DARS

Dopamine Augmented Rehabilitation in Stroke

Does Co-careldopa treatment in combination with routine NHS occupational and physical therapy, delivered early after stroke within a stroke rehabilitation service, improve functional recovery including walking ability and arm function?

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Other collaborators and the Sponsor contact are detailed in Appendix 1: Trial Management Group

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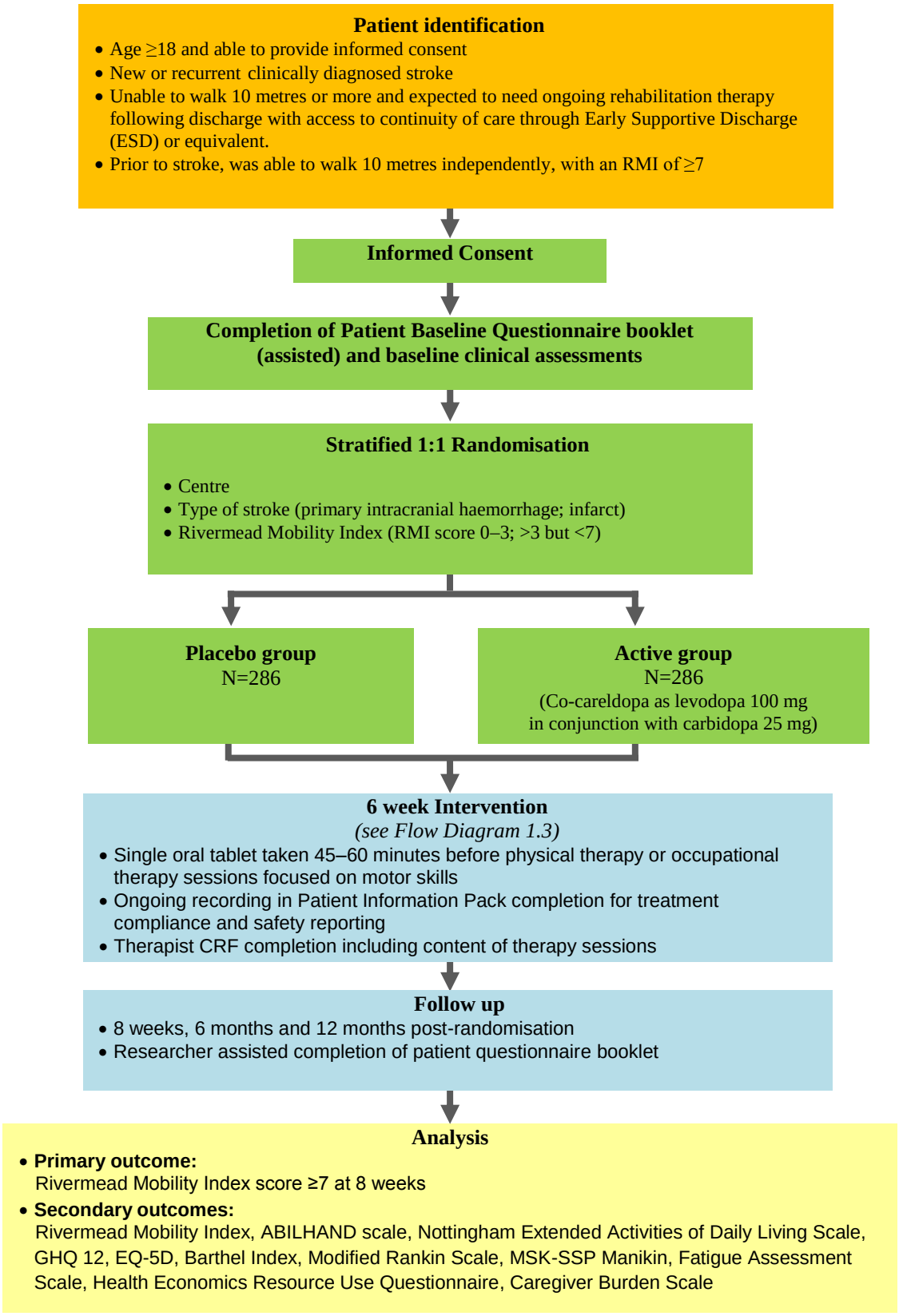
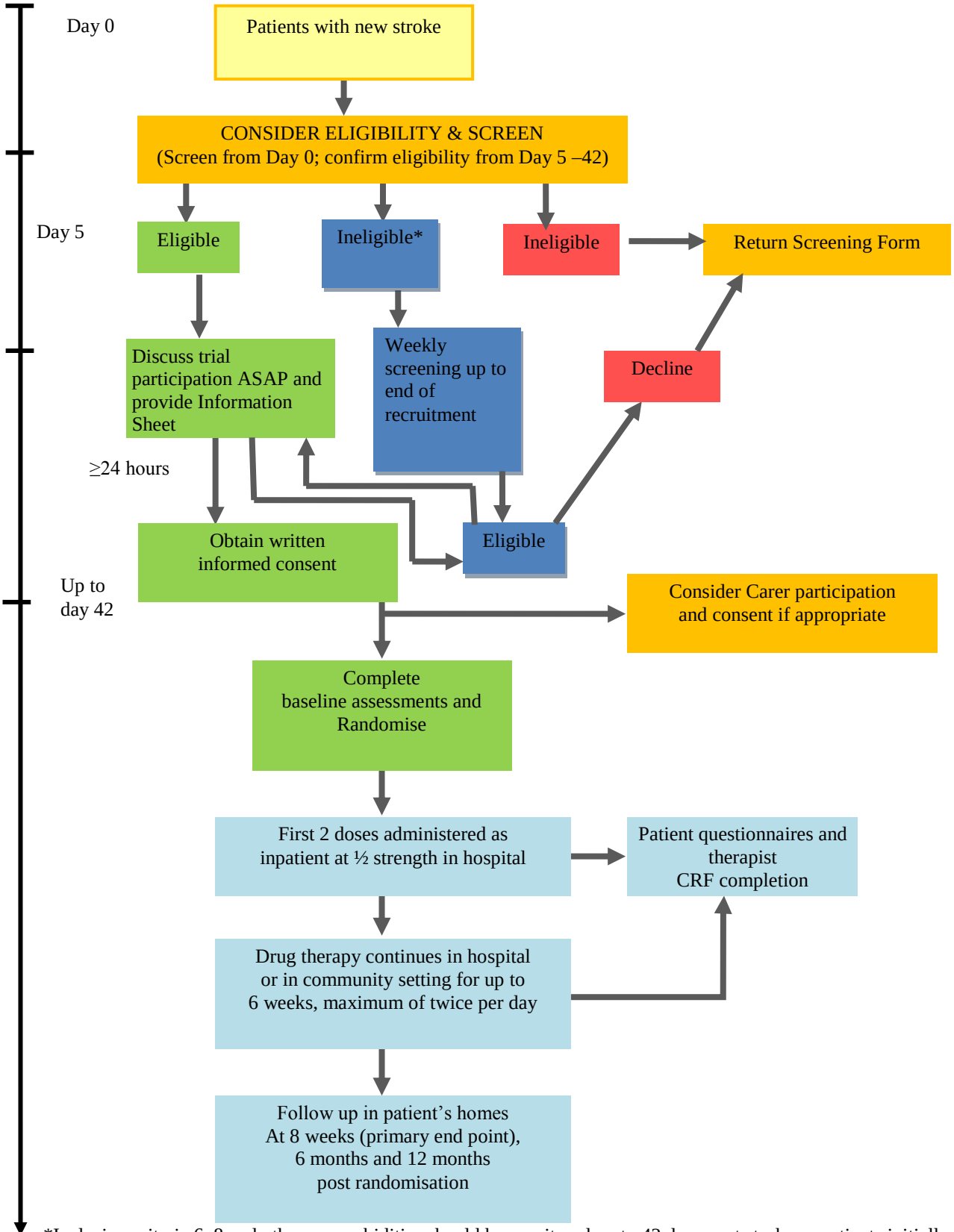
1.1 TRIAL FLOW DIAGRAM

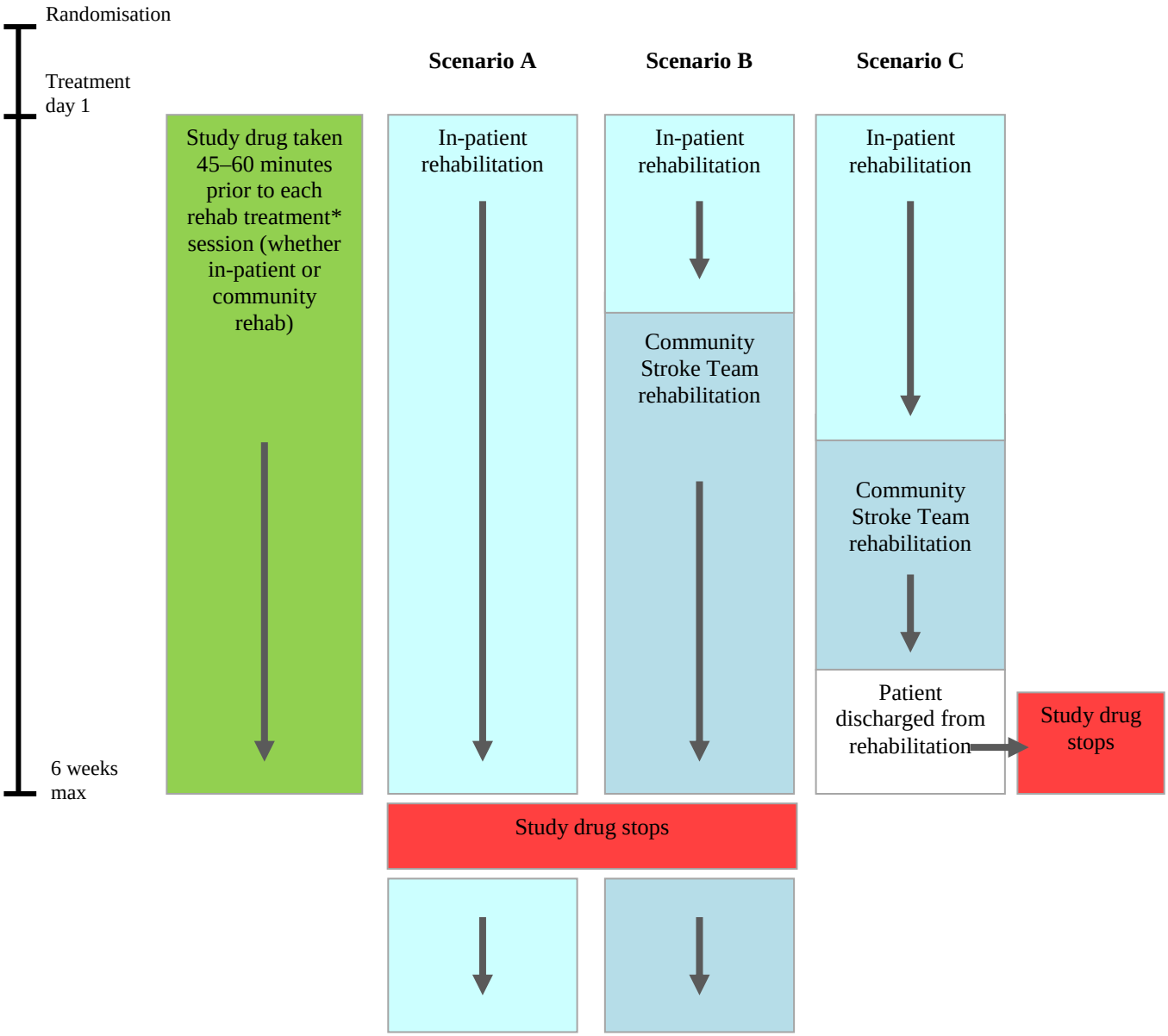


1.2 PATIENT RECRUITMENT PATHWAY - Flow Chart 1



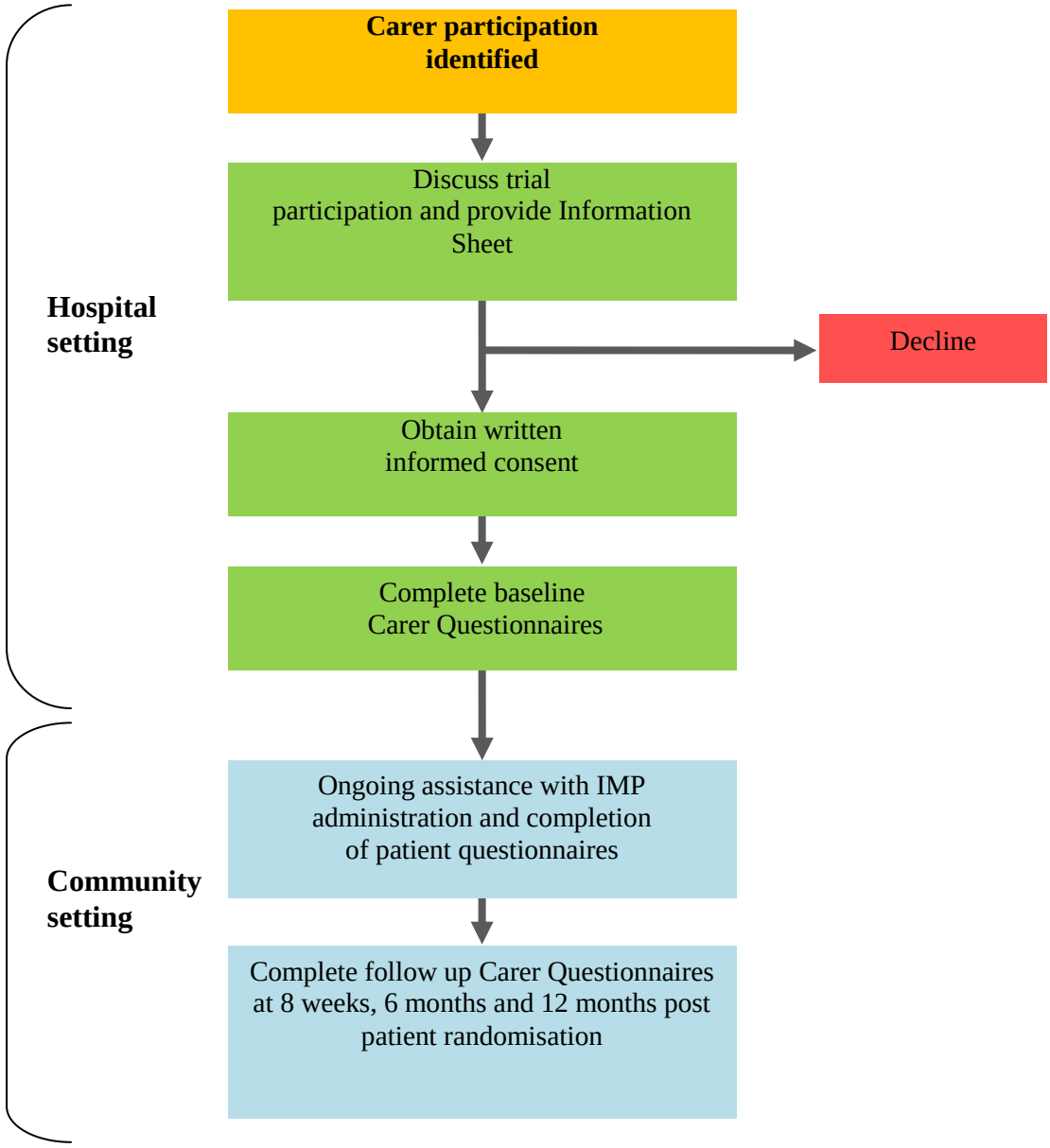
*Inclusion criteria 6, 8 and other co morbidities should be monitored up to 42 days post stroke as patients initially not meeting the eligibility criteria may improve within the 42 days post stroke.

1.3 PATIENT TREATMENT SCENARIOS - Flow Chart 2



* Rehabilitation treatment appropriate for drug administration within DARS is defined as an active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers and dressing, but not psychological input sessions or speech and language therapy, swallowing, splinting).

1.4 CARER PARTICIPATION PATHWAY – Flow Chart 3



2.0 GLOSSARY OF TERMS AND DEFINITIONS

2.1 DEFINITIONS

ABILHAND	ABILHAND Manual Ability Measure
AE	Adverse Event
BI	Barthel Index
BNF	British National Formulary
ADRM	Academic Department of Rehabilitation Medicine
CBS	Caregiver Burden Scale
CEA	Cost Effectiveness Analysis
CEACs	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EQ5D	European Quality of Life-5 Dimensions
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GHQ-12	General Health Questionnaire 12 (12 item version)
HRQoL	Health Related Quality of Life
ICC	Intracluster Correlation Coefficient
ICERs	Incremental Cost-Effectiveness Ratio
IMP	Investigational Medicinal Product
ITT	Intention To Treat
LRNs	Local stroke Research Networks
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRS	Modified Rankin Scale
MSK-SSP Manikin	Musculoskeletal symptoms/signs and pain Manikin
NEADL	Nottingham Extended Activities of Daily Living
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
NSA	National Stroke Audit
OT	Occupational Therapy
PI	Principal Investigator
PT	Physical Therapy
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life-Year
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMI	Rivermead Mobility Index
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SRN	Stroke Research Network
Stroke service/unit	Organised Stroke service/Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

2.2 GLOSSARY

Carer	An individual identified by the patient as the main informal carer, who provides the patient with practical support a minimum of once per week.
Code Break envelope	Code Break Envelopes are coded documents that allow the blind to be broken for the treatment allocation of an individual patient and are held by the CTRU Safety Team and an organisation/organisations responsible for the back-up of this process as per the protocol.
Kit number	Kit number is a random code used to identify each treatment code allocation and container of IMP (e.g. vial, box, bottle)
Rehabilitation	Occupational therapy / physical therapy which is addressing physical functioning (e.g. sitting practice, standing, dressing, kitchen skills).
Researcher	Research Nurse/therapist at each Trust who is responsible for the outcome assessment. This person may be employed by local Stroke Research Network or a DARS researcher.

3.0 BACKGROUND

3.1 STROKE

Stroke is the commonest cause of severe disability (annual UK incidence of first stroke is 100,000). Stroke has a huge impact leaving over a third of affected people with lasting disability affecting self care. One year after a stroke 31% are still dependent for outside mobility and 15% dependent for inside mobility. The number of disabled stroke survivors will increase due to ageing population demographics. The cost of stroke accounts for 6% of the total NHS and social services expenditure. Although acute stroke interventions such as thrombolysis can reduce mortality and morbidity, rehabilitation remains the cornerstone treatment for the majority of people with stroke. The role of high quality rehabilitation within comprehensive stroke services is widely acknowledged as described by the National Stroke Strategy.

Despite the clear benefits of organised stroke care at least 30,000 people in the UK each year are left with physical disability, increasing the long term societal costs of dependency and major impact of quality of life of those individuals and their families. Despite clear benefits of organised stroke care, a third of people with stroke are left with significant physical disabilities. Physical and occupational therapies have been shown to benefit people but residual disability for a large proportion of patients still remains a key issue in regaining full independence.

3.2 PHARMACOLOGICAL PRIMING OF THE BRAIN AND MOTOR SKILL ACQUISITION

There is emerging evidence from pilot studies which indicate that combining certain drugs with physical and occupational therapy may improve the recovery of arm and leg movements and thus essential day to day activities such as walking and getting dressed. These improvements are in addition to the benefits gained from physiotherapy and occupational therapy alone. These studies suggest that the nerve circuits in the brain respond better to the usual therapy when they are also exposed to drugs such as dopamine at the same time as having occupational or physiotherapy. A lot of this evidence comes from small studies.

3.3 RECENT STUDIES INVOLVING DRUGS AND LEARNING

Learning is an essential process by which recovery of mobility and arm function occurs after stroke, either through relearning to use the affected body parts and/or learning to compensate with the lesser affected side (e.g. one-handed dressing). These situations involve the patient becoming

attuned to the perceptions which guide skilled movement, such as vision and proprioception. At a clinical level, the patient practises motor skills with guidance and support from therapists (Pollock 2007). At a biological level, this practice leads to changes in behaviour (learning) through functional re-organization of the central nervous system (CNS) by a process of neural plasticity (Ward 2004).

Evidence from animal and human studies indicates an important role of noradrenergic / dopaminergic brain pathways in motor skill acquisition (Wise 2004, Ziemann 2006). Animal studies demonstrate that neural plasticity comprises cellular processes (e.g. changes in synaptic morphology, synaptic potentiation / depression, dendrite sprouting and alteration of axonal trajectories (Nudo 2006)). Involvement of adrenergic neurotransmitters in these processes raises the possibility of pharmacologically promoting neural plasticity by increasing catecholamine levels in the CNS (e.g. oral amphetamine increases the brain levels of dopamine, serotonin and norepinephrine) which can modulate long-term changes in synaptic function. Studies in rats suggest that amphetamines can promote relearning after experimental brain injury (Feeney 1982). Encouraged by this evidence, several clinical trials of amphetamines in stroke patients have been undertaken. A recent Cochrane review of 12 small clinical trials (344 patients) reports a trend towards improved motor function (Martinsson 2007) and suggested further studies to confirm an effect on motor recovery were warranted. There is no evidence of increased mortality / dependency with amphetamine administration in stroke patients. However, adverse sympathomimetic effects with amphetamines, such as tachycardia and hypertension are reported.

A growing body of evidence suggests that learning and motor skill acquisition occurs through the dopaminergic system rather than through direct noradrenergic action of general arousal. Therefore drugs that promote dopaminergic activity directly may be more appropriate as targeted brain modulators (Breitenstein 2006) in the context of motor skill acquisition, and be associated with fewer adverse cardiovascular effects.

Levodopa is a precursor of dopamine which crosses the blood-brain barrier and is converted to dopamine in the brain. Co-careldopa is a routinely available inexpensive medication that will be used to deliver 100mg of Levodopa through its combination with 25mg carbidopa. Co-careldopa is used to deliver Levodopa as this contains carbidopa a peripheral dopa-decarboxylase inhibitor which reduces the peripheral adverse effects of Levodopa. The peak effect is 0.5 to 2 hours after an oral dose and plasma half-life is 1 to 3 hours.

The impact of L-dopa (Levodopa) on motor function in stroke has been investigated in small scale clinical studies taking into account the temporal linkage between drug administration and physical therapy treatment (Scheidtmann 2001). This randomized controlled trial reported the effect of L-dopa (oral co-careldopa – 100 mg Levodopa/25 mg carbidopa) on motor function in 53 people who were 3 weeks to 6 months post stroke. All patients received daily physiotherapy sessions lasting 30 minutes for three weeks in a hospital setting. Motor function was assessed using the Rivermead Motor Assessment. Significantly greater improvement in RMA scores and walking ability were reported in the Levodopa treated group compared with placebo. The drug was well tolerated and no serious drug related adverse events were reported. The effect on function was still present 3 weeks after cessation of Levodopa. Although these results are encouraging the study has a number of limitations (Scott, 2002) including sample size, and the recruitment of some patients in the post acute phase of stroke when effects on neuroplasticity may be less.

3.4 RATIONALE FOR CURRENT STUDY

Co-careldopa provides an exciting and important opportunity to manipulate the brain's pharmacological environment at a time when physiological remodelling of the brain is occurring through conventional rehabilitation treatments. This not only has potential to enhance the effect of conventional therapies but also new rehabilitation interventions. Understanding the relationship between pharmacologically primed neuroplasticity and practice dependent neuroplasticity is of

major scientific interest in understanding how the brain adapts to injury.

In this study we will find out if combining Co-careldopa (a widely available and inexpensive form of the drug that is commonly used to treat Parkinson's Disease) with routine occupational and physical therapy enhances the effect of the therapy and further improves recovery of functionally useful arm and leg movement in people with new or recurrent clinically diagnosed stroke. The dose and timing of the medication within this trial reflects current evidence on use of L-dopa in this context (Rosser 2008; Kobari 1995; Salgado-Pineta 2006; Scheidtmann 2001). All study participants will receive the usual stroke care within their hospital and community rehabilitation settings. The study drug will be used with conventional rehabilitation treatment up to a maximum of 6 weeks and no more than twice per day. Those potentially suitable to take part in this study will be identified on admission to hospital with stroke and eligibility will be confirmed between Day 5 to Day 42 post-stroke. The study drug will be continued at home if the person is still having rehabilitation treatment after discharge from hospital.

4.0 AIMS AND OBJECTIVES

The aim of this study is to determine if combining Co-careldopa with routine occupational and physical therapy during early rehabilitation in people with new stroke admitted to a stroke unit enhances the effect of conventional rehabilitation treatments in terms of short and long term mobility and arm function.

4.1 PRIMARY OBJECTIVE

The primary objective is to compare the proportion of patients in both treatment groups who are walking independently at 8 weeks post-randomisation (as measured by a score of 7 or higher and who also answer ‘yes’ to item number 7 on the Rivermead Mobility Index).

4.2 SECONDARY OBJECTIVE

Impact on physical functioning and mood at 8 weeks, 6 months and 12 months

- To compare the proportion of patients who are walking at 6 and 12 months post-randomisation in the two groups (as measured by a score of 7 or higher on the Rivermead Mobility Index and who also answer yes on item number 7)
- To compare activities of daily living, mobility and dependency (Rivermead Mobility Index (continuous), Barthel Index, Modified Rankin, Nottingham Extended Activities of Daily Living Scale, ABILHAND) between groups.
- To compare psychological distress / mood between the two groups (General Health Questionnaire 12)
- To compare carer burden between groups using the Caregiver Burden Scale
- To investigate cost effectiveness of Co-careldopa and conventional rehabilitation treatments (EQ-5D to quantify care costs)

Investigate potential moderators and mediators of effect at 8 weeks, 6 months and 12 months

- To investigate whether baseline patient clinical characteristics and investigations (e.g. routine Brain CT scanning) help to predict those who might benefit from Co-careldopa augmented rehabilitation
- To investigate whether key factors (e.g. fatigue (Fatigue Assessment Scale)), concurrent musculoskeletal symptoms, signs and pain (using the MSK SSP manikin), and cognitive function (using the Montreal Cognitive Assessment) influence the short and long term effect of Co-careldopa on physical functioning

Investigation of implementation within NHS

- To assess the adverse event profile associated with combination treatment (NHS stroke rehabilitation treatment linked with Co-careldopa)
- To investigate the practical implications of delivering this intervention within routine NHS acute and early community care of people with stroke
- To assess acceptability of Co-careldopa treatment to stroke patients (study drug adherence will be measured and a semi structured interview will be undertaken with participants at the week 8 assessment)

5.0 DESIGN

DARS is a multi-centre, prospective, randomised, double-blinded, placebo controlled trial of NHS physical therapy and occupational therapy treatment alone vs. NHS physical therapy and occupational therapy treatment with 6 weeks Co-careldopa treatment for those admitted to acute stroke services after new or recurrent stroke. 572 people with stroke admitted to acute stroke services will be recruited. Each participant will be randomised to receive either the investigational medication (as Co-careldopa) or placebo within 5-42 days post stroke. Outcome measures will be obtained at 8 weeks, 6 months and 12 months following randomisation.

The double blind study design in which participants and study personnel will be blinded to group allocation will minimise bias by ensuring that Co-careldopa related intervention effects and information collection is the same between the active drug and placebo groups. Further minimization of bias and maximizing masking will be ensured by appropriate placebo and Co-careldopa preparation, blinding both patients and clinicians. Outcomes will be collected by assessors masked to the treatment allocation. All analyses will be undertaken blinded to treatment allocation until final analysis.

6.0 ELIGIBLITY

6.1 INCLUSION CRITERIA

Patients meeting all of the following criteria are eligible for trial entry. It is possible that a patient's condition may change during the 5 to 42 days post stroke and the patient must be reviewed during this period to assess eligibility:

1. New or recurrent clinically diagnosed ischaemic or haemorrhagic (excluding subarachnoid haemorrhage) stroke within 5 to 42 days prior to randomisation.
2. Cannot walk 10 metres or more indoors independently (i.e. without use of physical assistance)
3. Professionally scored Rivermead Mobility Index score of <7.
4. Expected to need rehabilitation treatment
5. Aged 18 years or above
6. Able to give informed consent[1]
7. Able to access continuity of rehabilitation treatment following discharge from hospital. This can be through early supported discharge scheme or hospital/community therapy according to local practice. It is important that continuity of rehabilitation is available within 5 days following discharge.
8. Expected to be able to comply with treatment schedule (e.g. swallow whole tablets)[1]
9. Expected to be in hospital for at least their first two doses trial medication

[1]Inclusion criterion numbers 6, 8 and other co-morbidities should be monitored up to 42 days post stroke as patients initially not meeting the eligibility criteria might improve and therefore meet the eligibility criteria within the 42 day post stroke period.

6.2 EXCLUSION CRITERIA

Patients meeting any of the following criteria are <u>not</u> eligible for trial entry:

1. Not expected to survive for 2 months following stroke
2. Diagnosis of Parkinson's disease, severe medical or surgical illness, severe psychosis
3. Known hypersensitivity or contraindications to Co-careldopa[2]
4. Symptomatic orthostatic hypotension
5. Needed physical assistance of at least one person to walk prior to stroke due to pre-existing co-morbidities (e.g. heart failure, osteoarthritis)
6. Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception whilst receiving treatment and for 1 month after treatment has finished
7. Patients currently participating in other interventional drug or treatment therapy trials*
8. Could not walk 10 metres or more indoors **prior** to their stroke (may have used a walking aid if necessary, but required no physical assistance). In this context physical assistance means help from one or more persons

*<u>**Enrollment of a trial participant in another trial will not necessarily exclude a patient from participating in the DARS trial.**</u> Potential trials for co-enrollment with DARS are considered by the Chief Investigator and Trial Management team with regards to:

1. It has been agreed with the Chief Investigator of the relevant studies.
2. It does not confound the results of DARS
3. It does not overburden the patient,
4. Attribution of causality to adverse events is not compromised
5. There are no potential interactions

Contact the CTRU for confirmation of trials where co-enrollment is permitted. An update of trials where co-enrolment is agreed will be also reported in the trial newsletter

7.0 RECRUITMENT AND RANDOMISATION

7.1 RECRUITMENT DETAILS

572 patients in total (286 in each arm) will be recruited from UK stroke services that have both an acute inpatient stroke rehabilitation facility and a service that allows rehabilitation treatments to be continued within the community setting. The latter may consist of early supported discharge or community stroke teams/services.

It is predicted that recruitment may be slower during the first 6 months as a consequence of the variable timescales for Trust approvals to be granted.

7.2 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 CTRU or appropriate Lead Investigator prior to the start of recruitment into the trial.

[2] Please refer to the trial supplied Summary of Product Characteristics (SmPC).

7.2.1 Screening

Patients admitted to stroke services after a new or recurrent stroke will be considered for trial entry. Potential patients should be identified on admission to the stroke unit and considered for enrolment up to 42 days post stroke.

Patients who are initially ineligible for the trial may subsequently become eligible during the 5 to 42 day period post-stroke. This applies to patients who are unable to give informed consent, have other co-morbidities or who cannot swallow whole tablets. These patients should therefore be identified early following admission and continue to be monitored until 42 days post stroke to determine if their condition improves and consequently become eligible for the trial.

Local Stroke Research Network staff, in liaison with ward nurses and therapists should identify potential participants and monitor their progress during their hospital stay.

7.3 INFORMED CONSENT

A verbal explanation of the trial will be provided by an authorised member of the research team (as specified on the Authorised Personnel Log) which may be the Local Stroke Research Network staff, ward nurses and / or therapists.

Information will be provided for the patient to consider in two stages. Firstly a simple sheet summarising the study in a few key bullet points will be given to eligible patients. Then, if having read the initial summary the patient is interested in receiving further information about the study they will be given the main Patient Information Booklet. This will include detailed information about the rationale, design and personal implications of the trial and may include showing the patient the Patient DVD. Following information provision, patients will have as long as they need to consider participation (a minimum of 24 hours) and will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to take part in the trial.

For Patients with aphasia, care should be taken to ensure that the information is given in a manner that can be easily understood and where practical arrangements are made to meet the patient's language, communication and other support needs.

The Principal Investigator or any other medically qualified members of the trial team who has received GCP training and is approved by the Principal Investigator are permitted to take informed consent. Only patients who are considered able to provide fully informed consent will be randomised into the study and their ability to do this documented in the patient's medical records.

Where the patient is able to provide fully informed consent, completion of the Consent Form in any of the following formats is considered valid written informed consent:

1. Patient signs and dates the Consent Form themselves.
2. Patient signs the Consent Form themselves but the date of consent on the Consent Form is written by someone else.
3. Patient is unable to sign or date the Consent Form.

Provision for completion of the consent form by a witness should be made where the patient can comprehend but are unable to sign or date the consent form (Options 2 or 3 above). This could their carer, a friend/family member or a local member of the clinical team who is not a part of the research team. The right of a patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be recorded in the patient's medical notes. The original consent form will be retained in the Investigator Site File, a copy of the consent form will be given to the patient, a second copy filed in the hospital medical records (as per local practice) and a third copy will be returned to the CTRU.

The responsibility for treatment with the trial drug or placebo and the prescription of study drug ultimately remains with the Principal Investigator. Should important new information become available that may be relevant to the safety or wellbeing of the participant, this will be notified to existing participants by the local researcher and detailed in updated consent documentation.

Where valid, informed consent is obtained from the patient and the patient subsequently becomes unable to give informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Ongoing trial participation should be at the discretion of the treating therapist in consultation with the local PI and patient's carer / family.

A trial participation card will be provided to each consenting patient, and he/she will be asked to carry this whilst taking part in the trial. The card will indicate the patient's involvement in a clinical trial, the name of the local investigator and emergency contact details. The patient should be instructed to show the card to any other medical or healthcare practitioners they consult during participation in the trial. In addition to this, the patient's GP will be notified of their participation by the research team using the trial approved GP letter and it must be made clear in the patient's hospital notes that they are a part of the DARS trial. It is recommended that a sticker or statement is added to the patient's notes to clearly indicate their participation in the trial in accordance with local policy.

7.3.1 CARER CONSENT

At the same time as the patient consents, consent will also be sought from carers to provide information relating to carer burden at 8 weeks, 6 months and 12 months after the patient's randomisation (see section 2 for trial definition of a carer). In addition, they will complete the EQ-5D and Health Economics Resource Use Questionnaire at baseline, 8 weeks, 6 months and 12 months.

The same principles as described above will be applied to the informed consent process for caregivers. With the exception that consent can be taken by a research nurse or other appropriately experienced/qualified personnel who have had GCP training and the process should be documented in the carers trial notes. As for the patients, the Carers will be free to withdraw from the study at any time without giving reasons.

Presence of a caregiver or Informed consent for a caregiver where present is not a prerequisite to patient participation.

A local researcher (e.g. Local Stroke Research Network research nurse or other authorised member of the trial team) will undertake the baseline assessment after consent and prior to randomisation.

7.4 SCREENING

Screening Logs should be completed for all patients considered for entry to the study and will include those patients who enter the trial and those who do not. Anonymised information will be collected on a regular basis including:

- Date screened
- Age

- Gender
- Ethnicity
- Eligible and consented
- Eligible but declined
- Reason not eligible for trial participation

7.5 RANDOMISATION

Informed written consent for entry into the trial must be obtained prior to patient randomisation.

Consenting eligible patients will be randomised between day 5 to day 42 days after stroke by the Local SRN nurse or trial-specific research nurse via the CTRU's automated 24-hour telephone randomisation system. Authorisation and PIN codes, which will be provided by the CTRU when all relevant study approvals are in place, will be required to access the randomisation system.

Participants who fulfil the eligibility criteria, and have given written informed consent, will be randomised on a 1:1 basis to receive either Co-careldopa or placebo and will be allocated a trial number and IMP kit code. Stratified randomisation will be used to ensure treatment groups are well-balanced for the following characteristics, details of which will be required at randomisation:

- Centre
- Type of stroke (primary intracranial haemorrhage; infarct)
- Rivermead Mobility Index (RMI score 0-3; >3 but <7)

The following information will also be required at randomisation:

- Patient details including initials and date of birth
- Name of person undertaking randomisation
- Name of treating Consultant
- Confirmation of eligibility
- Confirmation of written informed consent and date

DIRECT LINE FOR 24-HOUR RANDOMISATION: +44 (0)113 343 7957

Copies of the sealed Code Break Envelope will be produced by the Bilcare Ltd. Copies of the Code Break Envelopes will be held securely at the CTRU and those relevant to a participating site will be held in a secure location by each local pharmacy for use in an emergency only.

After randomisation the participating site will:

- Provide each patient with a Trial ID card which they should carry with them and present to medical staff should they be admitted to hospital during their time on trial, or should they visit their GP
- Provide the patient with the Patient Information Pack
- Patient DVD
- Dispense the trial medication
- Notify the GP of patients participation in the trial

8.0 TRIAL MEDICINAL PRODUCT MANAGEMENT

Within the trial, the following are classed are as Investigational Medicinal Products (IMPs):

Co-Careldopa (Sinemet®)

Co-careldopa Oral Tablet
Composition: Levodopa 100mg, carbidopa 25mg
A blinded, trial specific supply of Co-careldopa will be provided to all participating sites free of charge. Please refer to the trial supplied Summary of Product Characteristics (SmPC).

Note: The first two doses for each patient recruited will consist of Levodopa 50mg and carbidopa 12.5mg (Co-careldopa 62.5)

Placebo

The composition of the placebo has been agreed with Bilcare Ltd and approved by the MHRA.
A supply of placebo will be provided that has the same appearance as the active IMP. Please refer to the trial supplied simplified Investigational Medicinal Product Dossier (IMPD).

8.1 SUPPLY AND HANDLING OF IMP

Participating sites will be provided with study medication and corresponding code break envelopes in accordance with the Pharmacy and IMP Study Site Operating. In order to maintain the blind, Co-careldopa and matching placebo will be labelled with a unique kit number, which will be assigned to a patient upon randomisation. Once received by the pharmacy, the drug must be kept in accordance with the SmPC and simplified IMPD.

The trial medication must only be used to treat patients who are participating in the DARS trial and should only be accessible by authorised staff.

The site pharmacist will be notified of all patients randomised at that site, their trial number and IMP kit number by CTRU. The CTRU will arrange for supplies to be sent to each hospital pharmacy prior to the site opening to recruitment when all necessary approvals are in place. CTRU will keep a track of the amount of study medication available at each participating site and will request further supplies to be sent as required. In the event of an issue with supply, sites should contact CTRU.

A drug accountability log will be kept by the Pharmacy Department to record the dispensing of trial treatment packs. To supplement this the therapist who attends the home to provide the community based rehabilitation should also document whether the IMP has been taken on the trial case report forms.

Please refer to the DARS Pharmacy and IMP Study Site Operation Procedure for full details of the trial IMP management requirements.

8.2 IMP PACKAGING AND LABELLING

Packaging is considered to be a determinant in improving compliance rates for this trial. Push-through blister packs will be used to protect the IMP integrity. As well as the trial-specific label, the packs will also be appropriately labelled so that the study drug is taken prior to the rehabilitation sessions whether in the community or in hospital. The packaging will serve as a visual aid,

encouraging patients to take the trial medication at the appropriate times and giving the patient the ability to recognize whether or not they have taken the scheduled dose. Prescription information and educational materials will form part of the medication's packaging/labelling.

The packaging was developed through dedicated patient groups and obtaining preferences and opinions on proposed packaging and labelling using standardised questionnaires. The final design was manufacturer by Bilcare Ltd and enables one handed opening for easy access by the patient when self-administering at home.

As well as instructions to ensure compliance with the treatment schedule, IMP supplies will contain a trial specific label, complying with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). Co-careldopa and Placebo will both be labelled by Bilcare Ltd with identical labels. The pharmacy will be responsible for completing individual patient details on each label and adding the patient ID to the corresponding code-break envelope at time of dispensing.

8.3 REPLACING DISPENDED STUDY MEDICAITON

If the study medication (or Kit) is lost or damaged between randomisation and the end of the patients treatment period, the study medication should be replaced using the CTRU 24 hour system which will allocate a new kit.

Staff should complete the kit replacement Case Report Form prior to using the CTRU 24 hour system. A copy of which is available in the Investigator Site File and details of kit replacement. Further details are given in the Procedures for DARS Randomisation / Kit replacement Study Site Operating Procedure.

9.0 INTERVENTION DETAILS

9.1 TREATMENT REGIMEN DETAILS

Patients will be randomised to receive either Co-careldopa or Placebo, which they will be required to take as a single oral tablet 45-60 minutes before physical or occupational therapy sessions (this also includes programmed rehabilitation delivered by rehabilitation assistants). Rehabilitation treatment appropriate for drug administration within DARS is defined as active physical treatment (i.e. most physical and occupational therapy directed at motor skills such as walking, transfers, and dressing but not psychological input sessions or speech and language therapy). The dose and timing of the medication reflects current evidence on use of Co-careldopa in this context (Rosser 2008; Kobari 1995; Salgado-Pineta 2006; Scheidtmann 2001). As part of this trial a pragmatic approach will be taken. Although the IMP dose should be taken optimally between 45-60 minutes prior to the rehabilitation treatment session it is recognised that there may be occasions where, for example, the therapist is unable to contact the patient to remind them to take the tablet or the patient may forget. It is acceptable for the tablet to be taken within 0-15minutes before the start of therapy in these situations. The reason and timing for any deviation from the optimal timing will be recorded on the CRF whether this occurs in the hospital or home setting.

The use of intermittent single doses for short periods is anticipated to result in a low rate of adverse effects. Should adverse events arise, these will be managed in accordance with section 11.0 of the protocol.

The first two doses of the randomised treatment will be a half dose (i.e. 62.5mg Co-careldopa for those patients randomised to active drug) to reduce the risk of early adverse effects and reflecting

clinical practice. Blood pressure should be checked before administering the first dose of trial treatment, and if <90 systolic, discussed with the local PI. Subsequent doses of active drug will be 125mg Co-careldopa. The first doses of trial treatment will be clearly indicated as such within the drug blister packs (see section 9.2 Administration of Trial Drug).

If the patient is having more than two physical or occupational therapy sessions, the IMP must not be administered more than twice during any one 24 hour period**. The peak effect of Co-caredopa is 0.5 to 2 hours after an oral dose and plasma half-life is 1 to 3 hours. If the patient is scheduled to have two therapy sessions directly one after the other or within 3 hours of a dose of IMP then a repeat dose of IMP should NOT be given before the second of the therapy sessions.

For example:

- for an OT/PT session scheduled at 10.00 and a physiotherapy session scheduled at 11.00 then IMP should be given once at 0900-0915
- for an OT/PT session scheduled at 10.00 and a physiotherapy session scheduled at 1300 then first dose IMP should be given at 0900-0915 and the second IMP dose at 12.15
- for at OT/PT session scheduled at 10.00 and a physiotherapy session scheduled at 1400 then first dose of IMP should be given at 0900-0915 and second IMP dose 1300 - 1315

If the patient misses an IMP dose prior to a therapy session the patient may be given the IMP immediately prior to the session (see above).

Assuming a maximum of 2 sessions of physiotherapy or occupational therapy per day for 30 days over a six week treatment period, each patient will receive a maximum of 60 active or placebo tablets during their participation in the intervention phase of the trial. IMP with NHS rehabilitation treatments will be continued for a maximum of six weeks as long as it is deemed that the patient would benefit from ongoing rehabilitation.

The duration of treatment will be less if the patient is clinically deemed not to require further rehabilitation treatment. The decision about need for rehabilitation interventions (when to start, finish and type) will be made by the treating clinicians, therapists and nurses in consultation with patients and families as part of the routine management of the patient.

Four possible participant journeys could occur[#]:

- Patient receives all six weeks of IMP linked rehabilitation within the stroke unit
- Patient receives less than six weeks IMP linked rehabilitation within the stroke unit (e.g. due to withdrawal from trial for any reason or patient makes a good recovery and stroke unit staff indicate that further active OT and PT is not required)
- Patient receives all six weeks of IMP linked rehabilitation split between the stroke unit and community setting
- Patient receives less than six weeks of IMP linked rehabilitation between the stroke unit and community (e.g. due to withdrawal from trial for any reason or patient makes good recovery in the community and community stroke team indicate that further active OT and PT is not required)

The IMP should not be given if the patient develops (after randomisation) any contraindications to participating in the study as defined in the exclusion criteria above, Co-careldopa or it is deemed by the treating physician that continuing to participate in the study presents significant risk to the patient. The local researcher will complete the Withdrawal Case Report Form, indicating that the patient has been withdrawn from trial treatment and will fax this form to CTRU.

*** A 24 hour period starts from 00.00 to 23.59*

[#] *Possible patient pathways at each participating site will be identified during set-up and study training requirements of a particular service addressed*

9.2 ADMINISTRATION OF TRIAL DRUG

Administration of IMP within hospital setting

- The IMP will be first administered in an inpatient stroke unit after the patient has consented and been randomised. The patient will start the six week IMP treatment period whilst still in hospital. The participating site will therefore be able to closely observe patients for any early adverse events occurring as a result of the trial IMP.

- The IMP will be administered by appropriately trained stroke unit nursing staff who will record the time at which the IMP was given and sign that the IMP has been given. The first IMP dose will be given prior to the first scheduled OT or PT treatment after the patient has been randomised. At the start of the therapy session, the rehabilitation staff will ask the patient if they have taken the study drug and record the response on the treatment CRF. Also, the duration and type of PT / OT session will be recorded by the treating therapist on the treatment CRF.

Administration of IMP within home setting

- The patient will be assessed by the stroke unit nursing staff (prior to discharge from hospital) as to his/her ability to self medicate (in relation to the IMP) after discharge from hospital. Three scenarios may arise:

    - Deemed that the patient can self medicate independently
    - Deemed that the patient can self medicate with assistance from carer if present
    - Deemed that the patient is unable to self medicate due to cognitive, communication, or manual dexterity or other physical reasons and the person has no carer who would be able to administer the medication at the correct time. In this situation where possible the treating community therapist would assist the patient to take the IMP when he/she visits the patient's home (e.g. getting the patient a glass of water to allow the patients to administer the medication themselves).

- Once the patient has been discharged into the community, telephone reminders* approximately 1 hour prior to a therapy visit should be undertaken by treating community rehabilitation staff to prompt the patient to take the trial medication prior to the community rehabilitation session.

- At the start of the therapy session, the rehabilitation staff should ask the patient if they have taken the IMP and what time the IMP was taken. The timing and content of the PT / OT session should be recorded by the treating therapist on a simple standardised CRF proforma. Where IMP has not been taken it is recommended that the dose is taken as soon as the therapist arrives.

A telephone call should be made by the occupational or physiotherapist (or as determined by the local service configuration) to the patient once six weeks have elapsed following randomisation to request that the patient stops taking the study medication.

9.3 ADHERENCE TO TREATMENT

Ensuring that the patient takes the IMP at the correct time

Ensuring pharmacoadherance in the community setting is a greater challenge. There is no single effective approach and therefore a multi-modal approach incorporating best available advice from the recent Cochrane review (Haynes 2008), guidance provided by the U.K. National Patient Safety Agency and NICE guidance on pharmacoadherance will be used. The nature of the optimal packaging and ensuring maximum pharmacoadherence will be designed in collaboration with input from clinicians, pharmacy staff, manufacturer and patients. This will also include design and implementation of appropriate training for those dispensing the trial intervention both in the hospital and when patients are self medicating at home.

Within hospital setting:

- Within the stroke unit setting the nursing staff will administer the IMP in accordance with local Trust clinical governance processes.

Within community settings:

- The patient will be assessed by the stroke unit nursing staff (prior to discharge from hospital) as to his/her ability to self medicate (in relation to the IMP) after discharge from hospital.
- Telephone reminders one hour prior to the home based therapy session undertaken by treating community rehabilitation staff will prompt patients to take the trial medication prior to the community rehabilitation session.
- The package will serve as a visual aid, encouraging patients to take the trial medication at the prescribed times and giving the patient the ability to recognize whether or not they have taken the scheduled dose.
- Provision of understandable information sheets and educational materials will be part of the medication's packaging, which will also include an instructional area on the blister pack itself. The outer carton of the package contains space for dosing instructions, reminders and branding in large, readable fonts.
- Use of push-through blister packs will protect the IMP integrity.

Monitoring compliance with IMP administration

Within hospital setting:

- The IMP will be administered by appropriately trained stroke unit nursing staff who will record the time at which the IMP was given and add initials and date that the IMP has been given.
- The duration and content of the PT / OT session will be recorded by the treating therapist or rehabilitation assistant on a standardised CRF proforma. Where IMP has not been taken the reasons for this will be recorded on a CRF proforma by the nursing or therapy staff.

Within community settings

- At the start of the therapy session, the community rehabilitation staff will ask the patient if they have taken the IMP and what time the IMP was taken.
- The independent researcher undertaking the 8 week follow-up assessment will undertake a pill count and will sign the packaging to confirm this.
- The duration and content of the PT / OT session of each community based rehabilitation treatment session will be recorded by the treating therapist/rehabilitation assistant on a standardised CRF proforma. This will allow us to quantify the extent to which IMP was given in relation to community based OT/PT therapy sessions.
- The PT / OT treatment form should be completed for all eligible PT / OT sessions regardless of whether the trial drug was taken

The therapy staff (in conjunction with nursing staff if the participant is an in-patient) will be asked to

complete a tick box case report form intervention record for each participant, which includes therapy duration and type and whether the trial medication has been taken at the correct time. The local research network nurse at each recruiting centre will collate adherence information and complete relevant Case Report Forms and send them to the CTRU.

9.4 TREATMENT MODIFICATIONS

In exceptional or unforeseen circumstances the following modifications can be made to the treatment protocol:

There may be a delay in the randomised patient receiving the first IMP with therapy. In this instance the reason will be documented in the medical records and trial case record, for example, rehabilitation therapy may be delayed by up to 5 days.

Where IMP has not been taken at the appropriate time prior to a planned OT or PT session it is permissible that the IMP is taken just prior to the start of the OT/PT session - (see section 9.3)

If a patient has started the IMP and subsequently develops an intercurrent medical problem, the physician may decide to withdraw IMP administration temporarily on clinical grounds. If the patient recovers and there are no clinical contraindications to resuming IMP administration this should be allowable within the protocol as long as the patient can complete treatment by the 8 week follow-up and the treating clinician feels it is appropriate to do so.

Safety and treatment stopping rules for placebo will be as per active intervention.

9.5 EMERGENCY UNBLINDING

Whilst the safety of patients in the trial must always take priority, maintenance of blinding is crucial to the integrity of the trial. Unblinding is strongly discouraged and Investigators should only break the blind when information about the patient's trial treatment is clearly necessary, and will alter, the appropriate medical management of the patient.

Unblinding may be requested on the grounds of safety by the Chief Investigator, Local Principal Investigator or authorised delegate or treating physician. It is anticipated that requests for unblinding will most likely originate from a patient, carer (or friend/family member) or personal physician (e.g. GP) at the time of an adverse event or planned change in non-trial related drug therapy. Requests for unblinding will first be handled by the Local Investigator who will explore the reason for the request and evaluate the importance of knowledge of treatment assignment for patient safety. In the event of an SAE, all patients should be treated as though they are receiving the active medication.

Should an alternative to unblinding not be identified, and if unblinding is required to optimise clinical management of the patient, emergency unblinding may be employed. During Office Hours (Monday to Friday 9am-5pm other than bank holidays and the Tuesday following bank holiday Mondays), Investigators should telephone CTRU who will carry out the unblinding procedure. Outside of Office Hours, or where the Investigator is unable to contact CTRU, emergency unblinding may also be undertaken by contacting the local pharmacy department at the respective centre who will also hold code-breaking envelopes.

It is encouraged that requests for Emergency unblinding should be made directly with CTRU wherever possible.

CTRU TELEPHONE NUMBER FOR EMERGENCY UNBLINDING:
0113 343 4930

If emergency unblinding is performed at any stage during the trial, the decision as to whether the patient will continue trial drug is the responsibility of the local principal investigator. These patients should continue to be followed up, and all data collected will be used in the final analysis.

Once all patients at a participating site have completed trial treatment, all unopened code break envelopes will be returned to CTRU by the site pharmacy department. Code break envelopes must not be opened by local pharmacy for patients when they have completed trial therapy.

Further information on emergency unblinding can be found in the Emergency Unblinding Study Site Operating Procedure. The reason for emergency unblinding will be collected on the Emergency Unblinding Case Report Form.

9.6 WITHDRAWAL OF TREATMENT

The patient will not continue to receive the IMP after randomisation if he/she develops contraindications to Co-careldopa treatment or if the treating physician deems that the patient is at a significant health risk from continued participation in the trial. As the patients will be started on study medication in hospital we will be able to closely observe patients for presence of adverse medication related events.

Responsibility for care will remain with the attending clinical team. If treatment is stopped the patient will still be followed up unless the patient withdraws from follow-up. If a patient withdraws from the study prior to completion of the trial treatment, the primary reason for discontinuation will be determined and recorded. Patients will be made aware (through the information sheet and consent form) that should they withdraw, safety data will still be collected after their last dose and all data collected prior to the withdrawal date will be used in the final analysis.

10.0 DATA COLLECTION / ASSESSMENTS

10.1 ASSESSMENTS

Patients will be assessed at the following time points:

- Baseline - prior to randomisation
- 8 weeks* after randomisation
- 6 months after randomisation
- 12 months after randomisation

* primary end point

Patient outcomes at all follow-up time points (8 weeks, 6 and 12 months) will be collected via interview by the independent researcher (DARS researcher) in the patient's home,at the hospital or community facility and documented on paper CRFs which will be provided by CTRU.

Required data, assessment tools, collection time points and processes are described in detail in sections 10.2 to 10.4. This is summarised in table 1 below.

Patient data collection falls into the following categories:

(a) data to determine eligibility to participate in trial
(b) data to monitor and address adverse events
(c) data to monitor adherence to intervention and describe medical treatments
(d) data to capture the professional perspective on patient abilities and outcome

(e) data to capture the patient's own perception of abilities and outcome
(f) data to capture important baseline and follow up covariates that may influence primary and secondary functional outcomes
(g) data to allow economic evaluation

Table 1: Summary of Assessments

Assessment		**Timeline (months post-randomisation)**		
	Baseline	8 weeks (+/- 7 days)	6 months (+/- 14 days)	12 months (+/- 14 days)
Eligibility and consent	X			
Baseline data (researcher/nurse completed from routinely collected data and ward staff)				
Rivermead Mobility Index (professional perspective on patient's ability for stratification)	X			
Past medical history	X			
Lesion location and type (CT scan)	X			
Montreal Cognitive Assessment (MoCA)	X			
Randomisation (within 42 days post stroke)	X			
Patient questionnaires (completed via researcher interview with patient)				
Rivermead Mobility Index (patient's perspective on ability)	X	X	X	X
ABILHAND scale	X[1]	X	X	X
Nottingham Extended Activities of Daily Living Scale	X[3]	X	X	X
General Health Questionnaire 12	X	X	X	X
EQ-5D	X	X	X	X
Barthel Index (postal version but collected face to face)	X	X	X	X
MSK-SSP Manikin	X[1]	X	X	X
Fatigue Assessment Scale		X	X	X
Health Economics Resource Use Questionnaire	X	X	X	X
Carer questionnaires (Carer completed)				
Caregiver Burden Scale		X	X	X
EQ-5D	X	X	X	X
Health Economics Resource Use Questionnaire	X[1]	X	X	X
Qualitative follow-up				
Patient/therapist perspective regarding use of IMP		X		
Clinical follow-up data (researcher/therapist/nurse completed)				
Treatment data (rehabilitation and drug compliance)		X		
Modified Rankin Scale		X	X	
Montreal Cognitive Assessment (MOCA)		X	X	X
Serious and non-serious adverse event monitoring	Continuous reporting as occur			
New significant medical / surgical illness (e.g. for stroke, myocardial infarction, cancer, fracture, elective surgical procedures)			X	X

Patient Questionnaires were developed in collaboration with patient representatives (see section 8.2) to document all of the above data. We will asked up to 10 people with stroke to discuss with us (as part of protocol design) their opinion on the feasibility of capturing the functional information via face to face interviews using the questionnaires listed above (this includes time taken to complete the questionnaire).

[3] Pre-stroke score

The administration of all questionnaires will be in the same order for all patients at all time points (baseline, week 8, months 6 and 12). All the patient reported outcomes will be undertaken with a researcher through a face to face interview either at home, hospital or community facility. We anticipate the interview will last approximately two hours or less. The researcher will provide some assistance to help the participants complete the questionnaire (such as marking the response category based on the instructions of the participant). All participants will be offered comfort breaks during the face to face interviews as required and if the participant requests, the interview can be spread over two days.

Throughout the trial, patients and / or their carers will be encouraged to record items in the Patient Information Pack that they may wish to discuss with the therapist or DARS Researcher during their participation in the trial.

Before each OT/PT session, the therapist will verify that the patient has taken their trial medication and this will be recorded on a CRF. Following each therapy session, the therapist will also complete a short CRF detailing the intervention delivered. These CRFs will be collected by the DARS researcher at the 8 week follow-up visit.

The recruiting sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by CTRU, and to keep copies of all completed CRFs for the trial.

The DARS researcher should take copies of the completed baseline CRFs, patient, questionnaires and therapy CRFs and return the originals to CTRU.

10.2 BASELINE 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 data including the following:

- NHS number
- GP address and telephone number (for the researcher to inform the patient's GP of participation)
- Participants' contact details (for researcher to perform follow-up)
- Date of stroke and hospital admission
- Visual field defect
- Hemiparesis
- Past medical history
- Blood pressure
- Lesion type and location from Brain CT scan performed on admission using a standard proforma.

The researcher will also collect information from the patient (unless otherwise stated) via face to face administration of the questionnaires as listed in Table 1 Summary of Assessments.

BASELINE CT/MRI SCAN DATA

A codifying system based on a review of the literature and other available approaches will be used by the Research Fellow as a basis to capture this information with the assistance of neuroradiology expertise as required. All people with acute stroke should have a CT Brain scan on admission to identify presence of intracranial haemorrhage (National Stroke Strategy, RCP Stroke guidelines). This is to investigate whether any possible impact of co-careldopa on motor recovery is influenced

by the nature of the brain injury, as identified on routine neuroimaging. Therefore we anticipate that this data would be available for the majority of patients recruited to the study. The scans will be reviewed by the Research Fellow with the assistance of neuroradiology expertise as required and coded on standardised revised proformas. Collection of these data will carried out separately to other baseline assessments, and may occur later in the study.

TRANSFER OF SCANS

Once neuroimaging scans are available, an anonymised copy of the scans will be transferred to the CTRU on a CD or DVD. The site personnel will ensure the scans have been anonymised before transferring the scans for central review. The results of the scans will be used for the trial analysis of the lesion type characteristics.

10.2 DATA REQUIRED FOR STRATIFICATION AND RANDOMISATION

- Patient details including initials and date of birth
- Centre
- Name of person undertaking randomisation
- Name of treating Consultant
- Confirmation of eligibility
- Confirmation of written informed consent and date
- Type of stroke (primary intracranial haemorrhage; infarct)
- Rivermead Mobility Index (based on ward staff assessment of patient)

10.3 FOLLOW-UP TIME POINTS

Follow up data will be collected from both patients and consenting carers at 8 weeks, 6 months and 12 months post-randomisation.

10.4 FOLLOW-UP PROCESSES

The researcher will check with the patient's GP / PI to confirm participant status and address prior to contacting the patient at 8 weeks, 6 and 12 months post randomisation. When participant survival status has been established, contact will be made for follow-up. Where considered appropriate by the researcher, they may choose to send the questionnaires to the patient in advance of the scheduled appointment to allow the patient some time to prepare for the interview.

All participants who enter the study will be considered part of the intention to treat population and efforts will be made to follow them up whenever appropriate.

It is expected that each follow up visit will take a maximum of 2 hours per patient for the researcher to complete the data collection (to allow for comfort breaks for patient & carer as required). The data collection will be terminated if the patient or carer feels they are unable to continue. The reason will be recorded. If appropriate with the participant's consent, the researcher may arrange to continue the visit at another time.

Completion of Rivermead Mobility Index questionnaire may be completed via phone where it is not possible to arrange a face-to-face visit. This may only be conducted on a case by case basis and the site must have obtained approval from CTRU prior to the data being collected in this manner.

Carers will be provided with questionnaires to complete at the same time where possible. If the patient's carer is unable to attend the arranged visit, the researcher may leave the questionnaire with the patient to pass to the carer. Alternatively, the researcher may post the questionnaire directly to the carer. Under all circumstances, the carer will provided with an envelope in which to place their completed questionnaire and return this sealed, to the researcher.

10.5 OUTCOME DATA

The patient will complete the questionnaires at the above-mentioned time points as listed in Table 1 Summary of Assessments.

When patients are unable to complete such questionnaires independently, the DARS researcher will provide support - this may involve reading each question in turn and providing explanation as appropriate. The Researchers will receive standardised training on how to provide support. Where the patient is unable to provide a response the data will be recorded as missing.

The Researcher will also administer the clinical follow-up assessments as listed in Table 1 Summary of Assessments.

10.6 MEDICAL / REHABILITATION INTERVENTION AND IMPLEMENTATION DATA

Collected by Research team

During the six week period of IMP linked rehabilitation the therapy staff (in conjunction with nursing staff if the participant is an in-patient) will be asked to complete a therapy CRFs for each participant, which includes type, timing and therapy duration and whether the trial medication has been taken at the correct time.

Collected by independent researcher

At 8-weeks post-randomisation the following clinical data will be collected by the researcher:

- Investigational Medicinal Product data (including drug compliance, timing of doses)
- Adverse and Serious Adverse Event data (see section 11)
- Patient and Carer perspective of the use of Co-careldopa as part of the rehabilitation treatment regime will be assessed using a list of questions (with tick box response options plus room for qualitative feedback).
    - Ease of compliance with timing of treatment schedule
    - Ease of use of packaging
    - Clarity of instructions and labelling

At 6 and 12 months post-randomisation the following clinical data will be collected:

- New significant medical / surgical illness (e.g. stroke, cardio-vascular disease, cancer, fracture, elective procedures)
- Exit poll

10.7 ASSESSMENT INSTRUMENTS

Rivermead Mobility Index (RMI)
This is a robust unambiguous clinical cut-off indicator of Co-careldopa effect as it defines clearly the proportion of those walking at least 10 metres without assistance from another person. Changes on the RMI can also capture changes in posture and movement. The RMI has 15 items that measure the ability of patients to make postural adjustments (e.g. move in bed), transfer (e.g. between bed to chair, chair to toilet) and walk (indoors and outdoors) and it is scored from 0-15.

Barthel Index
Patient activities of daily living, disability and mobility will be assessed using the Barthel Index. This is a widely used instrument that is used to evaluate the patient's functional ability (e.g. bathing,

transferring from bed to chair, dressing, feeding, mobility, climbing stairs, toilet use, grooming, and bladder and bowel continence).

ABILHAND
The ABILHAND questionnaire is a Rasch derived person-centered measure of the manual ability in everyday bimanual tasks in people with chronic stroke designed to be administered on an interview basis. The patient is asked to rate his/her perception on the response scale as "Impossible", "Difficult" or "Easy" (0 = "Impossible", 1 = "Difficult" or 2 = "Easy"). The activities not attempted within the last 3 months are not scored and are entered as not applicable. The activities that the patient does not perform because they are too difficult must be scored as "Impossible".

Nottingham Extended Activities of Daily Living Scale
Physical and social independence will be measured using the Nottingham Extended ADL Scale (NEADL) (Nouri F, 1987). It was designed as a postal questionnaire and assesses aspects of physical and social independence performance across 22 items (score range 0 – 66) grouped in four categories (mobility, kitchen, domestic and leisure activities). It has been widely used as an outcome measure in rehabilitation trials. It has proven validity, reliability and has demonstrated responsiveness to change and able to discriminate between services.

General Health Questionnaire 12
Patient and carer emotional health will be assessed using the General Health Questionnaire 12 (GHQ12). This reflects the high priority patients and carers give to emotional well-being after stroke, is consistent with a patient-centred model of stroke recovery in which adjustment to disability is seen as a critical issue, reflects the high prevalence of psychological symptoms after stroke, and that psychological problems become more prevalent with time. It has been demonstrated that mood is associated with a range of other stroke effects and can be a determinant of physical functioning. The GHQ12 contains 12 questions addressing issues of decision making, loss of sleep and confidence, feelings of strain, enjoyment of daily activities, confidence and happiness.

Caregiver Burden Scale
Caregiver burden will be measured using a proven and reliable Caregiver Burden Scale. This 22-item scale will assess various aspects of caregiver burden including general strain, isolation, disappointment, emotional involvement and environment. If Co-caredopa accelerates functional independence for the patient, then this may translate into reduced carer burden.

EQ-5D
The non-disease-specific EQ-5D instrument (Krabbe P 2003) will be used to evaluate the health-related quality of life of patients. The EQ-5D measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on 3 levels (1 = no problems; 2 = some problems; 3 = severe problems). It was developed to yield utility values, which can be used to calculate quality-adjusted life year (QALY) gains or losses, and thus will facilitate the health economic evaluation.

Musculoskeletal Symptoms/Signs and Pain Manikin (MSK-SSP manikin)
MSK-SS manikin has been used in a self report epidemiological survey to identify pain in community dwelling persons. Musculoskeletal complaints are common in the general population and estimates suggest that 15% of the adult population have joint pain, with two out of three people over the age of 50 reporting recent musculoskeletal pain. Both stroke and musculoskeletal pain are common causes of disability and therefore in order to ascertain the long term impact of stroke interventions on disability one needs to take account the influence of existing or new musculoskeletal complaints (Chakravarty K 1993, Keenan, 2006).

Fatigue Assessment Scale
Fatigue is likely to be an important determinant of physical functioning in stroke and therefore important to measure for statistical modelling used in the secondary analyses. The FAS was

recommended in a review of fatigue scales because it had face validity, feasible to use with most patients, good test-retest reliability and high construct validity. It had low internal consistency compared to others but was deemed to be overall a reasonable tools to capture fatigue.

Modified Rankin Scale
This will be used so that results from this study can be related to other clinical trials (see National Stroke Trials database initiative).

Montreal Cognitive Assessment
This was designed as a rapid screening instrument for mild cognitive dysfunction (Pendlebury T 2010). It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Total possible score is 30 points; a score of 26 or above is considered normal. It is considered that cognition may affect outcomes, therefore this assessment will be conducted at all time points.

10.8 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last patient's last 8 week follow-up visit for the purpose of safety reporting. Long term follow up for purposes of the Main REC and Research Governance to one month after the last patient's last trial follow up visit constitutes the non-interventional phase of the trial.

11.0 PHARMACOVIGILANCE

11.1 GENERAL DEFINITIONS

11.1.1 ADVERSE EVENT

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment and can include:
• any unintentional, unfavourable clinical sign or symptom
• any new illness or disease or the deterioration of existing disease or illness
• any clinically relevant deterioration in any laboratory assessments or clinical tests.

11.1.2 ADVERSE REACTION

An adverse reaction is:

- All untoward and unintended responses to an investigational medicinal product related to any dose administered.

11.1.3 SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is defined in general as "any untoward medical occurrence or effect that:
• results in death,
• is life-threatening*,
• requires inpatient hospitalisation or prolongation of existing hospitalisation,
• results in persistent or significant disability or incapacity,
• consists of a congenital anomaly or birth defect.
• may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

*the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an SAE is serious in other situations.

Where an SAE is deemed to have been related to the IMP, the event is termed as a **Serious Adverse Reaction (SAR).**

Important SAE/SARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one or the other outcomes listed in the definition above, should also be considered serious.

11.1.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is a Serious Adverse Reaction which also demonstrates the following characteristic of being unexpected:

Unexpected- an adverse event, the nature, seriousness, severity OR outcome of which is NOT consistent with the applicable product information (e.g. Summary of Product characteristics)

The term 'severe' is used to describe the intensity (severity) of a specific event. This is not the same as 'serious' which is based on the patient event/outcome or action criteria.

11.2 OPERATIONAL DEFINITIONS OF AND REPORTING ADVERSE EVENTS AND REACTIONS

All adverse events identified by the patients or researchers, whether or not considered related to the trial drug (Co-careldopa or placebo) will be reported.

The following list of adverse events have been associated with Co-careldopa:

- Nausea
- Vomiting
- Taste disturbances
- Dry mouth
- Anorexia
- Arrhythmias
- Postural hypotension
- Syncope (unconsciousness for a short time as a result of reduced blood flow to the brain)
- Drowsiness (including sudden onset of sleep)
- Fatigue
- Dementia
- Psychoses (a distorted perception of reality)
- Hallucinations
- Confusion
- Euphoria
- Abnormal dreams
- Insomnia
- Depression
- Anxiety
- Dizziness
- Dystonia (involuntary contractions)
- Dyskinesia (inability to control voluntary movements)
- Chorea (sudden twitching of the face and shoulders)
- Deaths attributable to stroke or other unassociated factors

AEs, whether volunteered by the patient or carer, or discovered by the therapist or researcher, will be collected from randomisation up until the 8 week follow up appointment.

11.3 OPERATIONAL DEFINITION of SERIOUS ADVERSE EVENTS

11.3.1 EVENTS NOT CLASSED AS SAES

The following events **will not** be recorded as SAEs within this trial:

Hospitalisation for:

- Routine treatment or monitoring of the studied indication not association with any deterioration in condition.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
- Admission to hospital or other institution for general care, not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission.

Deaths not attributable to the trial treatment beyond 30 days after the last administration of the study agent will be reportable via collection on a standard Case Report Form, but will not be considered as SAEs.

11.3.2 EXPECTED SAES

Any reported Adverse Event described in section 11.2 that meets the definition of Serious as set out in section 11.1.3, will be classed as an expected SAE within this trial and therefore will **not** be reportable as a SUSAR.

When determining whether an SAE is expected or not, please also refer to the version of the Summary of Product Characteristics supplied in the Investigator Site File or the latest updated version as instructed by CTRU. Consideration should be given to the severity and outcome of the event when determining expectedness.

11.3.3 RECORDING AND REPORTING SAES AND SUSARS

As an inpatient, the local research team will monitor the patient for the occurrence of adverse events. Following discharge from hospital, detection of most adverse events will occur during spontaneous reporting by patients, their carers, attending therapists or via the scheduled visits by the researcher. Patients, their carers and/or families will be encouraged to contact the local research nurse or PI should they be concerned about an event or possible side-effect of trial treatment. Participants will be asked to carry Trial ID cards to facilitate this communication.

As an extra safety precaution, treating therapists referring a patient to their GP or arranging hospitalisation will also be asked to notify the local research team. The local researcher, research nurse or PI will follow up the details of the event in accordance with the timelines set out below. .

Each separate event is reported onto one SAE / SUSAR CRF and not combined into one form.

All SAEs / SUSARs occurring whilst on trial must be recorded on the SAE or SUSAR Form and faxed to the CTRU within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the original form should be posted to the CTRU in real time and a copy retained on site.

11.4 DATA ITEMS

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator
- whether the event would be considered expected or unexpected

Any follow-up information should be faxed to CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

11.5 ATTRIBUTION OF CAUSALITY AND EXPECTEDNESS FOR SAES

Assessment of causality and expectedness must be made by an authorised medic. If an authorised medic is unavailable, initial reports without causality and expectedness assessment should be submitted to the CTRU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter. Investigators should evaluate the causality and expectedness of all serious adverse events as though the patient is receiving active drug (Co-careldopa) and unblinding is strongly discouraged and should be avoided. If following an SAE, the decision is taken to unblind the treatment to allow optimum clinical management of the patient, the patient must stop taking trial medication. The Chief Investigator or designee should be consulted if necessary.

All SAEs assigned by the local investigator (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The CTRU will inform the MHRA, the main REC and the Sponsor of SUSARs within the required expedited reporting timescales.

CTRU staff who are not involved in the day to day running of the trial will be responsible for unblinding possible SUSARs for notification to the MHRA and main REC.

Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore expedited reporting. However, where SUSARs are thought to be associated with placebo (e.g. reaction due to excipient or impurity) the Sponsor will report such cases.

11.6 TIMELINES FOR REPORTING SAES AND SUSARS

SAEs

All SAEs occurring whilst on the trial (up until 30 days after the last dose of trial drug) must be recorded on the SAE CRF and faxed to the CTRU **within 24 hours** of the research staff becoming aware of the event.

SUSARS

All SAEs assigned by the local investigator as both suspected to be related to protocol treatment and unexpected will be reviewed by the Chief Investigator. Such SAEs will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The CTRU will inform the MHRA, the Main Research Ethics Committee (Main REC) and the Sponsor of SUSARs within the required expedited reporting timescales. All SUSARs occurring whilst on trial (until 30 days after the last of dose of IMP) must be recorded on the SUSAR CRF and faxed to the CTRU **within 24 hours** of the research staff becoming aware of the event.

CTRU FAX NUMBER FOR REPORTING SAE / SUSAR / DEATHS:
0113 343 1487

11.7 REPORTING PATIENT DEATHS

It is expected that, due to nature of the patient population, a proportion of patients may die as a result of their stroke, or other unassociated factors. Deaths occurring during trial treatment (and for 30 days thereafter) should be reported to CTRU as an SAE. Beyond 30 days after the end of trial treatment, deaths should be reported to CTRU on the appropriate CRF, but will not require expedited reporting unless they are associated with a Suspected Serious Adverse Reaction.

11.8 PREGNANCIES

All women of childbearing age (defined as women who had any menstrual bleeding in the last 24 months and who have not had a hysterectomy) should be informed of the potential risks to the unborn child should they fall pregnant whilst receiving treatment. Any woman who is pregnant at the time of eligibility assessment or is unwilling to use medically approved contraception whilst receiving treatment will be refused entry to the study. All women capable of having children must use at least 2 appropriate medically approved methods of contraception. Men whose partners are females capable of having children must use appropriate medically approved contraception.

Pregnancies occurring in participants of the study, or participants' partners during the study may therefore represent a safety issue. For this reason, where a pregnancy is known, this should be followed for outcome and any adverse outcome of pregnancy assessed for causality to the treatment received. All pregnancies should be reported immediately to the CTRU.

11.9 RESPONSIBILITIES

Principal Investigator:

1. Medical judgment in assigning to SAEs:
   - Seriousness
   - Causality
   - Expectedness
2. To ensure all SAEs are recorded and reported to the CTRU and to provide further follow up information as soon as available.
3. To report SAEs to local committees in line with local arrangements.

CTRU (as delegated by the Sponsor):

1. Expedited reporting of SUSARs to Competent Authority (MHRA in UK), Main REC and Sponsor in accordance with CTRU SOPs.
2. Preparing annual safety reports to Competent Authority, Main REC and Sponsor.
3. Notifying Investigators of SUSARs that occur within the trial.

Chief Investigator (or nominated individual in CIs absence):

1. Assign causality and expected nature of SAEs where it has not been possible to obtain local assessment by PI / Co-investigator.
2. Review all SAEs for seriousness, expectedness and causality in accordance with agreed process for the trial.
3. Review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and CI review with regards to SUSAR status, local assessment will not be overruled, but the CI may add comments prior to expedited reporting.

4. Assign code using the medDRA body system coding to all SAEs suspected to be related to trial treatment approximately monthly and prior to submission of annual safety reports.

In addition to the responsibilities set out above, it is expected that under the supervision of the local PI, the Researcher and Research Nurse will also have specific responsibilities.

12.0 HEALTH ECONOMICS

12.1 WITHIN TRIAL COST EFFECTIVENESS ANALYSIS

The objective of the economic evaluation is to identify the within trial and long term incremental cost effectiveness ratios for Co-careldopa augmented rehabilitation for stroke compared to usual care for individuals within stroke services after their first stroke.

12.2 WITHIN TRIAL COST EFFECTIVENESS ANALYSIS

12.2.1 MEASUREMENT OF RESOURCE USE

The primary analysis will take the perspective of the service provider including the costs of health and social care. NHS resource use associated with each treatment modality will be extracted through trial case report forms contained in the patient questionnaire (contact with primary, community and social care services together with hospital admissions and out-patient visits).

Detailed information will be collected regarding the six week period of Co-careldopa and placebo management from therapy and nursing staff **(see section 10)**. These intervention costs will provide a clearer picture of any additional unforeseen costs associated with Co-careldopa management within the 6 week administration.

Therapy and nursing staff will also provide resource use information associated with the physiotherapy or occupational therapy sessions (assuming a maximum of 2 sessions of either of the therapy session per day for 30 days over a six week treatment period). This will include staff time, facilities hire and any equipment used.

Secondary analysis will adopt a societal perspective taking account of productivity costs (time away from work) and out of pocket expenditures incurred by patients and their informal carers. The patient questionnaire will be used to collect these data together with a separate carer questionnaire.

Unit costs for health service staff and resources will be obtained from national sources such as the PSSRU, the BNF and NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimate in the analysis.

MEASUREMENT OF OUTCOMES

The primary analysis will be a cost-utility analysis based on the EQ-5D health state utilities. As economic evaluations are designed to inform resource allocation decisions, and in line with the NICE reference case, we will conduct an evaluation using quality-adjusted life years (QALYs) as the study outcome. A secondary within-trial analysis will estimate the incremental cost per patient achieving independent walking (as determined by a score of ≥ 7 on the Rivermead Mobility Index) at 8 weeks post-randomisation for Co-careldopa versus placebo.

The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. We will use the EQ-5D (Krabbe, 2003) instrument for this purpose and calculate the utility index employing the UK General Population Tariff (Dolan, 1997)The EQ-5D is a

very simple instrument to complete and will therefore be collected at baseline, 8 weeks, 6 and 12 months post randomisation. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the health-related quality of life differences between therapies (Manca A 2006)**.**

Discounting: There remains some uncertainty regarding the correct approach to discounting costs and benefits. The analysis will follow the recommendations current at the time. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum (Brouwer WB 2005, NICE 2008).

Within trial analysis: The primary, within-trial analysis will be a cost-utility analysis. This will be undertaken using the EQ-5D UK General Population Tariff to derive health state utilities Cost effectiveness analysis will be a within trial estimate of the incremental cost per QALY gained from Co-careldopa treatment compared with usual care.

If costs are greater and intervention more effective or if the intervention is cheaper and less effective, results will be presented as expected incremental cost effectiveness ratio (ICERs), expected net benefit (assuming lambda=£20,000) and a cost effectiveness acceptability curve.

12.2 WITHIN TRIAL – UNCERTAINTY ANALYSIS

Probabilistic analysis will be undertaken using non-parametric bootstrap simulation. Where necessary, censored data will be adjusted using appropriate techniques. The confidence region around the ICER will be estimated using appropriate statistical techniques (e.g. non-parametric bootstrap method). This stochastic analysis will enable a cost effectiveness acceptability curve to be produced illustrating the uncertainty surrounding the optimal decision.

12.3 WITHIN TRIAL – SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis will be undertaken to test the robustness of the results to parameter uncertainty. Monte Carlo simulations will be conducted to determine the effect of input parameter variation on the cost-effectiveness results. Sub-group analysis will be informed by the secondary analysis exploring potential response predictors. No interim analysis is planned unless requested to do so by DMEC.

12.4 LIFETIME ANALYSIS

A second CEA will adopt a lifetime horizon using a decision analytic cost effectiveness model developed with clinical investigators. The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team and after analysis of the adverse event data observed in the trial. The consequences in terms of patient-specific resource use will be measured using responses to the 8 week, 6 and 12 month assessments. This will capture information on quantity of primary and secondary health care use, use of personal social services, medication use and patient/carer costs.

It is likely that the model will be a Markov state model (or a generalisation of a Markov model). As far as possible the transition rates for the model will be estimated from the clinical trial data. Model parameters for which data could not be collected within the trial; e.g. long term outcomes following stroke, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature (NICE 2008, Weinstein MC et al 2006). It is likely that some model transition probabilities will be provided by previously conducted and planned literature reviews in the area.

13.0 ENDPOINTS

13.1 PRIMARY ENDPOINT

The primary endpoint is ability to walk independently at 8 weeks post-randomisation (defined by a score of 7 or above and who also answer 'yes' to item number 7 on the Rivermead Mobility Index) as collected by the DARS independent researcher. Eight weeks was chosen as the primary end point as all patients should have completed the Co-careldopa / placebo augmented rehabilitation program (maximum six weeks). This takes into account the variation of recruitment time within the first two weeks after stroke. Longer term outcomes are also important as the short term improvements in motor function during the early stages of recovery from stroke may later translate into extended activities of daily living such as return to driving and leisure (as measured by the Nottingham EADL) see section 13.2.

13.2 SECONDARY ENDPOINTS

PATIENT ENDPOINTS AT 8 WEEKS, 6 AND 12 MONTHS

- Independent walking ability at 6 & 12 months (corresponding to RMI item 7 and RMI ≥ 7)
- Rivermead Mobility Index (analysed as a continuous measure)
- Barthel Index
- ABILHAND
- Nottingham Extended Activities of Daily Living Scale
- GHQ-12
- EQ-5D
- Modified Rankin scale

CAREGIVER ENDPOINTS AT 8 WEEKS, 6 & 12 MONTHS

- Caregiver Burden Scale
- EQ-5D

QUALITATIVE FOLLOW UP AT 8 WEEKS

- Patient and Therapist perspective regarding use of IMP with rehabilitation treatment

CLINICAL FOLLOW UP DATA AT 8 WEEKS

- Treatment data (rehabilitation and drug compliance)

13.3 MODERATOR AND MEDIATOR VARIABLES

- Musculoskeletal Symptoms/Signs and Pain manikin (presence of joint pain; number of joints affected)
- Fatigue Assessment Scale
- Montreal Cognitive Assessment

13.4 SAFETY

- Number of SUSARS
- Number of SAEs
- Number not on randomised allocation at 6weeks
- Number of patients unblinded

14.0 STATISTICAL CONSIDERATIONS

14.1 SAMPLE SIZE

The calculations are based on the primary outcome of proportion of people walking independently eight weeks after randomisation. Independent walking is a robust and easily identifiable objective clinical outcome. The Scheidtmann study reports 42% (11/26) of L-dopa patients were walking independently at 6 weeks vs 26% (7/27) of placebo group patients. Our sample size calculation is based on these published data and will recruit 572 patients in total over 18 months. This will provide 90% power at 5% significance to detect 50% difference between the placebo and active treatment group in the proportion walking independently at 8 weeks post randomization as measured by the RMI score 7 or greater and who also answer 'yes' to item number 7. This assumes the same control rate of 26% and will ensure the minimum improvement that can be detected is 39% of patients on active treatment are walking independently by 8 weeks. This is slightly more conservative than the proportion improved in the Scheidtmann study. The primary ITT analysis will include all randomised patients as it will assume that patients who die or are lost to follow-up are unable to walk independently.

This sample size also provides 80% power to detect a small to moderate effect size of 0.3 in key secondary outcomes (e.g. ABILHAND - to measure functional upper limb activities; Nottingham Extended Activities of Daily Living Scale measuring instrumental activities of daily living such as outdoor mobility and household tasks). It is important that the study has sufficient power to detect real change in these secondary outcomes given that they are (a) important functional parameters in addition to walking and (b) are also likely to change if the treatment is effective. For all secondary analyses, loss to follow up has been estimated at 10% at 8 weeks (of those surviving stroke at 2 weeks), rising to 20% by 12 months. This loss to follow up will be minimised by data collection by research interview, but we have taken account for intercurrent illness, late mortality and study withdrawal.

14.2 ACCRUAL

Each centre will have a locally negotiated target of 1-2 patients per month over the duration of period. We plan to recruit up to 40 centres. There are typically 750 annual stroke admissions per acute city hospital. The protocol also allows for co-enrolment with other studies with prior consultation with the CI of the other studies and review of interactions relating between studies to patient safety monitoring, participant burden of assessment and interpretation of results.

15.0 STATISTICAL ANALYSIS

15.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the CTRU Statistician. The analysis plan outlined in this section will be reviewed and a final statistical analysis plan will be written before any analysis is undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator, the CTRU principal investigator and the senior trial coordinator. Any changes to the final analysis plan and reasons for change will be documented.

All analyses will be conducted on the intention-to-treat population defined as all participants randomised regardless of non-compliance with the intervention. An overall two-sided 5% significance level will be used for all endpoint comparisons. Appropriate methods will be used to handle missing data.

As DARS is a double-blind study, the Trial Statistician will be blinded to treatment group allocation

throughout the trial until the database has been downloaded for final analysis. Only the Safety Statistician, Supervising Trial Statistician, back-up Safety Statistician and Safety Data Manager will have access to unblinded treatment group allocation prior to final analysis.

15.2 FREQUENCY OF ANALYSES

Outcome data will be analysed once only, at final analysis, although statistical monitoring of safety data will be conducted throughout the trial and reported at agreed intervals to the Data Monitoring and Ethics Committee (DMEC).

15.3 ENDPOINT ANALYSIS

Primary and secondary analysis will be on an 'Intention to treat' basis, blind to random allocation, with statistical significance assessed at 5% level. Outcome measures will be analysed for each time point by regression models appropriate to the data type. Such analyses will adjust for patient-level covariates included as strata within the randomisation process including gender, type of stroke, centre and RMI; this will address the remaining inconsistencies between treatment groups and preserve the nominal significance level of the statistical tests being performed. Additionally, physical ability and lesion location will be adjusted for in the model.

15.4 PRIMARY ENDPOINT ANALYSIS

Primary analysis of independent walking ability at 8 weeks post-randomisation (defined by a score of 7 or above and who also answer 'yes' to item number 7 on the Rivermead Mobility Index) will be undertaken using logistic regression while adjusting for gender, type of stroke, centre, RMI at baseline and lesion location. It will be assumed for the primary outcome ITT analysis that patients who die or are lost to follow-up are categorized as "unable to walk independently". A sensitivity analysis will be undertaken to test the robustness of conclusions to this assumption.

15.5 SECONDARY ENDPOINT ANALYSIS

Independent walking ability (primary outcome, defined by item 7 on the Rivermead Mobility Index and a RMI score of 7 or more overall) will be analysed 6 and 12 months post-randomisation using a logistic regression model while adjusting for the patient level covariates gender, type of stroke, centre, RMI and lesion location. Other secondary endpoints will be analysed at 8 weeks, 6 and 12 months by regression modelling which is dependent on the type of outcome while adjusting for the same covariates and baseline outcome measurement: continuous endpoint analysis will use linear regression; binary endpoint analysis will use logistic regression and ordinal endpoint analysis will use ordinal logistic regression.

15.6 FURTHER SECONDARY ANALYSES

Potential predictors of response to Co-careldopa will be explored using baseline measurements taken for primary and secondary outcomes (see section 14). In addition we plan to model the relationship between potential moderator and mediator variables (for example, record of rehabilitation, compliance with medication,whether patients have had sufficient motor therapy, fatigue and musculoskeletal pain and CT/MRI scan data) and treatment effect. Sufficient motor therapy will be defined as at least 20 minutes of motor therapy in at least 80% of therapy sessions. Patients complying with medication are those receiving treatment 45-60 minutes before therapy begins in at least 80% of therapy sessions. This will enable us to determine which types of patients benefit most from treatment.

Sensitivity analyses will be conducted assessing the effect of patients lost to follow up by making various assumptions of their proceeding independent walking ability (primary outcome, defined by RMI) and other secondary outcomes. Due to the possibility of assistance on patient-completed questionnaires, analysis will investigate whether results are sensitive to varying responses between equivalent questionnaires completed with assistance or independently. A per-protocol analysis will be carried out to indicate whether results are sensitive to the exclusion of patients who violated the protocol (i.e. those patients randomised but subsequently found to be ineligible)

A standardised register of all patients referred to the participating stroke unit will be kept. Anonymised data will be used to identify systematic differences in those not recruited and those recruited. An exit poll undertaken by the stroke centre research nurse/researcher at eight weeks (patients and therapists), using the blinding index, will ascertain the level of masking to active drug.

15.7 SAFETY ANALYSES

The number of patients reporting a serious adverse event (up to 30 days after the last dose of treatment) and details of all serious adverse events will be reported for each treatment group.
The number of patients withdrawing from study treatment will be summarised by treatment arm, along with reasons for withdrawal.

All safety analyses performed prior to final analysis will be undertaken by the safety statistician (rather than the trial statistician), thus ensuring that the trial team remain blinded.

15.8 SUB-GROUP ANALYSES

No sub-group analyses are planned.

16.0 DATA MONITORING

16.1 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of patients, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule (i.e. an agreed list of data items to be reviewed) including safety data will be defined and agreed by the Trial Management Group (TMG) if necessary.

16.2 DATA MONITORING AND ETHICS COMMITTEE

An independent DMEC will be established to review the safety and ethics of the trial. Contents of the unblinded reports will be agreed between the DMEC and CTRU at the initial DMEC meeting during set-up. Six-monthly reports will be prepared by the CTRU for the DMEC during recruitment and follow-up. SAEs, SARs and SUSARs will be summarised by treatment group in a three-monthly safety report sent to the DMEC.

16.3 TRIAL STEERING COMMITTEE (TSC)

A TSC will be established to provide overall supervision of the trial, in particular, trial progress, adherence to protocol, patient safety, and consideration of new information. The committee will meet once during the set-up period and six monthly thereafter for the duration of the trial.

16.4 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspect of routine management will be brought to the attention of the TSC, and where applicable, to individual NHS Trusts.

17.0 QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

17.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006.

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify CTRU immediately of a serious breach (as defined by Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A “serious breach” Is a breach which is likely to affect to a significant degree:

a) The safety or physical or mental integrity of the subjects of the trial; or
b) The scientific value of the trial.

In the event of doubt or for further information or guidance the Investigator should contact the Senior Trial Co-ordinator at CTRU.

17.2 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000. Written informed consent will be obtained from the patients prior to trial entry. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw from the study at any time without giving reasons and without prejudicing his/her further treatment. The trial will be submitted to and approved by a main Research Ethics Committee (MREC) and the appropriate Site Specific Assessor for each participating site prior to entering participants into the trial. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

18.0 CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth, postcode, address and telephone numbers, NHS number, hospital number(s), GP name, address and telephone number
- patient and carer name, address and telephone number will be collected when a patient and carer are registered into the trial to facilitate follow-up by the researcher, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two patient and carer identifiers, usually their initials and date of birth. Forms containing the patient identifiable information must be sent to CTRU separately from clinical forms and will be stored separately at CTRU.
- appropriate storage, restricted access and disposal arrangements for participants' personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the patient's name must be obliterated by site before sending.
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent for further trial treatment and / or further collection of data, their data will remain on file and will be included in the final study analysis.

The trial staff at the participating site will be responsible for ensuring that any data / documentation sent to the CTRU is appropriately anonymised as per instructions given by CTRU in accordance with the trial procedures to conform with the 1998 Data Protection Act.

18.1 ARCHIVING

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Sponsor's archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

19.0 STATEMENT OF INDEMNITY

This trial is sponsored by the University of Leeds and the University of Leeds will be liable, in certain circumstances, for harm caused by the design of the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for harm to patients due to clinical negligence under this duty of care.

20.0 STUDY ORGANISATIONAL STRUCTURE

20.1 RESPONSIBILITIES

Chief Investigator

The Chief Investigator will have responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the Trial.

Clinical Trials Research Unit (CTRU)
The CTRU will have responsibility for conduct of the trial in accordance with relevant GCP standards and CTRU SOPs.

Clinical Research Fellow
To assist the Chief Investigator and the Clinical Trials Research Unit in the implementation and management of the DARs project (collating information on routine brain imaging and supporting developments of analytical models to investigate the effect of the intervention).

Health Economists
The Health Economics collaborators will assist the CTRU in protocol and CRF development and will be responsible for the selection and / or design of the economic questionnaires, collation of unit costs, and the conduct, interpretation and writing up of the economic evaluation.

Principal Investigator
Overall responsibly for conduct of the study at the participating site, including (but not limited to) assessment of eligibility, informed consent and patient safety.

LRN Staff
Assist in the informed consent process, and completion of screening and baseline assessments in collaboration with ward staff. Telephone contact with the patients as required.

Ward Staff
Administering IMP to patient whilst they are in hospital and assisting LRN staff in undertaking baseline clinical monitoring. Documenting timing that IMP was given. Reporting adverse events as described in section 11.

Therapists (in-patient)
Documenting type of therapy treatment given during each session. Reporting concerns about the patient's health, condition or trial medication to the hospital research staff.

Therapists (community)
Documenting type of therapy treatment given during each session and alerting patient by telephone reminder to take IMP at appropriate time. Reporting concerns about the patient's health, condition or trial medication sufficient to their GP or other healthcare professional (e.g. community nurse, hospital doctor, ward nurse).

Researcher
Trial-specific Researchers will have responsibility for the assessment and follow-up of participants identified for inclusion in the trial in their own homes. Each participating site will have an associated Researcher.

20.2 OPERATIONAL STRUCTURE

Trial Management Group (TMG)
The TMG, comprising the Chief Investigator, CTRU team and co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results**.** Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments (SSA), (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) appointing and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (vii) monitoring of screening, recruitment,

consent, treatment and follow-up procedures, safety, data quality and compliance (viii) interpretation of results and contribution to publications. The TMG will report to the DMEC and the TSC.

Clinical Trials Research Unit (CTRU)

The CTRU will provide set-up, implementation, and monitoring of trial conduct to CTRU SOPs and GCP and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006, including randomisation design and implementation, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis of clinical endpoints for the trial. In addition the CTRU will support main REC, SSA and R&D submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day to day running of the trial, including trial administration, database administrative functions, data management including safety reporting, all statistical analyses of clinical endpoints and drafting of publications.

Trial Steering Committee (TSC)

The Trial Steering Committee, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. Also, it will provide clinical and professional advice relating to the trial design, where relevant. The role of the TSC is to consider new information relevant to the trial, including reports from the Data Monitoring and Ethics Committee (DMEC) (where applicable) and the results of other studies, particularly if the results may have a direct bearing on the future conduct of the trial. It will include an Independent Chair, and not less than two other independent members, including a statistician. The Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress. The committee will meet annually as a minimum. The TSC will report to the Sponsor and funder.

Data Monitoring and Ethics Committee (DMEC)

The DMEC will review the safety and ethics of the trial by reviewing interim unblinded data during recruitment and will provide independent advice and recommendation, based on relevant clinical and professional expertise. The Committee will meet or communicate via teleconference approximately every six months. The DMEC is accountable to the TSC. The DMEC is responsible for escalating any issues for concern to the TSC.

21.0 PUBLICATION POLICY

<u>Authorship and acknowledgement</u>

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and by contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Co-Applicants and senior CTRU staff will be named as authors in any publication fulfilling the above criteria, and an appropriate first author agreed through discussion amongst the Trial Management Group (TMG) members. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of their roles in planning, conducting and reporting the trial. Other key individuals will be included as authors or

contributors as appropriate and at the discretion of the DARS TMG. Any disputes relating to authorship will be resolved by the TSC.

The Chairs and Independent members of the TSC and Data Monitoring and Ethics Committee (DMEC) will be acknowledged, but will not qualify for full authorship, in order to maintain their independence.

Relevant NIHR Clinical Research Networks' (e.g. Stroke Research Network) support should be acknowledged appropriately in trial publications.

Data source

Data from the CTRU database in Leeds must be used for data analyses for all abstracts and publications relating to the questions posed within the trial protocol. Furthermore, the statistical team at the CTRU must perform all such analyses. If any additional analyses outside the remit of the protocol are to be performed, the statistical team at the CTRU should be involved, if it involves data held on the CTRU databases.

Data release

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the results of the primary endpoint analysis, either for trial publication or oral presentation purposes, without the permission of the DMEC and the TSC.

The TSC will agree a publication plan and must be consulted prior to release or publication of any trial data.

Individual collaborators must not publish data concerning their participants, which is directly relevant to the questions posed in the trial, until the main results of the trial have been published. Local collaborators may not have access to trial data until after publication of the main trial results.

Processes for the drafting, review and submission of abstracts and manuscripts

The agreed first author of abstracts is responsible for circulating these to the other members of the Trial Management Group (TMG) for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:

- timely circulation of all drafts to all co-authors during manuscript development and prior to submission
- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the TSC (i.e. ensuring submission is in line with publication plan, and ensuring TSC receive the final draft prior to submission)

The first author is responsible for submission of the publication and must keep the TMG and all authors informed of the abstract's or manuscript's status. The TSC will be kept informed of rejections and publications as these occur. On publication, the first author should send copies of the abstract or manuscript to the TSC, the TMG, the Sponsor and to all co-authors, and ensure communication with the NIHR EME programme as outlined below.

NIHR Efficacy and Mechanism Evaluation (EME) programme requirements

In accordance with the NIHR EME programme's requirements, EME will be notified at least 28 days in advance of all published work related to the project throughout the course of the research. In addition to this, The EME Programme will be sent a draft final report by the project team within 14 days of the completion date. This will be peer reviewed and then published on the EME website.

Dissemination of results to participants

At the end of the trial, a lay summary of results will be published in the public domain accessible to participants. Participating investigators will be advised to direct patients to this information should they request information relating to the results of the trial.

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23.0 APPENDICES

APPENDIX 1: TRIAL MANAGEMENT GROUP

The TMG includes those listed as key contacts and the following Co-applicants:

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APPENDIX 2: COMMITTEE TERMS OF REFERENCE AND RESPONSIBILITIES

Trial Steering Committee

Terms of Reference

- To provide overall independent supervision of the trial
- To monitor trial progress and conduct, in particular the timely progress of the trial, adherence to the protocol and patient safety
- To provide clinical and professional advice relating to the trial design, where relevant

Roles and Responsibilities

1. To provide consultation regarding the trial design
2. To approve substantial amendments to the trial design during the course of the trial
3. To consider new information relevant to the trial, including reports from the Data Monitoring and Ethics Committee (DMEC) (where applicable) and the results of other studies, particularly if the results may have a direct bearing on the future conduct of the trial.
4. On consideration of new information relevant to the trial, make recommendations for appropriate action to the Sponsor / Funder. For example, changes to the trial protocol, additional patient information, or stopping or extending the study, to ensure that the rights, safety and wellbeing of the trial participants are the most important considerations and prevail over the interests of science and society.
5. Attend TSC meetings and provide availability for future TSC meetings
6. To ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and that due consideration is given to the implementation of the results into clinical practice.
7. To ensure that the trial is conducted in accordance with the principles of Good Clinical Practice

Reporting and Escalation

- The TSC reports to the Sponsor and Funder. The TSC is responsible for escalating any issues for concern to the Sponsor, specifically where the issue could compromise the integrity of the trial or data or patient safety.

Data Monitoring and Ethics Committee

Terms of Reference

- To monitor the safety, data and related ethics of the above trial
- To provide independent advice and recommendation based on relevant clinical and professional expertise, on the above.

Roles and Responsibilities

1. Agree to the trial objectives and design
2. Agree to any relevant statistical analysis plans (e.g. DMEC plans, interim analysis plans)
3. To consider interim safety data, un-blinded if considered appropriate, plus any additional safety issues for the trial and relevant information from other sources. Any recommendations relating to patient safety may be subject to expedited reporting to the Competent Authority and main REC
4. To review safety data to look for any emerging trends, including increases in severity or frequency of expected Serious Adverse Reaction / Event such that they would require expedited reporting to the Competent Authority and main REC
5. In the light of the above, and ensuring the ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee (TSC) and to recommend on the continuation of the trial (with consideration of any relevant stopping rules)
6. To consider new information relevant to the trial and the results of other studies, particularly if the results may have a direct bearing on the future conduct of the trial.
7. To consider any requests for release of interim trial data and to recommend to the TSC on the advisability of this
8. In the event of further funding being required, to provide to the TSC appropriate information and advice on the data gathered to date without jeopardising the integrity of the study
9. Attend DMEC meetings and provide availability for future DMEC meetings

Accountability & Escalation

The DMEC is accountable to the TSC. The DMEC is responsible for escalating any issues for concern to the TSC