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**Frailty, Inequality and Comorbidity: a cohort study in TIA and Stroke**

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**Short title:** Frailty & INEquality in STroke

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# SYNOPSIS

|  |  |
| --- | --- |
| Title | **Frailty and Co-morbidity in the East Midlands: a pilot study in TIA and Stroke** |
| Short title | *Frailty After Stroke in the East Midlands* |
| Chief Investigator | Dr Tim England |
| Objectives | Primary: To collect prospective data on recognised clinical frailty scales and co-morbidity scores to validate for their use in future prospective randomised controlled trials  Secondary: To demonstrate the feasibility of establishing and collecting data from a TIA/stroke frailty cohort at centres in the East Midlands; to provide pilot data to inform future power calculations by measuring frailty, multi-morbidity, socio-economic status, clinical events, hospital re-admission, functional outcome, dependency, cognition, mood and quality of life. |
| Study Configuration | Multi-centre, prospective population-based longitudinal cohort study |
| Setting | Stroke Units and Rapid Access TIA clinics in the East Midlands |
| Number of participants | 200 |
| Eligibility criteria | Inclusion: Age>40; TIA, ischaemic or haemorrhagic stroke (IS, ICH) in the last: 4 weeks (subacute group) or 4 weeks to 3 years (chronic group); Written consent from participant or proxy  Exclusion: Probable stroke mimic (e.g. migraine, functional neurology, brain tumour); Life e  xpectancy <3 months; Not expected to complete follow up at day 90 (e.g. homeless, out-of-area); Level of consciousness prohibits engagement in baseline measures. |
| Description of interventions | Questionnaires at baseline and Day 90 |
| Duration of study | Study Duration: 24 months: Regulatory approvals, protocol and training: months 1-3; patient recruitment 4-18; final follow-ups 16-21; data clean, analysis and presentation of results 21-24. Data collected period: 1st patient recruited (month 4) to final patient’s final visit (month 21).  Participant Duration: 90±7 days. |
| Methods of analysis | The impact of frailty on day 90 modified Rankin scale will be assessed using ordinal and binary (mRS 0-2 v 3-6) logistic regression with adjustment for baseline co-variates age, sex and CCI. We will test whether the use of different frailty scales has an impact on predicting functional outcome (day 90 mRS) according to varying degrees of frailty using eFI, CFS and PRISMA-7 scales.  A similar approach will be adopted in exploring the effect of frailty on quality of life, disability (BI), mood, cognition, fatigue and health deprivation scores using appropriate statistical tests (ordinal/binary/linear regression) with covariate adjustment.  The cohort will be dichotomised according to presence of frailty, comparing baseline/day 90 outcomes: binary data compared with chi-squared, Fisher’s Exact test or logistic regression with adjustment of baseline prognostic factors; continuous data compared using t-test and ANCOVA with adjustment for baseline covariates.  The sensitivity, specificity, positive predictive value and negative predictive value of the presence of frailty in predicting a poor outcome (mRS 3-6) will be assessed. |

# ABBREVIATIONS

BI Barthel Index

CCI Charleston Co-morbidity Index

CFS Clinical Frailty Scale

CI Chief Investigator overall

CRF Case Report Form

DSRS Dysphagia Severity Rating Scale

eFI Electronic Frailty Index

GCP Good Clinical Practice

MoCA Montreal Cognitive Assessment

mRS modified Rankin Sclae

NHS National Health Service

OCSP Oxford Clinical Stroke Project

PI Principal Investigator at a local centre

PIS Participant Information Sheet

PRISMA-7 Program of Research on Integration of Services for the Maintenance of Autonomy

QoL Quality of Life

REC Research Ethics Committee

R&D Research and Development department

TIA Transient Ischaemic Attack

UoN University of Nottingham

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# STUDY BACKGROUND INFORMATION AND RATIONALE

Stroke is the commonest cause of neurological disability and death in the UK (>100,000/year). The majority of strokes occur in the older generation (58% aged >70), whilst over one third (38%) occur in middle-aged adults [Public Health England, PHE 2018]. Within the East Midlands, the prevalence of stroke is amongst the highest in England: Derby and Derbyshire CCG have 2.1% stroke prevalence, Nottingham North and East 2.02%, compared to rates in Greater London of ~1% [NIHR Open Data Platform Research Targeting Tool 2019]. Moreover, the levels of diversity within the East Midlands are extreme with cities such as Nottingham and Derby amongst 20% of the most deprived areas in England; Leicester is also the first minority majority city in the UK. The association between mortality from cardiovascular disease (including stroke) and health inequality (measured by deprivation score) is also stark, a linear relationship between the two (Figure below, derived from Local Authority Health Profile, PHE). Nottingham and Leicester are in the bottom 10 Local Health Authorities nationally identified in terms of premature mortality from cardiovascular diseases. It is therefore imperative to understand how diversity and inequality across the region relate specifically to prevalent cardiovascular disorders: transient ischaemic attack (TIA) and stroke.



Risk of TIA and stroke are also increased in the older population, both age and frailty negatively impacting on morbidity and mortality. Frailty describes a decline in function across several organ systems, linked to ageing, but progressing at different rates in individuals. However, the influence of frailty on stroke outcomes (including physical function and cognition) is not well understood. There are several commonly used and validated outcome measures of frailty including Rockwood’s clinical frailty scale (CFS, 9-point scale form very fit to terminally ill), the Electronic Frailty Index (EFI) and PRISMA-7 (recommended in NICE CG56 on multi-morbidity), but these have not been prospectively validated in populations with TIA and stroke. The recognition and management of frailty has recently been identified as a priority for research in multiple conditions in later life (James Lind Alliance Priority Setting Partnership).[1]

We therefore plan to identify patients assessed through the rapid access TIA clinics and stroke units in the East Midlands with the aim to explore the relationships between frailty, co-morbidity, health inequality and clinical outcomes. These data will help inform future trial design in the frail elderly population with stroke and enable us to tailor more appropriate, potentially cost saving approaches to treatment. We plan to demonstrate that we can perform frailty measures reliably in the TIA and stroke population and then explore how measures of frailty and inequality (postcode and deprivation score) relate outcome measures used routinely in stroke and with other relevant clinical endpoints (cognitive decline, recurrent vascular events, treatment adherence, identification of atrial fibrillation).

We will aim to recruit 200 participants over a 12 month period. This will allow us to determine the distribution of the frailty scale across different stroke subtypes and provide associations testing scale validity. The distribution amongst the frail population will allow future sample size estimates for larger RCTs. Ultimately, we would like to know whether we can we approach our TIA & stroke populations using frailty to stratify intervention use, and thereby focus our treatments more appropriately. We can then use this approach to test the efficacy of current and future interventions.

# STUDY OBJECTIVES AND PURPOSE

## PURPOSE

**Hypothesis**

Frailty, co-morbidity and health inequality negatively impact stroke outcomes. Understanding the relationship between frailty, multi-morbidity, inequality and outcome will inform the design of trials for current and future health care interventions in an ageing stroke population.

**Aims**

**Pilot study**

* To initiate a stroke cohort to inform the relationship between frailty, multi-morbidity, socioeconomic status and clinical outcome in TIA and stroke.

**Aims beyond pilot study**

* To design a prospective pragmatic non-inferiority randomised controlled trial testing the impact of de-escalating treatment in frail patients with TIA and stroke e.g.
  + stop versus continue statin treatment;
  + short (3-6 months) versus guideline anti-platelet use;
  + stop anti-hypertensives versus guideline
* To inform stroke services within the East Midlands regarding the influence of frailty, multi-morbidity and treatments on functional and cognitive outcomes, and explore their relationship between socioeconomic regions to identify health inequalities, thus informing the direction healthcare resource (e.g. improving compliance, identification of atrial fibrillation and cognitive decline, advanced care planning).

## PRIMARY OBJECTIVE

**Pilot study**

* To collect prospective data on recognised clinical frailty and co-morbidity scores to validate their use in future prospective randomised controlled trials

## SECONDARY OBJECTIVES

* To demonstrate the feasibility of establishing and collecting data from a TIA/stroke frailty cohort at centres in the East Midlands
* To provide pilot data to inform future power calculations by measuring frailty, multi-morbidity, socio-economic status, clinical events, hospital re-admission, functional outcome, dependency, cognition, mood and quality of life.

# STUDY DESIGN

## STUDY CONFIGURATION

**Design:** prospective population based longitudinal cohort study in 200 participants from Stroke Units and Rapid Access TIA clinics in the East Midlands

**Primary outcome**

* Frailty Scale Validity in Stroke and TIA [2]
  + Concurrent criterion validity: To demonstrate how frailty scales correlate with functional outcome (modified Rankin Scale) when taken at the same time point
  + Predictive criterion validity: To demonstrate how frailty scales at baseline correlate with the stroke-related clinical measures assessed at a later timepoint (day 90 modified Rankin Scale [mRS] and Quality of Life [QoL])
  + Responsiveness: sensitivity to change, refers to how well frailty instruments identify longitudinal changes

Frailty measures will include

* + CFS: Clinical Frailty Scale, [3]
  + EFI: Electronic Frailty Index, if available/accessible [4]
  + PRISMA-7: Program of Research on Integration of Services for the Maintenance of Autonomy Questionnaire [5]
  + FI-CGA: Rockwood Frailty Index Comprehensive Geriatric Assessment [6]

**Secondary Outcomes**

* In addition to mRS [7] and QoL, frailty scales will be correlated against: Disability (Barthel Index, BI),[7] Dysphagia (Dysphagia Severity Rating Scale, DSRS),[8] Cognition (Montreal Cognitive Assessment, MoCA),[9] mood (Zung Depression Scale),[10] inequality score (English Indices of Deprivation); fatigue and co-morbidity (number of co-morbidities and comorbidity score (Charleston Comorbidity Index, CCI and Cumulative Illness Rating Scale (CIRS, and part of FI-CGA)[11, 12]
* Feasibility of data collection: data completeness, attrition by day 90

**Measures**

**Baseline** (performed by CRN research nurse either by face-to-face questionnaire if in hospital/clinic, or from information collected through postal questionnaire and subsequent telephone call):

* demographics (age, sex, ethnicity, risk factors);
* TIA/stroke phenotype (OCSP) and aetiology (TOAST);
* Postcode (linked to English Indices of Deprivation, which includes scores on income, employment, education, crime, housing and living environment);
* Frailty (PRISMA-7, CFS, EFI, FI-CGA);
* Education
* † Weight;
* Co-morbidity; CCI
* Polypharmacy;
* Modified Rankin Score, mRS); Barthel Index (BI);
* † Walking speed, timed up and go;[13]
* † Grip strength (both hands, documenting hand dominance, exclude limb if hemiparesis present);
* Cognition (MoCA if face-face, [9] TICS-M if telephone [14, 15]);
* Mood (Geriatric Depression Scale)
* Dysphagia (DSRS)
* Fatigue (Fatigue Assessment Scale)[16]

† performed only with face-to-face interview

**On Discharge**

* Final diagnosis
* Neuro-imaging report – presence of cerebral atrophy, small vessel disease, old strokes (potential indicators of brain frailty); if MRI, reported cerebral microhaemorrhages

**Day 90 ± 7 c**entral follow up coordinator via telephone):

* Frailty (PRISMA-7, CFS, EFI, FI-CGA);
* mRS; BI;
* Cognition (TICS-M);
* Mood (GDS);
* Quality of life (EQ5D-5L);
* Mortality and cause;
* Presence of an advanced care plan; community DNACPR or RESPECT form;
* Recurrent vascular and clinical events (including non-fatal and fatal stroke and MI; cardiovascular death, atrial fibrillation);
* Re-admission (any cause);
* Medication;
* Place of residence, social care package;
* Fatigue (Fatigue Assessment Scale)

**Sub-studies**

At a later time-point, there may be opportunity to validate the frailty scores in other specific populations, such as those with Chronic Kidney Disease, Acute Kidney Injury, Diabetes and Chronic Obstructive Airways Disease, in line with the NHS long-term plan.[17] The protocol will be adapted and amendments made as appropriate according to future resource.

## STUDY MANAGEMENT

The Chief Investigator (TE) has overall responsibility for the study and shall oversee all study management. The Trial Management group will consist of Dr Tim England (TE) and Prof Adam Gordon, and will meet quarterly.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

## DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: 21 months: Regulatory approvals, protocol and training: months 1-3; patient recruitment 4-15; final follow-ups 16-18; data clean, analysis and presentation of results 19-21. Data collected period: 1st patient recruited (month 4) to final patient’s final visit (month 18).

Participant Duration: 90±7 days

### End of the Study

The end of the study will be the last visit of the last participant.

Final Data analysis and write up will occur outside of the study period.

## SELECTION AND WITHDRAWAL OF PARTICIPANTS

### Recruitment

200 adult patients presenting to clinical stroke and TIA services to be recruited from centres in the East Midlands:

(1) University Hospitals of Derby and Burton NHS Foundation Trust

(2) Nottingham University Hospitals NHS Trust Stroke Services, Nottingham City Hospital (NCH)

(3) University Hospitals of Leicester NHS Trust Stroke Services, Leicester Royal Infirmary

(4) Northampton General Hospital NHS Trust

(5) Sherwood Forest Hospitals NHS Foundation Trust (King’s Mill Stroke Unit)

If the potential participant is approached in the hospital setting, a member of the patient’s usual care team will approach the patient or their consultee (where a patient lacks capacity to consent) on admission to the respective stroke unit or TIA/stroke clinic. The investigator or their nominee, e.g. from the research team or a member of the participant’s usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

In another approach, potential participants will be sent a letter of invitation to complete the questionnaire. Their details are acquired from a routine collected database of patients admitted through the stroke services (via SSNAP – Sentinel Stroke National Audit Programme). Letters/questionnaires will be sent after information on vital status is confirmed from their GP. On return of the questionnaire, the research nurse/practitioner will call the participant to clarify any data queries.

### Eligibility criteria

### Inclusion criteria

* Age>40;
* TIA, ischaemic or haemorrhagic stroke (IS, ICH) in the last:
  + 6 weeks (subacute group)
  + 6 weeks to 3 years (chronic group)
* Written consent from participant or proxy

### Exclusion criteria

* Probable stroke mimic (e.g. migraine, functional neurology, brain tumour);
* Life expectancy <3 months
* Not expected to complete follow up at day 90 (e.g. homeless, out-of-area)
* Level of consciousness prohibits engagement in baseline measures

### Expected duration of participant participation

Study participants will be participating in the study for 90±7 days.

### Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator (e.g. failure of participant to adhere to protocol requirements, disease progression, withdrawal of consent). The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

### Informed consent

The following procedure will be used for giving information and obtaining informed consent for this non-interventional study:

**Patient has capacity to provide consent:**

All participants who are able to will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the study. The Investigator (or nominee) will explain the details of the study and provide a Participant Information Sheet. The Investigator will answer any questions that the participant has concerning study participation. Potential participants will be given as long as they need to consider whether to consent. If the participant is unable to write (e.g. in the presence of dominant hand weakness, ataxia or dyspraxia), witnessed verbal consent may be recorded on the consent form.

**Patient lacks capacity to give consent**

The participant’s attending clinical care team will determine lack of capacity. If the potential participant lacks capacity to give informed consent the following procedure will be employed.

**Consultee present:** If a consultee (relatives or other representative such as partner or close friend, able to represent the patients views and wishes) is present, they will be provided with brief information about the study. The Investigator (or nominee) will explain the details of the study and provide a Relative Information Sheet. The Investigator will answer any questions that the consultee has concerning study participation. They will be given as long as they need to consider whether to give advice.

**Relatives not present:** If the patient lacks capacity and no consultee is present, we will not recruit the patient into the study.

Participants who originally lacked capacity (and were entered into the study following agreement from a consultee) but then regain capacity will need to give informed written consent to continue in the study. The participants’ decision to withdraw would overrule the decision of the consultee

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient’s hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant’s participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

**For Postal Questionnaires:**

Completion and subsequent return of questionnaires will be taken as informed consent and separate written informed consent will not be sought.

## STUDY REGIMEN

There are two time-points of assessment:

1. Baseline. Participants will initially be assessed/approached in one of two ways:
   1. Whilst in hospital (subacute group) – either on the stroke unit, TIA clinic or stroke outpatient clinic. They will be approached according to ‘Recruitment’ (page 13). The questions asked at baseline are covered in ‘Measures’ (page 12). They will also perform the following face-to-face assessments: weight; grip strength; walking speed and timed-up-and-go.
   2. Via postal questionnaire (chronic group) – potential participants will be sent a letter of invitation to complete the questionnaire from a database of patients admitted through the stroke services (via SSNAP – Sentinel Stroke National Audit Programme). Letters/questionnaires will be sent after information on vital status is confirmed from their GP. On return of the questionnaire, the research nurse/practitioner will call the participant to clarify any data queries.

The proportions in each group will be monitored over the course of the study

The frailty scales CFS, FI-CGA and PRISMA-7 are simply administered through a few questions. The eFI, however, will require hospital staff to access System One (routinely held data on primary care database) with their own hospital access or via the general practitioner.

The questions asked at baseline are covered in ‘Measures’ (page 12).

1. Day 90. A second point of contact will be made 90 days later, covering questions laid out on page 12. This will be conducted via the telephone after information on vital status is confirmed from their GP. If we are unable to contact the participant, a questionnaire will be sent in the post. This approach has been successful in our previous stroke trials (e.g. ENOS, TICH-2, TARDIS, RIGHT-2, RECAST).[14, 18-21]

Reasons for re-admission and specific clinical outcomes will be collected according to those listed in the Day 90 measures

There are no further assessments made in this study after day 90 but the participants will be asked if they will allow us to approach them in the future for other potential studies.

At both timepoints (baseline and day 90), the data will be collected by the research nurse/practitioner and entered into a web-based electronic database. Completed questionnaires are classed as source data and will be retained in the study archives, but personal identifiers will be removed.

The participants usual care will not be affected in any way.

### Criteria for terminating the study

It is unlikely that the study will need to halt prematurely. We will consider stopping the study in the event of poor recruitment rates, reviewed as part of the trial management meetings.

# ANALYSES

### Methods

**Primary outcome**

Correlations between frailty scores and ordinal and/or continuous measures will be assessed using Spearman’s rank correlation.

**Secondary outcomes:**

The impact of frailty on day 90 modified Rankin scale will be assessed using ordinal and binary (mRS 0-2 v 3-6) logistic regression with adjustment for baseline co-variates age, sex and CCI. We will test whether the use of different frailty scales has an impact on predicting functional outcome (day 90 mRS) according to varying degrees of frailty using eFI, CFS and PRISMA-7 scales.

A similar approach will be adopted in exploring the effect of frailty on quality of life, disability (BI), mood, cognition, fatigue and health deprivation scores using appropriate statistical tests (ordinal/binary/linear regression) with covariate adjustment.

The cohort will be dichotomised according to presence of frailty, comparing baseline/day 90 outcomes: binary data compared with chi-squared, Fisher’s Exact test or logistic regression with adjustment of baseline prognostic factors; continuous data compared using t-test and ANCOVA with adjustment for baseline covariates. Mortality and binary outcome events will be analysed using cox regression analyses with covariate adjustment.

The sensitivity, specificity, positive predictive value and negative predictive value of the presence of frailty in predicting a poor outcome (mRS 3-6) will be assessed.

**Subgroups**

Separate analyses will be performed in the following subgroups

Subacute stroke; Chronic stroke; TIA; Ischaemic Stroke; ICH

The Chief Investigator (or nominee) and trial statistician will analyse the data.

### Sample size and justification

The majority of validation studies rarely provide sample size justification *a priori*, and 90% of articles have sample sizes equal to or greater than 100.[22] We have selected a sample size of 200 given that we want to assess the cohort in both subacute and chronic stroke. Exploring frailty in a stroke specific cohort and the impact on functional outcome in a prospective study is novel. The distribution of functional outcome in frail vs non-frail groups will help generate estimates of sample size calculations for larger interventional trials.

# ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

# ETHICAL AND REGULATORY ASPECTS

## ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider’s Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice and the UK Department of Health Policy Framework for Health and Social Care, 2017.

## 

## INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study records. A second copy will be filed in the participant’s medical notes and a signed and dated note made in the notes that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

For Questionnaires:

Completion and subsequent return of questionnaires will be taken as informed consent and separate written informed consent will not be sought

## 

## RECORDS

### Case Report Forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy)

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant’s name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

### Source documents

Source documents shall be filed at the investigator’s site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

### Direct access to source data / documents

The CRF and all source documents shall made be available at all times for review by the Chief Investigator, Sponsor’s designee and inspection by relevant regulatory authorities.

## 

## DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study’s participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant’s medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

# QUALITY ASSURANCE & AUDIT

## INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

## STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

## STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator/Academic Supervisor,, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the study database will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

## RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

## DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

## STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant’s medical team and all appropriate medical personnel responsible for the participant’s welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

# PUBLICATION AND DISSEMINATION POLICY

Results of the trial will be submitted for publication in a peer review journal. The results will be presented to audiences at local and national meetings that involve the public and patients (e.g. the Nottingham Research Showcase and the UK stroke forum)

# USER AND PUBLIC INVOLVEMENT

This study has not yet had any user and public involvement. Service users from local groups (e.g. Stroke persons Involvement Group) will be approached in the next phase.

# STUDY FINANCES

### Funding source

This study is funded by the NIHR Clinical Research Network East Midlands and by a NIHR Senior Investigator Award.

### Participant stipends and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care.

# SIGNATURE PAGES

Signatories to Protocol:

**Chief Investigator:** (name)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date: \_\_\_\_\_\_\_\_\_\_\_

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