FAST INdICATE: Study protocol version 7.3

Project title

Clinical efficacy of functional strength training for upper limb motor recovery early after stroke: neural correlates and prognostic indicators

Background

Existing research

This proposed trial is directed at an important focus for stroke rehabilitation, namely, the ability of stroke survivors to use their arm and hand again for everyday activity such as picking up a cup, unscrewing the top off a coffee jar and doing up buttons/zips. Difficulty performing such everyday tasks is common as upper limb neuromuscular weakness occurs in approximately 77% of people with stroke[1]. Limitation of ability to perform such everyday tasks seriously affects stroke survivors' capacity for independent living. Yet at six months after stroke only 38% of people who receive rehabilitation recover some dexterity[1]1. Better methods of upper limb rehabilitation are required urgently.

Systematic reviews indicate that repetitive task-specific activity, i.e. practising everyday object-related tasks such as picking up a cup, may improve motor function (for example[2]). Building on these findings randomised controlled trials of Constraint-Induced Movement Therapy (CIMT) and Robot-Assisted Therapy (RAT) have been conducted. CIMT is effective between 3 and 9 months after stroke[3] but early after stroke, is no more effective than an equal dose of usual therapy[4]. Of key importance is that CIMT is suitable only for patients with at least 10 degrees of active movement of the paretic thumb and 2 or more paretic fingers[5, 6]. This high level of function excludes many early stroke survivors[6]. RAT has been used in a wider group of stroke survivors but has also been found to be no more effective than an equal dose of usual therapy[7]. In both cases it may have been the intensity of therapy rather than the specific approach which led to clinical improvement. Thus, the question of whether a novel treatment aimed at upper limb function can provide *additional* benefit, over and above usual therapy, to patients with the greatest need early after stroke remains unanswered.

Functional strength training (FST) is a new therapy combining task-specific exercise and strength training aimed at patients with substantial to moderate paresis early after stroke and is based on evidence from experimental and clinical studies[8-12][8-12]. Importantly, preliminary data indicates FST may be more effective than standard therapy of equal intensity [13]. FST is based on findings that the largest impact on upper limb functional recovery after stroke may result from the combination of loss of muscle strength and dexterity with the former having more impact[8, 9]. A systematic review of muscle strength training after stroke found positive effects on both strength and functional activity[10] but increases in muscle strength may not translate into improvements in functional activity unless strengthening activity is provided as part of training of everyday functional activities[14]. Functional training and muscle strength training have therefore been combined to form FST. FST emphasises improving the power of shoulder/elbow muscles to enable appropriate placing of the hand and improving the production of appropriate force in hand muscles to achieve the specific grasp.

Preliminary evidence suggests that FST is more effective than no therapy[15] and our own early phase trial, with 30 participants, provides proof-of-concept that FST given in addition to conventional physical therapy (FST+CPT) is more beneficial than either the routine amount of CPT or extra intensity CPT (CPT+CPT) early after stroke[13]. The median (IQR) change in Action Research Arm Test score (ARAT) for the three groups was: CPT, 11.5 (21.0); CPT+CPT, 8.0 (13.25); and CPT+FST,19.5 (22.0). For the Nine Hole Peg Test (9HPT; clinically important difference = 0.02 pegs/sec) the median (IQR) changes were: 0.08 (0.17) for CPT; 0.05 (0.22) for CPT+CPT; and 0.11 (0.27) for CPT+FST. These

median changes show a trend in favour of the CPT+FST group which was also found in measures of pinch force and elbow flexion force[13]. In addition, the results of our early phase trial indicate that delivery of CPT+FST is feasible and is acceptable to stroke survivors early after stroke (mean 20 (SD 14) days). These findings justify continuing research into the potential benefits and mechanisms of action of FST and using data from this early phase trial to inform a sample size calculation for a subsequent Phase II trial.

The evaluation of FST through properly designed clinical trials is crucial. We are aware, however, that a potentially serious barrier to the development of any novel treatment for post-stroke motor impairment arises from a poor understanding of its mechanisms of action and, in particular, whether it is likely to work in all types of patients [16]. Both the CIMT and RAT trials recruited patients based on clinical phenotype, but in order to target a therapy to those patients most likely to benefit this may not be sufficient[17]. Restoration of physiological or psychological function after stroke is thought to result at least in part by promoting activity-driven change in the organisation of surviving brain regions and networks[18]. Consequently, it is increasingly recognised that large rehabilitation trials of this type will need to include more sophisticated baseline measures of residual brain structure and function in order to understand both the mechanisms of action of the treatment and the characteristics of 'responsive' patients[16, 17, 19, 20]. The tools used for this purpose to date have been (i) MRI-based diffusion tensor imaging (DTI) or transcranial magnetic stimulation (TMS) to assess corticospinal system damage, and (ii) functional magnetic resonance imaging (fMRI) to assess changes in functional organisation of brain networks. FMRI studies of cerebral reorganisation after stroke demonstrate that non-primary cortical motor regions, such as premotor and supplementary motor areas, can take on new and functionally relevant roles in motor performance that help to support recovered function[21, 22]. This shift is greatest in patients with more damage to the corticospinal system as assessed with either DTI[23] or TMS[24]. The use of neuroimaging and neurophysiological data for the purposes of prediction, as proposed in the current study, is less common, but recent methodological advances have made this feasible[25, 26]. For example, both the pre-treatment level of brain activity in primary motor cortex during the performance of a motor task (functional measure)[27], and the degree of damage to descending motor white matter pathways (structural measure)[28] were associated with clinical improvement in 24 chronic stroke patients undergoing two weeks of a robotic-based therapy. These studies are encouraging but if we are to realistically incorporate such data into models that can accurately predict therapeutic response, larger numbers of patients are clearly required. In the current study we propose, in over 180 patients, to characterise the structural and functional properties of each patient's residual motor network before and after treatment using cutting edge neuroimaging and neurophysiological methods. We hypothesise that individual differences in baseline and treatment induced changes in structural and functional organisation of motor networks will help us to understand (i) the relationship between FST-induced behavioural gains and brain reorganisation, (ii) whether FST works via the same mechanism in all patients and (iii) in whom FST is likely to have the greatest impact.

Progress in the area of stroke rehabilitation has been hampered by a paucity of large-scale projects in which neuroscientists and clinicians have been able to work together and so inform each other's approach to a single clinical problem such as the treatment of upper limb weakness[22, 29]. Here we propose to combine neuroscience and clinical science expertise in the largest study of its kind in order to investigate underlying mechanisms of motor recovery in a representative sample of patients early after stroke with substantial to moderate upper limb motor impairment using a well-characterised physical therapy which has sufficient evidence of efficacy to support further trials.

Risks and benefits

Ethical approval will be in place before this trial begins. All participants will be told that they are free to withdraw from the trial at any time, without giving a reason and without any effect on their current or future healthcare. The risk of harm for any participant in this proposed trial is low. There is, however, a small risk that FST could be associated with an overuse syndrome expressed by experience of pain or fatigue. We will check regularly for these adverse events in all participants (assessment of safety).

All participants will benefit from a more detailed assessment of their upper limb function than is available to them in routine clinical practice and also from regular checks for potential adverse events. In our experience of conducting trials early after stroke this can benefit both experimental and control participants as clinical information about health and safety issues can be provided to the clinical team

without compromising research. In addition, all participants will receive an extra amount of therapy that is thought to be important for enhancing recovery.

All participants will undertake the clinical measures at three times (1)~~,~~ at baseline before randomisation; (2) at outcome after the 6 week intervention period; and (3) at 6 months after stroke. On each occasion this is expected to take between 30 minutes and one hour. In addition, all participants will undertake the explanatory measures detailed below at baseline and 6 weeks post baseline. The explanatory measures will be completed within 10 working days of the clinical measures. Throughout the measurement sessions we will monitor participants for fatigue and discomfort and allow adequate rest periods or stop the session as appropriate for individuals.

All imaging and TMS measures to be used are routine protocols currently in standard use in many laboratories. The risks associated with any TMS or MRI study concern exposure to strong magnetic fields and potential for claustrophobia or mild discomfort. We will guard against these risks by thoroughly screening subjects prior to entry to ensure that those with exclusion criteria (e.g. non-MR-safe metallic implants, claustrophobia) do not participate. In addition, subjects will be offered ear protection and padding for the head/back to minimise discomfort. The TMS design employed will use only single stimulation, both of which is generally regarded as a standard and safe method~~s~~ for probing central motor function in health and disease. There is a very small risk that stimuli could provoke a seizure in susceptible individuals, but we follow published guidelines that reduces this to a minimum. In 5 years of testing in our laboratories, no seizures have been provoked.

Rationale for current study

Stroke is the single largest cause of adult disability worldwide[29]. Each year, in England alone, approximately 110,000 people suffer a stroke and approximate annual costs are: £2.8 billion direct health and social care costs; £1.8 billion to the wider community in terms of lost productivity and disability; and £2.4 billion in costs to informal carers[30]. The majority of this cost is the result of "rehabilitation and life after stroke" [30]. The impact on the NHS is unlikely to fall because the benefits of better preventative and acute care are likely to be offset by an increase in the percentage of older people in the population to 23% in 2031 (16% in 2003), in whom most strokes occur. Stroke rehabilitation is a research priority for the NHS[31] and more widely for Europe[32].

It is known that physical therapy for motor impairment after stroke is generally effective[33], that motor recovery occurs most rapidly in the first three months after stroke[34] and that during this period the CNS probably has most potential for reorganisation[21]. Further progress in the provision of effective therapy for patients early after stroke requires deeper understanding of the process of CNS recovery associated with clinical improvement (mechanisms) and determining which physical therapies should be provided (clinical efficacy) for which stroke survivors (prognostic indicators)[8, 18, 20, 29, 32].

Further progress, therefore, requires neurological 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 [17, 20, 28]. This is important because there is a need to establish knowledge of mechanism to improve understanding of why treatment works or does not work[35]. "*Not having such knowledge might hinder development of novel and potentially more efficacious interventions in the long term*" [35].

Investigating efficacy and mechanisms together in this proposed Phase II trial will provide robust information to ensure that subsequent Phase III trials investigate the effectiveness of FST targeted at the underlying CNS mechanisms of upper limb motor deficits early after stroke in those people most likely to respond. This approach is of critical importance in subsequent trials of neurorehabilitation interventions so that potentially important clinical effects are not diluted by attempting to treat patients for whom other interventions might be more appropriate[16]. More generally, the results of this proposed trial, using CPT and FST as probes of CNS recovery, are expected to contribute to knowledge of the CNS mechanisms of upper limb recovery after stroke. The need for such research is well recognised[17, 20, 29]. Our recently completed early phase trials of defined physical therapies early after stroke show that such investigations are feasible and also provide new information[13, 36, 37].

Clinical Relevance

Discussion of the need for further research with clinical therapists has revealed potential confusion with using the label “CPT” to denote the extra routine therapy. This potential confusion arises because the extra, experimental CPT does not cover every aspect of routine CPT. It does, however, cover what clinical therapists think of as therapy which is designed to enhance ability to produce movement of good quality. We have therefore renamed “CPT” as Movement Performance Therapy (MPT). The label has changed but the content has not.

Objectives

The primary driver for this research, generated by our early phase work, is the clinical hypothesis that FST for the paretic upper limb plus the standard amount of protocol-driven CPT (CPT+FST) produces greater improvements in motor impairment and functional ability and is more cost-effective than CPT+MPT in people with substantial to moderate upper limb motor impairment early after stroke. For example, decrease in motor impairments will reduce duration of treatment and thereby reduce hospital stay. The scientific premise driving this research is that detailed understanding of the interaction between the treatment and each patient’s residual functional architecture will more likely enable physical therapies to be targeted at recovery mechanisms in those stroke survivors most likely to respond. Combining structural and functional brain imaging and neurophysiological measurements together with well-defined physical therapies in such a large cohort of patients is a unique and valuable undertaking which is expected to enhance understanding of neurological recovery and thus further enhance upper limb stroke rehabilitation. The results are expected to lead to important advances in healthcare that will increase the ability of stroke survivors to lead independent lives and participate more fully in society. Specific objectives to be achieved by the end of the trial are:

1. To determine whether CPT+FST commenced early after stroke produce greater improvements in upper limb motor recovery than CPT+MPT (clinical efficacy)
2. To identify the similarities and differences in the neural correlates of clinical improvement in upper limb motor function in response to (a) CPT+FST and (b) CPT+MPT (understanding neural and behavioural mechanisms)
3. To determine whether any pre-treatment parameters or any combination of pre-treatment parameters; (a) clinical severity, (b) anatomical location/volume of infarction (derived from structural brain imaging), (c) residual functional anatomy (derived from fMRI), (d) residual structural cortico-cortical and cortico-spinal connectivity (derived from DTI), and (e) brain-muscle functional connectivity (derived from TMS),are sufficiently predictive of improvement in upper limb motor function to enable physical therapy to be targeted at those stroke survivors most likely to respond (new scientific/clinical principles)
4. To find the likely cost-effectiveness of CPT+FST (inform design of a subsequent Phase III trial)

Achieving these objectives before undertaking a Phase III RCT conforms with the MRC Framework for Design and Evaluation of Complex Interventions to Improve Health[38].

Methods and Design

The FAST INDICATE trial is a randomised, controlled, observer-blind, 2-group, multi-centre Phase II trial to determine efficacy of CPT+FST for enhancing upper limb recovery, with embedded explanatory measures to determine prognostic indicators for and neural correlates of response to CPT+FST and CPT+MPT (see figure 1 for a trial overview).

We considered using a 3-group design (i.e. CPT, CPT+MPT, CPT+FST) identical to that used in our Phase I study, but the results of that study suggested that the type of therapy is more influential than the intensity (amount) of therapy. The primary driver for the current proposed Phase II trial, therefore, is to test whether we can replicate the findings that CPT+FST enhances motor recovery more than CPT+MPT in a larger group, and whether stroke survivors with different characteristics might respond differently to the two forms of physical therapy. Thus, the results of this proposed trial will inform the design of a subsequent Phase III, definitive, trial. For example, if we find that those participants with low functional integrity of the corticospinal tract are unlikely to benefit from either therapy, then the

subsequent definitive trial will exclude people so affected. Consequently, our proposed 2-group design will refine our hypothesis whilst avoiding the extra cost involved in undertaking a 3-group trial at this stage in development of the definitive Phase III trial.

The trial was developed with and is supported by the Glasgow Clinical Trials Unit (UKCRN and UKSRN registered) and the Norwich Clinical Research Trial Unit (UKCRC registered). The trial design adheres to the updated CONSORT 2010 Statement and the extension for trials assessing nonpharmacologic treatments, particularly in respect to provision of sufficient description of the experimental and comparator treatment to enable replication[39, 40].

Eligible patients (study population)

Participants will be recruited from stroke services (Birmingham, Staffordshire and Norfolk) and will be followed up until 6 months after stroke wherever they are residing.

The inclusion criteria are

- adults aged 18+ years,
- 2 - 60 days after stroke when they provide informed consent. This time period has been chosen because some people who may meet the criteria for this trial are discharged from stroke services a few days after stroke and they need to be provided with the opportunity to participate. As brain recovery occurs mostly in the first 3 months after stroke participants will be within what is considered to be the critical time window for neural re-organisation;
- stroke in anterior cerebral circulation territory, cortical and/or subcortical, confirmed by clinical neuroimaging;
- sufficient voluntary muscle contraction in the paretic upper limb to generate the beginning of prehension i.e score at least 11/33 for Motricity Index pinch section;
- unable to complete the Nine Hole Peg Test (9HPT) in 50 seconds or less (maximum time for test);
- no obvious spatial neglect as defined by a score of 0 or 1 on the Extinction and Inattention sub-scale of the NIH Stroke Scale.
- have no obvious motor dyspraxia or communication deficits as assessed by ability to imitate action with the non-paretic upper limb. This will be assessed by the Research Therapist sitting alongside the potential participant. The Research Therapist will perform 5 upper limb activities and potential subjects will be asked to observe with intent to imitate and then perform the activities. The accuracy of imitation of observed activity will be assessed on the 3-point scale used by Decety[41]: 2 = correctly reproduced action; 1 = incorrectly reproduced action; 0 = not reproduced. Those scoring 8/10 or above will be considered to have the ability to imitate and therefore be included in this proposed trial;
- were able, prior to the index stroke, to use the paretic upper limb to lift a cup and drink from it;
  It is expected that the results of this proposed Phase II trial will identify those less likely to benefit and thus reduce the heterogeneity in the study population for subsequent trials.

Screening and assessment for suitability

All participants admitted into the recruiting sites will be screened for potential eligible for the study.

The clinical team, research nurses, or research network colleagues will collect the following anonymised information. (This information will be used only to facilitate the screening process and will not be retained in the study database).

- Unique ID
- Name of recruiting site
- Date screened
- Stroke-in anterior cerebral circulation territory, cortical and/or subcortical, confirmed by clinical neuroimaging (Y/N)
- Adults aged 18+ (Y/N)
- 2 – 60 days post stroke when provided informed consent (Y/N)
- Able, prior to the index stroke, to use the paretic upper limb to lift a cup and drink from it (Y/N)
- Medically stable (Y/N). This is operationally defined as "medically stable as confirmed by the stroke service medical team responsible for the individual's stroke care".
- Have sufficient voluntary muscle contraction in the paretic upper limb to generate the beginning of prehension i.e. score at least 11/33 for Motricity Index pinch section (Y/N) *(Only If routinely clinically assessed)*
- Interested (Y/N)

Medical and functional characteristics change over time following a stroke. It is possible that an individual may not be suitable on one occasion but has the potential to recover to the point where they fulfil the trial criteria. In these cases the screening professional will monitor the progress of an individual until it is clear whether or not they are potentially suitable for this trial (see figure 2).

The researchers will also collect the following information after obtaining written informed consent. To avoid confusion with screening, this will be referred to 'suitability assessment' (see figure 4). The relationship of screening and the suitability assessment within the participant eligibility pathway can be observed in figure 2.

- Consented (Y/N)
- Have sufficient voluntary muscle contraction in the paretic upper limb to generate the beginning of prehension i.e. score at least 11/33 for Motricity Index pinch section (Y/N)
- Unable to complete the Nine Hole Peg Test (9HPT) in 50 seconds (max time) or less (Y/N)
- No obvious motor dyspraxia or communication deficits as assessed by ability to imitate action with the non-paretic upper; score 8/10 or above (Y/N)
- A score of 2 on the extinction and inattention scale on the NIH Stroke Scale (Y/N)
- Other anonymous and important notes (such as 'amputee').

Participants who are assessed for suitability but do not meet the inclusion criteria may be re-assessed for suitability if the candidate indicates his/her wish for this to happen, the exclusion time limit has not been met and the researcher has reasonable reason to believe the participants performance may change sufficiently to meet the inclusion criteria.

Recruitment Process

Participating sites will be required to have obtained all relevant local ethical and management approvals and have undertaken a site initiation meeting with the CRTU or appropriate Lead Investigator prior to the start of recruitment into the trial.

Local Stroke Research Network staff, in liaison with ward nurses and therapists in the acute stroke service, will identify potential participants at least 2 days post stroke, explain the nature of the study and provide information. Potential participants will be given at least 24 hours to decide whether they would like to take part.

Participant Identifiable data

The following data will be collected from medical case records of patients who satisfy the eligibility criteria and have provided written informed consent. Local research network nurse or other appropriate member of the local stroke team will assess patients and collect participants' contact details (such as address and telephone number for arranging appointments and dissemination of research findings). (This information will not be retained in the study database).

Ethical considerations, providing information and written informed consent

In keeping with Good Clinical Practice (GCP), participants will be screened by an appropriate person with local governance and ethical permission. Working with the clinical teams in each trial setting and adhering to the conditions of our ethical approval**,** we will screen all people with a diagnosis of stroke for suitability for this proposed trial. Information will be provided by a person not involved in the clinical care of the patient but trained in providing information and taking consent. Those people identified as meeting the study criteria will be provided with written and verbal information about the trial (including potential risks and benefits), encouraged to discuss potential participation with others as they deem appropriate and given sufficient time to fully consider the likely implications of the research before making a decision.

In extenuating circumstances whereby a patient may be scheduled for discharge within 24 hours of first being approached by the research team, they will be provided with a Participant Information Sheet prior to discharge and then offered the opportunity to respond to the invitation to participate if they choose to do so.

However, the patient will not be rushed into any decisions; they will still be provided with ample opportunity to discuss their decision with family, friends and/or their health care practitioner if they wish.

The subsequent time required between a patient first being approached about the trial and consented will be at the discretion of those taking consent. As fully trained and experienced members of their clinical teams, they will be able to judge whether or not a potential participant needs more time to consider their involvement in the trial before consenting.

Consent may be witnessed if the patient has capacity but cannot hold or operate a pen due to stroke related weakness or other co-morbidity. All participants will be told that they are free to withdraw from the trial at any time, without giving a reason and without any effect on their current or future healthcare.

Randomisation

The randomisation sequence will be generated before the trial and will stratify by clinical centre, time after stroke (up to 30 days and 31-60 days) and ability to use the paretic upper limb as assessed by the Nine Hole Peg Test (9HPT; substantial = move 1 peg or less in 50 seconds and moderate = move 2-8 pegs in 50 seconds; healthy older adults can move 9 pegs in 18 seconds or less). An independent telephone IVRS randomisation service will maintain concealment of the treatment allocation from investigators, research therapists and blinded assessors prior to randomisation of a participant.

Assessment and follow-up

Time-points for outcome and follow-up measures

Clinical efficacy measures will be made before randomisation (baseline), the working day (±7 days) after the 6-week intervention ends (outcome) and 6 calendar months (±14 days) after the index stroke (follow-up – this is**;** a key time-point for stroke rehabilitation). Explanatory and cost-effectiveness measures will be made within 10 days after the clinical efficacy measures at baseline and at outcome. All of the aforementioned measures will be made by Assessors who are blinded to treatment group allocation. To assess whether blinding of Assessors was achieved we will ask assessors, at the 6-month follow-up point, to guess which group they think participants were assigned to. Agreement with actual allocation will be assessed with the Kappa statistic. Every effort will be made to include all randomised participants at outcome and follow-up even those who drop out of the intervention. All participants omitted from these measures will be accounted for in terms of reason for omission (CONSORT guidelines).

Interventions

The intervention phase will last for 6 weeks after the completion of baseline measurements. All participants will receive routine CPT and the same amount of either extra MPT or FST.

All participants will receive routine CPT because there is insufficient evidence of the effectiveness of FST to justify non-provision of established therapy. Thus, experimental FST will need to be delivered in addition to routine CPT, but this will introduce the potential influence of intensity of therapy raised by systematic review findings (e.g.[42]). These systematic reviews are, however, confounded by the inclusion of trials that compared different types of therapy as well as different intensities (e.g.[42]). Our proof-of-concept trial, therefore, employed a 3-group design namely: CPT; CPT+CPT; and CPT+FST[13]. The findings of this trial are outlined in the existing evidence section above. In summary, we found that the median score improvement in the CPT+CPT group between baseline and outcome was essentially the same as the CPT group and was smaller than the CPT+FST group for five of the six measures made[13]. The implication is that the interaction between type and intensity of therapy needs to be evaluated in a definitive three-group Phase III trial. Such a trial will be expensive and complex. We have therefore designed this proposed efficacy trial to compare MPT and FST whilst controlling for intensity and to identify which stroke survivors might be most likely to respond to which type of therapy. Thus the findings of this proposed trial will either refine the hypothesis for or justify the cost of subsequent Phase III trial(s). The control intervention with the most clinical and research relevance is therefore CPT+MPT and our data suggest that this may not reduce the potential effect size.

Routine CPT will be provided by the clinical physiotherapists using a modified version of the standardised treatment schedule (treatment recording form and descriptive booklet) developed in partnership with clinical therapists[43] and used in our earlier trial[13].

Content of CPT includes soft tissue mobilisation, facilitation of muscle activity/movement, positioning, and education for patient/carer[43]. Emphasis is given to interventions provided by a therapist facilitating and guiding movement (therapist-dependent) to provide sensory input to optimise joint alignment in preparation for voluntary movement. Some repetitive practice of functional tasks is included but without systematic progression in resistance to movement.

Training will be provided for clinical physiotherapists to use the treatment schedule and record interventions given. They will document content and amount of treatment provided each day.

- In each clinical centre the extra therapy will be provided by a Research therapist responsible for delivering either only the extra MPT (control) or only the FST (experimental) therapy. This minimises the potential confounder of therapist bias. We will not tell clinical staff which Research Therapist is providing which treatment. This strategy is expected to minimise the potential for therapist bias, however, this possibility will not be eliminated completely and it needs to be appreciated that allocation to different types of exercise therapy is less concealable than to**,** for example**,** an active or placebo drug.

If participants are discharged from in-patient rehabilitation before the end of the 6-week intervention period then they will either attend an out-patient setting or the research therapist will visit them in their 'home' to receive their allocated treatment. If it is most suitable for any participant to travel to an out-patient setting then a pre-paid return taxi journey will be provided.

Control intervention: Participants allocated to the control group will participate in additional MPT[45] prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week (with the exception of public holidays for pragmatic reasons) for up to 6 weeks (CPT+ MPT group). Experimental MPT was formerly called experimental CPT in our earlier trials. The content of extra experimental MPT remains the same as the routine CPT described earlier in this section. Training in delivering the intervention will be provided before the trial begins. Fidelity to the protocol will be assessed at the beginning and at regular points throughout the trial with little prior warning to the therapist.

Experimental intervention: Participants allocated to the experimental group will participate in additional FST prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week (with the exception of public holidays for pragmatic reasons) for up to 6 weeks (FST+CPT group). FST will also be provided according to a treatment schedule consisting of standardised treatment activities. Training and fidelity assessment will be exactly the same procedure as for the control intervention. FST involves repetitive progressive resistive exercise during goal-directed functional activity, with the therapist providing verbal prompting and feedback (therapist-independent). The emphasis is on producing appropriate muscle force for the functional activity being practised. FST is based on the key elements of normal upper limb function, i.e. positioning the hand and then using it to manipulate objects, and is therapist-independent whilst maintaining participant safety. The focus is on: improving the power of shoulder/elbow muscles to enable appropriate placing of the hand; improving the production of appropriate force in arm and hand muscles to achieve the specific grasp; and specific interventions for the wrist and finger muscles to maximise ability to manipulate objects. FST, therefore, is designed to increase power of shoulder and elbow muscles, increase power of muscles for grasp, and improve production of appropriate force at the optimum time for shoulder/elbow movement and object manipulation. The initial level of resistance is the maximum load which still permits five repetitions of movement/action through the available range of muscle length. Treatment is progressed systematically using repetition and increase in the resistance to movement by changing the limb's relationship to gravity, amount of friction to overcome (e.g. shoulder flexion performed in side-lying while (a) in a sling, (b) on a skateboard, then (c) on a towel on a table) and increasing the size and weight of items (e.g. empty cup followed by cup with increasing amounts of water). Content of FST is divided into: specific movements for muscle groups (e.g. emphasis on elbow flexion/extension); upper limb gross movement patterns underlying functional activity (e.g. shoulder flexion/external rotation + elbow extension to reach forward); hand reaching/retrieval activity (e.g. reaching to grasp something on a shelf whilst seated); hand grip activities; hand manipulation involving entire everyday movements and using objects such as screw top canisters, pegs, food items (e.g. bag of dried pasta), mugs and pens. These movements are extended into more complex everyday activities such as using the paretic upper limb to: place different food items into a shopping bag and then lift the bag onto a shelf; tighten/loosen nuts/bolts; open a bottle and drink from it and pour tea from a pot. In line with current research findings on maximising motor learning, feedback and instructions during FST encourage an external focus of attention in participants (focusing on effects of

movements (e.g. whether the teapot has been lifted off the table) rather than focusing on the arm/hand (e.g. amount of shoulder movement when lifting the teapot)[43] and informative verbal feedback on performance[44, 45]on at least 50% but less than 100% of attempts to encourage self-evaluation for motor learning[46]. Training in delivering the intervention will be provided before the trial begins. Fidelity to the protocol will be assessed at the beginning and at regular points throughout the trial, with little prior warning to the therapist.

Key differences between MPT and FST are outlined in the following table.

	Type of Therapy **Movement Performance Training**	**Functional Strength Training**
Description of Therapy		
	Therapist-dependent therapy with an emphasis on preparation and joint alignment via tactile/proprioceptive input. The patient is encouraged to practise grasp/release and reaching for objects or to a point in space, but not as part of a functional task, i.e. reaching for a cup to drink. Instead, for example, they would reach for a therapeutic object such as a cone and move it from one table to another.	Therapy incorporating specific functional tasks or specific strength training movements using everyday objects, in preparation for functional tasks using a therapist-independent approach whilst maintaining patient safety. Verbal prompting is used rather than tactile/proprioceptive input by the therapist. Activities are progressed using repetition, size and resistance.
Progression of Therapy		
Repetition	≤5 repetitions of the same specific task	1 to 5 sets of 5/10 repetitions of the same specific task
Resistance progression – less able subjects	No systematic progression in treatment activities although different weights of objects may be used for treatment activities.	Systematic progression in treatment activities with gravity eliminated or assisting movement, to moving against gravity, or from movements with reduced friction to overcome (e.g. sliding with skateboard beneath) to sliding with towel on table)
Resistance progression – more able subjects	No systematic progression in treatment activities although different weights of objects may be used for treatment activities.	Systematic progression in activities from light to heavy objects or resistance, starting with a resistance which allows a 5-repetition maximum load (and no more) throughout the available range of muscle length. Load is increased when 5 sets of 10 repetitions are achieved.
Size progression	Different sizes of objects may be used in treatment activities but with no systematic progression to make the activity more challenging.	Systematic progression from medium to very small (e.g. to improve pinch grasp) or medium to very large objects (e.g. to improve size of hand opening for power grasp), so that tasks are progressively more challenging.
Distance progression	Different distances of target objects may be used but with no systematic progression to make the activity more challenging	Systematic progression from near to far objects, so that tasks are progressively more challenging
Speed progression	Different speeds of movements may be used in treatment activities but with no systematic progression to make the activity more challenging	Systematic progression from slow to faster movements towards objects so that tasks are progressively more challenging

For both MPT and FST the 6 week intervention period reflects a maximum possible duration.

It is anticipated that the intervention therapy may not be given when; (1) the participant is otherwise unwell (2) on the day of a research assessment (3) the participant is out of the area due to holiday or other personal reasons, or (4) there is a public holiday. In any of these instances, this will be recorded.

Settings

Participants will be screened from either acute in-patient or rehabilitation (in-patient or out-patient) settings in services provided around Birmingham, North Staffordshire and Norfolk. Participants will be recruited from their current residence (permanent or temporary including hospitals) and followed up wherever they go thereafter so long as research governance and ethical permission has been obtained. The extra MPT or FST will be delivered in either the settings described above or, in a NHS or University setting in which case a pre-paid return taxi journey will be provided.

The clinical outcome and follow up measures and the health economics explanatory measure will be completed in any of the above settings. Neuro-imaging will take place in a NHS or University neuro-imaging department. TMS measurements will take place in a University or NHS setting.

Sample size

The clustered data structure (patients within therapist within treatment group) is accounted for in the design and analysis. We follow the strategy proposed by Roberts[47] for randomised trials of this type where two different groups of health professionals deliver the intervention and control therapy. The minimum clinically important change in ARAT score of around 6 points translates to an improvement of one level on 6 of the 19 upper limb tasks tested. There are no intra-class correlation coefficient (ICC) estimates in the literature for physiotherapy interventions being assessed using any of our proposed outcomes. ICC values are known to be lower where patient rather than process of care outcomes are being measured, with the ICC being expected to be somewhat lower than 0.05 for patient outcomes[48]. This sample size calculation is based on actual ARAT data from our previous early phase trial[13]. Assuming an ICC of 0.01 in both treatment arms and three centres with a separate therapist for each randomised arm, a sample size of 99 participants per group would have 80% power to detect a clinically important mean difference of 6.2 in ARAT change when analysing data using a two sample t-test, with Satterthwaite correction, applying a 5% 2-sided significance level and allowing for potentially different standard deviations in the CPT+MPT (7.9) and CPT+FST (19.3) groups. To account for clustering in the design (participants within therapist within randomised treatment at each study site) a sample size inflation factor 1+(m-1)*ICC is applied where m is the cluster size and ICC is the intra-class correlation coefficient. We have investigated this using the SSC software (Health Services Research Unit, University of Aberdeen). Here we have three study sites each with two therapists. Assuming that recruitment is evenly distributed across therapists, the sample size is therefore inflated to 129 evaluable participants per group. The corresponding mean differences in ARAT change that would be detectable in a study of this size for ICCs of 0.02 and 0.03 would be 7.0 and 7.8 respectively, showing that the design is fairly insensitive to assumptions about the ICC. Finally, to allow for an attrition rate of 10% (7% in our previous single centre trial[13]), 144 participants per group will be recruited - total sample size of 288.

For the explanatory measures, the experience of the Oxford research team (HJ-B) indicates that, of those meeting the criteria for this proposed trial, at least 70% will consent to participate. The London research team's (NW) experience of acquiring these explanatory data is that more than 95% of those eligible for trial MRI scanning consented over the last 10 years. Of those that consent in both centres, more than 90% tolerate the measures and complete the study. This is based on extrapolation from studies with similar requirement e.g. multiple visits, imaging+TMS. For example, in a just completed longitudinal study in which 25 patients underwent TMS and MRI before and after 2 weeks treatment, all consented and all tolerated the procedures. There were no drop-outs. We anticipate, therefore, that using our established, successful, procedures we will continue being successful in recruiting participants to, and maintaining their involvement in the explanatory measures for this proposed trial.

Based on this experience we expect that at least 201 (70%) of the 288 participants will consent to explanatory measures at baseline. At outcome we expect that at least 181 (90%) of these participants will complete explanatory measures. Thus, we anticipate that 181 sets of explanatory measures will inform identification of prognostic indicators for the two forms of therapy and determine whether there are any similarities and differences in the neural correlates of improvement in upper limb motor function in response to the two forms of therapy. Thus, our sample size will be much greater than other explanatory studies of upper limb motor recovery early after stroke where a recent systematic review of neuroimaging studies of upper limb recovery within 6 months after stroke concluded that n=14 has been the largest sample size to date[49].

Measures

Clinical efficacy measures (objective 1) participants will be studied at all 3 time points. Measurements will be undertaken in all centres with subjects seated in an upright chair (except for some items of Wolf Motor Function Test), which allows for a posture in which knees and hips are maintained at 90°. A table will be available for placement in front of participants so that when appropriate for the measurements the forearms can be supported on the table with elbows directly below the gleno-humeral joint. The primary outcome measure will be:

A. The Action Research Arm Test (ARAT: mean 10 minutes). The ARAT consists of four sub-sections (grasp, grip, pinch and gross movements) each of which involves 3-6 items which are scored from 0 (unable) to 3 (normal performance). Scores for each sub-section are combined and the total possible score is 57. The ARAT is a measure of the primary focus of both interventions i.e. improved upper limb function. A standardised protocol for conduction and scoring will be used [50].

The secondary outcome measures will be:

B. Wolf Motor Function Test (WMFT: mean 15 minutes). This 15-item test has been designed for use with stroke survivors which measures both performance time and quality of movement of 15 functional tasks including both simple actions (e.g. placing forearm on table) and complex tasks (e.g. turning key in lock). The WMFT has been demonstrated to have high validity and reliability[51, 52], to assess a range of functions not in the ARAT, and is widely used in stroke rehabilitation research.
C. Upper limb strength for hand muscles (mean 15 minutes) – with a myometer held in a secure position. Force values will be obtained during 3 trials, with the greatest value obtained used for data analysis. Tasks will be:
   i. Hand Grip Force and Pinch Grip Force - The upper limb position for both pinch and grip force will be standardised[46]and the myometer will be set to 'zero' after the subject is positioned with their hand/digits around the bars, 'at rest'. Instruction is "squeeze as hard as you can".

Explanatory measures (objectives 2 & 3). Clinically suitable participants will be studied twice; pre-treatment (baseline) and immediately post-treatment (outcome). MRI and TMS data will be acquired at all three clinical centres, using comparable 3T MRI systems and Magstim TMS systems. Applicants are experienced in multi-centre imaging studies[53-55]and we are therefore aware of the importance of maintaining consistency and data quality across sites and of treating multi-centre data appropriately and have systems in place to do this. Once testing begins, data from all sites will be sent promptly to UCL for rigorous quality control prior to statistical processing as described below. Quality control assessments will include manual checks (e.g, subject motion) and automated checks (e.g., signal to noise, motion correction parameters, range checks). These procedures should enable consistent and comparable data to be acquired across sites. A factor of centre will be included in all group level statistical analyses applied to imaging and TMS data to adjust for any centre effects.

The acquisition of explanatory data will be led and supervised by co-applicants with much experience in this area (NW and HJ-B). To maximise recruitment to and minimise attrition from explanatory measures we will provide potential and actual participants with: full explanations and opportunities to ask questions; plenty of time to be made comfortable; and plenty of time to practice the tasks. In addition we will ensure that full training is given to all trial centre teams so that the Oxford and London expertise is extended to all concerned. We will also set up comprehensive monitoring and supervision arrangements to avoid difficulties, and if this is not possible to ensure they are minimised. Our experience is that when these procedures are used then the dropout rate is very low.

D. Structural brain imaging (all conducted in same location in same session)

i. Structural MRI approx 5 mins). T1-weighted, 1x1x1mm whole brain image will be analysed at UCL. Automated normalisation, segmentation and lesion identification will be performed as recently described[56] using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/). This approach has a high sensitivity for delineating brain lesions and identifying tissue classes thereby dealing well with atrophy and white matter disease. Outputs include normalised lesion maps as well as grey and white matter maps consisting of voxel-wise values representing grey or white matter density. These maps will provide quantitative data to aid characterisation of the lesion site.

ii. BO field map (approx. 1 minute). Will provide a map of the static field which allows for off-line correction of image distortions.

iii. Diffusion Tensor Imaging (approx.12 mins). DTI data will be acquired at 2x2x2mm and analysed at Oxford University. A diffusion tensor model will be fitted to data at each voxel to allow for maps of diffusion parameters (fractional anisotropy (FA), mean diffusivity (MD), and eigenvalues) to be generated for each participant at each scanning session. Probabilistic tractography (implemented within FSL[56] (www.fmrib.ox.ac.uk/fsl) will be used to generate pathways of interest across the group[24] This will allow us to test whether integrity of specific pathways is predictive of response to intervention and also to test for any intervention-mediated change in path integrity, as has been previously demonstrated for healthy subjects learning new motor skills [57]

iv. Dual-echo T2-weighted and proton density whole brain MRI (approx. 2 minutes) will be acquired at 1x1x3mm resolution to allow for accurate delimitation of stroke volumes and also for the detection of other pathological changes such as white matter hyperintensities.

E. Functional imaging of brain activity (fMRI; 7 minutes)

A key purpose of FST is to improve the production of appropriate force in different muscles to enhance grasping and manipulation of objects by the paretic hand. We will therefore use a grip force task for fMRI. As all participants will be able to produce the beginnings of prehension (see study population section) they will be able to perform the fMRI grip task. Participants will be scanned whilst performing handgrips with the affected hand. For this purpose, a foam ball will be secured in the participants affected hand. The experiment is conducted in a block design (5 gripping blocks and 5 resting blocks, with each block lasting 18 seconds). During the gripping block, participants will make a hand grip lasting 1.5-2 seconds in response to an auditory cue delivered every 3 seconds (5 hand grips). Subjects will be trained in how to perform the task prior to scanning. The hand grip paradigm has been successfully used in the study of patients with a wide range of motor impairment[22, 58, 59].

Analysis of neuroimaging data will follow standard approaches using SPM12. Normalisation of scans will use the recently published unified model as implemented in SPM12[60]. Single subject results will include voxel wise values for magnitude of brain activity during (all) handgrips. In addition, we will use Dynamic Causal Modelling (DCM) for fMRI[61] to measure effective connectivity between brain regions (coupling parameters) during handgrip.

F. Brain-muscle connectivity (40 minutes)

Single pulses of TMS, using a standard figure of eight coil, will be given over the hand area and the arm area of primary motor cortex of the stroke hemisphere and, when possible within time constraints and participant tolerance, the non-stroke hemisphere. MEP data will be recorded and analysed using EMG data collection software. EMG recordings of MEPs over both contralateral and ipsilateral forearm/arm/hand muscles (e.g wrist extensors and biceps, and hand muscle) will allow for characterisation of recruitment curves in the activated muscle groups. The recruitment curves for one or both hemispheres, will be constructed by measuring the amplitude of the motor evoked potential at between 100, and 160% (where possible) of active motor threshold [62]. The resulting stimulus/response gradient is a sensitive reflection of the functional integrity of the corticospinal system[58].

A consecutive series of participants who have already completed baseline brain-muscle connectivity measures and recruited in predefined Norfolk sites will be invited to participate in a supplementary brain muscle connectivity assessment to provide information on the stability of the baseline brain-muscle connectivity data collected acutely after stroke. The existing evidence suggests that TMS measures are stable (reliable) in healthy adults (Malcolm et al., 2006; Cacchio

et al., 2011) and in people later after stroke (Cacchio et al., 2011; Koski et al., 2007; Wheaton et al., 2009). Although there is no reason to suspect instability of TMS measures early after stroke, the repeated measures design will allow this possibility to be tested robustly.

Once participants have completed the baseline brain-muscle connectivity measures written information on the supplemental assessment will be provided. The supplementary assessment will be between 1-3 days following completion of the baseline brain-muscle connectivity measures and will be identical to the explanatory assessment at baseline, detailed above. Written informed consent will be obtained before the supplementary assessment is undertaken and potential participants will be provided with sufficient time to fully consider the likely implications of the additional research before deciding whether or not to consent.

To robustly assess reliability the appropriate power is needed. To achieve an ICC of 0.8 with a confidence interval between 0.7 and 0.9 a sample size of 51 participants are desired.

The supplementary brain-muscle connectivity data and the baseline brain muscle connectivity data will be used as part of a PhD project under the supervision of the Principal Investigator, Professor Valerie Pomeroy, and Dr. Niamh Kennedy. Dr. Niamh Kennedy is leading the day-to-day management of the TMS measures working to the trial lead provided by Professor John Rothwell.

Cost-effectiveness measurement (objective 4)

An economic analysis is necessary as the estimation of cost-effectiveness is an iterative process, and early information on costs and effects can be used to inform the design of subsequent phase III studies[63]. For costs we will seek to identify what resource items should be monitored in a future study (i.e. what major cost drivers are likely to be affected by the intervention). The resources to be monitored will include those associated with input by the research therapist, length of stay in the original admission and any subsequent re-admission, and other health and non-health care contacts (further therapy, nursing care, social services, out-patient visits, etc.). Additionally, we will monitor the resources incurred by the patient and their families, including transportation, and the care they receive, and provide. Appropriate unit costs will then be assigned to these resource items in order to provide an indication of the relative costs for those receiving CPT+FST compared to CPT+MPT.

In line with NICE guidelines[64] the EQ-5D[65]will be the main measure of effect in the cost-effectiveness analyses. The information on the costs and QALY (Quality Adjusted Life Year) gain (calculated from the EQ-5D) will be drawn together in order to give an indication of the likely cost-effectiveness of CPT+FST. Additionally, the level of uncertainty associated with that decision will be estimated.

Adverse Event Reporting

Definitions

Definitions will be as defined in the Norfolk and Norwich University Hospitals NHS Foundation Trust and University of East Anglia joint Standard Operating Procedures for the Identifying, Recording and Reporting Adverse Events. However, events will not be reported to the NNUH, but rather the UEA as sponsor. The full operating procedures can be found at http://www.nnuh.nhs.uk/Dept.asp?ID=681

MPT or FST Expected Adverse Reactions

Pain and Fatigue are of clinical interest in informing the results of the trial. There is a small possibility that either therapy could be associated with an overuse syndrome as expressed by a participant's experience of pain or fatigue.

a. Pain will be considered to be a Adverse Reaction if (i) a participant reports the onset or increase of paretic upper limb pain (verbally or behaviourally), (ii) the pain is sustained over four therapy sessions and (iii) if the therapist and clinical team are unable to account for this in any other way than involvement in this trial. This will be addressed by the therapist adjusting the therapy as appropriate or, if indicated, stopping the extra therapy on either a permanent or temporary basis. The date of Adverse Reaction will be the date of the fourth therapy session.
b. Fatigue will be considered to be a Adverse Reaction if (i) a participant demonstrates a decrease of two levels in the Motricity Index upper limb score on two consecutive therapy sessions and (ii) the therapist and clinical team are unable to account for this in any other way than involvement in this trial. This will be addressed by the therapist adjusting the therapy as appropriate or, if indicated, stopping the extra therapy on either a permanent or temporary basis. The date of Adverse Reaction will be the date of the second therapy session.

Stroke related Expected Adverse Events

- Death
- A fall requiring hospitalisation
- Further vascular events (including recurrent strokes, myocardial infarction, bowel ischemia)
- Cardiac, renal or liver problems
- Epileptic seizures
- Revascularisation
- Major Bleed
- A fall
- Infections
- Mood disturbances
- Spasticity or contractures
- DVT

Neuroimaging Expected Adverse Reactions

- Acoustic noise due to rapid gradient switching. Hearing protection will be provided
- Potential quench of cryogens and asphyxiation - a hazard only if the vent fails
- Operating at a field strength of 3 Tesla, our scanner falls into the second category 'upper level' (NRPB) which corresponds to 'first level controlled operating mode' (IEC). The MHRA advises that visual supervision of a conscious patient by an MR Operator will be sufficient to ensure the safety of the subject
- Potential for RF burns - correct input of subject weight will ensure Specific Absorption Rate (SAR) limits are not exceeded.
- The scanner has a laser alignment beams which is a Class 2 laser product. The instructions "Do not stare into the beam" will be given

- Claustrophobia – subjects will have an ‘attention button' to indicate that they wish the scan to be stopped and to be withdrawn from scanner.
- Peripheral nerve stimulation (experienced as pain or tingling in nerve distribution when entering magnetic field or during scan) - this would result in withdrawal from scanner room and MRI would not be performed or would be stopped. The symptoms go away as soon as removed from magnetic field.

TMS related Expected Adverse Reactions

- Seizure

Reporting of adverse events

All Adverse Events, including those which are expected, will be recorded from date of randomisation to end of trial (see below). Adverse events will be reported to the Data Monitoring and Ethics Committee, set up in accordance with the Medical research Council Guidelines for Good Clinical Practice [66].

Study co-ordination

The study will be co-ordinated and managed by the Chief Investigator and Clinical Trials Manager and at the University of East Anglia. They will collaboratively provide overall project co-ordination and ensure that the trial runs according to relevant ethical and regulatory standards, and that all aspects of the study are performed to the highest quality.

Data collection

Each centre will be provided with a Protocol, Standard Operating Procedures, Intervention protocols and CRFs. Data will be sent to the Robertson Centre for entry and quality control in a secure standardised manner in keeping with the Data Management Plan produced by the Robertson Centre for Biostatistics.

Pre-study site visits

Before the study commences each centre will receive a training visit by CTM or delegate. These visits will ensure that the research team at each site (including principal investigators, co-investigators, research therapists and blinded assessors) fully understand the protocol, CRFs and the protocols for the study.

Monitoring site visits

During the study the CTM or delegate will perform monitoring visits to each centre at regular intervals. The purpose of these visits is to ensure compliance to the protocol and that ethical and regulatory guidelines are met. These visits also provide an opportunity for further training if required (eg new staff). Central review of study data will also be performed throughout the study.

Close out site visits

After the end of the study each centre will receive a site visit from CTM to resolve any outstanding queries or adverse events and to verify the correct storage of study documentation.

End of Trial

Participants are considered to have reached the end of the trial when the first of the following occurs; (1) completion of 6 month outcome assessment (2) withdrawal of consent (3) SAE resulting in withdrawal of participant or death, (4) loss to follow-up. If during therapy pain or fatigue (as defined above) occurs, the extra CPT or FST will be temporally or permanently stopped depending on whether or not the symptoms dissipate.

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. A single formal analysis will take place at the end of the study. Interim data summaries will be made available to the independent Data Monitoring and Ethics Committee (DMEC).

Clinical efficacy (objective 1)

Continuous outcome variables will be compared between treatment groups using a normal multilevel model. Change from baseline to day 43 outcomes will be modelled, adjusting for the baseline value, time after stroke category and 9HPT score category patient-level covariates. Therapist will be included in the model as a zero-mean random effect. We will test, by comparing the log-likelihood, whether a separate random effect variance is required for therapists delivering each treatment arm or whether a pooled variance is sufficient. Where the outcome distribution deviates from a normal distribution, a log or other appropriate transformation will be applied. In particular, analysis of the WMFT primary endpoint will be performed following a log transformation as this outcome is positively skewed. The effect of treatment will be summarised using the adjusted mean difference and 95% confidence interval. Adjusted mean differences for log-transformed variables will be exponentiated to give an adjusted mean percentage difference.

Binary outcomes will be compared between treatment groups using a multilevel logistic regression model. Day 43 values will be modelled, adjusting for the baseline value and the 9HPT score category patient-level covariates. The effect of treatment will be expressed as an odds ratio and 95% confidence interval. Therapist will be included in the model as a zero-mean random effect. We will assess, using a Wald test, whether a separate random effect variance is required for therapists delivering each treatment arm or whether a pooled variance is sufficient.

Secondary analyses will include the sensitivity to incomplete follow-up, descriptive analysis at each time-point, statistical modelling of follow-up measures at 6 months, and a per-protocol analysis. For the safety analysis the number and percentage of participants experiencing each category of pre-specified adverse event will be summarised by treatment group.

Mechanisms – explanatory measures (objective 2)

We will have the following explanatory measures at baseline and after 6 weeks therapy on over 180 participants; (i) TMS and DTI based measures related to corticospinal system integrity, (ii) normalized lesion maps, (iii) voxel-wise measures of grey and white matter density, and (iv) voxel-wise measures of brain activity during hand grip and its modulation by changing force. We will not need to group participants according to an arbitrary definition of lesion site (cortical/subcortical) as this information will be included in the segmented lesion map. Clinical motor scores will also be recorded. We will adjust for the time after stroke category.

Objective 2 seeks to identify similarities and differences in the neural correlates of clinical improvement in upper limb motor function in response to CPT+FST and CPT+MPT. Associations will therefore be investigated between change from baseline in clinical outcomes and change from baseline in each of these explanatory measurements. These will be assessed within each treatment group and overall. We will make every possible effort to record and adjust for potential baseline confounding variables, such as baseline motor score.

The relationship will be explored further via multilevel linear regression which will include therapist as a random effect, and will assess whether the changes in neuroimaging and/or neurophysiological measures are strongly associated with clinical improvements in the individual patient. We acknowledge the potential value of structural mean models (SMM)/causal inference (CI) and are aware of additional complexity due to clustering in the design. Therefore we will investigate an extension of SMM/CI as a potential exploratory analysis[67].

Mechanisms – explanatory measures (objective 3)

Objective 3 aims to determine whether baseline measurements, either individually or in combination, are sufficiently predictive of improvement in upper limb motor function to enable physical therapy to be targeted at those stroke survivors most likely to respond.

Baseline measurements considered will be (i) TMS and DTI based measures related to corticospinal system integrity, (ii) normalized lesion maps, (iii) voxel-wise measures of grey and white matter density, (iv) voxel-wise measures of brain activity during hand grip and its modulation by changing force, (v) clinical variables including motor scores. An interaction term between treatment group and each variable from (i)-(v) in turn will be added to the normal linear model for ARAT used in the clinical efficacy analysis of Objective 1. Continuous baseline variables will be categorized as high or low, the cut-point being at the median of the observed data. We will adjust for the time after stroke category. Statistical significance of the interaction term will be assessed and the treatment effect calculated within each of the high and low subgroups of the interaction variable.

We then propose a further analysis, to develop within each treatment group a multiple regression model to predict change in ARAT clinical outcome using baseline measurements. This will determine the subset of baseline variables independently associated with response to treatment and will allow for a different group of baseline predictors within each treatment group. Principal components analysis will be used to reduce the dimensionality of the predictor variables while retaining a meaningful interpretation of the principal components. An alternative approach that will also be considered is a machine learning approach such as that applied by Saur[26].

The stability (test-retest reliability) of the brain-muscle connectivity between the baseline assessment and the supplementary assessment (between 1-3 days later) will be explored using Intra-class correlation coefficient together with the limits of agreement analysis. The Intra-class correlation will reflect the degree of correlation as well as the agreement between the two tests (Portney and Watkins, 2000). The limits of agreement will examine the agreement across multiple tests, and will determine if there is a biased pattern of error such as systematic error versus random error between tests (Bland and Altman, 1986; Portney and Watkins, 2000). The combination of these two statistical tests will robustly determine the absolute reliability of brain-muscle connectivity acutely after stroke.

Funding and external supervision

FAST INDICATE is co-ordinated by the Efficacy and Mechanism Evaluation programme (www.eme.ac.uk),funded by the MRC and NIHR, with contributions from the CSO in Scotland, NISCHR in Wales and the HSC R&D, Public Health Agency in Northern Ireland. It is managed by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton. EME reference: 10/60/30

Indemnity

"The University of East Anglia (UEA) is the named recipient of the grant and Sponsor. Details of insurance can be found at https://intranet.uea.ac.uk/fin/insurance/clinicaltrials or obtained from Research and Enterprise Services researchsponsor@uea.ac.uk"

Ethical arrangements

The National Research and Ethics Service (NRES) granted a favourable opinion to the trial on the trial and assigned reference 11/EE/0524

Research governance

The University of East Anglia (UEA is the named recipient of the funding and with the University of Glasgow Clinical Trials Unit and Norwich Clinical Research Trials Unit will be responsible for the overall setup and delivery of the trial. The UEA has subcontracted with each University, detailing the funding and delegated responsibilities each has to the UEA in the set-up and delivery of the trial. Each University will employ and indemnify its allocated research staff and ensure that they and the applicants are given the allocated time to research and manage the project. Each University will also secure appropriate management and governance arrangements with their local NHS Trusts for their part of the trial. All employed research staff 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 delivery of functional strength training does not require the administration of medicinal products, therefore this is not a trial within the scope of the Clinical Trials Directive defined by the Medicines and Healthcare products Regulatory Agency (MHRA).

Trial documentation will be archived securely for a period of 10 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**.** The custodian will be the Chief Investigator.

Responsibilities

Chief Investigator (or nominated individual in CIs absence):

1. Review all SAEs for seriousness, expectedness and causality in accordance with agreed process for the trial.
2. All other responsibilities as assigned by regulating bodies, the funder or the sponsor not otherwise delegated.

In addition to the responsibilities set out above, responsibilities will be delegated by the CI and CTM to PIs, research therapists, blinded assessors, research technicians and others as appropriate and recorded on delegation logs.

Principal Investigator:

1. Reviewing all Adverse Events for Seriousness and Causality
2. Clinical judgement in assigning to Serious Adverse Events:
    - Seriousness

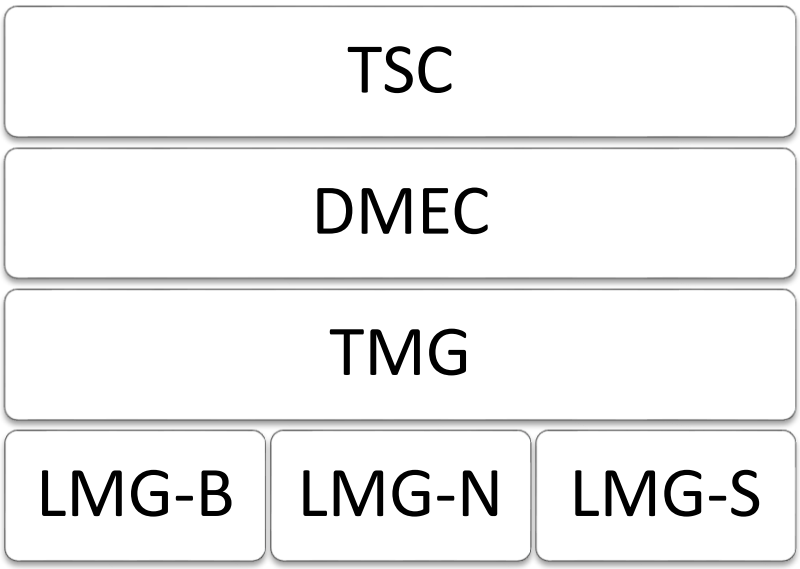
- Causality
- Expectedness

3. To ensure all SAEs are recorded and reported and to provide further follow up information as soon as available.
4. To report SAEs to the CTM, and local bodies as appropriate, in line with local arrangements.
5. All other responsibilities as listed on SSI form for the site which he or she has authorised.

Clinical Trial Manager

1. Preparing reports to Main REC, Sponsor, Funder and other such bodies
2. Providing strategic supervision and management of the project

Trial Management



The Trial Steering Committee will provide supervision on behalf of the Trial Sponsor (University of East Anglia) and the Trial Funder (NIHE EME) and to ensure that the trial is conducted as set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice.

The DMEC will monitor un-blinded comparative data and make recommendations to the TSC on whether there any ethical or safety reasons why the trial should not continue based on the available data.

The Trial Management Group will meet every 3 months and provide strategic oversight of the trial and will be composed of members the trial team and service users.

Three Local Management Groups (Birmingham, North Staffordshire, and Norfolk respectively) will meet each month and provide operational management of the trial.

Trial Steering Committee (TSC)

The TSC will meet once a year throughout the life of the trial (or more frequently if advised by the Chair). We will follow the guidelines provided by the National Institute of Health Research (NIHR) Efficacy and Mechanisms Evaluation (EME) guidelines

(http://www.eme.ac.uk/investigators/pdfs/TSCGuidelines.pdf) and the Medical Research Council Guidelines for Good Clinical Practice [66] on the scope and composition of the TSC.

The TSC will be quorate when the Independent Chair, one or more independent member, CI and/or the CTM are in attendance either in person or by tele or video conference.

Data Monitoring & Ethics Committee (DMEC)

The DMEC will meet once a year throughout the life of the trial (or more frequently if advised by the Chair), approximately 4 weeks before the TSC meet so that the DMEC can make a recommendation to the TSC on the continuation of the trial. We will follow the guidelines provided by the National Institute of Health Research (NIHR) Efficacy and Mechanisms Evaluation (EME) guidelines (http://www.eme.ac.uk/investigators/pdfs/DMECGuidelines.pdf) and the Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials [66] on the scope and composition of the DMEC.

The DMEC will be quorate when the Independent Chair and one or more independent members are in attendance.

Trial Management Group (TMG)

The TMG will meet by a combination of physical and tele/video conferencing before the trial starts and approximately every 4 months thereafter.

The TMG will be quorate when the CI and/or CTM, and two or more other members are in attendance. Members will be invited as determined by the agenda.

Local Management Groups (LMGs)

Frequency

Local Management Groups (LMGs) will meet approximately every two months except when the TMG meets in which case it will be waived. Core Business will include

The LMG will be quorate when the CTM and PI are in attendance.

Service users

Patient and Public Involvement in Research (PPIRES: www.norfolhealthresearch.nhs.uk) members' comments have informed the present version of this protocol.

Collaborator Expertise

The interdisciplinary team has substantial expertise in: stroke rehabilitation research, neuroimaging, neurophysiology, health economics, clinical trials, clinical stroke rehabilitation, statistics, large external grant administration, project management, research staff supervision and user involvement. All clinical sites are currently undertaking similar local projects and have appropriate expertise and collaborative clinical networks in place to enable the successful conduction and completion of this proposed trial.

- Professor Pomeroy leads an internationally competitive stroke rehabilitation research group who since 2002 have published over 50 papers in peer-reviewed scientific journals. She is experienced in conducting large stroke rehabilitation trials.
- Dr Ward has an international reputation for neuroimaging research.
- Dr Johansen-Berg has research expertise in structural (MRI, DTI) and functional (fMRI) brain imaging and brain stimulation (TMS, tDCS) in stroke survivors and healthy adults.
- Dr van Vliet leads innovative research in recovery and upper limb physical therapy after stroke
- Professor Burridge has expertise in physiotherapy and measurement of motor impairment
- Dr Hunter has clinical and research expertise in stroke rehabilitation.
- Professor Lemon currently has Wellcome Trust and MRC funding for research on control of hand function, including use of TMS for exploration of cortico-cortcal interactions during skilled grasp.
- Professor Rothwell has over 20 years experience with transcranial magnetic stimulation and is an expert in the pathophysiology of movement disorders.
- Professor Wing has expertise in behavioural and neurophysiological methods for studying sensory motor control of upper limb reach, grasp, grip and lift in normal and hemiparetic stroke participants.
- Dr Weir has over 15 years experience in biostatistics research, the majority of which has focused on applications in acute stroke.
- Alex McConachie is the Assistant Director of Biostatistics, Robertson Centre for Biostatistics, University of Glasgow
- Dr Barton has conducted economic evaluations within a number of pragmatic RCTs.

Site Website

The official trial website is located at www.fastindicate.com

Figure 1: Trial Overview

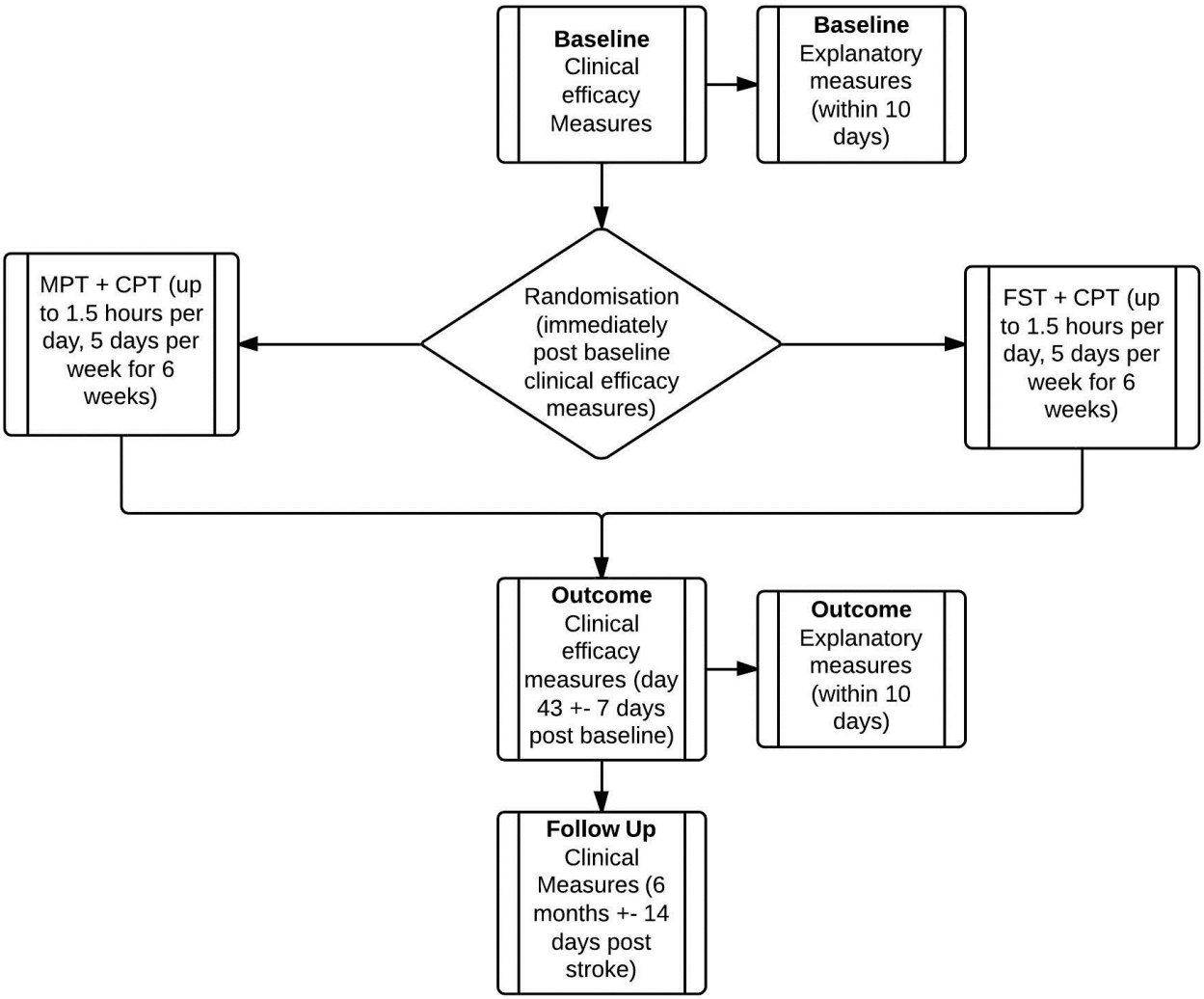


Figure 2: Initial screening

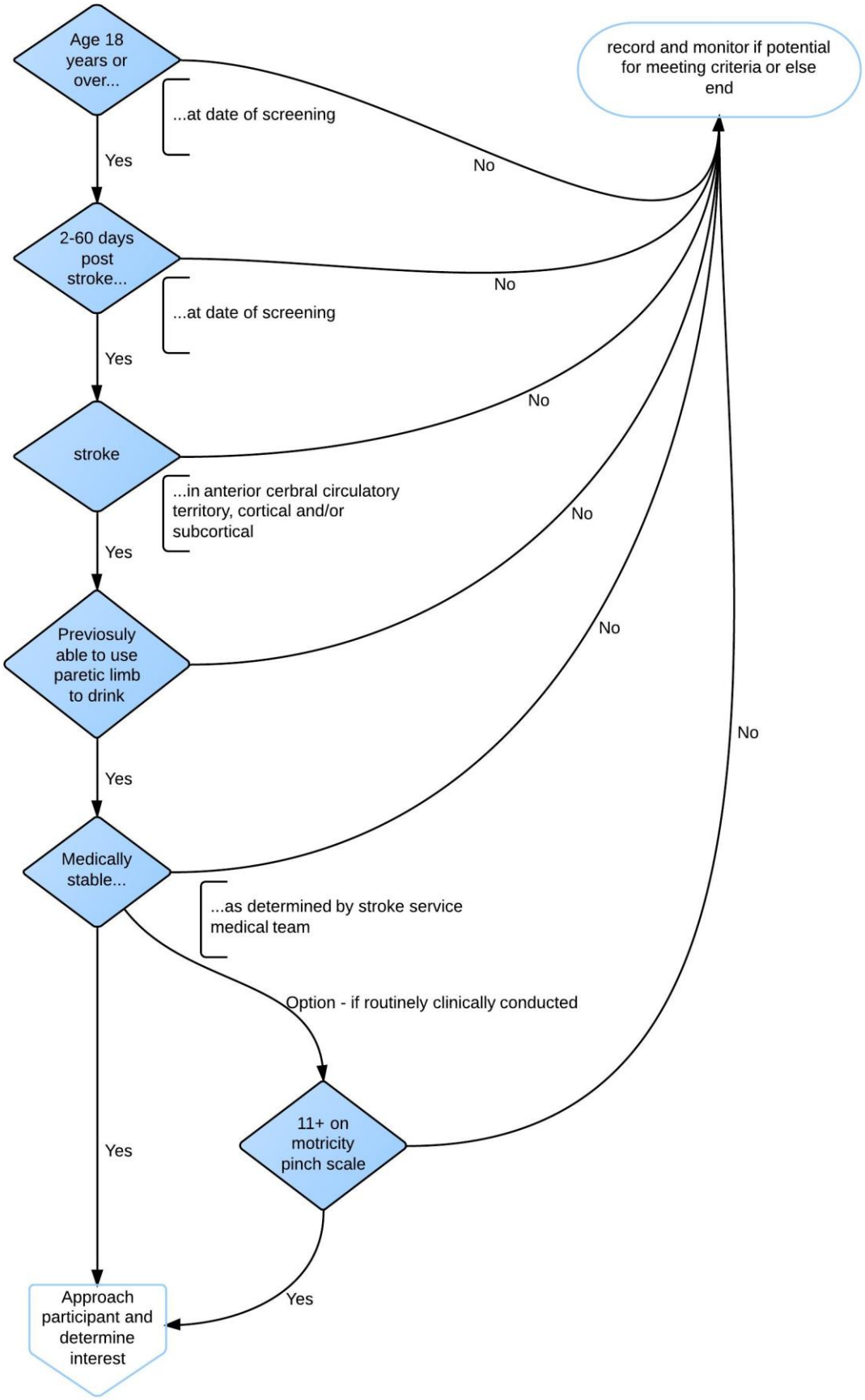


Figure 3: Participant eligibility pathway

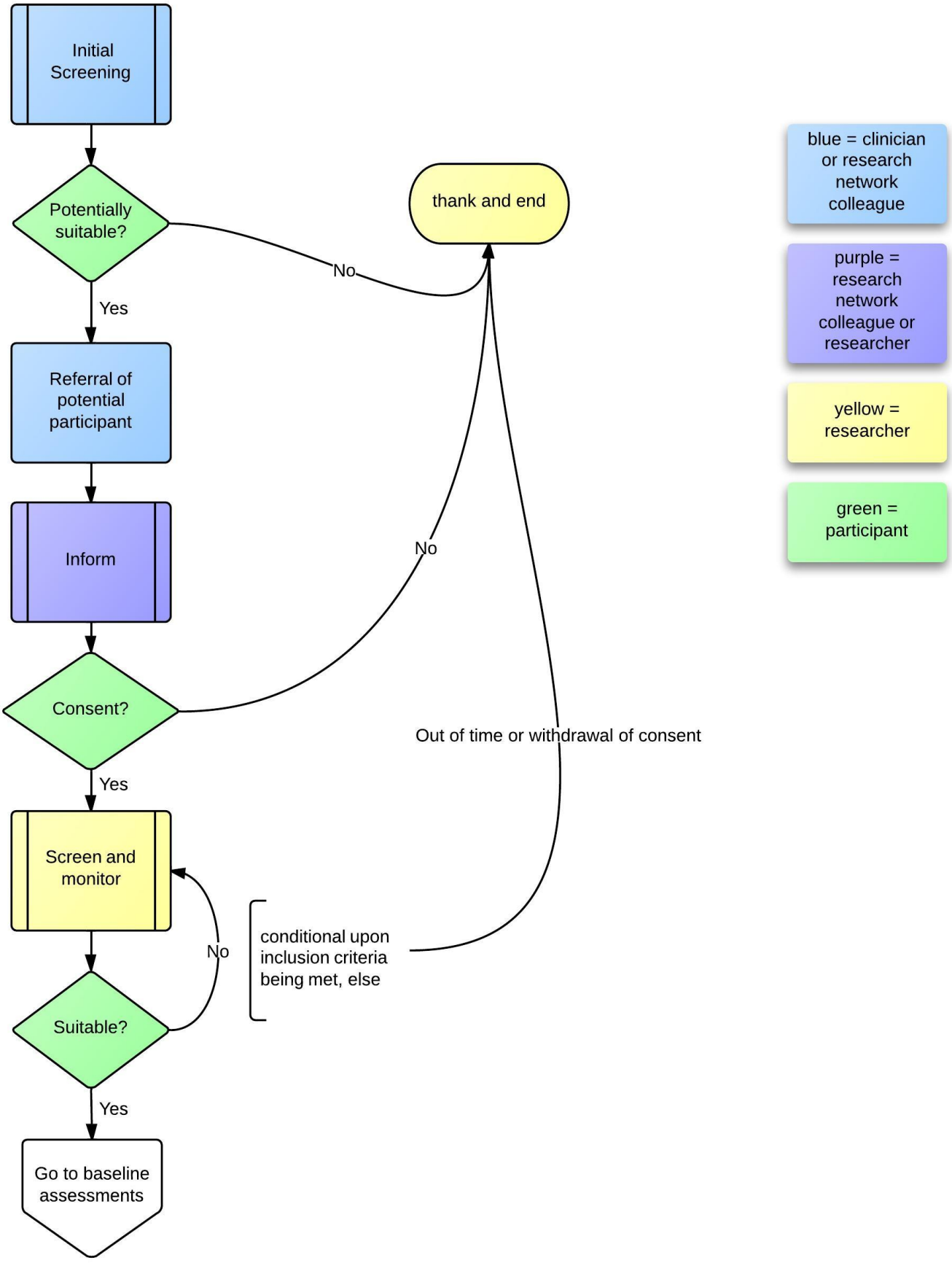
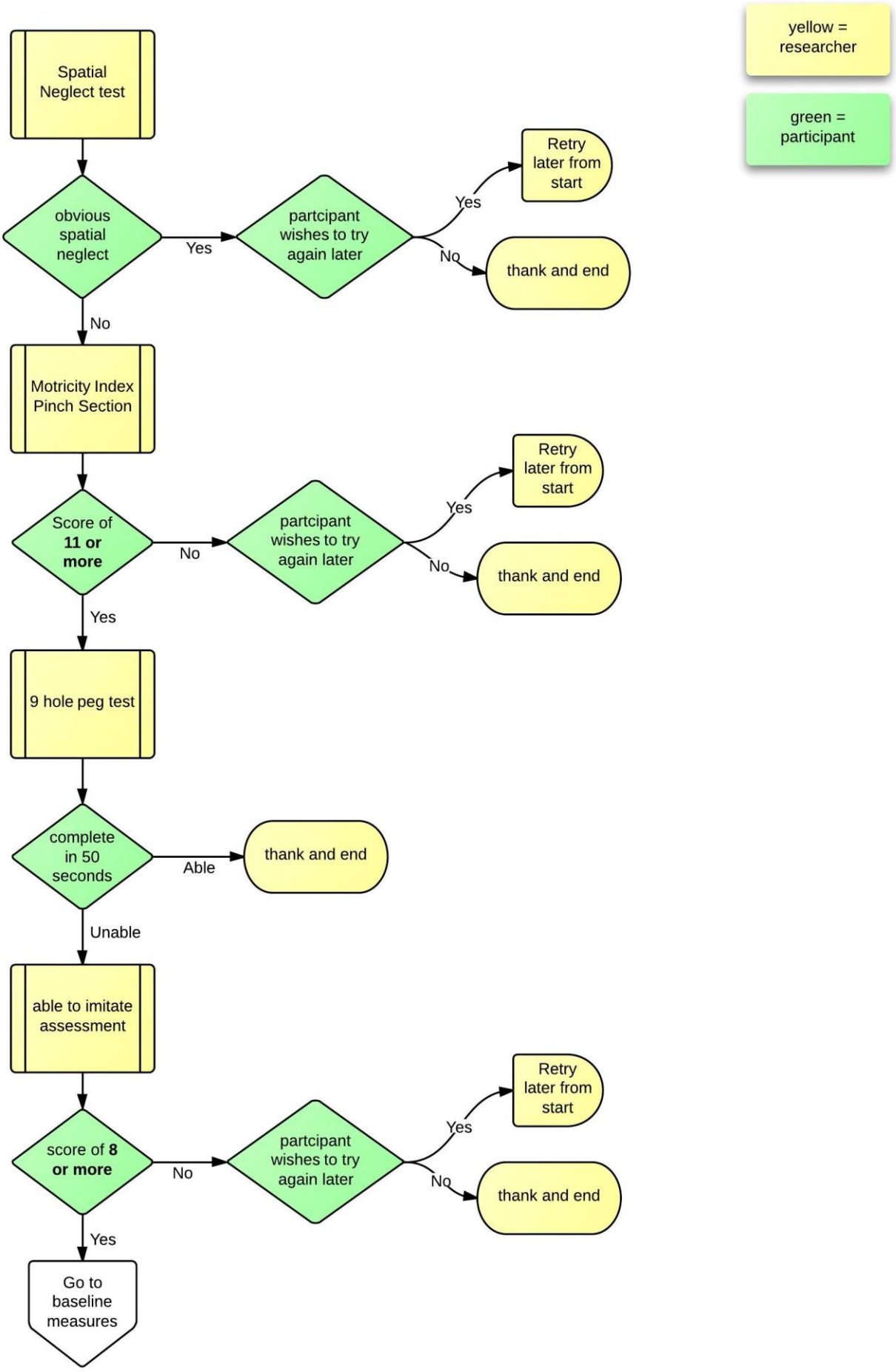


Figure 4: Post-consent Suitability assessment



Abbreviations used in protocol

ARAT, Action Research Arm Test; CI, Causal Interference; CIMT, Constraint-Induced Movement Therapy; CNS, Central Nervous System; CONSORT, Consolidated Standards of Reporting Trials; CPT, Conventional Physical Therapy; CRTU, Clinical Research Trials Unit; CTM, Clinical Trials Manager; DCM, Dynamic Causal Modelling; DMEC, Data Monitoring and Ethics Committee; DTI, Diffusion Tensor Imaging; EME, Efficacy Mechanism Evaluation programme; EMG, Electro-Myogram; fMRI, Functional Magnetic Resonance Imaging; FA, Fractional Anisotropy; FST, Functional Strength Training; GCP, Good Clinical Practice; ICC, Intra-class Correlation Coefficient; ISI, ; IVRS, Independent Telephone Randomisation Service; LMG, Local Management Group; MD, Mean Diffusivity; MEP, Motor Evoked Potential; MHRA, Medicines and Healthcare products Regulatory Agency; MPT, Movement Performance Training; MRC, Medical Research Council; MRI, Magnetic Resonance Imaging; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PPIRes, Patient and Public Involvement in Research Group; QALY, Quality Adjusted Life Year; RAT, Robot-Assisted Therapy; RCT, Randomised Controlled Trial; SMM, Structural Mean Models; SPM8, Structural MRI (8mins); tDCS, Transcranial Direct Current Stimulation; TMG, Trial Management Group TMS, Transcranial Magnetic Stimulation; TSC, Trial Steering Committee; UCL, University College London; UEA, University of East Anglia; UKCRC, UK Comprehensive Research Collaboration; UKCRN, UK Clinical Research Network; UKSRN, UK Stroke Research Network; WMFT, Wolf Motor Function Test; 9HPT, Nine Hole Peg Test

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