TITLE PAGE:

Title:
Evaluation of a home-based standing frame programme in people with progressive Multiple Sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis.

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Evaluation of a home-based standing frame programme in people with progressive Multiple Sclerosis (SUMS): a pragmatic, multi-centre, randomised, controlled trial and cost-effectiveness analysis.

ABSTRACT / SUMMARY

Background:

People severely impaired with progressive Multiple Sclerosis (MS) spend much of their day sitting, with very few options to improve motor function. In response, secondary physical and psychosocial complications can occur. Effective and feasible self-management strategies are needed to reduce sedentary behaviour and enhance motor function. We aimed to assess the clinical and cost-effectiveness of a home-based, self-managed, standing frame programme.

Methods:

A pragmatic, multi-centre (n=8, two regions in the United Kingdom), randomised controlled superiority trial of people with progressive MS and severe mobility impairment, with assessor-blinded outcome assessment using clinician and patient rated measures at baseline, 20 and 36 weeks. Following baseline assessment, participants were randomised (1:1) by computer-generated assignment to either a standing programme plus usual care or usual care alone. The intervention consisted of two home-based physiotherapy sessions (60 minutes each) to set up the standing programme, supported by 6 follow-up telephone calls (15-minutes/call). Participants were asked to stand for 30 minutes, 3 times weekly, over 20 weeks, with encouragement to continue in the longer term, although no further physiotherapy support was provided.

The primary clinical outcome was motor function (Amended Motor Club Assessment, AMCA) at week 36, analysed in the intention-to-treat (ITT) population. A 9-point AMCA change was considered clinically meaningful *a priori*. Adverse events were collected by a daily pre-formatted patient diary throughout the 36 weeks. An economic evaluation established the resources required to provide the standing programme, estimated intervention costs, and conducted a cost-effectiveness analysis.

The trial registration is ISRCTN69614598.

Findings:

Between 16th September 2015 and 28th April 2017, 285 people with progressive MS were screened for eligibility and 140 were randomly assigned; 71 (intervention) and 69 (control). Of these, 122 completed the primary outcome (intervention = 61, control = 61) for the ITT analysis. Most people in the intervention group (66%) stood regularly over the 36 week trial period. Standing resulted in a significant increase in AMCA compared to usual care alone, with fully adjusted between-group difference in AMCA at 36 weeks of 4.7 points (95% confidence interval: 1.9 to 7.5). For the patient diarised adverse events (AEs), there was a disparity between the two groups in the frequency of short-term musculoskeletal pain (standing group = 486 of all 1188 AEs (41%); usual care group = 160 of all 736 AEs (21%)) which was potentially related to the intervention. The musculoskeletal pain lasted for over seven days in five people (standing group = 2; usual care group = 3. No serious AEs related to the study occurred. The additional quality-adjusted life-years (QALYs) in the standing programme group were 0.018, and the estimated incremental cost-per-QALY was approximately £14,700.

Interpretation:

The standing programme significantly increased motor function in people with severe progressive MS, although not to the degree that was considered *a priori* as clinically meaningful. This is one of the first physiotherapy interventions proven to be effective in this group of people. We have demonstrated that the programme is feasible as a home-based, self-managed intervention which could be routinely implemented in clinical practice in the United Kingdom.

Funding:

UK National Institute of Health Research (Research for Patient Benefit Programme) (PB-PG-1013-32047), United Kingdom.

RESEARCH IN CONTEXT

Evidence before this study

The long-term management of people with progressive Multiple Sclerosis (MS) is challenging, particularly when mobility and balance impairments become severe. To investigate the evidence-base for the use of standing frames in people with progressive MS, we searched electronic databases (MEDLINE, AMED, CINAHL, EMBASE, PsycINFO and PEDro) for manuscripts published in English, in adults >18 years, from database inception until 1st August, 2018. Search terms were "multiple sclerosis" and "standing frames" or "standing tables" or "standing wheelchairs". Reference lists from identified papers were checked and www.clinicaltrials.org and the ISRCTN registry searched. No adequately powered randomised controlled trials (RCTs) evaluating the clinical or cost-effectiveness of this intervention were identified. Our search revealed one systematic review of standing in people with upper motor neurone disorders which cited one small pilot RCT in MS (n=6), and one mixed methods study (AB case study design plus interviews, n=9), neither of which exclusively recruited people with progressive MS. To our knowledge, no RCTs of standing frame use in people with MS have been undertaken since our literature search.

Added value of this study

To our knowledge, the SUMS study is the largest RCT of physical rehabilitation in people with progressive MS. It is the first assessor-blinded, multi-centre, RCT to investigate the clinical and cost-effectiveness, safety, and tolerability of a supported standing frame programme plus usual care (intervention) versus usual care alone (control) in people with progressive MS whose standing balance and walking is severely limited. The study is an important addition to the evidence-base for supported standing, for which high-level evidence is currently lacking.

Implications of all the available evidence

The use of a home-based, self-managed standing frame programme can provide a significant improvement in motor function at an estimated incremental cost of approximately £14,700 per quality-adjusted life-year (QALY) and a 0.52 to 0.61 probability of being cost-effective at the National Institute of Health and Care

Excellence threshold of £20,000 to £30,000 per QALY. The intervention was well tolerated in people with MS who were unable to walk or whose mobility is limited to a maximum of 20 metres with a bilateral walking aid. The standing programme significantly increased motor function in people with progressive MS although not to the degree that was considered *a priori* as clinically meaningful. Participants varied in their response to standing, but on average, longer standing times were associated with significantly greater improvements in motor function, with the confidence intervals containing the *a priori* clinically meaningful improvement.

MAIN BODY OF TEXT

Introduction

Multiple Sclerosis (MS) is a progressive, neurological condition, impacting all aspects of people's lives. Affecting approximately 2.5 million people worldwide, it substantially and adversely impacts on an individual's quality of life. MS is associated with high direct and indirect costs to people with MS, their families and society. These costs are highly correlated with increasing immobility.[1]

Mobility is a major concern for people with MS.[2] It is estimated that within 10-15 years of diagnosis, approximately 80% of people will experience impaired mobility. Eventually, an estimated 25% are wheelchair dependent.[3] Mobility spans more than walking, and includes standing, transferring and moving in bed.[4] These are important activities for maintaining independence, particularly for people who are severely physically impaired. Individuals with progressive MS spend much of their day sitting[5], often with limited ability to change position. In response, insidious yet preventable secondary complications can occur including muscle wasting, reduced skin integrity, spasms, constipation, depression and lowered self-esteem.[6] These problems can compound the primary neurological disability, accelerating loss of independence, and can even be mistaken for disease progression. Furthermore, prolonged sitting time is associated with increased risks of morbidity and mortality.[5] The clinical significance of these issues is underlined by their consistent prominence in policy documents for long-term neurological conditions.[4,7]

There is strong evidence that increasing physical activity can improve mobility and minimise secondary health problems in people with mild to moderate MS[8], and evidence suggests that this may also be the case for people with severe MS.[9,10] Despite this, up to 78% of people with MS do not participate in meaningful physical activity.[11] There are considerably more barriers to keeping active when mobility impairment is severe[12]. Interventions have typically been resource intensive, entailing regular supervised sessions by a physiotherapist or sports therapist, within an outpatient or hospital setting, and relying on expensive equipment which cannot be used within the home environment.[9,10] Moreover, data are currently lacking regarding adherence when supervision ceases.

Finite healthcare resources mean on-going supervision of physical activity programmes is rarely possible. Effective self-management strategies, which are low cost and realistic to implement, are needed for people with severe physical limitations to optimise their engagement in physical activity. Regular supported standing using standing frames, which can be used within people's homes, is one such option. Standing frames enable individuals with restricted mobility and balance, lower limb or trunk control, the opportunity to spend time in supported standing. Proposed benefits of standing include strengthening antigravity muscles, providing prolonged weight-bearing muscle stretch, enhancing respiratory function, and maintaining bone density[6]. Whilst preliminary evidence demonstrates benefit for their use in in people with MS[13-15], no appropriately powered RCTs have been undertaken. In line with Newman et al's systematic review[6] findings, we concluded it was important to determine whether a home-based standing frame programme was clinically effective and to explore its cost-effectiveness in people with severe, progressive MS.

Methods

The trial methodology, previously published in detail[16], is briefly described in line with current guidelines[17-20].

The trial is registered with the International Standard Randomised Controlled Trials Number: ISRCTN69614598.

Study Design and Participants

This was an individually-randomised, controlled, pragmatic, multi-centre, superiority trial with blinded outcome assessments in people with progressive MS. Participants were randomised to receive either usual care or usual care plus standing programme, with blinded assessments at baseline and 20 weeks post-randomisation (aligned with end of the protocolised intervention period for those allocated to the intervention group) and again 16 weeks later (36 weeks post-randomisation).

Participants were recruited through eight healthcare organisations, including National Health Service (NHS) Trusts, Social Enterprises and third sector MS Therapy Centres, in two regions (Devon/Cornwall and East Anglia) of the United Kingdom

(UK). Individuals were invited consecutively until the allocated number of frames (dependent on commissioning costs) at each healthcare organisation had been reached. Key inclusion criteria were: individuals aged over 18 years with a diagnosis of progressive MS (primary or secondary) according to McDonald's criteria[21], and scoring 6.5–8.0 on the Expanded Disability Status Scale (EDSS). Key exclusion criteria were: within three months of ceasing an MS disease modifying drug, receiving steroid treatment within the last month or participating in another clinical trial. Full inclusion/exclusion criteria are reported in the protocol paper.[16]

In this ethically approved study (NRES Committee South West – Frenchay, REC reference number: 15/SW/0088) participants were provided with written informed consent before enrolment or undertaking any study-related procedures.

Randomisation and Masking

The 1:1 allocation sequence was undertaken using random-sized permuted blocks, stratified by region (Devon/Cornwall or East Anglia) and baseline EDSS score (≤7.0 or ≥7.5). It was computer-generated in conjunction with an independent statistician who had no further involvement in the trial. The randomisation list and programme that generated it were stored in a secure network location within the UKCRC-registered Peninsula Clinical Trials Unit (PenCTU), accessible only to those responsible for providing the system. Randomisation took place following baseline assessment, with the blinded assessor inputting the participant details directly into the randomisation website.

It was not possible to blind trial participants, carers or treating physiotherapists due to the nature of the intervention. However, outcome assessors (research therapists) were blinded to treatment allocation and all assessments were conducted independently and away from the participant's home. At each assessment time-point, research therapists were asked whether they were unblinded to group allocation, with 89% and 87% answering no at weeks 20 and 36, respectively. The trial statisticians were blinded for the primary analysis of the primary outcome.

Interventions

Participants allocated to the standing group were issued with a wooden Oswestry Standing frame (Theo Davies & Sons, Wrexham, North Wales, http://www.oswestry-frames.co.uk/), funded via the UK NHS commissioning process and delivered to the person's home prior to the first physiotherapy session. The person with MS and their standing assistant (typically their spouse) engaged in two face-to-face, home-based, one-hour physiotherapy sessions, aimed at setting up, implementing and progressing the standing programme according to ability, supplemented by on-line advice and DVDs. These were supported by six scripted telephone calls which utilised a behaviour change approach[22] to increase the participant's self-efficacy, intended to enhance long-term engagement.

In line with previous research[14] participants were asked to stand in the frame for 30 minutes, three times per week over 20 weeks and to record the frequency and duration of each stand in a daily diary. This allowed for a graduated introduction to standing. At the end of the 20 week period participants were encouraged to continue to regularly stand although no further physiotherapy support was provided. On trial completion, participants were able to keep the frame, providing they used it at least once per week.

Use of standing frames is a recognised core skill for UK trained neurological physiotherapists. To standardise and optimise implementation of the intervention, educational materials were provided and assessment of fidelity undertaken[16].

All participants received their usual health and social service input throughout the study period.[16] This input was recorded on a self-report health and social care resource form, which included changes in medication.

Outcomes

Validated outcome measures included clinician-rated assessments and self-reported questionnaires. The primary outcome was motor function as measured by the Amended Motor Club Assessment (AMCA)[23] at the primary end-point of 36 weeks post-randomisation. This was developed for use by physiotherapists in a clinical setting to assess motor function in people with MS and has demonstrated validity, reliability and responsiveness.[14,23,24] The AMCA score (range 0-76) is the sum of two sub-scores. The functional activity sub-score (16 items, each scored 0 - 3) comprises

key functional activities of the trunk and lower limbs, such as rolling in bed, sit-to-stand, sitting and standing balance. The lower limb movement sub-score (14 items, each scored 0 - 2) rates motor impairment by grading hip and knee flexion, knee flexion and dorsiflexion in lying, sitting and standing positions.

Secondary outcomes, at weeks 20 and 36, measured explanatory physical impairments[16] (length of hip flexors, hamstrings and ankle plantarflexors [manual goniometry], knee extensor strength [hand-held dynamometer], spasm frequency [Penn Spasm Frequency Scale] and forced expiratory volume at one second [hand-held spirometer]); clinical outcomes (bowel and bladder control [bladder and bowel control scales], sitting balance [modified functional reach in sitting] and falls frequency); and quality of life (29-item Multiple Sclerosis Impact Scale (MSIS-29 version 2)). AMCA at week 20 and the two AMCA sub-scores at 36 weeks were also measured as secondary outcomes. Participants were classified as “fallers” if they self-reported falling on two or more days during three different periods: (i) up to week 20; (ii) up to week 36; and (iii) between weeks 21 and 36.

All participants were asked to record new symptoms, falls and medication changes in a daily pre-formatted diary. Intervention participants were asked to record frequency and duration of standing sessions and any adverse events experienced.

An embedded qualitative component explored the contemporaneous subjective experiences of using a standing frame within daily life, through audio-recorded diaries by a sub-group of intervention participants. These data will be reported in a future publication.

Statistical Analysis

The target sample size was based on comparing AMCA scores at week 36 between allocated groups, adjusting for baseline AMCA score, and detecting a minimally clinically important difference (MCID) of nine points, assuming estimated standard deviation of AMCA of 20 and estimated correlation between baseline and week 36 AMCA of 0.55.[16] Detection of a nine point between-group difference with 80% power, and at the 5% significance level, required follow-up data from 55 participants per

group. We allowed for 20% loss to follow-up/non-completion of primary outcome and set the recruitment target at 140 participants.

The analyses were pre-specified in a statistical analysis plan (SAP) approved by the Trial Steering Committee before analysis commenced (available at https://www.plymouth.ac.uk/research/sums), except the method of analysis of spasm frequency, as detailed below. Primary analyses were adjusted for the stratification factors (region and baseline EDSS) as fixed effects and baseline scores where appropriate (i.e. fully adjusted models); results adjusted for baseline scores only are also presented. Estimated between-group differences are presented with two-sided 95% confidence intervals (CIs), with the two-sided significance level for hypothesis testing set at 5%. The analyses were conducted using Stata SE version 14.2.

The primary analysis population was defined as all participants who completed baseline and 36-week assessments. The primary analysis of the primary outcome, AMCA score at 36 weeks, followed an ITT approach, regardless of compliance to the intervention, and utilised an analysis of covariance (ANCOVA) approach. As pre-specified in the SAP, Complier Average Causal Effect (CACE) sensitivity analyses were conducted on the 36 week AMCA scores. This method provides an unbiased estimate of the intervention effect, based on those who complied with the standing intervention protocol.[25] The agreed SAP listed six scenarios that could trigger a CACE analysis[25] (appendix, pp 2), if at least 20% of participants allocated to the intervention group were classed as non-compliers in the scenario. The CACE analysis, triggered for all six scenarios, used two-stage least squares instrumental variable regression, with treatment allocation as the instrument for the binary compliance variable and adjustment for baseline AMCA, region and EDSS category.[25]

A repeated measures model was fitted to the post-baseline AMCA scores, including adjustment for baseline AMCA, stratification variables and the interaction term between allocated group and time point. Between-group pairwise comparisons at 20 and 36 weeks were calculated using marginal linear predictions and CIs from the fitted model.

All secondary outcomes were analysed on an ITT basis, utilising an ANCOVA approach, for both fully adjusted models and models with adjustment for baseline measures only, except spasm frequency and falls. Ordinal logistic regression was pre-specified for the analysis of the 5-level Penn Spasm Frequency Scale, however, due to insufficient numbers in some of the response categories, a dichotomisation of no spasms/mild spasms versus infrequent spasms/>1 per hour/>10 per hour was agreed. Logistic regression was used to analyse the dichotomised Penn Spasm Frequency Scale and the binary outcome of fallers/non-fallers with adjustment for stratification factors.

Cost-effectiveness Analysis

A within-trial cost-effectiveness analysis was conducted. This estimated the additional costs of delivering the intervention, costs associated with health, social care, carer and patient resource use, and quality-adjusted life-years (QALYs) over the 36 week trial period. The primary perspective was the UK NHS and Personal Social Services (PSS), with a broader societal perspective considered in sensitivity analyses. Detailed methods are provided in appendix, pp 3-9.

Patient Involvement

People with MS were actively involved throughout, including development of the research questions, study design, trial management and steering groups, writing study materials and dissemination activities.

Role of the Funding Source

This was an investigator-initiated study. The sponsor and funders had no role in study design, data collection, data analysis, data interpretation, or report writing. All authors had full access to all study data and responsibility for writing the manuscript. The corresponding author had the final responsibility to submit for publication.

Results

Figure 1 outlines the flow of participants in the trial. Recruitment took place from 16th September 2015 to 28th April 2017. Participants were aged on average 59.1 years and 64.3% (90/140) were female (table 1). Baseline characteristics were broadly consistent across the allocated groups. Some imbalances in sex and type of MS were observed:

43.7% (31/71) males in the standing group versus 27.5% (19/69) in the usual care group and 39.4% (28/71) primary progressive MS in the standing group versus 23.2% (16/69) in the usual care group. There was an imbalance in baseline AMCA motor function score, with mean (SD) of 26.1 (13.9) points in the standing group and 30.2 (14.6) points in the usual care group (table 2).

Clinical effectiveness

At the primary end-point, 36 weeks post-randomisation, the pooled standard deviation of AMCA at week 36 was 16.9 points, with a correlation between baseline and week 36 AMCA of 0.86. Individual-level changes in AMCA between baseline and week 36 assessments by allocated group are shown in appendix, pp 10. The AMCA at week 36 was significantly higher in the standing group than the usual care group, with fully adjusted between-group mean difference of 4.7 points (95% CI: 1.9 to 7.5, p=0.001) (table 2). Results of the analysis adjusted for baseline AMCA only were similar.

Analyses of both 36-week AMCA sub-scores and short-term AMCA at 20 weeks showed significant fully adjusted between-group mean differences in favour of the standing group. Short-term, statistically significant differences in favour of the standing group were observed at 20 weeks in hip goniometry, knee extensor strength and both the physical and psychological components of the MSIS-29 scale (appendix, pp 11-13). Longer term, at 36 weeks, significant differences were observed in hip and ankle goniometry in favour of the standing group; the short-term differences in MSIS-29 were not sustained at 36 weeks (appendix, pp 14-16). The proportion of participants having ≥2 falls over weeks 21-36 was significantly lower in the standing group, with odds ratio of 0.43 (95% CI: 0.20 to 0.94, p=0.035), but there was no significant between-group difference over weeks 1-20 or the full 36 week study period. Falling days per person year (PPY) was 9.9 amongst the overall sample over the 36 weeks.

Eighteen Serious Adverse Events (SAEs) were reported in 15 participants (usual care group = 7, standing group = 8; three participants each experienced two SAEs), none of which occurred during or in relation to the standing intervention. These were in line with expectation: urinary tract infections (n=8), cardiovascular events (stroke,

n=2; arrhythmia, n=1), breast cancer (n=1), falls (n=3, of whom two fractured a hip), respiratory infections (n=2), and burns (n=1). In two individuals, pressure sores on the heels developed following hospital admission. For one participant, this resulted in the inability to continue frame use following hospital discharge despite regular use pre-hospitalisation

“New symptoms”, recorded via pre-formatted daily diaries, forms the basis of our AE reporting, distinct from the SAE data. Overall, 1924 symptoms were recorded (standing group = 1188, usual care group = 736) (table 3). These were expected in people with MS[3]. There was disparity between the groups in the frequency of short-term musculoskeletal pains such as aching leg muscles (standing group = 486 of all 1188 AEs [41%]; usual care group = 160 of all 736 AEs [21%]), which was potentially related to the intervention. The musculoskeletal pain lasted for over seven days in five individuals (standing group = 2; usual care group = 3).

Pre-specified sensitivity analyses of the primary outcome with additional adjustment for variables with observed baseline imbalance (sex; type of MS) showed no difference in conclusion from the primary analysis results. The planned CACE sensitivity analyses realised results consistent with the primary analysis, although under the CACE approach the average between-group mean differences were larger and all of the CIs included 9.0 (figure 2). The repeated measures modelling gave similar results to the primary analysis, with a significant between-group difference in mean AMCA score at week 20 of 3.7 points (95% CI: 1.2 to 6.2, p=0.004) and at week 36 of 4.5 points (95% CI: 2.0 to 7.0, p<0.001).

Cost effectiveness

The estimated mean (SD) intervention cost per participant was £808 (£91) (appendix. pp 17). The main cost drivers were the standing frame (£504) and physiotherapist home visits (£76). Mean costs to the NHS/PSS over the follow-up period (adjusted for cost at baseline, EDSS category and region) were approximately £539 less for the standing group than the usual care group, excluding the cost of the intervention itself. With the addition of the intervention cost, adjusted mean costs to the NHS/PSS were approximately £268 greater for the standing group (table 4, and appendix, pp 18-26). The amount of informal care used by this population was

substantial, and application of a national average hourly rate to this time gave an adjusted informal care cost of approximately £3,643 less in the standing group (table 4, and appendix, pp 18-26). The mean EQ-5D increase from baseline to 36-week follow-up was 0.042 for the intervention group and 0.01 for the usual care group. This equated to an adjusted mean of 0.018 additional QALYs over the period of follow-up (table 4).

The cost-per-QALY of the intervention from the perspective of the NHS/PSS was approximately £14,700 (appendix, pp 27). Uncertainty around this estimate is illustrated in the cost-effectiveness plane of bootstrapped replicates of incremental costs and incremental QALYs (appendix, pp 28). These simulations suggest that on 87% of occasions the intervention group would have greater QALYs over the period of follow-up than the usual care group. The bootstrap replicates also indicate a 0.52 probability of the intervention being considered cost-effective at a willingness-to-pay threshold of £20,000 per QALY and a 0.61 probability at a threshold of £30,000 per QALY. Broadening the analysis perspective beyond health and social care, in line with the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine[26], increased the apparent cost-effectiveness of the intervention.

There were little missing data, and hence multiple imputation was not employed. Sensitivity analyses explored: i) the broader societal perspective; ii) taking account of the 10-year life of the frames and the NHS's policy of equipment re-use. For both scenarios the intervention appeared dominant in terms of cost-effectiveness (appendix, pp 29-30).

Discussion

Our results provide high-quality evidence that, compared with usual care alone, regular frame standing plus usual care provides significant improvement in motor function (the primary outcome) in people severely physically impaired with progressive severe MS. Statistically significant differences were also found in favour of the standing group in terms of hip and ankle joint range and quality of life (secondary outcomes). This standing intervention was demonstrated to be feasible for people with progressive MS to self-manage with the help of a standing assistant, and for physiotherapists to implement within routine clinical practice.

Less clear cut is whether the outcome of the standing intervention was clinically meaningful. Interpretation is difficult because of the limited evidence to define what constitutes an MCID on the AMCA. We relied upon the only two physiotherapy studies we were aware of which had used the AMCA; both suggested a nine point improvement was clinically relevant in people with severe MS[14,24]. A nine point change could mean, for example, that a person could have improved so that they could balance in sitting to dress themselves (3 points), transfer independently (3 points), and stand without having to use their hands for balance (3 points). However, an improvement in any single one of these functional activities may constitute a clinically meaningful change. This is supported by the audio narrative accounts of the changes experienced by SUMS study participants (see https://www.plymouth.ac.uk/research/sums). When considering the design of future studies, further exploration is needed regarding the MCID on this measure for severely impaired individuals.

Our CACE analysis showed that accounting for compliance to the intervention resulted in a larger estimated intervention effect, with the pre-specified MCID of nine points on the AMCA scale contained within the CIs for all six compliance definitions. This suggests a positive association between compliance with the intervention and the motor benefits gained. This is consistent with theoretical expectation, and the results of (low methodological quality) studies of standing frame use in other neurological populations.[6]

To sustain any benefits gained from physical activity, individuals need to maintain long-term engagement; a particular challenge for people with disability.[27] Evidence is lacking regarding long-term adherence in people with MS to such interventions, however non-adherence rates are as high as 80% for chronic conditions where interventions may aim to slow down decline rather thana 'cure'.[27] Two-thirds of the standing group participants continued to stand regularly in the frame over the 36-week period, which, in light of the literature, we consider as high. Furthermore, 70% requested to keep the frame on completing the study, thus lending support that the intervention was both feasible and acceptable.

Behavioural change techniques were an integral component of the standing intervention. To complement the physiotherapy advice and support, individuals had access to paper-based, DVD and online resources, designed to equip them and their standing assistants with the knowledge and skills necessary to undertake this activity within their own homes. Aimed at enhancing self-efficacy[22], this approach was considered essential since self-efficacy is a key determinant of physical activity behaviour in people with MS[28] and is typically low.[12]

Tolerability of an intervention is important for adherence and so capturing AEs potentially associated with the intervention was important. We achieved this using daily, self-report, pre-formatted diaries. However, free text description of AEs were often ambiguous, making it difficult to determine whether they were new symptoms. It is challenging, therefore, to precisely state what proportion of these broad-ranging symptoms are related to the standing intervention. Bias in reporting of AEs is also possible as the standing group recorded details of each standing session in the same diaries, potentially triggering reporting of new symptoms more comprehensively than the usual care group. Overall, however, the data suggest this intervention is well tolerated; the AEs were typically transient (<7 days), musculoskeletal in nature (aches and pains), and occurred early in the programme when participants were likely adjusting to recommencement of regular standing. Importantly, physiotherapists should inform people that short-term musculoskeletal aches and pains may occur, and provide education about how to manage this. From a methodological perspective, effective and reliable systems for collecting AE data in rehabilitation trials should be further investigated.

There are a number of strengths of this study. To our knowledge this is the largest randomised controlled physical rehabilitation study undertaken in severely impaired people with progressive MS. It is the first definitive multi-centre RCT to assess the clinical and cost-effectiveness, safety and tolerability of a home-based, self-managed standing frame programme in this client group. The study was originally planned to have 80% power based on conservative assumptions[16]; with our observed standard deviation being lower, and correlation between baseline and week 36 AMCA score higher, than anticipated, we are able to estimate the intervention effect with increased precision. Our cost-effectiveness analysis assumed that a new standing

frame would be purchased for everyone in the intervention group; however, given the NHS policy of equipment re-use, and the average 10-year life of a frame, our cost-effectiveness estimate is likely to be conservative.

A further strength is that this is a pragmatic trial. To maximise generalisability of the results we minimised our exclusion criteria. The intervention was delivered by physiotherapists working within the NHS, who did not undergo specific training to deliver the intervention, making it likely that similar results would be gained on implementation within usual practice. It is noted, however, that our findings cannot automatically be generalised to other countries which do not have a similar organisational context. Publication of our educational resources on a freely available website (https://www.plymouth.ac.uk/research/sums) aims to enhance shared, evidence-based, decision making about the impact of introducing this intervention to people's daily life.

This study has several limitations. Our primary economic outcome measure was QALYs, in line with NICE guidance. The difference in EQ-5D scores (used to calculate QALYs) between the standing frame and usual care groups at 36-weeks does not reach the MCID for the EQ-5D described by Marra et al.[29] Therefore, it could be argued that the QALY gain is not perceptibly different from zero, implying that the intervention is not cost-effective. However, the standing frame intervention does appear effective from the patient perspective when considered across outcome measures, and specifically according to the primary clinical outcome measure. Our main analysis may have been restrictive in identifying benefits of the intervention, and a broader societal perspective may have been preferable.

The usual care group was not offered an intervention and hence we cannot exclude that placebo effects contributed to the benefits experienced by the standing group. However, the primary outcome was clinician-rated and measured by a blinded assessor which should limit the impact of this. Nevertheless, further research is needed to disentangle the intrinsic effects of standing from non-specific effects due to, for example, attention. It is also possible that drug interventions may have contributed to any changes. However, participants were excluded if there had been any recent changes in disease modifying therapies, and asked to record any

medication changes throughout the study period; the two groups were balanced in terms of medication changes, hence this is unlikely to account for the between-group differences.

In conclusion, there is a paucity of evidence-based, self-management interventions which are recommended for people severely impaired with progressive MS who have limited available treatment options. We hope this intervention will now be offered and reimbursed more widely as a management option for this population.

AUTHORS STATEMENTS AND FORMS

Role of the Funding Source

This was an investigator-initiated study. The sponsors and funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and were responsible for writing the manuscript. The corresponding author had the final responsibility for content and the decision to submit for publication.

Contributors

JF, WH, LJ, SC and AB developed the study. JF, WH, LJ, SC, AB, AH, JZ contributed to trial design, data interpretation, and writing of the report. RD contributed to data acquisition, data interpretation, and writing of the report. SC and BJ were responsible for the statistical analysis and data interpretation. All authors approved the final draft of the manuscript.

Declaration of Interests.

The authors have no conflicts of interests to declare.

Data sharing.

The SUMS study protocol and statistical analysis plan are publically available at https://www.plymouth.ac.uk/research/sums. Individual participant data that underlie the results will be made available (following de-identification) on a controlled access basis, subject to suitable data sharing agreements. Requests for data sharing should be made to the Chief Investigator (CI, Freeman) in the first instance. Requesters will be asked to complete an application form detailing specific requirements, rationale and proposed usage. Requests will be reviewed by the CI and study Sponsor who will consider the viability and suitability of the request and the credentials of the requester. Where access to requested data is granted, requesters will be asked to sign a data sharing agreement. Requested data will be made available, along with supporting documentation (e.g. data dictionary) on a secure server or via other secure data transfer method.

Acknowledgements.

The study was fully funded by the National Institute of Health Research (Research for Patient Benefit Programme) (PB-PG-1013-32047), United Kingdom. The authors are indebted to all participants of the SUMS trial. We are grateful to physiotherapists at each NHS site who were instrumental for the successful implementation of the standing programmes, and to Steve Hooley, Emily Rogers and Danielle Munford who undertook the blinded assessments. We thank David Russell and Helen Cherry who were our patient representatives, Carol Lunn our study administrator, Professor Paul Ewings for methodological advice, and Pauline McGlone (Chief Operating Officer Clinical Research Network South West) for her assistance with negotiating excess treatment costs.

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Figure 1: CONSORT Flow Diagram.

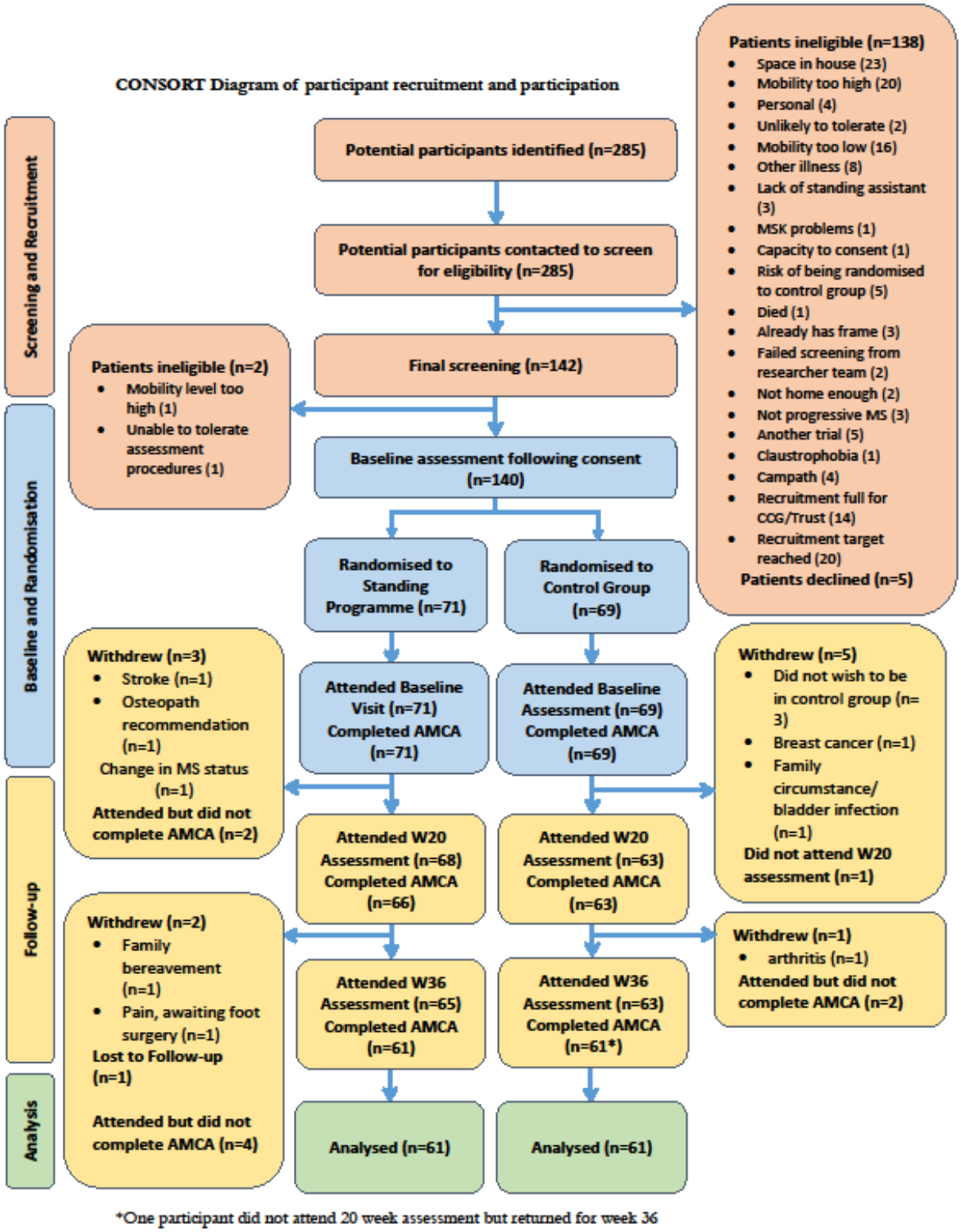
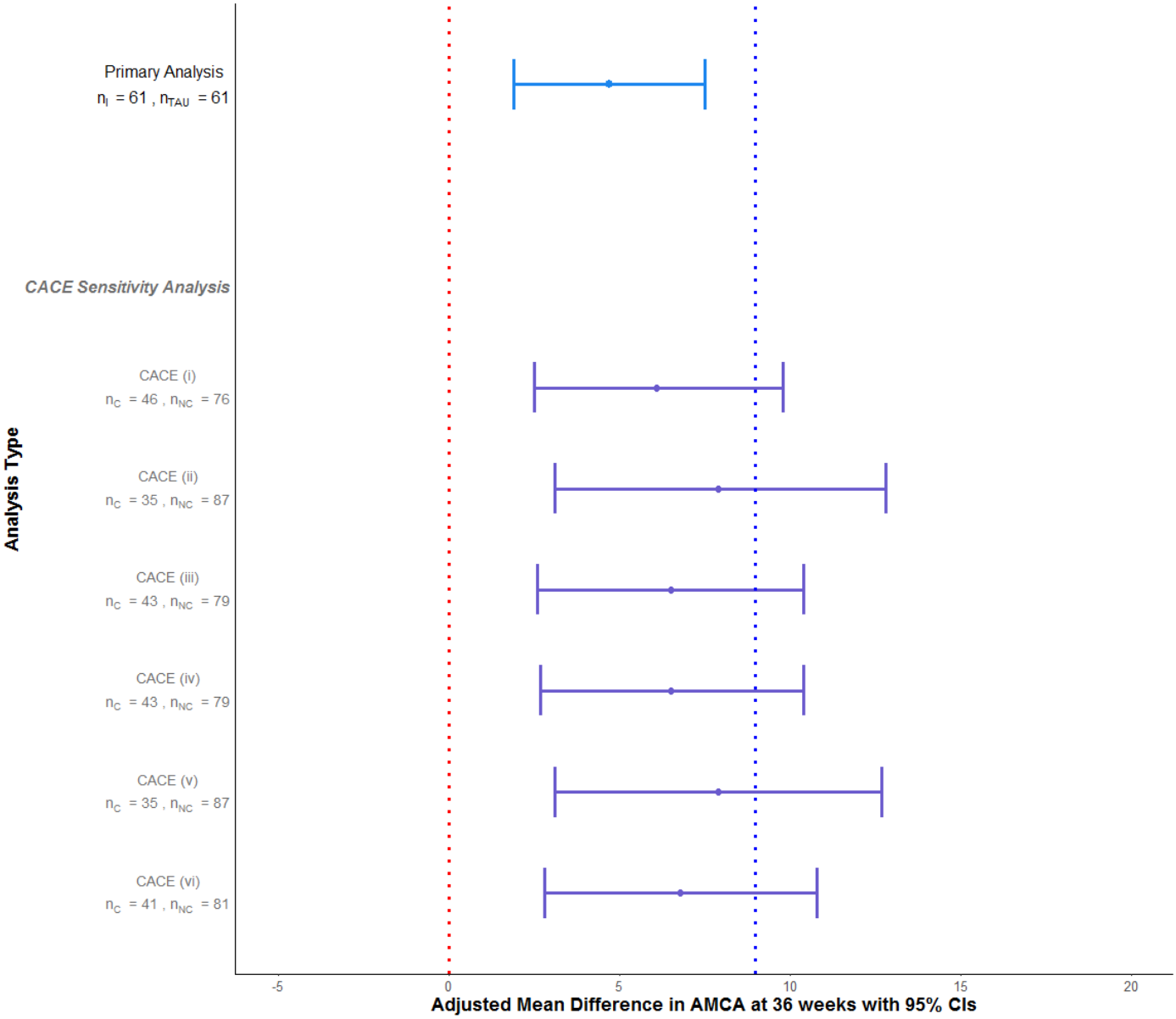


Figure 2: Fully Adjusted mean difference in the primary outcome, AMCA at 36 weeks, for (a) the primary analysis and (b) the CACE sensitivity analyses under the six compliance definitions, with corresponding 95% confidence interval (CIs).



Note: n_I is number of participants in intervention group; n_{TAU} is number of participants in control group; n_C is number of compliers; n_{NC} is number of compliers plus control group participants

Table 1 – Demographic Data and Baseline Characteristics

% (n) unless specified	**Standing Group (n=71)**	**Usual Care Group (n=69)**	**All (n=140)**
Mean (sd) [range] **Age** (years)	58.5 (9.5) [34.9, 75.2]	59.6 (9.3) [39.8, 80.7]	59.1 (9.4) [34.9, 80.7]
Mean (sd) [range] **EDSS Score**	7.3 (0.6) [6.5, 8]	7.2 (0.6) [6.5, 8]	7.3 (0.6) [6.5, 8]
EDSS Score			
6.5	33.8 (24)	26.1 (18)	30.0 (42)
7.0	15.5 (11)	24.6 (17)	20.0 (28)
7.5	15.5 (11)	23.2 (16)	19.3 (27)
8.0	35.2 (25)	26.1 (18)	30.7 (43)
Sex			
Male	43.7 (31)	27.5 (19)	35.7 (50)
Female	56.3 (40)	72.5 (50)	64.3 (90)
Type of MS			
Primary Progressive	39.4 (28)	23.2 (16)	31.4 (44)
Secondary Progressive	60.6 (43)	76.8 (53)	68.6 (96)
Most Recent Relapse			
> 1 year	87.3 (62)	91.3 (63)	89.3 (125)
Within three months	2.8 (2)	2.9 (2)	2.9 (4)
Within six months	2.8 (2)	0.0 (0)	1.4 (2)

% (n) unless specified	**Standing Group (n=71)**	**Usual Care Group (n=69)**	**All (n=140)**
Within 12 months	1.4 (1)	2.9 (2.9)	2.1 (3)
Unknown	5.6 (4)	2.9 (2.9)	4.3 (6)
Occupation			
Unemployed	7.0 (5)	4.3 (3)	5.7 (8)
Student	0.0 (0)	1.4 (1)	0.7 (1)
Part Time Work	2.8 (2)	10.1 (7)	6.4 (9)
Full Time Work	1.4 (1)	1.4 (1)	1.4 (2)
Age Retired	9.9 (7)	11.6 (8)	10.7 (15)
Medically Retired	78.9 (56)	71.0 (49)	75.0 (105)
Indoor Walking Aid			
1x Stick	4.2 (3)	2.9 (2)	3.6 (5)
2x Stick	9.9 (7)	11.6 (8)	10.7 (15)
Frame	38.0 (27)	43.5 (30)	40.7 (57)
Wheelchair	66.2 (47)	69.6 (48)	67.9 (95)
Outdoor Walking Aid			
1x Stick	2.8 (2)	2.9 (2)	2.9 (4)
2x Stick	8.5 (6)	8.7 (6)	8.6 (12)
Frame	15.5 (11)	21.7 (15)	18.6 (26)
Wheelchair	94.4 (67)	92.8 (64)	93.6 (131)

% (n) unless specified	**Standing Group (n=71)**	**Usual Care Group (n=69)**	**All (n=140)**
Wheelchair Use			
None	5.6 (4)	5.8 (4)	5.7 (8)
Occasionally	5.6 (4)	4.3 (3)	5.0 (7)
Monthly	2.8 (2)	1.4 (1)	2.1 (3)
Weekly	18.3 (13)	14.5 (10)	16.4 (23)
Daily	67.6 (48)	73.9 (51)	70.7 (99)
Medical History			
Nil of note	19.7 (14)	18.8 (13)	19.3 (27)
Osteoarthritis	8.5 (6)	13.0 (9)	10.7 (15)
CHD/Hypertension	21.1 (15)	13.0 (9)	17.1 (24)
Diabetes	11.3 (8)	1.4 (1)	6.4 (9)
COPD	8.5 (6)	1.4 (1)	5.0 (7)
Migraine	9.9 (7)	7.2 (5)	8.6 (12)
Other Neurological	5.6 (4)	4.3 (3)	5.0 (7)
Depression	38.0 (27)	43.5 (30)	40.7 (57)
Osteoporosis	7.0 (5)	11.6 (8)	9.3 (13)
Other	35.2 (25)	33.3 (23)	34.3 (48)

Table 2 – Primary Outcome: AMCA score at 36 weeks. Primary Intention to Treat (ITT) Analysis and Complier Average Causal Effect (CACE) Sensitivity Analyses

	Mean (sd) [range] of AMCA				Fully Adjusted Analysis[1]	Analysis Adjusted for Baseline only
	Standing Frame (n=71)		Usual Care (n=69)		Mean Difference (Standing – Usual Care) (95% CI)	Mean Difference (Standing – Usual Care) (95% CI)
	Baseline (n=71)[2]	Week 36 (n=61)[2]	Baseline (n=69)[2]	Week 36 (n=61)[2]		
ITT Analysis	26.1 (13.9) [3.0, 59.0]	29.3 (17.2) [1.0, 68.0]	30.2 (14.6) [6.0, 66.0]	28.2 (17.0) [0.0, 68]	4.7 (1.9, 7.5) p=0.001	4.6 (1.6, 7.6) p=0.003
	Compliers		Non-compliers + Usual Care			
	(n = 49)[2]	(n=46)[2]	(n=91)[2]	(n=76)[2]		
CACE: Best 16 Weeks	26.2 (13.7) [3, 56]	29.9 (16.0) [6, 65]	29.1 (14.6) [6, 66]	28.4 (17.5) [1, 68]	6.1 (2.5, 9.8) p=0.001	6.1 (2.2, 9.9) p=0.002

	(n=36)[2]	**(n=35)[2]**	**(n=104)[2]**	**(n=87)[2]**		
CACE: Worst 16 Weeks	28.2 (13.4) [8, 56]	31.6 (16.4) [8, 65]	28.1 (14.7) [3, 66]	27.9 (17.1) [1, 68]	7.9 (3.1, 12.8) p=0.001	7.9 (2.8, 13.0) p=0.003
	(n=46)[2]	**(n=43)[2]**	**(n=94)[2]**	**(n=79)[2]**		
CACE: Weeks 5-20	26.7 (14.0) [3, 56]	30.5 (15.9) [6, 65]	28.8 (14.5) [6, 66]	28.1 (17.5) [1, 68]	6.5 (2.6, 10.4) p=0.001	6.5 (2.3, 10.6) p=0.002
	(n =46)[2]	**(n=43)[2]**	**(n=94)[2]**	**(n=79)[2]**		
CACE: Best 32 Weeks	26.6 (14.0) [3, 56]	32.4 (16.6) [6, 65]	28.0 (14.5) [6, 66]	27.7 (17.5) [1, 68]	6.5 (2.7, 10,4) p=0.001	6.5 (2.4, 10.5) p=0.002
	(n=36)[2]	**(n=35)[2]**	**(n=104)[2]**	**(n=87)[2]**		
CACE: Worst 32 Weeks	28.4 (13.9) [8, 56]	32.4 (16.6) [6, 65]	28.0 (14.5) [3, 66]	27.5 (16.9) [1, 68]	7.9 (3.1, 12.7) p=0.001	7.8 (2.8, 12.9) p=0.002
CACE: Weeks	**(n=42)[2]**	**(n=41)[2]**	**(n=98)[2]**	**(n=81)[2]**		
	27.3 (13.8)	31.9 (15.7)	28.5 (14.6)	27.5 (17.4)	6.8	6.8

5-36	[3, 56]	[6, 65]	[4, 66]	[1, 68]	(2.8, 10.8) p=0.001	(2.6, 11.0) p=0.002

[1] Adjusted for baseline AMCA Score, region and EDSS category; [2] n is the total number of participants who provided data at that time point

Table 3

Self-reported adverse events according to allocated group

Self-reported Symptoms lasting < 7 days	**Usual Care group (n = number of events*)**	**Standing Frame group (n = number of events*)**
Pain	180	551
Categorised according to organ classification		
Musculoskeletal	*160*	*486*
Neurological	*12*	*16*
Abdominal	*6*	*9*
Gynaecological	*2*	*0*
Renal	*0*	*2*
Respiratory	*0*	*1*
Spasms	197	231
Fatigue	184	60
Urinary tract infection	36	45
Numbness / sensory disturbance	33	41
Tremor /shaking	24	7
Weakness	23	24
Constipation / diarrhoea	17	7
Vertigo	9	22
Virus	5	31
Chest Infection	5	16
Leg or back stiffness/ tightness	2	23
Headache	3	3
Visual disturbance	3	3
Seizures	2	0
Balance problems	2	5
Loss of bladder control	2	0
Slurred speech	1	0
Multiple Sclerosis Relapse	1	1
Confusion	1	0
Rash	1	0
Toe infection	1	0
Shingles	1	0
Bladder spasms	1	2
Blood in urine	1	0
Nausea /vomiting	1	2
Low sodium	0	1
Ankle swelling	0	4
Depression	0	1
Shortness of breath	0	3
Tennis elbow	0	1
Low blood pressure	0	3
Bruising	0	1
Total number of adverse events* lasting < 7 days	**736**	**1188**

Adverse events lasting >7days	**Usual Care group (n=number of participants)**	**Standing Frame group (n=number of participants)**
Urinary tract infection	4	10
Chest infection	5	10
Nervous system: *Spasms* *Fatigue* *Weakness* *Stiff legs*	6 *4* *1* *1* *0*	4 *2* *2* *0* *1*
Bowel difficulties	3	0
Infection	0	1
Psychiatric (depression)	0	1
Musculoskeletal pain	3 *coccyx pain (18 days)* *heel pain (9 days)* *hip pain (22 days)*	2 *back pain (11 days)* *joint ache (14 days)*
Total number of participants reporting adverse events lasting > 7 days	**21**	**28**

*n = the number of days on which the adverse event was self-reported (i.e. event days rather than number of participants reporting the adverse event)

Table 4 – Estimated costs and EQ-5D values by group, and adjusted cost and adjusted QALYs differences, over 36-week follow-up

	Standing frame intervention (n=71)		**Usual care (n=69)**		**Difference adjusted for baseline covariates***
Resource item	*n*	*Mean (SD) £*	*n*	*Mean (SD) £*	*Mean (95% CI)** £*
Primary care	65	594.58 (831.29)	62	470.46 (681.94)	15.79 (-199.74, 248.23)
Secondary care	65	1,787.40 (4,155.02)	62	2,074.17 (3,836.70)	-284.82 (-1,368.04, 1,077.62)
Personal social services	65	477.58 (1,359.09)	62	947.28 (3,086.93)	-10.78 (-408.81, 369.46)
Total NHS/PSS (excluding standing frame intervention)	65	2,859.56 (4,958.43)	62	3,491.91 (5,408.15)	-539.27 (-1,953.60, 1,138.40)
Standing frame intervention	54	807.74	-	-	-
Total NHS/PSS	65	3,667.30 (4,958.43)	62	3,491.91 (5,408.15)	268.47 (-1,093.79, 2,051.38)
Patient personal costs	65	2,999.25 (6,951.45)	62	2,117.50 (3,437.69)	709.07 (-998.70, 2,469.58)
Informal care	65	16,047.16 (9,944.57)	62	18,624.35 (13,589.22)	-3,643.34 (-6,020.19, -1,348.18)
Total costs (NHS, PSS, patient and informal care)	65	21,905.97 (12,147.65)	62	24,233.75 (13,464.93)	-2,192.41 (-5,755.23, 1,163.43)
Measure: time point	*n*	*Mean (SD) [range]*	*n*	*Mean (SD) [range]*	*Mean (95% CI)**
EQ-5D: Baseline	71	0.224 (0.272) [-0.352 to 0.813]	69	0.251 (0.274) [-0.265 to 0.778]	
EQ-5D: 20 weeks	68	0.294 (0.269) [-0.256 to 0.813]	63	0.271 (0.304) [-0.319 to 0.779]	
EQ-5D: 36 weeks	65	0.266 (0.303) [-0.307 to 0.767]	63	0.262 (0.293) [-0.358 to 0.836]	

QALYs (based on the EQ-5D) over the 36-week follow-up	65	0.189 (0.174) [-0.125 to 0.549]	62	0.183 (0.182) [-0.142 to 0.544]	0.018 (-0.014, 0.051)

*Cost (specific to each cost component)/EQ-5D value at baseline, EDSS category (>=7.5,<7.5) at baseline, and region
** From bootstrap with 10,000 replication.