Clinical efficacy of the **S**oft-Scotch **W**alking **I**nitial **F**oo**T** (SWIFT) Cast on walking recovery early after stroke and the neural-biomechanical correlates of response

Lay summary

Weakness of the leg and foot is common after stroke. This affects peoples' everyday lives. For example, being unable to cross the road in the time allowed at most Pelican crossings. Current therapies often have disappointing outcomes. Some treatments may be beneficial but this largely depends on patients' ability to participate actively in functional exercise. Patients with substantial weakness, however, those who most need therapy, may not be able to do this. A common problem limiting ability to practice walking is when the affected foot cannot be held in the correct position in relation to the lower leg. The present study will investigate whether a splint designed to maintain a correct position of the foot on the leg will enable people to participate in more walking re-training and thus have a better outcome after stroke.

The proposed study will be a two-group clinical trial. All participants will receive standardised conventional physical therapy. Participants will be randomly allocated to receive either the splint (SWIFT Cast) or no extra intervention. The outcome measures that will be used to assess whether the SWIFT Cast is beneficial will be: walking speed and ability to walk independently. The measures will be made before treatment begins, after 6 weeks treatment and 6 months after stroke. The trial is designed to find whether the benefits of using the SWIFT Cast justify a subsequent larger trial. Embedded in the trial are some measures which aim to increase understanding of how the central nervous system (brain and spinal cord) recovers after damage caused by stroke. We know that central nervous system recovery occurs due to reorganisation of nerve networks in the brain and spinal cord. We do not know how we can use physical therapies to encourage beneficial reorganisation so that we can improve outcomes for stroke survivors. We also do not know which stroke survivors should receive which physical therapies.

Neuroimaging of the brain has provided our current understanding but this cannot give us the specifics that we need to guide treatment decisions to improve ability to walk after stroke because of technological limitations. A way forward is provided by using biomechanics to investigate biological mechanisms of walking recovery after stroke (e.g. how movement at different joints is co-ordinated and how muscle activity moves body segments and maintains balance). Biomechanics involves measurement of movement and postural control during walking in free space without application of either radiation or magnetic fields. We will combine brain imaging to define the stroke damage with biomechanics to define the biological mechanisms of walking with clinical measures of ability to walk. We will therefore be able to find how the biological mechanisms of walking change over time in the two groups of participants and whether these changes are associated with improvements in ability to walk. Thus we will gain insight as to how different forms of physical therapy might be working in stroke survivors with different parts of their brain damaged by the stroke.

Every person recruited as a participant in this clinical trial will first be required to provide written informed consent. No routine treatment will be with-held from participants in this clinical trial whether people are allocated to the SWIFT Cast group or not.

Background to this trial

Stroke is the single largest cause of adult disability. Each year in England approximately 110,000 people suffer a stroke. Each year the approximate costs are: £2.8 billion direct health and social care costs (more than the cost of coronary heart disease); £1.8 billion to the community in terms of lost productivity and disability; and £2.4 billion in costs to informal carers[1]. The majority of this is related to "rehabilitation and life after stroke" [1]. Although better preventative and acute care interventions have decreased incidence and mortality rates the impact on the NHS is unlikely to decrease. This is because the majority of strokes occur in people aged over 65 years and the percentage of older people in the population will increase to 23% in 2031 (16% in 2003). The ageing population therefore presents a challenge to the NHS to improve stroke rehabilitation. Thus recovery of walking after stroke is an important health problem that limits functional independence as at least 300,000 people in England alone are living with moderate/severe disability as a result of stroke[1]. Evaluation of stroke rehabilitationis identified as a research priority for the NHS in the National Stroke Strategy[2].

It is known that physical therapy for motor problems in stroke survivors is generally effective[3], the majority of motor recovery may occur in the first three months after stroke[4] and that during this period the CNS might have most potential for reorganisation[5]. Progress now requires determination of the process of CNS recovery associated with clinical improvement (mechanisms) and which physical therapies should be provided (efficacy) for which stroke survivors (prognostic indicators)[6]. Addressing these questions requires biomechanical and neuro-structural investigation of the efficacy of well-characterised interventions for which proof-of-principle is established and at the same time using these interventions to determine how the CNS responds in the presence of different stroke lesions. The rationale for investigating efficacy and mechanisms together in an Phase II trial such as this present proposal has been summarised by van der Wilt and Zielhuis[7]:

a. effectiveness and mechanism are closely linked - “an intervention is always based on an idea or a model of how the symptoms of a disease present and how an intervention might exert its effect.”;
b. “an intervention can be effective, even though it is based on an erroneous assumption about its mechanism of action”;
c. “the effectiveness of an intervention can be assessed, without enquiring into its mechanism of action. Although such a study might produce important information, it does not improve knowledge of the underlying pathophysiological processes. Not having such knowledge might hinder development of novel and potentially more efficacious interventions in the long term”. In terms of motor recovery after stroke knowledge of CNS recovery processes is expected to aid further development of therapies so that they can be targeted closer to the underlying CNS deficits.

Hence investigating efficacy and mechanisms together in this proposed trial should provide robust information to ensure that subsequent Phase III trials investigate the effectiveness of a SWIFT CAST targeted at the underlying CNS mechanisms of walking deficits early after stroke in those people most likely to respond More generally, the results of this proposed trial, using a SWIFT CAST as a probe of CNS recovery, are expected to contribute to knowledge of the CNS mechanisms of walking recovery after stroke. The need for such research has been highlighted by the Academy of Medical Sciences[6].

Introduction

This trial is directed at a key focus for stroke survivors, namely, the ability to walk again. Walking is a critical pre-requisite for functional independence. Yet, at discharge from rehabilitation, stroke survivors may only walk at 0.55 metres per second (m/s) well below normal (1.2 to 1.4 m/s) and not even fast enough to cross a road before the lights change (0.8m/s)[8]. At one year after stroke only approximately 60% of total possible recovery (measured by the Fugl-Meyer Leg Assessment) may be acheived[9]. Current methods of walking rehabilitation are under-evaluated and have mostly evolved from clinical experience and unsystematic application of neurophysiological principles[10]. There is an urgent need for better methods of gait rehabilitation which are based on a scientific understanding of how the central nervous system (brain and spinal cord:CNS) recovers after stroke[1].

A modified systematic review found that clinical improvement in motor function after stroke is accompanied by brain reorganisation[11]. The patterns of brain reorganisation associated with motor recovery, mostly assessed via functional magnetic resonance imaging (fMRI), include[12-15]:

- different sites of activation relative to healthy adults and over time;
- change in laterality of activation e.g. from contralesional to ipsilesional;
- involvement of distributed sensorimotor networks including areas not normally involved in movement execution;
- focusing of activation over time particularly in ipsilesional sensorimotor cortex;
- activation in peri-infarct cortical region.

More specifically, different areas of the motor execution system, including ipsilesional pre-motor cortex, ipsilesional supplementary motor area and contralesional primary motor cortex (M1), may be associated with recovery. Best recovery may be related to remaining intact functional connectivity[13] and/or to activation in spared M1[13].

These findings can only be used to a limited extent to inform a) the provision of physical therapies targeted at enhancing recovery of walking early after stroke and b) prognostic indicators for response to these. Most fMRI studies use models of upper limb movement to investigate participants who: are able to perform the movements required for fMRI (high level of motor function at baseline); have no contraindications to fMRI (e.g. no implanted metal); are 10-20 years below the mean age of stroke survivors; and, are late after stroke. Clinical usefulness is also limited by the different physical therapy interventions employed[17] and variations in lesion sites[18,19.] Exactly how these changes relate to recovery of walking early after stroke therefore remains unclear.

The limitations of fMRI can be avoided by using biomechanical investigations of mechanisms of walking. Biomechanics involves the investigation of human movement performance and control as expressed in the kinematics and kinetics of body segments. Detailed biomechanical gait analysis can be achieved in the clinical environment using video based movement analysis systems such as the one proposed for use in this study in which video film is replayed at slow speed or using freeze frame facilities. Such systems have been widely used in sports biomechanics. Measures of efficiency of gait can be made as expressed by rapid, smooth and symmetrical forward progression of the body including: suitable foot placements and timings and joint angular displacements. These measures can be made during everyday functional tasks in free space without application of either radiation or magnetic fields. Thus valid and reliable measures of the end product of neural activity in the CNS can be recorded in most patients early after stroke and used to advance knowledge of which physical therapies to use with stroke survivors[20-22]. This is important as it is known that excitability of the anterior horn cell is not just influenced by descending neural information via the corticospinal pathways but also via the reticulospinal system [23] and enhanced propriospinal activity[24]. Recently, changes in brain activation, as measured by near infra-red spectroscopy, have been found to be significantly correlated with improvements in biomechanical measures of gait[24] giving further validation to this biomechanical approach. When used with participants with well-characterised lesions, described by structural neuroimaging, who are representative of stroke survivors early after the ictus biomechanics offers an opportunity to increase understanding of how well-defined physical therapies can enhance the recovery process in the CNS after stroke[25-27]. In addition structural neuroimaging will increase understanding of how brain damage is linked to prognosis for response to such restorative therapies. Although several brain areas have been associated with lower limb weakness and/or gait deficit after stroke (e.g. posterior third of the internal capsule and medial centrum semi-ovale[28]) whether these are related to response to specific restorative therapies remains unknown. Combining biomechanics and structural neuroimaging (neuro-biomechanics) will enhance understanding of how the CNS recovers as it will enable investigation of the influence of the brain lesion on movement performance. Using this information to inform clinical decisions about which targeted therapies should be provided (efficacy) for which stroke survivors (prognostic indicators) requires investigation using well-defined physical therapies with a scientific rationale.

Walking is probably the most complex automatic activity in humans and requires correct biomechanical alignment of body segments. Indeed walking requires co-ordination of muscles in the lower limbs, upper limbs, spine, torso, neck and head[26]. The required movement control (tempo-spatial coordinated

activation of muscle/s to generate appropriate force to produce coordinated and controlled movement during the desired task) emanates from activity in a widely distributed CNS network[29,30]. Walking is therefore a neuro-biomechanical activity which cannot be investigated adequately using fMRI to elucidate the CNS mechanisms of walking recovery after stroke (limitations outlined in section 3.1). Hence better understanding of the neuro-biomechanical correlates of 'spontaneous' and therapy-enhanced walking recovery is expected to be informative about the recovery process in the CNS after stroke[25-27]. The most well known example for the benefits of using neuro-biomechanics is the improvements in clinical outcomes that have resulted from its use with children with cerebral palsy to enable precise characterisation of the underlying mechanisms of walking deficit and thus information to guide the most appropriate surgical[31] and orthotic intervention[32].

Compared with the walking performance of healthy adults, stroke survivors exhibit asymmetry (e.g. shorter stance time on paretic side)[33] due to abnormalities such as: initial contact on ground with a foot-part other than the heel; hyperextension of knee in mid/late stance; and flexion of hip in terminal stance[34]. Reviews suggest that task-orientated goal-directed functional training may improve outcome after stroke. When patients have sufficient voluntary activation for repetitive voluntary contraction of paretic muscles they can participate in this form of walking training. If, however, they have substantial weakness, providing such training presents a challenge. Furthermore, if the paresis results in substantial biomechanical gait abnormality (e.g. abnormal initial foot contact) it is possible that abnormal patterns of walking could a) have a detrimental effect on re-organisation of neuronal networks; and, b) lead to maladaptive changes in the musculoskeletal system (e.g. contracture, disuse atrophy), which are associated with poorer functional ability. Consequently it is important to have repetitive practice of a biomechanically normal walking pattern as soon as possible early after stroke.

An ankle foot orthosis (AFO) may achieve this aim by positioning the foot in relation to the lower leg so that normal alignment is optimised. This leads to suitable segment orientations relative to gravity and correct alignment of the line of weight bearing through the leg, normal joint moments at hip, knee and ankle which help control the limb and provide shock absorption and propulsion and energy storage and return so that an efficient gait is produced[26]. Clinical use of an AFO early after stroke has been recommended by an International Consensus Conference[35] and identified as an area for clinical improvement by NHS Quality Improvement Scotland (michelle.miller2@nhs.net). Research evidence is, however, limited. In preparation for this proposed trial we have undertaken a modified systematic review of studies investigating the effects of an AFO on people with inability to take weight through the paretic leg and/or foot drop within 3 month of the ictus. Two of the 39 identified studies met the inclusion criteria but sample sizes were small. Our review suggested that wearing an AFO produced immediate improvement in walking. Preliminary evidence for benefit on walking has also been found by an upcoming Cochrane review although this is insufficient to recommend clinical use early after stroke[36]. Proof-of-concept is established and robust evaluative studies are now required.

The optimal type of AFO is considered to be a device customised for individuals by an orthotist[35]. Obtaining such an AFO within an appropriate timescale early after stroke, however, is problematic and an International Consensus Conference recognised that that a non-customised device could be used "where there is a need for early mobilisation before a custom orthosis can be provided" [35]. Off-the-shelf AFOs can be applied immediately by the treating physiotherapist but cannot be individually cast or tailored which is a substantial disadvantage for the often experienced complex presentations after stroke. Hence these are not widely acceptable. A better clinical alternative is a soft-scotch ankle-foot cast (SWIFT CAST) made by a researcher with appropriate biomechanical training which can be provided to stroke survivors within 24 hours. We, VP and RS, have conducted a pilot study (unpublished) of the immediate effects of a SWIFT CAST on gait parameters of 10 stroke survivors. The SWIFT CAST produced immediate increase in mean walking speed of 0.04 (SD 0.077) m/sec with a biomechanically improved gait. Thus proof-of-principle for using a SWIFT Cast has been established. In addition, a Quality Improvement Scotland scoping project on AFO use early after stroke, undertaken by PR, indicated the readiness of the stroke community to adopt this intervention into clinical practice. A Phase II trial to investigate efficacy is now required. A search of the Current Controlled Trials Register, HTA website and world wide web found no ongoing trials of orthotics early after stroke.

In summary this trial aims to determine: the clinical efficacy of a Researcher-made ankle-foot cast on reduction of walking disability early after stroke; the process of CNS recovery associated with clinical improvement (mechanisms); and which stroke survivors may be most likely to respond (new scientific/clinical principles). The results are expected to lead to important advances in healthcare focused on increasing the ability of stroke survivors to lead independent lives.

Research objectives

The primary driver for this research is the clinical hypothesis, generated by our pilot work, that an individualised and rapidly produced ankle-foot cast (SWIFT CAST) used in addition to protocol-driven conventional physical therapy (CPT) early after stroke is more cost-effective than protocol-driven CPT alone for walking recovery. The scientific premise driving this research is that detailed understanding of how the central nervous system recovers after stroke will enable physical therapies to be targeted at recovery mechanisms in those stroke survivors most likely to respond. Progress is hampered as the predominant means of investigation, fMRI, has technological limitations and physical therapies used to investigate the central nervous system have been poorly defined. Neuro-biomechanics together with well-defined physical therapies provides a novel way forward. This research will determine clinical efficacy of a SWIFT CAST, as a precursor to a subsequent Phase III trial, and use this and protocol-driven CPT to investigate neuro-biomechanical correlates of clinical improvement. Specific questions are:

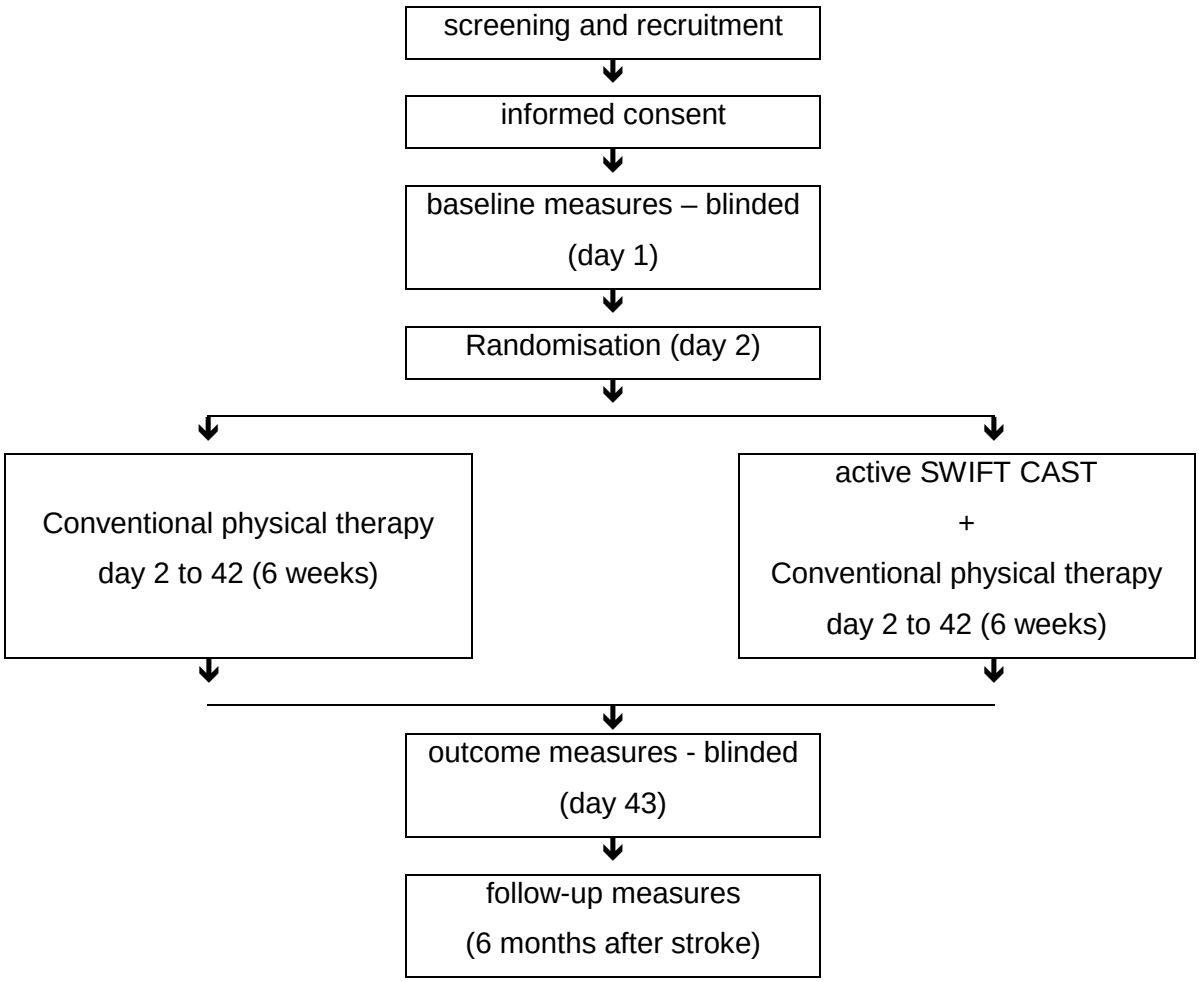
1. Does the use of a SWIFT CAST provided as an adjunct to CPT enhance walking recovery early after stroke more than CPT given alone? (clinical efficacy);
2. What are the biomechanical correlates of clinical improvement in walking in response to SWIFT CAST and protocol-driven CPT? (understanding biological and behavioural mechanisms);
3. Is site of stroke lesion (structural MR) and/or biomechanical characteristics sufficiently predictive of improvement in walking to enable targeting therapy at stroke survivors likely to respond? (new scientific and clinical principles).

In addition, the combination of structural imaging, biomechanics and protocol-driven physical therapy is a novel combination in stroke rehabilitation research and we are therefore also asking:

4. Should neuro-biomechanics and protocol-driven physical therapy be used together with structural neuroimaging to enhance knowledge generated by stroke rehabilitation research? (development/testing of new methodologies).

Research design

Randomised, controlled, observer-blind Phase II trial. The randomisation sequence will use minimisation with a) ability to walk independently as assessed by: the Functional Ambulation Category (FAC) (higher functioning = score 3-5 of FAC and lower functioning = score **I**-2 of FAC[37]), b) involvement of the primary motor cortex (MI) in stroke lesion (yes/no); and c) clinical centre (Norwich/Glasgow). An independent telephone randomisation service will be used. Bias protection is thus provided by blinding of assessors, concealment of randomisation order and group allocation via independent telephone service.



Study population

Participants will be recruited from in-patient stroke services and will be followed up until 6 months after stroke wherever they are living. Study criteria (combined inclusion and exclusion) are:

- aged 18+ years, 3-42 days after stroke, infarct or haemorrhage, confirmed through routine clinical imaging;
- fit for rehabilitation i.e. peripheral oxygen saturations 90%+ on air, resting pulse <101 beats/ minute;
- walking ability from FAC score 1 to FAC score 5 (section 5) but with a) abnormal initial floor contact and/or b) impaired ability to take full body weight through the paretic lower limb in stance;
- no contractures at hip, knee, ankle or forefoot or loss of skin integrity over the paretic foot or lower limb. Contracture is defined as "persistent loss of full passive range of motion at a joint resulting from structural changes in connective tissues"[38] and measured using manual goniometry using the non-paretic lower limb as the comparator;
- can follow a 1-stage command i.e. sufficient communication/orientation for interventions in this trial.

Planned interventions

After completion of baseline measurements the intervention phase will last for six weeks. All participants will receive conventional physical therapy (CPT) deemed appropriate for their presentation by the clinical physiotherapists using a standardised treatment schedule[39]. The treatment schedule consists of a recording form and explanatory manual describing the treatment and we have used this successfully with clinical physiotherapists in our recently completed trials comparing CPT and functional strength training for the upper limb [40] and lower limb[41]. The clinical physiotherapists providing CPT will be trained to use the treatment schedule and will document content and amount of treatment provided each day. The records of treatment provided for all participants will be collected by **Researcher** each week.

***Control intervention*.** Participants allocated to the control group will receive CPT. A SWIFT CAST will not be provided. They will, however, have a video analysis of their gait (described in experimental intervention) to ensure that assessment is exactly the same as in the experimental group. If participants discontinue CPT before the end of the 6-week intervention period then every effort will be made to include individuals in the outcome and follow-up measures (intention to treat principle).

***Experimental intervention*.** Participants allocated to the experimental group will receive a soft-scotch ankle-foot cast (SWIFT Cast) in addition to CPT[42]. A SWIFT Cast is a lightweight, semi-rigid cast extending from the metatarsal heads to the head of the fibula. It positions the paretic foot in relation to the shank so that plantarflexion and/or excessive pronation/supination of the foot is minimised during walking so that the ground reaction force vector assumes the normal direction: passing in front of the knee at floor contact, through the knee in mid-stance and behind the knee in terminal stance. It is made from Soft Cast and Scotch (3M PLC UK). The SWIFT Cast is lightweight (100-200g), semi-rigid and porous.

The SWIFT Cast will be made by the Researcher who will be trained in the procedure**.** This training will take place before any participants are recruited and will be ongoing throughout the trial to maintain consistency in trial procedure. The Researcher will make the SWIFT Cast on the first day of the intervention phase and fit it on the second day.
The SWIFT Cast will be made with a participant in a supported sitting position that allows hips, knees and ankles to be at 90^0. One Researcher will apply the materials required whilst an assistant other will maintain the paretic ankle and foot in the plantigrade position, avoiding either pronation or supination at the subtalar joint. Stockinet layers are applied to the shank, proximally to the level of the knee joint line, distally to approximately 2.5 cm beyond the level of the toes. Using an indelible pencil the stockinet will be marked with a trim line based on designs of a traditional ankle foot orthosis. Broadly the trim line will bisect the foot sagitally on both sides, pass behind the malleoli and up the lower leg along a central line, roughly dividing this section in two. A cutting spacer is then inserted between the two layers, laterally and anterior to the ankle, running on top of the 4^{th} and 5^{th} metatarsal bones. A roll of soft cast bandage is applied below the head of the fibula, with half layered overlaps as it is wrapped around the lower leg. A figure of eight wrap is used around the ankle, and continued until the toes are covered. A 6-layer Scotch back-slab is then applied from the level of the head of the fibula to end of toes. Another soft-cast bandage is applied, in the same fashion as the first, 1 cm from the proximal end. A wet crepe bandage is applied, covering the whole SWIFT Cast. The SWIFT Cast is then moulded to maintain arch support and align the ankle (described above). The SWIFT Cast is left to dry for 5 minutes maintaining this alignment with assistance from the second therapist, and is cut off along the cutting spacer. The SWIFT cast is then removed and cut along the trim lines, the edges are smoothed and taped over with Leucotape The SWIFT Cast is then left to set for 24 hours. Velcro straps are applied around the ankle and just below the knee to secure the SWIFT Cast to the paretic lower limb[42].
To ensure safe walking and to provide the necessary and corrective shoe to foot force required for successful use of the SWIFT Cast a strong plaster shoe (Darco Multifit Surgical Trauma Shoe rounded toe, Markell Shoe Co, USA) is fitted over it. To assess whether the SWIFT Cast enables appropriate joint alignment. The participant will stand and step/walk forward whilst being filmed in the sagittal plane using a digital camcorder. The gait achieved by the participant will be observed using slow motion and freeze frame facilities and viewed on a suitable computer monitor. The video will be used to check that the heel is on the floor at initial contact to ensure there is no knee hyperextension

instance, that the tibia progresses smoothly forward during stance and that the hip extends in terminal stance (i.e. minimising gait abnormalities see introduction). If alignment is incorrect then a wedge will be placed under the heel in the plaster shoe to tilt the tibia slightly forwards (tuning) and the filming and assessment will be repeated. A range of wedges will be available to allow for the appropriate angle to be given to each participant so as to produce the optimal gait. Any pelvis asymmetry arising from leg length asymmetry will be corrected using an insole in the shoe on the non-paretic foot.

During physical therapy sessions the SWIFT Cast will be worn for weight-bearing re-training of walking. As gait improves there will be periods of walking re-training without wearing the SWIFT Cast which are aimed at re-education of lower limb movement control. All walking re-training interventions will be drawn from the CPT treatment schedule[39] as deemed appropriate by clinical physiotherapists. Outside of physical therapy sessions participants will be requested to wear the SWIFT Cast for the whole of their waking day initially. As gait improves the Research Physiotherapist will adjust use of the SWIFT Cast as clinically appropriate. Each participant will keep a diary, assisted by nursing staff if appropriate, to record the number of hours that the SWIFT Cast is worn each day and to make free comments about its use. Each time the SWIFT Cast is applied/removed the lower limb will be assessed for skin integrity (adverse event monitoring below). If a participant is discharged from an in-patient care setting during the 6-week intervention period then he/she will continue wearing the SWIFT Cast in their home. This is on the provision that the participant is regularly visited by a community care team to ensure that skin integrity is monitored. Those who are not seen by a community team will discontinue to wear the SWIFT CAST at home but will follow the intention-to –treat principle and still complete outcome measures.

If an individual regains a normal gait pattern (section 6) when walking independently without the SWIFT Cast during the 6-week intervention phase then its use will be discontinued as it will not be clinically indicated. Discontinuation of use of a SWIFT Cast might also occur due to adverse events (see below). If an individual discontinues using a SWIFT Cast before the end of the planned 6-week intervention phase then the time period for which it was worn will be recorded. Every effort will be made to ensure that individuals who discontinue use of a SWIFT Cast participate in the outcome and follow-up measures (intention to treat principle).

Measurement battery

Rationale for measures to be used. In this phase II trial the efficacy of the SWIFT Cast (question 1) will be investigated using a combination of clinical measures of functional ability recorded with a clinical gait analysis system (i.e. simple, inexpensive, objective, gait assessment techniques which do not need access to an expensive 3D movement analysis system) together with subjective yet widely used functional ability assessments. This clinical measurement battery can therefore be used in a subsequent multi centred phase III trial should the intervention be shown to have sufficient efficacy.

In addition, the clinical gait biomechanical assessment techniques together with structural brain imaging will be used to provide a scientific measurement battery to investigate the neuro-biomechanical correlates of and prognostic indicators for response to a SWIFT Cast and to CPT (questions 2 & 3).

The entire measurement battery will be used to inform a decision as to whether or not combining investigation of clinical efficacy of well-defined physical therapies with measurement of neurobiomechanical correlates is an appropriate methodology to advance knowledge about which therapies are beneficial for which stroke survivors and why they might work (question 4).

Whenever possible, the structural neuroimaging will be added to routine clinical neuroimaging and will take no longer than 20 minutes. The clinical and biomechanical measures are expected to require one hour at each measurement point as in reality several measures can be made during one trial of walking forwards (see below). Thus the proposed measurement battery has been designed to be efficient in terms of addressing more than one important question and also in terms of the time and effort required of participants.

In common with published stroke rehabilitation research the primary outcome measure for clinical efficacy is walking speed. This is not the sole issue, however, as walking speed can increase at the expense of gait efficiency as reflected clinically by symmetry of foot falls and joint actions particularly the sagittal kinematics of the knee. These will therefore be measured within the clinical assessment battery. These measures can be used both to evaluate clinical efficacy and to increase knowledge of the underlying mechanisms of clinical improvement and avoid the limitations of fMRI (section 3.1). This comprehensive analysis of the walking mechanism is required clinically particularly because:

a. the hypothesised action of an orthotic device such as a SWIFT Cast is that it improves the relationship between the ground reaction force and the lower limb joints leading to reduced (more normal) moments generated at the lower limb joints and a smooth forward progression of the tibia from an inclined backwards position at heel strike to an inclined forwards position at toe off[35]. The only way to investigate this hypothesis is through biomechanical gait analysis. This approach has been applied successfully for children with cerebral palsy in whom surgery and orthotic intervention is now based on biomechanical data[32]. Furthermore an International Consensus Conference criticised published research into the effects of orthotics after stroke for not measuring gait biomechanics as it "greatly reduces the validity of the research project as it is impossible to judge whether or not the biomechanical design of the orthosis is appropriate"[35]. Hence failure to report the biomechanics of a SWIFT Cast will mean that orthotists will not accept the findings of the proposed trial or adopt the intervention if it is found in subsequent Phase III trials to increase walking speed.

b. an upcoming Cochrane review of the effects of orthotic devices on walking after stroke highlights the clinical controversy around their use[36]. "The Bobath concept which is the most widely used approach to stroke physiotherapy in Britain and Europe traditionally discourages the use of orthoses believing that they prevent or delay the recovery of normal movement. Although physiotherapists perceive their practice has become more eclectic in recent years and that they now embrace the use of orthoses ---- studies of physiotherapists actual (rather than perceived) every day clinical practice indicate that physiotherapists rarely prescribe or use orthoses" [36]. Hence a comprehensive analysis of the biomechanics of gait is required to investigate whether or not a SWIFT Cast promotes the persistence of an abnormal gait or delayed recovery of walking. The demonstration of clinical efficacy to physiotherapists will require biomechanical evidence of normality of gait to allay concerns that walking speed is achieved at the expense of gait efficiency.

In summary, biomechanical gait analysis is crucial for investigation of the main question (clinical efficacy) and in conjunction with structural neuroimaging (neuro-biomechanics) will also provide information about underlying mechanisms of response to and prognostic indicators for a SWIFT Cast. Structural neuroimaging cannot be omitted from the measurement battery as this would mean that biomechanical values of the end result of CNS activity obtained at each measurement point will not be able to be related to the origin of gait abnormalities i.e. the site and extent of the stroke lesion in the brain – it has been shown that the infarct does not change from 3 weeks onwards[44]. We have positive experience of conducting full biomechanical analysis of functional activities (including walking and sit-to-stand) in a similar group of stroke survivors to those to be included in the proposed trial[45]. In our recently completed phase II trial of functional strength training we conducted full biomechanical analysis in a specialised gait laboratory with 94 people at baseline and the attrition rate at outcome (after 6 weeks intervention) was 9%. This indicates that people find biomechanical analysis acceptable early after stroke. Consequently the biomechanical measures of clinical efficacy are suitable for continued use in any subsequent multicentre phase III trial.

Primary outcome measure – walking speed: during walking forwards in a straight line at participant-selected speed. Each participant will be asked to undertake 4 walks. Walking speed will be measured in the middle of the walkway using 2 inexpensive infra-red light beams placed 3 metres apart on shoulder-high stands and connected to an electronic timer. Subjects who cannot walk without support, i.e. a FAC score of 2 or less (support of 1 person), will be deemed to have a walking speed of zero.

Secondary outcome measures – ability to walk independently, functional mobility, ability to walk with a normal gait pattern and structural brain imaging

- Functional Ambulation Category (FAC)[37] ranges from unable to walk (score 0) to able to walk independently on level/non-level surfaces (score 5). This measure is clinically relevant to walking function and has been found to have strong inter-rater and test-retest reliability[45];
- Modified Rivermead Mobility Index[46]: This reliable and clinically relevant scale measures functional mobility including turning over in bed, standing up, walking indoors and ascending stairs. This measure is used widely in stroke rehabilitation research.
- Efficiency of gait measured by: a) peak angular velocity of the knee during walking as a sensitive objective measure of gait performance[47] b) the ratio of step times on the paretic and non-paretic lower limbs as a measure of temporal symmetry; c) the ratio of step lengths on the paretic and non-paretic lower limbs as a measure of spatial symmetry; d) the ratio of sagittal angular velocity of the knee of the paretic and contra-lateral lower limbs as a measure of joint symmetry; and e) the angle of the tibia with respect to the vertical at initial contact, foot flat, mid stance and terminal contact as a measure of smooth forward progression of the lower leg. These measures are made simultaneously with walking speed using the clinical gait analysis equipment (see primary outcome). They can be undertaken easily in a clinical environment using a technique developed by Wall and applied by Rowe and others in which the participant walks across a 10 metre long mat on which a high contrast grid has been printed while being video recorded from the side view[43]. The resultant video can be played back in slow motion and timed using a multi-lap stopwatch to determine the step times. It can also be viewed frame by frame and using the grid the spatial location of the feet during the walk can be determined to give step lengths. The average angular velocity of the knee during stance can be estimated for the gait cycle in which the participant is perpendicular to the camera by measuring the angle of the maximum and minimum knee angles using a computer generated goniometer[43], subtracting one from the other and then dividing them by the time between the two occurrences. Finally the angle of the tibia with respect to vertical can be determined by using the freeze frame mode and the computer generated goniometer.
- MR scan (baseline only): In order to have an accurate delineation of the cerebral lesion, the structural neuroimaging will be done 3-8 weeks after onset[44]. To achieve accurate delineation of the lesion will mean that, for some participants, the structural neuroimaging will not be undertaken at exactly the same time point as other baseline measures. Standard FLAIR and T1-weighted SPGR high-resolution "volume" data sets will be obtained prospectively from all subjects at baseline using a standardized acquisition sequence including field inhomogeneity correction and identical voxel size; data sets will be collected and processed in a single laboratory under J-CB's supervision. Following harmonisation of image characteristics for different scanners[48] lesions will be automatically segmented on the FLAIR data set[44] using appropriate seeding and then the lesion contours will be projected onto the T1-SPGR data set following reslicing. All T1-SPGR data sets will then be spatially normalised to the MNI template (including lesion masking if necessary[49]) using SPM2.

Adverse event monitoring will also be undertaken and this is described below in assessment of safety.

Assessment at outcome and follow up

Every effort will be made to include all randomised participants at outcome and follow-up and all participants omitted from these measures will be accounted for (intention-to-treat principle).

Assessment of efficacy

The measurement points are before randomisation (baseline) the working day (± 2 days) after the 6-week intervention ends (outcome) and 6 months (± 2 weeks) after stroke (follow-up). Measures will be made by Assessors blinded to treatment allocation. A Research Fellow, blinded to treatment allocation, will independently process the clinical biomechanical data to ensure accuracy of value extraction. All measures will be made without the SWIFT Cast as it is designed as a temporary adjunct to physical therapy interventions aimed at enhancing motor recovery rather than as a permanent device to compensate for motor impairment.

Between the end of the 6-week intervention (outcome) and before the follow-up measure (6 months after stroke) all participants will receive routine CPT as deemed appropriate by clinicians in the clinical

service who are providing their rehabilitation care. Randomisation before baseline (section 5) is expected to control for potential differences in participant characteristics between groups.

Assessment of safety

The risk of serious adverse events resulting from use of a SWIFT Cast is low. There is however a small possibility that using a SWIFT CAST could be associated with loss of skin integrity on the shank and/or foot and an overuse syndrome as expressed by participant experience of pain or fatigue.

Adverse event monitoring – skin integrity and potential overuse syndrome

a. *Viability of skin* will be assessed each time the SWIFT Cast is applied/removed by clinical staff/Researcher using the Stirling 2-digit Scale[50]. The Researcher will also perform a twice weekly check of participants allocated to the control condition. The results of the skin integrity assessment will be recorded in participants' diaries. If the threat of loss or actual loss of skin integrity occurs then appropriate routine clinical care will be provided. Use of the SWIFT Cast will be discontinued only if the clinical team deem that this is the best way of providing appropriate care for decrease in skin integrity.

b. *Pain* will be considered to be an adverse event if a participant reports onset or increase of paretic lower limb pain (verbally or behaviourally) on 4 consecutive days and the clinical team consider that are unable to account for this in any other way.

c. *Fatigue* will be considered to have occurred if there is a decrease of 1 level of FAC on 4 consecutive days and the clinical team cannot account for this in any other way e.g. sleep difficulty. Researcher will twice weekly for all participants irrespective of group allocation.

Sample size

A formal power calculation is not yet possible but we estimate that with a sample size of 110 the study has 80% power at 5% significance to detect a clinical improvement of 0.13 m/s for walking speed with a standard deviation of improvement of 0.24 m/s (based on CPT group from our recently completed study of an exercise intervention early after stroke[45]). This sample size will detect a clinical improvement of 1.1 points on the FAC assuming a standard deviation of 2 points. To allow for an attrition rate of approximately 10% this study will recruit 120 participants (60 in each group).

For estimation of sample size for biomechanics clinical efficacy data we have used angular velocity of the knee during the stance phase of walking as our earlier work has shown this to be a sensitive objective measure of gait after stroke[47]. The estimated sample size, based on our published data[47], provides 98% power to detect a clinically important difference of 15.4 degs/sec with a standard deviation of 19.2 degs/sec.

For the investigation of the correlation of biomechanical data with response to therapy a formal pre-specified power analysis is complicated. However with 60 participants per group we would have 80% power to detect a correlation coefficient between response to therapy and gait parameters of 0.35. Similarly, a formal pre-specified power analysis is complicated for VLSM mapping (section 11) since we cannot know the number of individuals with lesions in each voxel. However, power would be maximised for a voxel with 50% (30 within a treatment arm) of individuals with a lesion and 50% with no lesion, this would have 80% power to detect a difference in outcomes of 0.74 standard deviations.

Statistical analysis

In accordance with the intention-to-treat principle all participants will be analysed according to the group to which they were randomly allocated. The clinical efficacy analysis will be carried out using analysis-of-covariance (ANCOVA) adjusting for the baseline values, variables used for stratification and any factors imbalanced between the two groups. If the assumptions of ANCOVA are not met non-parametric techniques will be used. We will investigate whether the intervention increases the rate of adverse events using a Poisson regression model. Secondary analyses will focus on the sensitivity to incomplete follow-up, analysis at each time-point and a per-protocol analysis and the analysis of the secondary outcome measures. Adverse events will be recorded and we will investigate whether the

intervention increases the rate of adverse events using Poisson regression. All analyses will be carried out using Stata. The analysis will also be used to estimate the parameters required to design a subsequent Phase III trial.

The exploratory analysis of biomechanical data will use correlation and multivariate regression techniques as required.

For structural neuroimaging data the relationship between binary lesion-segmented images and clinical response to therapy will be computed on a voxel-by-voxel basis using modified voxel-based lesion-symptom mapping (VLSM), a validated and widely used method that allows us to map across patients the statistical relationship between presence of lesion in each voxel and behavioural measures, here the clinical variables, response to treatment and the biomechanical variables[51,52]. VLSM data will be used for two purposes. First within each group and for each voxel we will use a t-test to evaluate difference in the outcome measures between those with a damaged voxel and those without a damaged voxel. Second, an interaction test across groups will be performed to identify which voxels are associated with different levels of efficacy. A suitable approach adjusting for multiple testing will be used[53]. For structural neuroimaging data the relationship between binary lesion-segmented images and clinical response to therapy will be computed on a voxel-by-voxel basis using voxel-based lesion-symptom mapping (VLSM), a validated and widely used method that allows the mapping across patients of the statistical relationship between presence of lesion in each voxel and behavioural variables[51,52]. The presence or absence of lesion in each voxel is decided by determining the contours of the final cerebral infarct on the 3D structural MRI scan done 3-8 weeks after the stroke; any voxel inside the infarct contours is declared “lesioned” and any voxel outside it “non-lesioned”. Segmenting the infarct is standard procedure in stroke imaging research and is based on sophisticated software that automatically segments the infarct by thresholding of the MRI signal from a “seed” placed manually in the centre of the infarct by an experienced stroke imaging researcher. J-CB has extensive experience in using this software and access to it free of charge. VLSM data will be used for two purposes. First within each group and for each voxel we will use a t-test to evaluate difference in the outcome measures between those with a damaged voxel and those without a damaged voxel. Second, an interaction test across groups will be performed to identify which voxels are associated with different levels of efficacy. A suitable approach adjusting for multiple testing will be used[52]. We will also use VLSM data to determine which areas of the brain are associated with response to therapy using the predefined response criteria above. The proportion of lesioned voxels in each brain area will be used as possible explanatory factors. Furthermore, we shall compare the predicted response to therapy from three models: a) using only biomechanical data; b) using only VLSM data; and c) using both biomechanical and VLSM data both graphically using agreement plots and ROC curves.

Research Governance

The University of East Anglia (UEA) is the named recipient of the grant and with the Norwich Clinical Trials Unit is responsible for the overall setup and delivery of the trial. UEA has subcontracted a) the University of Strathclyde to run the trial in Glasgow and to process and analyse the biomechanics data, and b) the University of Cambridge to analyse the MRI scans. Each University will employ and indemnify its allocated research staff and ensure they and the applicants are given the allocated time to research and manage the project. Each University will secure appropriate management and governance arrangements with local NHS Trusts for their part of the trial. All research staff employed and trial applicants will have Good Clinical Practice training. Non-NHS staff actively engaged in clinical contact will have honorary clinical contracts or research passports which enable clinical research in the NHS settings involved.

The SWIFT Cast is not a regulated device as defined by the Medicines and Healthcare products Regulatory Agency (MHRA directive 16, p4). We will therefore comply with the MHRA Guidance Notes for Manufacturers of Custom-made Devices.

In accordance with the MRC code of good practice in clinical trials and the CONSORT guidelines we will document all decisions regarding eligibility for entry, consent giving, inclusion, exclusion and attrition.

We will convene a Trial Steering Committee (TSC) to provide overall supervision and ensure good conduct of the trial (e.g. adherence to the Declaration of Helsinki and good practice in the area of user involvement). This will be undertaken by nominating potential members to the EME Programme Board who will then appoint people to the TSC. Members of the TSC will be: an independent Chair (independent from the lead investigator and her institution), two further independent members, the applicants, and two public representatives. The TSC will meet twice during the first year and once during the second year. A condition of funding is that Observers from the EME programme will be invited to all TSC meetings and a copy of all TSC papers and reports will be supplied to them.

Despite the low potential risk of adverse events/adverse reactions/serious adverse reactions/serious suspected adverse reactions and serious suspected unsuspected adverse reactions occurring as a result of participating in this trial an independent Data Monitoring and Ethics Committee will be convened. The IDMEC will report directly to the chair of the TSC. The TSC will therefore be notified of any adverse events. If adverse events are found to affect participants the TSC will ask the trial statistician to inspect the un-blinded data and inform the Chair of the TSC of any potential intervention related problems. Because there is a low risk of adverse events and those that could occur are not expected to be serious it is unlikely that we will need to stop the trial.

We propose retaining relevant trial documentation for a period of 20 years after the end of data collection to comply with the Good Clinical Practice regulations and to ensure availability of data for any subsequent systematic reviews and meta-analyses. Documentation will be archived in secure facility in the University of East Anglia and the custodian will be the Principle Applicant.

Project timetable and milestones

Recruitment of research staff will be undertaken before the trial begins and we will make every effort to synchronise start dates for staff. Approximately 24 months will be required for recruitment of the 120 participants, 5 per month. Three months will be needed at the beginning of the trial for training of staff and to set up trial procedures. Six months will be required after recruitment to complete all follow-up measures. Three months will be required to finish neuro-biomechanical data processing and write up results. Consequently a total of 3 years will be needed to undertake this proposed research.

Milestones	**Project months**					
	1-6	7-12	13-18	19-24	25-30	31-36
Staff trained and trial procedures set up in centres						
Clinical trial registration completed						
15 participants recruited with baseline measures						
45 participants recruited with baseline measures						
75 participants recruited with baseline measures						
Neurobiomechanical processing training completed						
105 participants recruited with baseline measures						
120 participants recruited with baseline measures						
Follow-up completed						
Statistical analysis completed						
Draft paper and final report written						

Service users

An earlier version of this protocol was reviewed by the Patient and Public Involvement in Research Group (PPIRES: www.norfolkhealthresearch.nhs.uk/nhr/309/47.html). Feedback was positive and no concerns were raised about the trial. Service user involvement will continue to be provided by PPIRES whose members will be involved in activities such as the design of information sheets/informed consent forms and the Trial Steering Group.

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Chief Investigator	Date	Signature