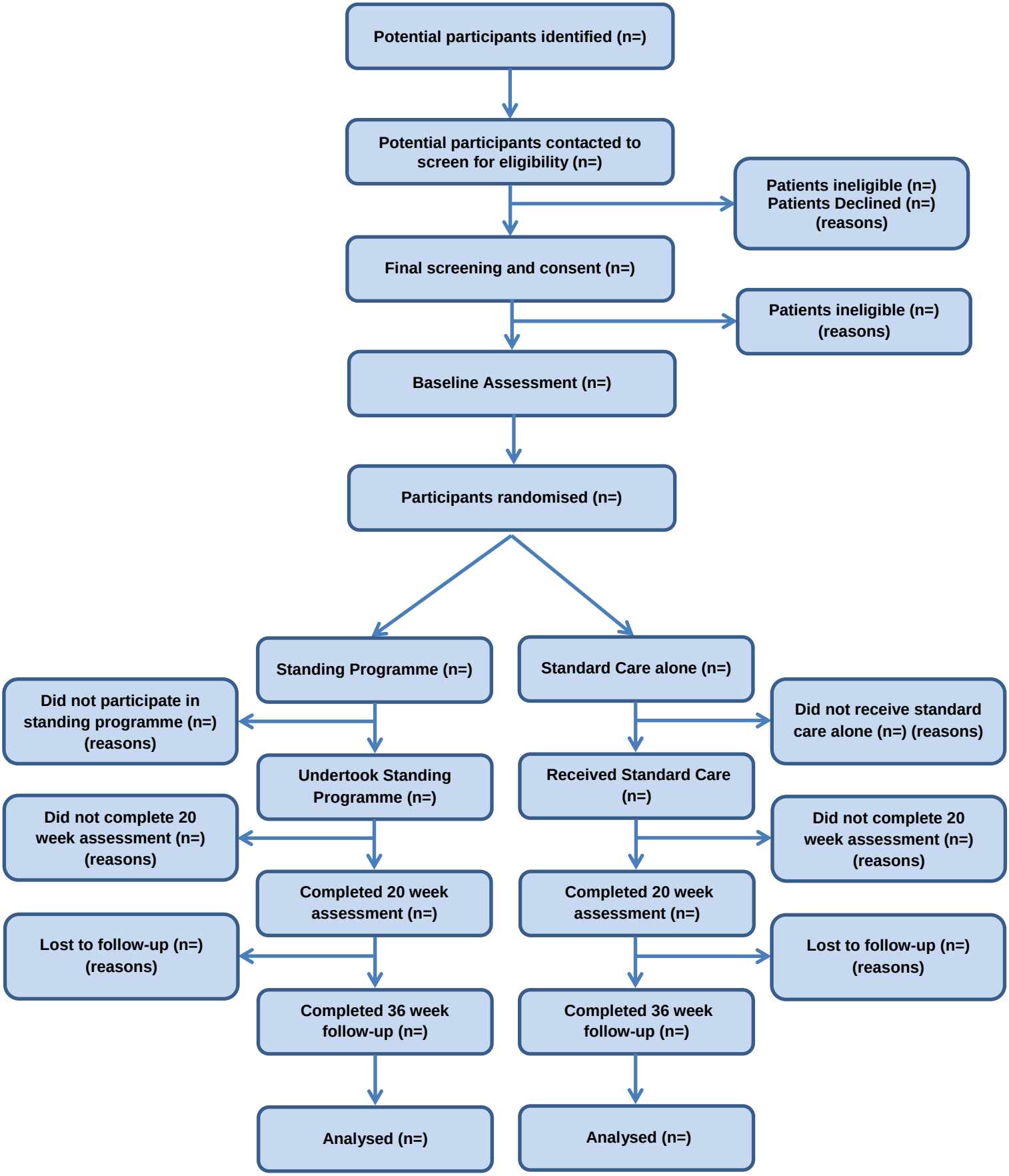

Figure 2: Example table – demographic data

	Standing Programme (n=)	Usual Care (n=)	Total (n=)
Mean (sd) [range] Age (years)			
Gender			
Male (%)			
Female (%)			
Region*			
South West (%)			
East Anglia (%)			
Type of MS			
Primary Progressive (%)			
Secondary Progressive (%)			
Most Recent Relapse			
>1 year (%)			
Within 3 months (%)			
Within 6 months (%)			
Within 12 months (%)			
Unknown (%)			
Indoor Walking Aids			
1x Walking Stick (%)			
2x Walking Stick (%)			
Frame (%)			
Wheelchair (%)			
Outdoor Walking Aids			
1x Walking Stick (%)			
2x Walking Stick (%)			
Frame (%)			
Wheelchair (%)			
Assistive Device			
None (%)			
AFO (%)			
FES (%)			
Other (%)			
Wheelchair Use			
None (%)			
Occasionally (%)			
Monthly (%)			
Weekly (%)			
Daily (%)			
EDSS Category*			
≤7.0 (%)			
≥7.5 (%)			

*Stratification Factor

Figure 3: Example Table – baseline data

	Standing Programme (n=)	Usual Care (n=)	Total (n=)
Mean (sd) [range] AMCA Score*			
Knee Extensor Strength			
Mean (sd) [range]			
Goniometry			
Mean (sd) [range] hip			
Mean (sd) [range] hamstring			
Mean (sd) [range] ankle			
Median (IQR) [range] **Spasm Frequency**			
Mean (sd) [range] **respiratory capacity**			
Median (IQR) [range] **Bowel Control**			
Median (IQR) [range] **Bladder Control**			
Mean (sd) [range] **reach in sitting**			
Falls frequency			
Mean (sd) [range] **MSIS Physical Impact Score**			
Mean (sd) [range] **MSIS Pschological Impact Score**			

*Primary Outcome

Figure 4: Primary outcome analysis

		Standing Programme (n=)	Usual Care (n=)	Adjusted Analysis[1]		Unadjusted Analysis	
				Mean Between-Group Difference (95% CI)	p-value	Mean Between-Group Difference (95% CI)	p-value
Primary Analysis	Mean (sd) [range] difference in AMCA at baseline vs week 36						
Sensitivity Analysis [1]	Mean (sd) [range] difference in lower limb AMCA at baseline vs 36 weeks						
	Mean (sd) [range] difference in functional activities AMCA at baseline vs 36 weeks						

[1] Adjusted for stratification factors region and EDSS score (≤7.0 or ≥7.5)

Figure 5: Secondary analysis of the Primary Outcome utilising repeated measures

(TBC)

Figure 6: Secondary outcome analysis – knee extensor strength and goniometry

(note a similar table will be completed for the week 20 outcomes)

		Standing Programme (n=)	Usual Care (n=)	Adjusted Analysis[1]		Unadjusted Analysis	
				Mean Between-Group Difference (95% CI)	p-value	Mean Between-Group Difference (95% CI)	p-value
Knee Extensor	Mean (sd) [range] difference in knee extensor at baseline vs week 36						
Length of hip flexors, hamstrings and ankle plantar-flexors	Mean (sd) [range] difference in hip flexor at baseline vs 36 weeks						
	Mean (sd) [range] difference in ankle plantar-flexor at baseline vs 36 weeks						
	Mean (sd) [range] difference in hamstring at baseline vs 36 weeks						

[1] Adjusted for stratification factors region and EDSS score (≤7.0 or ≥7.5)

Figure 7: Secondary outcome analysis – respiratory capacity, reach in sitting and MSIS score (note a similar table will be completed for the week 20 outcomes)

	Standing Programme (n=)	Usual Care (n=)	Adjusted Analysis[1]		Unadjusted Analysis	
			Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	p-value
Mean (sd) [range] difference in respiratory capacity at baseline vs week 36						
Mean (sd) [range] difference in sitting reach at baseline vs week 36						
Mean (sd) [range] difference in MSIS physical score at baseline vs week 36						
Mean (sd) [range] difference in MSIS psychological score at baseline vs week 36						

[1] Adjusted for stratification factors region and EDSS score (≤7.0 or ≥7.5)

Figure 8: Secondary outcome analysis – Spasm Frequency, bowel and bladder control (note a similar table will be completed for the week 20 outcomes)

		Standing Programme (n=)	Usual Care (n=)	Adjusted Analysis[1]		Unadjusted Analysis	
				Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	p-value
	Median (IQR) [range] difference in average spasm frequency at baseline vs week 36						
Bowel control scale	Mean (sd) [range] difference in bowel control score at baseline vs 36 weeks						
	Median (sd) [range] difference in bowel control score at baseline vs 36 weeks						
Bladder control scale	Mean (sd) [range] difference in bowel control score at baseline vs 36 weeks						
	Median (sd) [range] difference in bowel control score at baseline vs 36 weeks						

[1] Adjusted for stratification factors region and EDSS score (≤7.0 or ≥7.5)

Figure 9: Safety data – reporting of AEs and SAEs

	Adverse Event			Serious Adverse Event		
	Related to trial	Unrelated to trial	Total	Related to trial	Unrelated to trial	Total
Mild (%)						
Moderate (%)						
Severe (%)						

APPENDIX B: Correspondence with Lorraine De Souza regarding the allocation of a score of 0 to participants who could not attempt AMCA exercises.

Hi Lorraine,

Hope all is well with you.

I hope you don't mind me picking your brains, but Jenny and I are using the AMCA in our standing frame study and we were wondering how you dealt with any measures from a research point of view which were marked as 'X' (i.e.not tested). Did you score them as '0' for the analyses?

Hope you have a lovely Christmas and a very happy and healthy 2018.

Very best wishes,

Wendy

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Dear Wendy

Yes we scored as zero if testing was futile. That is that it would be impossible for the participant to attempt.

Hope this helps.

Have a great Christmas and a very Happy New year

Best wishes
Lorraine

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University Ambassador for Equality and Diversity