A trial to **e**valuate an e**xt**ended **r**eh**a**bilitation service for **s**troke patients (**EXTRAS**)

Study Protocol

Version 5: 24 September 2014

Study Funder:
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Protocol signature page

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Site investigator signature:

I have read and agree to version 5 of the protocol, dated 24 September 2014 entitled "**A trial to evaluate an extended rehabilitation service for stroke patients (EXTRAS)**".

I am aware of my responsibilities as an Investigator under the Research Governance Framework for Health and Social Care. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Name……Signature …… Date ……

Affiliation……..

Glossary

Abbreviation	Definition
AE	Adverse Event
ADL	Activities of Daily Living
AR	Adverse Reaction
CEA	Cost-effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CRF	Case Record Form
CSRI	Client Services Receipt Inventory
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTO	Clinical Trial Officer
CTU	Clinical Trial Unit
CUA	Cost-utility analysis
DMEC	Data Monitoring and Ethics Committee
EADL	Extended Activities of Daily Living
ESD	Early Supported Discharge
HAD	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
NIHR	National Institute for Health Research
NIHSS	National Institute of Health Stroke Scale
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Patient Information Sheet
OHS	Oxford Handicap Scale
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
R+D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIS	Stroke Impact Scale
SRN	Stroke Research Network
TIA	Transient Ischaemic Attack
TMG	Trial Manangement Group
TSC	Trial Steering Committee
VISTA	Virtual International Stroke Trials Archive

Protocol summary

Title: A trial to **e**valuate an e**xt**ended **r**eh**a**bilitation service for **s**troke patients (EXTRAS)

Chief Investigator: Professor Helen Rodgers.

Sponsor: Northumbria Healthcare NHS Foundation Trust.

Funder: NIHR HTA programme (ref: 10/37/01).

Study design: Multicentre randomised controlled trial with health economic and parallel process evaluations.

Study setting: Twelve or more NHS stroke services which provide Early Supported Discharge (ESD).

Study participants: Adults with a new stroke (and their carer if appropriate) being discharged from hospital under the care of an early supported discharge team.

Study intervention: An extended stroke rehabilitation service provided for 18 months following completion of routine Early Supported Discharge. The extended stroke rehabilitation service will provide regular contact with a senior ESD team member who will lead and coordinate further rehabilitation.

Study control: Usual care post Early Supported Discharge. Usual care may involve referral of patients to a range of rehabilitation services upon completion of ESD in accordance with local clinical practice.

Randomisation: Central independent web based service.

Primary outcome: Extended activities of daily living (Nottingham Extended Activities of Daily Living Scale) at 24 months post randomisation.

Secondary outcomes: For patients: health status, quality of life, mood and experience of services will be measured at 12 and 24 months. For carers: quality of life, carer stress and experience of services will be measured at 12 and 24 months. Resource use and adverse events will also be collected.

Blinding: Outcomes will be undertaken by blinded assessor.

Parallel qualitative process evaluation: Implementation and delivery of the extended stroke rehabilitation service in different settings will be described. Semi-structured interviews with a subsample of study participants and staff will be conducted to gain insight into their perceptions and experience of intervention and control rehabilitation services.

Sample size: Allowing for 25% loss to follow up, 510 participants are needed between intervention and control groups to provide 90% power to detect a difference in mean Nottingham EADL score of 6 (scored 0-66, SD=18) with a 5% significance level.

Study duration: 5 years.

Background

There are approximately 300,000 disabled stroke survivors in the UK.[1] Although one third of patients remain disabled 12 months after acute stroke the longer term provision of stroke rehabilitation is sparse. Input from a therapist or nurse with specialist expertise in stroke rehabilitation is rare beyond 6 months post discharge. Stroke patients and their informal carers are frequently disappointed and frustrated that longer term rehabilitation is not more widely available and a recent survey reported that just under half of stroke survivors experienced unmet needs.[2]

In 1988 the King's Fund reported that stroke care in the UK was disorganised and haphazard.[3] Since then a number of randomised controlled trials, Cochrane reviews, and independent patient data meta-analyses have clearly demonstrated that stroke units and early supported discharge (ESD) services are effective ways to improve patient outcomes and the quality of care following stroke.[4, 5] These services are referred to as 'organised stroke care' and their key features are multidisciplinary stroke specialist expertise and coordination of care.[6, 7] The National Stroke Strategy[8] was launched in England in 2007 and has achieved significant improvements in stroke services, particularly in TIA and acute stroke care, via the Stroke Improvement Programme.[9] However, the National Audit Office reviewed NHS progress in improving stroke care in 2010 and reported:

'*There is a lack of research based evidence on the benefits and costs of clinical and other support for long term stroke care. …. In particular, clinical evidence on the effectiveness of rehabilitative therapies a year or more after stroke is lacking. One of the top three suggestions for improving rehabilitation that patients and carers in our survey made was to provide physiotherapy for longer after stroke; but commissioners told us that there was insufficient evidence available to them to be able to conclude on the relative benefits and costs of longer term provision of, for example longer term provision of speech and language therapy, occupational therapy or physiotherapy'*.[10]

Poor coordination and limited provision of community stroke services in England was again highlighted in the 2011 Care Quality Commission report 'Supporting life after stroke'.[11]

There is no clear evidence of the clinical and cost effectiveness of longer term rehabilitation following stroke. A Cochrane review of therapy based rehabilitation services for patients living at home more than one year after stroke concluded that it was unclear whether rehabilitation provided after one year can improve recovery.[12] The review included 5 trials (487 participants) and no improvements were seen in case fatality; personal activities of daily living; extended activities of daily living; patient mood; and carer mood. All studies were single centre with sample size sizes ranging from 49-170 (median 94). Only 3 studies (n=168) assessed extended activities of daily living.

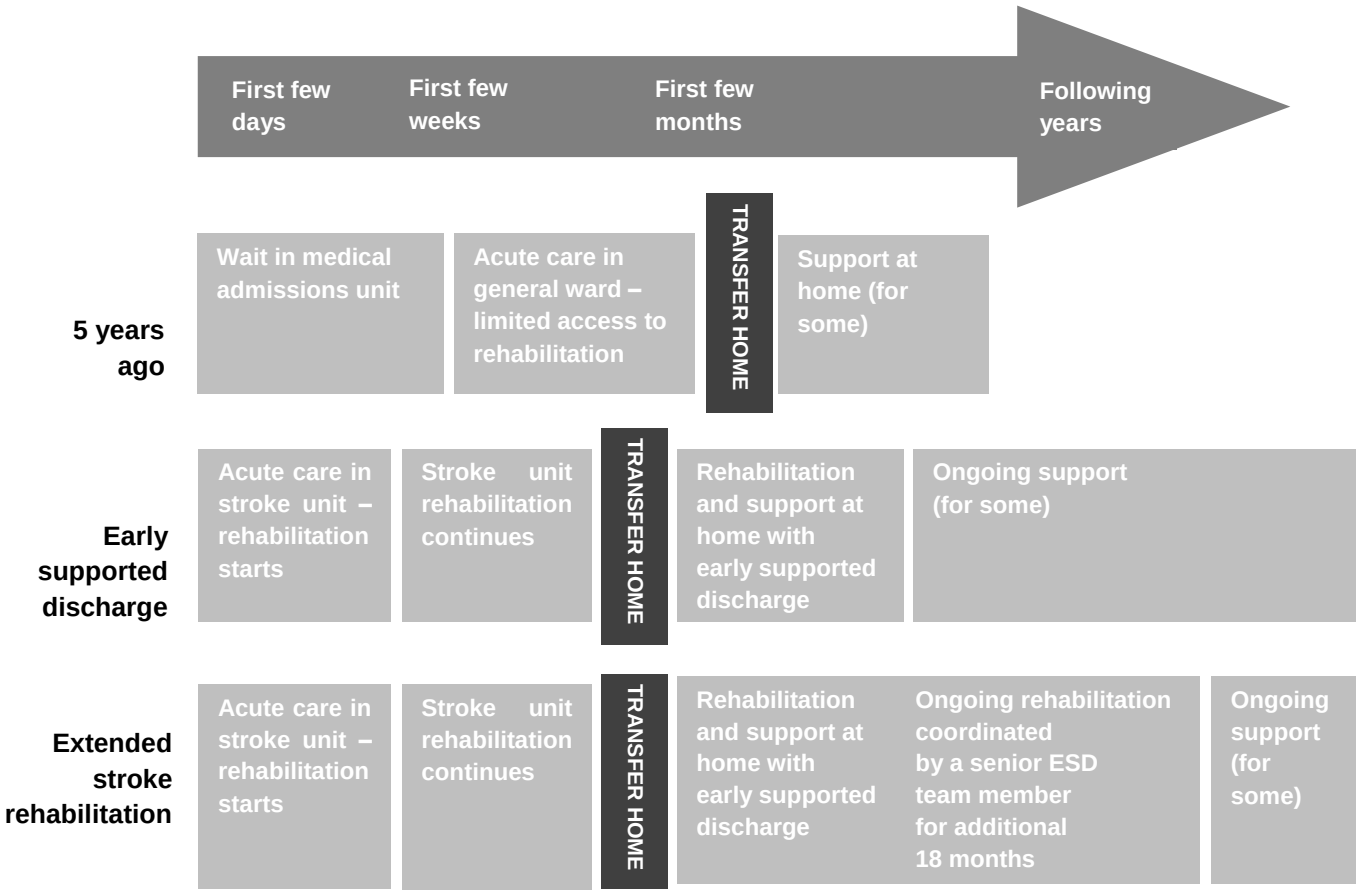
However, therapy-based rehabilitation services for stroke patients at home provided soon after discharge have been shown to be effective.[13] A Cochrane review included 14 trials (n=1617). Nine studies (n=996) reported extended activities of daily living outcomes. Therapy-based rehabilitation services improved this group of patients' ability to perform extended activities of daily living (OR 0.17 (95% CI 0.04 – 0.30)). There was no statistically significant heterogeneity between trials. It is unclear how many participants received stroke unit care and ESD was available in one study.

ESD services offer patients the opportunity to continue rehabilitation in their own home following a period of stroke unit care. ESD provided by a specialist multidisciplinary team leads to better clinical outcomes, increased satisfaction with care and reduced NHS costs.[4] ESD is a core component of an evidence based stroke service and it is the current 'gold standard' for an early community rehabilitation service for stroke patients with ongoing rehabilitation needs who are discharged to their own homes.[8] Typically an ESD team becomes involved with discharge planning with patient, family and stroke unit staff at an early stage of admission. Prior to discharge from hospital a member of the team undertakes a home visit (with the patient) or an environmental visit (without the patient). Rehabilitation and ongoing care provided by a specialist ESD team begins immediately after discharge. The duration and intensity of ESD therapy depends upon patient need. The discharge policy of ESD services varies with some services defining a maximum period of input of 3 months. ESD teams do not usually retain any contact or involvement with patients once their input has

ceased. Following discharge from ESD services the concept of 'organised stroke care' disappears. Patients who have ongoing rehabilitation needs may be referred to a range of services most of which do not offer specialist stroke rehabilitation e.g. neurorehabilitation teams; day hospital; community rehabilitation services. Patients report difficulties re-accessing rehabilitation services and the National Stroke Strategy requires that stroke patients and carers should be reviewed by primary care services at 6 weeks and 6 months post discharge and annually thereafter.[8] The Care Quality Commission report and the recently published National Quality Board System Alignment in Stroke Report recognises that progress in assessment and review following hospital discharge is patchy.[11, 14]

This project will evaluate an extended stroke rehabilitation service. The service will extend 'organised stroke care' beyond ESD to include longer term community stroke rehabilitation. Figure 1 shows the changing pathway of stroke care and how the extended stroke rehabilitation service proposed in this research project will extend organised stroke care.

Figure 1: Changing pathway of stroke care and proposed extended stroke rehabilitation service (adapted from Care Quality Commission: Supporting life after stroke)[11]



Study aim and objectives

Aim

To determine the clinical and cost effectiveness of an extended stroke rehabilitation service.

Objectives

- To determine whether an extended stroke rehabilitation service (intervention) improves patient outcomes compared to usual care (control). The primary outcome is extended activities of daily living at 24 months. Secondary outcomes: health status; quality of life; mood; experience of services (12 and 24 months).

- To determine whether an extended stroke rehabilitation service improves carer outcomes compared to usual care. Outcomes are: quality of life; carer stress; experience of services (12 and 24 months).

- To determine the cost effectiveness of an extended stroke rehabilitation service.

- To document how the extended stroke rehabilitation service is implemented and delivered in different settings.

- To seek the views and experiences of patients, carers, and rehabilitation staff about the community rehabilitation they have received or provided.

- To explore the impact of the severity of activity limitation, pre-stroke heath status, and comorbidity upon the effectiveness of the intervention.

Study design

This project will use a multi-method approach to evaluate the extended stroke rehabilitation service. A pragmatic observer-blind parallel group multicentre randomised controlled trial (RCT); health economic evaluation; and process evaluation including a qualitative description of the experience of patients, carers and rehabilitation staff will be conducted. The RCT will commence as an internal pilot and continue to the full study if the progression criteria are achieved.

Study setting

The study will take place in 12 or more NHS stroke services that provide ESD. ESD services will meet the following criteria:

- The ESD service is a multidisciplinary stroke team who provide community rehabilitation following discharge from hospital.
- The ESD service provides stroke rehabilitation at home within 48 hours of patient discharge from hospital.
- The ESD service provides stroke rehabilitation for a specified period of time and/or has clear criteria for discharge of patients from the service.

Study participants

Adults with a stroke who fulfil the following criteria are eligible:

Inclusion criteria

- Age 18 years and over
- Confirmed diagnosis of new stroke (first ever or recurrent)
- Will be discharged from hospital under the care of an early supported discharge team or are currently receiving this service.

Exclusion criteria

- Unable to participate in a rehabilitation programme which focuses upon extended activities of daily living.

A carer is the main family member or friend, who will provide support after discharge. He/she may not necessarily be co-resident with the patient. If a stroke patient has no carer or a carer does not wish to participate in the study, the patient may still participate in the study.

Case ascertainment, recruitment and consent

1. Patients

Potential patients will be identified and recruited by SRN Clinical Trial Officers (CTOs) and/or senior members of the ESD team at each participating stroke service. SRN CTOs are part of the hospital stroke team and they liaise regularly with other stroke unit staff to identify which patients may be invited to participate in stroke research studies. Potential patients may be recruited prior to discharge from hospital or whilst receiving care from the routine ESD service. Although the extended stroke rehabilitation service will not commence until routine ESD services end, identification and recruitment of patients in hospital or during ESD will maximise recruitment opportunities. An eligibility screening log will be completed for all stroke patients considered for the study and subsequently included or excluded. This log will ensure potential patients are only approached once.

Consent for patients with mental capacity

For potential patients with mental capacity to consent to research, a SRN CTO/ESD senior team member will approach the patient, discuss the study and provide a study information sheet. After allowing sufficient time for potential participants to decide whether to take part in the study (>24 hours) and an opportunity to ask questions, consent will be obtained in writing. Where a patient has mental capacity but is unable to sign the consent form (e.g. because of weakness of the dominant hand following stroke), consent will be confirmed orally in the presence of a witness (an individual not otherwise involved in the trial) who will sign the consent form on behalf of the participant.

Consent for patients with aphasia

We wish to include stroke patients with communication difficulties due to aphasia as we believe the extended stroke rehabilitation service being evaluated in this study is of potential benefit to these stroke patients and their carers. A set of 'easy access' study documentation has been developed specially for use with patients with aphasia. To recruit and consent patients with aphasia, a SRN CTO/ESD senior team member will approach the patient, discuss the study and provide them with the 'easy access' information sheet. After allowing sufficient time for the information to be considered (>24 hours) and an opportunity to ask questions, consent will be obtained in writing using the 'easy access' consent form. SRN CTOs/ESD senior team members are experienced in communicating with patients with aphasia but specialist advice can be sought from their local stroke speech and language therapist if required.

Consent for patients without mental capacity

We wish to include stroke patients who do not have mental capacity and who are therefore unable to consent for themselves. Exclusion of patients with mental incapacity would mean exclusion of patients with more disabling strokes who may gain from the extended stroke rehabilitation service.

For potential patients who lack mental capacity to consent to research, a SRN CTO/ESD senior team member will identify a personal consultee to approach and discuss the study with. This will be a person who is in a position to advise on the wishes and feelings of the potential patient in relation to taking part in this research project. Due to the nature of the study, potential patients lacking in capacity will need to have a relative/friend (carer) who would be prepared to assist with the extended stroke rehabilitation service reviews and outcome assessments as these are unlikely to be possible without their support. In most cases, it is anticipated that the identified consultee will be the patient's carer. This carer may therefore also be approached about their own participation in the study. If the carer does not wish to participate in the study, it is still possible for the patient to participate provided the carer will provide the necessary support for reviews and outcome assessments.

The identified consultee will be provided with a consultee information sheet. After allowing sufficient time to consider the patient's wishes and feelings (>24 hours), and an opportunity to ask questions, the consultee will be asked to complete a consultee declaration form if they believe the patient would have no objection to taking part in the study.

If a patient regains capacity during their participation in the study, they will be informed about the study, given a 'recovered capacity' patient information sheet and asked to provide their own consent to continue in the study on a 'recovered capacity' consent form. If a patient does not wish to continue in the study, they will be withdrawn. Data collected prior to withdrawal will be used in the study analysis.

Loss of capacity to consent to research during participation in the study

If a patient who has provided their own consent loses capacity to consent to research during their participation in the study, we will seek advice from a personal consultee about their continuing participation in the study. This will be a person who is in a position to advise on the wishes and feelings of the patient in relation to the research study. On entering the study, patients will be asked to nominate a relative or friend who they would like to be their consultee should they lose capacity to consent to research. Due to the nature of the study, patients who lose capacity will need to have a relative or friend (carer) who would be prepared to assist with the extended stroke rehabilitation service reviews and outcome assessments to continue in the study, as these are unlikely to be possible without their support. This person will be identified in the event of loss of capacity to consent to the research. However, where a patient has a carer (who may also be participating in the study) we anticipate that this carer will be approached to provide support for reviews and outcome assessments.

In the event of loss of capacity to consent to this research, the nominated consultee will be given a 'loss of capacity' consultee information sheet. If a consultee believes the patient would have no objection to continuing in the study, they will be asked to complete a 'loss of capacity' consultee declaration form. If the consultee believes that the patient would not wish to continue in the study, the patient will be withdrawn from the study. Data collected prior to withdrawal will be used in the study analysis.

Original consent forms/declaration forms will be retained in the investigator site file. A copy of the form (s) will be filed in the medical notes and a further copy given to the patient/consultee. A letter will be sent to the patient's GPs to inform them about participation in this study. Consent for this will be sought on the consent form/declaration form.

The information sheets and consent forms will be available in English. However, interpreters and translation of written material will be possible through local NHS arrangements should potentially eligible patients require this.

2. Carers

Potential carers will be identified by ESD senior team members whilst the patient is receiving routine ESD care. At the time of patient discharge from routine ESD services, if the patient has an identified carer, she/he will be provided with an invitation letter, study information sheet, study carer baseline questionnaire and pre-paid envelope (addressed to the study co-ordinating centre). Provision of the invitation letter and study documents may be in person by an ESD senior team member, by post by the local study team, or by a consented patient. These three options are being used to maximise potential opportunities for carers to take part in the study as carers are not always present at staff visits.

The invitation letter will ask a carer to complete and return the baseline questionnaire, if she/he is willing to participate in the study. A formal written consent form will not be undertaken, return of the questionnaire to the study co-ordinating centre will be taken as consent to participate in the study. Further questionnaires will subsequently be issued or posted at the study assessment time points.

Recruitment assessment

A patient recruitment assessment will be performed by a SRN CTO/ESD senior team member. This will be undertaken after informed consent has been obtained and within four days prior to planned discharge from hospital or during routine ESD care. The following data will be collected: demographic data, pre-stroke level of extended activities of daily living (Nottingham EADL Scale[15]), pre-stroke health status (Oxford Handicap Scale[16]), date of hospital admission, date of stroke, stroke type and subtype, National Institute of Health Stroke Scale[17] (NIHSS), comorbidity, pre-stroke resource usage (adaptation of the Client Service Receipt Inventory[18-20](CSRI)).

To enable contact with the research team for follow up assessments, patients will also be asked for their contact details and contact details of their next of kin and general practitioner. A study 'change of circumstances' form will be issued to be returned to the study team if appropriate.

Baseline assessment

A patient baseline assessment will be performed by a senior ESD team member or a SRN CTO at discharge from routine ESD services and immediately prior to randomisation. The following data will be collected: date of hospital discharge, date of ESD discharge, Abbreviated Mental Test Score[21], Sheffield Aphasia Screening Test[22], extended activities of daily living (Nottingham EADL Scale[15]), health status (Oxford Handicap Scale[16]), quality of life (Euroqol EQ-5D[23]) and mood (Hospital Anxiety and Depression Scale[24]). Contact details will also be confirmed. As it is intended that the majority of 12 month and 24 month outcome assessments will be conducted by telephone interview, ability to take part in a telephone interview will be recorded. Patients will also be asked for their preferred time of contact for the telephone interview.

Carers will receive a baseline questionnaire with the study invitation letter. The questionnaire will collect the following data: demographic data, quality of life (Euroqol EQ-5D[23]) and carer stress (Caregiver Strain Index[25]).

Randomisation

Randomisation will be by a central independent web based service hosted by Newcastle University Clinical Trials Unit. Participants will be stratified according to stroke service and randomised to intervention and control in a 1:1 ratio using permuted block sequences. Randomisation will be performed by an appropriately trained ESD team member or SRN CTO at each research site when a patient is discharged from routine ESD services. Stroke patients and carers will be randomised as a single unit.

Study control treatment

Usual care and provision of booklet about stroke care and rehabilitation

Stroke patients in the control group will receive usual ESD care with subsequent referral to other rehabilitation services post discharge from ESD if required and in accordance with usual care. Patients who have ongoing rehabilitation needs following completion of ESD may be referred to a range of services e.g. neurorehabilitation teams; day hospital; and community rehabilitation services.

In addition, both control and intervention group participants will receive a booklet about stroke care and rehabilitation. The booklet will be 'Care after stroke or transient ischaemic attack. Information for patients and their carers' written by the Intercollegiate Stroke Working Party[26]. This publication is written for stroke patients and carers. It describes what a stroke is, assessment, acute management and rehabilitation. It is based on the National Clinical Guideline for Stroke[27].

Study intervention treatment

Extended stroke rehabilitation service and provision of booklet about stroke care and rehabilitation

Stroke patients in the intervention group will receive an extended stroke rehabilitation service for 18 months following completion of rehabilitation with their ESD team. This will be in addition to usual care. They will also receive the Intercollegiate Stroke Working Party booklet about stroke care and rehabilitation.

The extended stroke rehabilitation service consists of reviews by a designated senior member of the ESD team at 1, 3, 6, 12, and 18 months post discharge from routine ESD. We have chosen to evaluate a model where care is coordinated rather than delivered by a senior member of the ESD team as this model could potentially be delivered throughout the UK. The role of specialists coordinating rather than delivering rehabilitation has been shown to be effective in other conditions.[28]

Each review will consist of:

1. A semi-structured interview to identify the patient's progress, current rehabilitation needs and service provision. The interview will address both everyday activities (personal care, meal times, domestic activities, indoor mobility, outdoor mobility, shopping, hobbies, driving), social participation and wider issues (mood, memory, pain, communication, medical issues) which may be problematic for stroke survivors. The views of both the patient and carer (where appropriate) will be sought.

2. Joint rehabilitation goal setting. From the identified progress and rehabilitation needs, up to five individual rehabilitation goals will be set by the patient (and carer) in collaboration with the senior ESD team member who conducts the review. The focus of joint goal setting will be increasing participation in everyday activities. The physical, psychological and social factors which may impact on goal attainment will be considered. At each review, progress towards goals from the previous review will be assessed prior to further goal setting. Achievement of goals will be recorded using a Goal Attainment Scale[29].

3. Action planning. The patient (and carer) will agree an action plan for each rehabilitation goal. This may include:

- Verbal advice and encouragement
- Discussion with the stroke team, rehabilitation team, primary care team, or social services involved in care
- Signposting to local activities, community organisations or voluntary services
- Referral to stroke services, rehabilitation services or primary care services for further assessment and treatment if required according to local guidelines and/or service provision.

The majority of the reviews will be done by telephone. The senior ESD team member will know the patient and carer as he/she will have treated the patient as part of the ESD service. However, if the patient and/or carer are unable to participate in a telephone review, a home visit will be undertaken. Patients will be given a study appointment card which will also contain a short checklist of rehabilitation issues to be covered in each

review. This is to allow patients (and carers) time to consider the topics to be discussed prior to the interview. Patients with aphasia will receive an 'easy access' version of the appointment card.

All senior ESD staff taking part in the trial will receive an extended stroke rehabilitation service manual and training in delivery of the new service. The extended stroke rehabilitation manual describes how to conduct the reviews including guidance on exploring rehabilitation needs, goal setting and appropriate interventions to meet a patient's needs.

Subsequent to each review the ESD therapist/nurse may contact services currently involved in the patients care to discuss progress, goals and care plan.

A summary of the review and recommendations for rehabilitation will be sent to the patient, patient's GP, stroke physician, and therapists who are currently involved in care. Patient's with aphasia will receive an 'easy access' version of the letter.

Outcome assessments

Outcomes will be assessed at 12 months (+/- 7 days) and 24 months (+/- 7 days) following randomisation.

Patient outcome assessments will be undertaken by telephone by a researcher based in the study co-ordinating centre. For participants who do not have a telephone or who are unable to communicate by telephone, outcomes will be collected by postal questionnaire. If a patient is unable to participate in a telephone interview or complete a postal questionnaire, outcome assessments will be undertaken by staff trained by the study team.

To arrange a telephone interview, a letter or email (according to patient preference) will be sent to each patient with an appointment and a copy of the outcome assessment questionnaire, one week in advance. If the appointment is not convenient, it will be rearranged. If a patient is not contactable, the researcher will ring him/her on further occasions over seven days at different times of the day. One of these calls will be in the evening if the person may be working. If there is still no response, the researcher will contact SRN staff and/or the GP surgery to check the contact details and see if he/she has died, been admitted to hospital or moved away. If a patient has died, data about use of services prior to death will be collected from health records by SRN staff. Where patients have not been contactable by phone, an attempt to collect outcome data will be made by postal questionnaire. A letter, the questionnaire and a pre-paid return envelope will be mailed from the co-ordinating centre. Postal reminders to complete the questionnaire will be sent after two and four weeks if a questionnaire has not been returned.

For patients unable to participate in a telephone interview, a letter, the outcome assessment questionnaire and a pre-paid return envelope will be mailed from the co-ordinating centre one week in advance of the due date. Postal reminders to complete a questionnaire will be sent after two and four weeks if a questionnaire has not been returned.

For patients unable to participate in a telephone interview or complete a postal questionnaire, an identified member of staff will make contact with the patient (or next of kin) and arrange a visit to conduct the assessment.

The following data will be collected from patients: extended activities of daily living (Nottingham EADL Scale[15]), health status (Oxford Handicap Scale[16]), quality of life (Euroqol EQ-5D[23]), mood (Hospital Anxiety and Depression Scale[24]), experience of services (adaption of an experience survey designed by Northumbria Healthcare NHS Foundation Trust) and resource utilisation (adaptation of the Client Service Receipt Inventory (CSRI)[18-20]).

Carers outcome assessments will be undertaken by postal questionnaire. This is because the Caregiver Strain Index asks some sensitive questions about the impact of stroke upon the carer.[25] In our experience, the patient will often be in the same room as the telephone and/or may overhear the assessment. The carer and patient may find this distressing and/or the carer may modify their answers. Carer questionnaires will be

mailed from the co-ordinating centre one week in advance of the outcome assessment due date. Postal or telephone reminders to complete a questionnaire will be used after two and four weeks if a questionnaire has not been returned. The carer outcome questionnaire will collect the following data: quality of life (EuroQoL EQ-5D[23]), carer stress (Caregiver Strain Index[25]) and experience of services (adaption of an experience survey designed by Northumbria Healthcare NHS Foundation Trust).

Blinding

Due to the nature of the intervention, it is not possible to blind stroke patients or carers to treatment allocation. Patient outcome assessments will be collected by a researcher blinded to treatment allocation who will be based in the study coordinating centre. After each assessment the researcher will be asked to record whether they have unintentionally become aware of treatment allocation due to conversation with the participant. Success of patient outcome assessment blinding will be reported. Carer outcome assessments will not blinded as they will be self-reported by postal questionnaire.

Therapists outwith the ESD team who provide usual care to the control group post discharge from ESD will not be informed that a patient is participating in the study.

Study withdrawal

No specific study withdrawal criteria have been pre-set. Stroke patients and/or carers may withdraw from the study at any time for any reason. If a patient wishes to discontinue receiving the extended stroke rehabilitation service, they will be encouraged to remain in the study for the purposes of data collection in line with the study schedule. If they wish to discontinue data collection, they will be asked to participate in an 'end of study' assessment at the time of withdrawal. Data collected prior to withdrawal will be used in the study analysis unless consent for this is specifically withdrawn. Should a decision to withdraw from the study be made, a reason for withdrawal will be sought but patients and/or carers can chose to withdraw without providing an explanation.

Investigators, senior ESD team members and/or a patients consultee (in the case of mental incapacity) may also withdraw participants from the study at any time if they feel it is no longer in their interest to continue, for example, because of intercurrent illness or adverse events.

Safety evaluation

The safety of the extended stroke rehabilitation service will be evaluated by examining the occurrence of all adverse events and serious adverse events in accordance with National Research Ethics Committee (NRES) guidance for non CTIMP trials.

Definitions

Adverse event (AE): Any untoward medical occurrence in a participant to whom a study intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE, therefore, does not necessarily have a causal relationship with the treatment. In this context, "treatment" includes all interventions (including comparative agents) administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

Related AE: An AE that results from administration of any of the research study procedures. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a study procedure qualify as 'related adverse events'. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Causality: The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. All adverse events judged as having a reasonable suspected causal relationship to a study procedure (i.e definitely, probably or possibly related) are considered to be related adverse events. If any doubt about the causality exists, the local investigator (PI) should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the main REC and other bodies will be informed of both points of view.

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Unexpected Adverse Event: An adverse event that is not listed in the study protocol as an expected occurrence in the circumstances of this study.

Serious Adverse Event (SAE): an untoward occurrence that:-

- Results in death
- Is life-threatening (refers to an event in which the subject 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 were more severe)
- Requires hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Recording and reporting of adverse events

All adverse events will be recorded. This will occur for the duration of a patient's involvement in the study. Recording will take place at the study outcome assessments by including the following questions in the outcome proforma: "are there any new medical problems since the last study assessment?" In addition, we will specifically enquire about:

1. Injurious falls as these may be an unwanted consequence of increased participation in extended activities of daily living.
2. Placement in residential or nursing care (short and long term).

Events considered to be SAEs will subsequently be documented onto a separate study SAE form, and a causality and expectedness assessment will be performed. As study investigators or other members of the research team may become aware of SAEs at times other than at outcome assessment appointments, the SAE form will also be used to directly capture these events.

All SAEs, regardless of causality or expectedness, will be reported to the Chief Investigator and trial sponsor (Northumbria Healthcare NHS Foundation Trust). The initial report can be made by telephone or email to the study co-ordinating centre who will inform the Chief Investigator and trial sponsor. All provisional reports must be followed by a fully completed SAE form. If incomplete information is available at the time of this initial report, further information must be provided on a follow up form as soon as it is available. The main REC will be notified of related and unexpected SAEs within 15 days of the Chief Investigator becoming aware of the event. AE data will be processed with routine study data.

Statistical analysis

Primary analysis

The primary outcome is the Nottingham EADL score at 24 months. Analysis will be on the basis of intention to treat. Mean scores will be compared between intervention and control groups using multiple linear regression including terms for sites and patient-level covariates such as baseline scores.

Secondary analyses

Secondary outcomes will be compared between intervention and control groups using multiple linear regression including terms for sites and patient-level covariates such as baseline scores. Further exploratory descriptive analyses will examine the impact of the severity of activity limitation, pre-stroke health status, and comorbidity upon the effectiveness of the intervention; there is not sufficient power to perform any formal subgroup analyses.

Interim analysis

The Data Monitoring and Ethics Committee (DMEC) will decide on the need for any interim analyses and stopping rules at their first meeting.

Sample size

There is consensus that a difference of 6 points (scored 0-66, SD 18) on the Nottingham EADL Scale is clinically important and power calculations for previous multicentre rehabilitation trials have been based upon this difference.[20, 30] Responses from 382 patients split equally between intervention and control groups will provide 90% power to detect a difference in mean Nottingham EADL of 6 points. Based on attrition in other stroke rehabilitation trials, we believe that there may be up to 25% attrition between study randomisation and the 24 month (primary) outcome assessment. To allow for this, we aim to randomise 510 participants into the study.

Although participants may be recruited any time from within four days prior to discharge from hospital until discharge from ESD, many are likely to be recruited prior to discharge from hospital. There may be several weeks between recruitment and randomisation and some participants may withdraw from the study during this time. Our current estimate is that up to 15% may drop out before randomisation. The target recruitment sample size will be kept under review and recruitment will cease when we estimate that 510 participants will be randomised. Reasons for loss from the trial will be recorded.

Economic analysis

The economic evaluation will include both a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA).[31] The CEA will be undertaken using the Nottingham EADL Scale[15] at 24 months as the measure of effect. The result of the CEA will be an incremental cost effectiveness ratio (ICER).[32] In order to quantify the uncertainty associated with the ICER the stochastic analysis will be conducted with the results presented as a cost effectiveness acceptability curve (CEAC).[33] The CEAC will show the probability that an extended stroke rehabilitation service is cost-effective compared with usual post ESD care, given the observed data, for a range of maximum monetary values that decision makers may be prepared to pay for unit change in Nottingham EADL Scale.[15] The CUA will compare changes in health related quality of life, based on responses to the EuroQoL EQ-5D[23], at baseline and 24 months across both arms of the trial. These data will be combined with study participant's mortality to estimate quality adjusted life years (QALYs). Both costs and QALY data will be combined into an incremental cost per QALY. Both analyses will be carried out from

the perspective of the National Health Service, but we will also take societal perspective by including costs borne by the participants themselves and their informal carers by obtaining information about time away from employment and time spent providing care. Resource utilisation will be assessed at 12 and 24 months using an appropriate adaptation of the Client Service Receipt Inventory (CSRI).[18-20] We will identify all the relevant financial costs associated with providing the intervention. Relevant costs will be categorised as either fixed costs or variable costs, where fixed costs are those resources that are required to set up and run the service and variable costs are those required to treat an individual patient. Where appropriate, discounting[31] will be applied to financial costs and outcomes. Financial costs will be attached to the items of service used using data from the Personal Social Services Research Unit.[34] Because the financial consequences of an extended stroke rehabilitation service may extend beyond the 24 month timeframe of the trial, and may have significant financial cost and quality of life implications; for example a reduced incidence of hospitalisation related to falls or need for residential or nursing home care, a Markov model will be developed that can be used to predict outcomes up to 60 months given status at 24 months. Transition probabilities and cost associated with each state in the model will be obtained from published literature and where no published evidence exists expert opinion will be sought. Other forms of uncertainty such as variation in unit prices will be explored within the deterministic sensitivity analyses, where appropriate these CEACs will also be produced for these analyses.

Parallel process evaluation

Parallel process evaluations of complex interventions being tested by randomised controlled trials are increasingly recommended.[35] They can provide information about unanticipated consequences, reasons for success, how an intervention can be improved, and identify contextual factors associated with variations in outcome.[36] This process evaluation will investigate the operation of the extended stroke rehabilitation service collecting both quantitative and qualitative data. This will include:

i) Mapping the rehabilitation and follow up services provided for stroke patients in each site at the start and end of the study.

ii) Documenting how the new service is implemented and delivered in different settings. A senior ESD team member at each site will complete a standard proforma at each assessment. This will consist of a progress update, rehabilitation undertaken since the previous assessment, services received and progress toward rehabilitation goals. The senior ESD team member will record the patient's current rehabilitation needs, assessment and advice given to the patient and carer. Details of new referrals to other services will be recorded. Data will be entered at each study site onto a web-based database.

iii) Seeking the views and describing the experiences of patients and carers about the rehabilitation services they received. Semi-structured interviews will be conducted with a purposive sample of patients and caregivers who received the extended stroke rehabilitation service and usual care. Sampling will use variables of age, gender, ethnicity, level of disability and geographical location of research sites for participant selection. Equal numbers of control and intervention group participants will be selected to allow comparison between the two groups. A topic guide will be devised drawing on relevant literature.[37-40] The interviews are likely to include questions on their views and perceptions about their ability to undertake extended activities of daily living; enablers and barriers; perceptions of provision of rehabilitation to support extended activities of daily living; and perceptions of unmet need. Interviews will take place after final outcome assessment. The topic guide will be refined by pilot interviews with a small sample (approximately four) of patients and their carers. The guide will then be used with up to 60 patients and/or patient/carer dyads with final numbers determined when 'data saturation' is considered to have been achieved through on- going analysis.[41] All interviews will be digitally recorded, transcribed and entered onto NVivo for data management.

iv) Seeking the views and experiences of senior members of the ESD teams and community rehabilitation staff about the services provided to the intervention and control groups. Semi-structured 1:1 interviews will be conducted with a purposive sample of rehabilitation staff who were involved in the study. Sampling will ensure the involvement of the range of healthcare professionals delivering the intervention. A topic guide will be developed following a small pilot sample of unstructured interviews

with two senior ESD team members who provided the extended stroke rehabilitation service and two members of community rehabilitation services. Interviews will investigate their experience in delivering rehabilitation to improve extended activities of daily living; the longer term needs relating to extended activities of daily living of people with stroke and their carers; and views about the extended stroke rehabilitation service compared to usual care. Interviews will then be undertaken with 2-3 members of the community teams in all study sites. Since interviews conducted during the recruitment may have the undesired effect of changing staff practice, these will be undertaken within six weeks of the end of trial recruitment.

Interview data analysis

Transcribed interviews will be checked and corrected for errors by the interviewer. Analysis will follow standard approaches that entail familiarisation with the material, coding and category development to identify the main patterns of responses, consistencies and divergences across and within interviews and to identify similarities and differences between and within group testing.[42] Common experiences, outlier views and significant differences by category of respondent will be identified. A sub-sample of interview data will be independently analysed by a study co-investigator and compared to the analysis undertaken by the interviewer.

We will use accepted approaches to demonstrating rigour in qualitative research[43], including clear documentation of research methods and processes, transparency in the use of data collection schedules, independent coding and analysis by researchers, systematic exploration of alternative explanations for the processes claimed to explain our findings and as far as possible and the involvement of study participants in a discussion of the initial analyses.

Pilot study

This study will commence as an internal pilot trial. Three to six research sites will be set up and participant recruitment and treatment will be monitored for 9 months. If the internal pilot trial is considered a success, the full trial will continue. The internal pilot will be considered a success if:

i) three pilot sites are set up and recruiting.
ii) the study has recruited a minimum of 22 patients (60% of predicted recruitment at month 9).
iii) the extended stroke rehabilitation service is being provided at each site and participants who have reached the first review dates have been assessed and treatment recommendations made according to protocol.

Ethics and regulatory issues

The study sponsor is Northumbria Healthcare NHS Foundation Trust. The study will be conducted in accordance with Research Governance Framework for Health and Social Care.[44] Ethical and NHS Trust approvals will be sought. The study coordinating centre will require a written copy of local approval documentation before initiating each participating centre and accepting participants into the study.

Confidentiality

Personal data will be regarded as strictly confidential. Original paper case record forms containing study data will be stored in the investigator site file at each research site, or for the outcome assessments conducted from Newcastle University, in the study file in the co-ordinating centre. All study files will be securely stored and access restricted to staff involved in the study. All data will be uploaded onto a secure web-based electronic database run and maintained by Newcastle University. Access to this database will be password protected and limited to staff at research sites or Newcastle University who are involved in the study.

The study will comply with the Data Protection Act, 1998 and Caldicott Guardian approval for use of patient

identifiable data will be sought in line with local requirements. All trial documentation will be retained for future audit and inspection in line with the sponsor policies.

Trial monitoring, quality control and quality assurance

The Chief Investigator will have overall responsibility for study conduct. The Principal Investigators will be responsible for the day-to-day study conduct at their individual sites.

The trial will be managed by a co-ordinating centre based at Newcastle University who will provide day-to-day support for the sites and provide training through investigator meetings, site initiation visits and routine monitoring visits. A Trial Management Group (TMG) will be convened and meet regularly during the study.

Quality control will be maintained through adherence to Newcastle Biomedicine Clinical Research Platform SOPs, the study protocol and research governance regulations. General monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits. The main areas of focus will include consent, serious adverse events and essential documents in study files. All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

A Trial Steering Committee (TSC) will be convened. This will comprise of an independent chair (Professor Peter Langhorne, Glasgow University), at least two other independent members, one or two Co-Investigators, a patient and/or a carer representative, the chief investigator, the trial statistician and the project manager. The TSC will agree a charter of operation and meet at least annually during the study. Representatives from NIHR HTA and the study sponsor will be invited to attend TSC meetings.

An independent data monitoring and ethics committee (DMEC) will be convened to undertake independent review. This will comprise of 3-4 members including expert healthcare professionals and a statistician. The DMEC will be chaired by Professor Ian Ford (Glasgow University). The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMEC will have access to unblinded outcome data before the trial ends. The DMEC will agree a charter of operation and meet at least annually during the study.

The study may be subject to inspection and audit by Northumbria Healthcare NHS Foundation Trust under their remit as sponsor.

Funding

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Indemnity

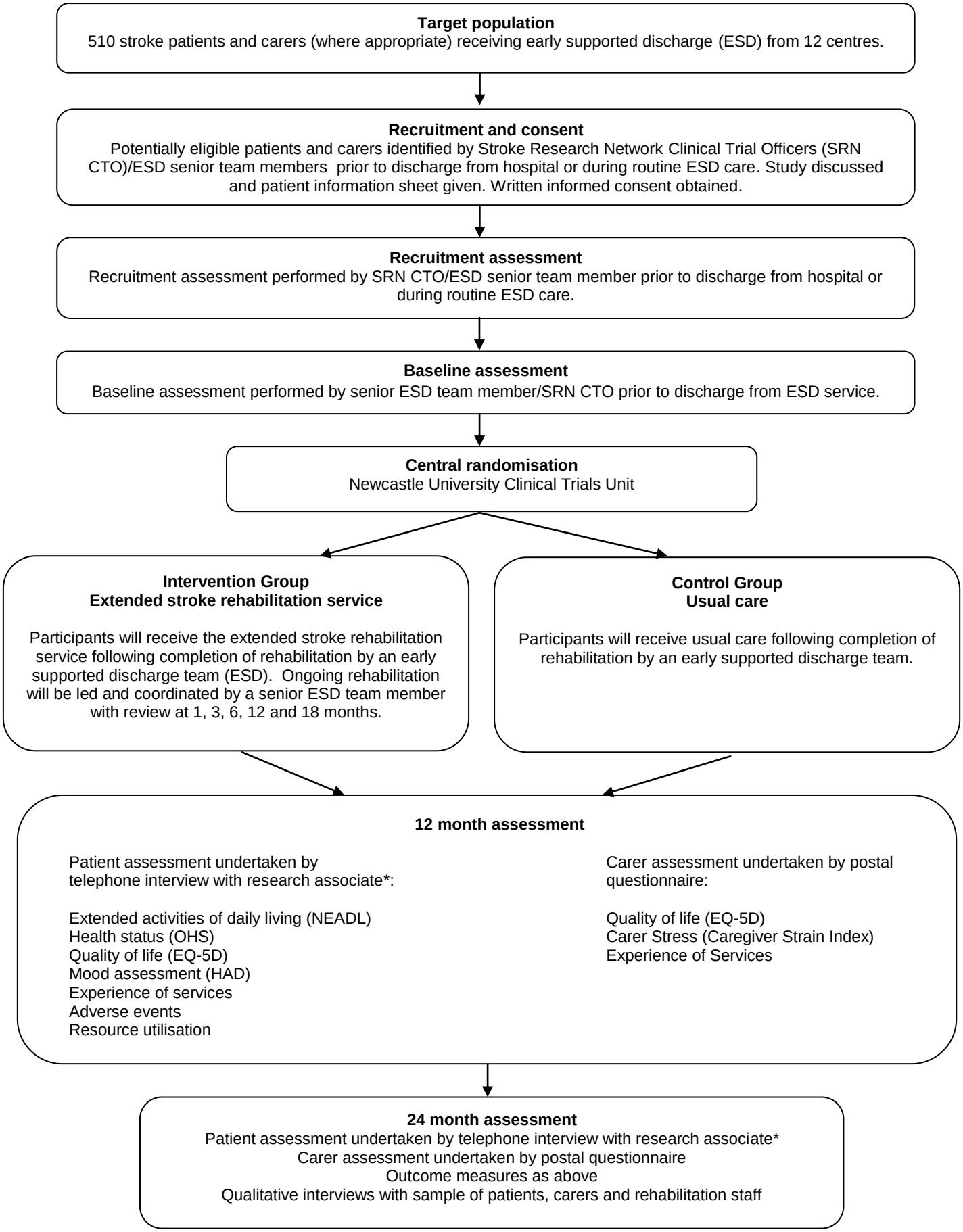
NHS Trusts participating in the study have liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS indemnity covers NHS staff and academic staff with honorary contracts conducting the trial for potential liability in respect of negligent harm arising from the conduct of the study. Northumbria Healthcare NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantative contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the university. This is a non-commercial study and there are no arrangements for non-negligent compensation.

Dissemination of results

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator.

The study will be presented at national and international conferences, and reported in peer reviewed journals and a HTA monograph. Reports will be written for the study sponsor and regulatory bodies. A summary of the results will be sent to study participants and carers. Anonymised data will be provided to research databases as requested (e.g. the Cochrane Collaboration, the Virtual International Stroke Trials Archive (VISTA)) to enable future meta-analyses.

Trial summary



* If patient unable to use telephone a postal questionnaire or face to face interview will be arranged.

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Appendix 1: Summary of study schedule

	Initial study approach	Recruitment assessment[1]	Baseline assessment	Extended rehabilitation review 1 (1month)	Extended rehabilitation review 2 (3month)	Extended rehabilitation review 3 (6 month)	Extended rehabilitation review 4 (12 month)	Outcome assessment 1 (12 month)	Extended rehabilitation review 5 (18 month)	Outcome assessment 2 (24 month)
Study discussed and PIS given	x									
Informed consent[1]		x								
Contact details		x	x					x		x
Demography		x	x[2]							
Pre-stroke level of extended activities of daily living (Nottingham EADL scale)[1]		x								
Pre-stroke health status (OHS)[1]		x								
Details of stroke[1]		x								
Medical history[1]		x								
Level of extended activities of daily living assessment (Nottingham EADL scale)[1]			x					x		x
Health status assessment (OHS)[1]			x					x		x
Quality of life assessment (EQ-5D)			x					x		x
Mood assessment (HAD)[1]			x					x		x
Carer stress assessment (Caregiver strain index)[2]			x					x		x
Randomisation			x							
Issue of stroke care and rehabilitation booklet			x							
Rehabilitation needs review [1,3]				x	x	x	x		x	
Rehabilitation goal setting and/or review [1,3]				x	x	x	x		x	
Experience of services								x		x
Resource utilisation (CSRI)[1]		x						x		x
Adverse Events[1]								x		x

1. Patients only, 2. Carers only, 3. Intervention group only

Appendix 2: Project Gantt chart

ID	Task Name	Start	Finish
1	**PHASE 1: PRE-PROJECT WORK**	Thu 01/09/11	Sun 30/09/12
2	Develop assessment tool for extended rehab service	Thu 01/09/11	Thu 31/05/12
3	Develop manual of interventions for extended rehab service	Thu 01/09/11	Thu 31/05/12
4	Develop stroke rehabilitation information booklets	Thu 01/09/11	Thu 31/05/12
5	Finalise study protocol	Wed 01/02/12	Thu 31/05/12
6	Prepare study documentation	Wed 01/02/12	Thu 31/05/12
7	Complete REC application (via IRAS)	Sun 01/04/12	Thu 31/05/12
8	Complete global R&D application (via IRAS)	Sun 01/04/12	Thu 31/05/12
9	Await REC and global R&D approvals	Fri 01/06/12	Sun 30/09/12
10	Recruit NHS research sites and dedicated study therapists	Thu 01/09/11	Sun 30/09/12
11	Agree NHS excess treatment costs	Thu 01/09/11	Sun 30/09/12
12	Recruit TSC and DMEC Members	Thu 01/09/11	Sun 30/09/12
13			
14	**PHASE 2: INTERNAL PILOT TRIAL**	Mon 01/10/12	Mon 30/09/13
15	Complete R&D (SSI) applications for three pilot sites	Mon 01/10/12	Mon 31/12/12
16	Set up study randomisation service	Mon 01/10/12	Mon 31/12/12
17	Set up study online data entry system	Mon 01/10/12	Mon 31/12/12
18	Train SRN CTOs and study therapists in three pilot sites	Mon 01/10/12	Mon 31/12/12
19	Pilot recruitment	Tue 01/01/13	Sun 30/06/13
20	Review success of internal pilot trial	Mon 01/07/13	Mon 30/09/13
21			
22	**PHASE 3: MAIN TRIAL**	Tue 01/10/13	Sat 30/09/17
23	Continued recruitment sites 1-3	Mon 01/07/13	Sat 31/01/15
24	R&D (SSI) applications/approvals and training for sites 4-6	Tue 01/10/13	Tue 31/12/13
25	Participant recruitments sites 4-6	Wed 01/01/14	Sat 31/01/15
26	R&D (SSI) applications/approvals and training for sites 7-9	Wed 01/01/14	Mon 31/03/14
27	Participant recruitment sites 7-9	Tue 01/04/14	Sat 31/01/15
28	R&D (SSI) applications/approvals and training for sites 10-12	Tue 01/04/14	Mon 30/06/14
29	Participant recruitment sites 10-12	Tue 01/07/14	Sat 31/01/15
30			
31	Total participant recruitment pilot/main trial	Tue 01/01/13	Sat 31/01/15
32	Provision of extended rehabilitation service pilot/main trial	Wed 01/05/13	Wed 30/11/16
33	12 month outcome assessments	Wed 01/01/14	Sun 31/01/16
34	24 month outcome assessments	Thu 01/01/15	Tue 31/01/17
35	Parallel process evaluation data collection	Wed 01/10/14	Fri 31/03/17
36	Research site governance monitoring	Tue 01/01/13	Tue 31/01/17
37			
38	**Data Handling and Reports**	Tue 01/01/13	Sat 30/09/17
39	Data monitoring and cleaning	Tue 01/01/13	Mon 31/07/17
40	Final data analyses	Wed 01/03/17	Mon 31/07/17
41	HTA final report writing	Tue 01/03/16	Sat 30/09/17
42	HTA 6 Monthly Reports	Mon 01/04/13	Mon 03/04/17
53	REC Annual Reports	Tue 01/10/13	Mon 03/10/16
58			
59	**Meetings**	Sun 01/05/11	Sat 30/09/17
60	Applicant Group Meetings	Thu 01/09/11	Fri 01/09/17
74	TSC Meetings	Mon 01/10/12	Mon 03/04/17
85	DMEC Meetings	Mon 01/10/12	Mon 03/04/17
96	Trial Management Group Meetings	Thu 01/09/11	Fri 01/09/17