Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and The Medicines for Human Use(Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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CHIEF INVESTIGATOR

Professor Keith Muir
SINAPSE Chair of Clinical Imaging & Consultant Neurologist
Institute of Neurosciences & Psychology
University of Glasgow
Southern General Hospital
Glasgow, G51 4TF
Tel: 0141 201 2494
Fax: 0141 201 2510
Email: keith.muir@glasgow.ac.uk

CO-INVESTIGATORS

Professor Lalit Kalra
Professor of Stroke Medicine
Department of Neurosciences
Academic Neurosciences Centre
King's College London
London, SE5 8AF
Tel: 020 3299 3487
Fax: 020 7848 5186
Email: lalit.kalra@kcl.ac.uk

Professor Ian FORD
Director, Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit
The Robertson Centre for Biostatistics
Boyd Orr Building
University of Glasgow
G12 8QQ
Tel: 0141 330 4048
Email: Ian.Ford@glasgow.ac.uk

Professor Joanna WARDLAW
Professor of Applied Neuroimaging and Hon. Consultant Neuroradiologst
Division of Clinical Neurosciences
Western General Hospital
Crewe Rd
Edinburgh, EH4 2XU
Tel: 0131 537 2943
Fax: 0131 332 5150
Email: joanna.wardlaw@ed.ac.uk

PROJECT MANAGER

Dr Ewan A DOUGALL
Clinical Project Manager
Glasgow Clinical Research Facility
Tennent Institute
38 Church Street
Western Infirmary
Glasgow
G11 6NT
Tel: 0141 232 9530
Fax: 0141 232 9516
Email: ewan.dougall@ggc.scot.nhs.uk

TRIAL STATISTICIAN

Dr Alex McCONNACHIE
Assistant Director of Biostatistics
Robertson Centre for Biostatistics
University of Glasgow
Boyd Orr Building
University Avenue
G12 8QQ
Tel: 0141 330 4744
Email: alex.mcconachie@glasgow.ac.uk

DATA CENTRE

Dr Sarah WEEDEN
Clinical Trials Manager
Robertson Centre for Biostatistics
University of Glasgow
Boyd Orr Building
University Avenue
G12 8QQ
Tel: 0141 330 4744
Fax: 0141 330 5094
Email: sarah.weeden@glasgow.ac.uk

CHAIR OF DATA SAFETY MONITORING COMMITTEE

Dr Andrew M DEMCHUK
Director, Calgary Stroke Program
Room 1162
Foothills Medical Centre
1403 29 St NW
Calgary, AB Canada T2N 2T9
Tel: 403-944-8671
Fax: 403-944-1602
Email: ademchuk@ucalgary.ca

CHAIR OF TRIAL STEERING COMMITTEE

Prof TG ROBINSON
Professor of Stroke Medicine
Department of Cardiovascular Sciences
University of Leicester
Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary
Leicester LE2 7LX
Tel: 0116 252 3187
Fax: 0116 252 5847
Email: tgr@leicester.ac.uk

PHARMACOVIGILANCE

Dr Eleanor DINNETT
Pharmacovigilance Office
Pharmacovigilance Office
Glasgow Clinical Trials Unit
Robertson Centre for Biostatistics
Boyd Orr Building
University of Glasgow
Glasgow G12 8QQ
Tel: 0141 330 4744
Fax: 0141 357 5588
Email: Eleanor.dinnett@ggc.scot.nhs.uk

SPONSOR

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Sponsor's Representative:

Dr Erica PACKARD
Academic Research Co-ordinator
NHS Greater Glasgow and Clyde
Research and Development Central Office
1st Floor
The Tennent Institute
38 Church Street
Western Infirmary
Glasgow
G11 6NT
T: 0141 232 9448
E: erica.packard@ggc.scot.nhs.uk

FUNDING BODY

National Institute for Health Research Efficacy and Mechanism Evaluation programme
Evaluation, Trials and Studies Coordinating Centre
University of Southampton
Alpha House, Enterprise Road
Southampton SO16 7NS

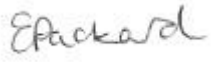
Penumbra and **R**ecanalisation **A**cute **C**omputed **T**omography in **I**schaemic **S**troke **E**valuation **(PRACTISE)**

Chief Investigator: **Professor Keith Muir**
SINAPSE Chair of Clinical Imaging & Consultant Neurologist
Institute of Neurosciences & Psychology
University of Glasgow
Southern General Hospital
Glasgow, G51 4TF

Signature: 

Date: 16 Jan 2015

Sponsor Representative: **Dr Erica PACKARD**
Academic Research Co-ordinator
NHS Greater Glasgow and Clyde
Research and Development Central Office
1st Floor
The Tennent Institute
38 Church Street
Western Infirmary
Glasgow
G11 6NT

Signature: 

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LIST OF ABBREVATIONS

AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
AVM	Arteriovenous Malformation
CI	Chief Investigator
CNS	Central Nervous System
CMH	Cochran-Mantel-Haenszel
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CT	Computed Tomography
CTA	Computed Tomography Angiography
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTP	Computed Tomography Perfusion
ECG	Electrocardiography
eCRF	Electronic Case Record Form
EME	Efficacy and Mechanism Evaluation
GCP	Good Clinical Practice
IA	Intra-Arterial
ICH	Intra-Cerebral Haemorrhage
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ration
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCCT	Non-contrast Computed Tomography
NIHR	National Institute for Health Research
NIHSS	National Institute of Health Stroke Scale
NRES	National Research Ethics Service

LIST OF ABBREVATIONS (cont.)

PI	Principal Investigator
PV	Pharmacovigilance
R&D	Research and Development
REC	Research Ethics Committee
RFA	Rankin Focussed Assessment
rtPA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
SICH	Symptomatic Intra-Cerebral Haemorrhage
SIRS	Systematic Image Review System
SITS	Safe Implementation of Thrombolysis
SIVM	Studies of Intra-cranial Vascular Malformations
SmPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
TSC	Trial Steering Committee

STUDY SYNOPSIS

Title of Study	Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation (PRACTISE)
Study Centre	Approximately 10 hyperacute stroke centres across the UK
Duration of Study	42 months
Primary Objective	1. To evaluate the utility of additional multimodal CT imaging in acute ischaemic stroke patients considered clinically eligible for IV rtPA, compared to standard clinical imaging (non-contrast CT).
Secondary Objective	1. Compare diagnostic interpretation of CTP processed by individual scanners at local centres with diagnostic interpretation of CTP processed by a uniform central analysis. 2. Evaluate the sample size requirements, feasibility, and optimal design of a larger study to test the effect of different diagnostic imaging strategies on functional outcome
Primary Endpoint	• Proportion of patients receiving IV rtPA
Secondary Endpoints	• mRS distribution at 3 months (ordinal shift analysis) • Proportion with favourable outcome at 3 months defined by mRS 0-1 and mRS 0-2 • Favourable early treatment response defined by NIHSS 0-1 or improvement by ≥8 points at 24h • Proportion with Symptomatic Intra-cerebral Haemorrhage (SITS-MOST and ECASS-3 definitions) • Mortality • Proportion of patients excluded from IV rtPA • Inter observer agreement on interpretation of CTP comparing locally processed with centrally processed scans • Inter observer agreement on interpretation of CTA
Rationale	More complex imaging in acute stroke is widely hypothesised to be valuable, but this remains unproven, and to date there has been no prospective, randomised study evaluating the role of multimodal imaging in defining individual patient treatment decisions in acute stroke, especially within the current time window for routine IV rtPA use. Multidetector CT scanners capable of multimodal CT are widely available in the NHS, but adoption of CTP and CTA into clinical management has varied widely among centres, with no standardisation. It is not known whether benefits from potentially improved patient selection will outweigh the disadvantages of additional resource utilisation, radiation and contrast exposure, and treatment delay. It is also possible that in order to realise benefit from better patient selection, post processing will require to be standardised, since there is well-documented variation in processing methods and data presentation for diagnostic decisions across equipment manufacturers.

Rationale (cont.)	If additional diagnostic testing identifies a subgroup of patients that are more or less likely to respond to treatment and hence influences treatment decisions favourably, then these should be adopted as standard practice. This would require substantial changes to many NHS Radiology and stroke departments, additional costs and training, and an agreement on standard approaches, all non-trivial and non-cheap problems. An additional question to be addressed is whether the different processing approaches used in different scanners are equivalent, and whether a unified processing approach improves diagnostic accuracy.
Methodology	Prospective, multicentre, randomised, controlled trial comparing the current evidence-based imaging (control, NCCT) with additional multimodal CT imaging (CT + CTA + CTP).
Sample Size	400 patients (200 in each group) to be initially recruited. (2-3 patients per centre per month)
Screening	All patients being considered for IV thrombolysis following ischaemic stroke
Randomisation	IVRS administered via Robertson Centre for Biostatistics in a 1:1 ratio of multimodal imaging: standard non-contrast CT
Main Inclusion Criteria	• Current Clinical diagnosis of stroke • Written informed consent from patient, legal representative or consultee • Male or non-pregnant female ≥18 years of age • Within 4.5 hours of onset as defined by time since last known well
Main Exclusion Criteria	• Contraindications to thrombolytic drug treatment for stroke • Known impaired renal function precluding CT contrast administration • Known allergy to radiological contrast • Severe concurrent medical condition that would prevent participation in study procedures or with life expectancy ≤ 3 months.
Statistical Analysis	The Robertson Centre for Biostsatistics will manage IVRS and statistical analysis. Trial eCRF and database will be provided and managed by the Robertson Centre for Biostatistics. Image management and the imaging database will be provided by the University of Edinburgh. All statistical analyses will be conducted according to a Statistical Analysis Plan, which will be authored by the Trial Statistician and agreed by the Trial Steering Committee.

TABLE 1.SCHEDULE OF ASSESSMENTS						
Study Procedure	**Visit 1** Pre randomisation	**Visit 2** Randomisation and Investigations	**Visit 3** Treatment	**Visit 4** 24 h (22-36h)	**Visit 5** Day7(±2) or discharge if earlier	**Visit 6** Day 90(±7)
Informed Consent from patients, legal representative or consultee	✓					
Review Inclusion/Exclusion Criteria	✓					
Medical history	✓					
Demographic data	✓					
Modified Rankin score	✓					✓
Physical examination, NIHSS	*			✓	✓	
Laboratory: eGFR, glucose	*					
Blood pressure	*				✓	
Randomisation using IVRS		✓				
CT Brain		*		**		
CT Perfusion		✓				
CT angiogram		✓				
IV rtPA decision and administration if appropriate			✓			
Adverse events evaluation			✓	✓	✓	✓

✓ Study specific procedure
* Clinically routine procedure (data captured for study)
** Clinically routine in some patients

1 INTRODUCTION

1.1 BACKGROUND

Stroke is the third commonest cause of death worldwide and the largest single cause of adult disability. Around 125,000 people suffer a first stroke each year in the UK, with a total cost to society of >£7 billion per annum as a result of hospital care, loss of capacity to work, disability and social care needs.

Around 85% of all strokes are due to arterial occlusion (ischaemic stroke), for which the only licensed acute treatment is the thrombolytic drug, intravenous (IV) recombinant tissue plasminogen activator (rtPA, also known as alteplase). Thrombolytic treatment is highly effective if delivered <4.5 hours after symptom onset, but is currently given in only a minority of patients even in experienced centres: current estimates are that <5% of ischaemic strokes are treated with rtPA in the UK, despite more than one third of hospitalised stroke patients reaching hospital within 3 hours of onset.[1] Diagnostic uncertainty in particular causes clinicians to under-utilise thrombolysis, and encompasses two key issues: first, whether the diagnosis is ischaemic stroke or a "stroke mimic;" and second, whether an individual stroke is severe enough to warrant treatment that carries risk, since rtPA carries a risk of iatrogenic intra-cerebral bleeding (symptomatic intra-cerebral haemorrhage, SICH).

Brain imaging is an essential component of diagnosis in patients with suspected acute stroke, and at present relies on computed tomography (CT), primarily to exclude patients with non-ischaemic stroke diagnoses. Non-contrast CT (NCCT) of brain identifies intra-cerebral haemorrhage (accounting for about 15% of incident clinically-diagnosed strokes) with high sensitivity and specificity, and can also identify many non-stroke structural pathologies that mimic stroke symptoms (e.g. brain tumours, subdural haematomas). However, in the target population of those with ischaemic stroke, NCCT has low sensitivity because the changes in brain tissue attenuation are subtle and difficult to recognise soon after the stroke. Clinicians therefore make treatment decisions based on the exclusion of contraindications on NCCT rather than on positive confirmation of diagnosis and extent of ischaemia. Coupled with perception of treatment risk, difficulty in accurately defining severity based on clinical findings alone, and anxiety that stroke mimics that lack brain imaging abnormalities may be subjected to risk, the poor sensitivity of NCCT is a factor in restricting treatment. Evidence indicates that this results particularly in treatment not being given to patients with less severe strokes, despite this group having a high rate of disability when untreated,[2] and there being evidence of similar treatment benefits among these patients.

Multimodal brain imaging offers additional information on brain vasculature and brain perfusion that increase diagnostic certainty, and most importantly, identify the severity and extent of brain ischaemia. The combination of CT perfusion (CTP) and CT angiography (CTA) represents a practical and widely available extended imaging protocol for acute stroke. However, whether the additional resource use, radiation and contrast exposure for patients, and time for acquisition, processing and interpretation, is associated with benefit has not been established.

1.2 EXISTING RESEARCH

Why are patients not treated with IV rtPA? The major reason for not treating ischaemic stroke patients who present within the time window and are otherwise eligible, with rtPA is uncertainty about the clinical diagnosis, and severity, of stroke.2,3 In particular, as many patients are not treated because of mild or improving symptoms, as receive IV rtPA. In one hospital series, 27% of those presenting definitely within 3h of onset were treated (representing 7% of all ischaemic stroke admissions regardless of time to presentation), but 31% were excluded because of a clinically mild, or improving, deficit.2 In a local series of thrombolysis cases, 26% of patients referred from peripheral hospitals not being transferred due to mild or improving symptoms, and 36% of those who were transferred not being treated for the same reasons.3 In the UK, data from the Safe Implementation of Thrombolysis (SITS) registry identify a bias towards treating more severely affected patients compared with other European countries. However, patients who are not treated because of mild deficits often have poor outcome: around 1 in 3 are dead or disabled at 3 months.2 Imaging findings are a predictor of those patients who initially improve but later deteriorate, most notably the presence of a persistent intracranial arterial occlusion,[4,5] which is associated with a high risk of subsequent deterioration. A substantial proportion of patients who are currently referred for treatment are not given rtPA, yet could benefit from therapy if clinicians had better information about the state of the affected brain tissue and arteries.

Existing routine imaging has poor sensitivity for ischaemic stroke in the relevant time frame. For moderately severe stroke, NCCT sensitivity was 57-66% within the first 5 hours of onset in a clinical trial of rtPA.[6] However, in a more general population that included mostly less severe patients, sensitivity of 23% was reported.[7] Changes on NCCT in the first 4.5h after stroke are subtle and difficult to recognise,[8] and also reflect a mixture of irreversible and potentially reversible tissue damage.[9] While clinical scores correlate with outcome, they are unreliable surrogates of the volume of tissue at risk due to problems such as insensitivity to neurological features of non dominant hemisphere strokes.[10,11] CT perfusion imaging has sensitivity reported to be 88% and specificity of 95%, while CT angiography had sensitivity of 95% and specificity of 100% for ischaemic stroke, but based on a small retrospective cohort of patients.[12]

Multimodal imaging yields information on stroke severity and tissue viability that may stratify patients. NCCT gives no information on two key physiological determinants of tissue viability, brain perfusion and vascular anatomy, that are likely determinants of treatment response.[13,14]

Perfusion imaging can discriminate potentially salvageable brain tissue (the “ischaemic penumbra”) from irreversibly damaged tissue. Studies in very small numbers of patients suggest that perfusion characteristics stratify patients into three broad groups:[15]

1. those with extensive irreversible damage due to severe hypoperfusion, in whom rtPA probably does not help, and indeed may be harmful;[16]
2. those who have spontaneously reperfused, in whom outcome is likely to be good even without treatment; and finally,
3. the target population for thrombolytic treatment, in whom there is a large volume of hypoperfused tissue that remains viable.

1.2 EXISTING RESEARCH

Stratifying individual patients based on perfusion imaging has been proposed to improve patient selection for appropriate IV rtPA use, both by reducing risk of iatrogenic intra-cerebral haemorrhage (ICH) and poor outcome in those with no potential salvageable tissue, and by identifying patients with clinically mild deficit but extensive ischaemia who may be at high risk of deterioration. Support for this concept has come from several observational studies using multimodal magnetic resonance imaging (MRI). The non-randomised Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study in patients given IV rtPA beyond the conventional time window identified potential increased ICH risk when thrombolytics opened an occluded vessel in the presence of extensive severely hypoperfused tissue.[16].16 A prospective, non-randomised multicentre study using multimodal MRI in 1210 patients suggested that selecting patients for IV thrombolysis by the presence of large volumes of salvageable tissue, and excluding from treatment those with large volumes of very severely hypoperfused tissue, reduced the risks of poor outcome and ICH after IV rtPA.[17] Similar imaging has been used for case selection in clinical trials that seek to extend the time window for thrombolysis (eg DIAS-1 [18] (1) with the novel thrombolytic desmoteplase). The only clinical trial designed to evaluate the efficacy of IV rtPA in patients with and without MRI features of penumbra, the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET),[19] failed to find a significant differential treatment effect largely because of lack of standardised perfusion imaging processing and small sample size,[20],[20] but supported the concept. Systematic review of trials that utilised predominantly MRI-based selection for thrombolysis beyond the current time window confirmed that studies have been too small to identify a convincing advantage for treatment,[21] and two ongoing trials (DIAS 3 and DIAS 4) that used CTA or MRA-based selection in a late time window (4.5-8h) have respectively shown no treatment effect or were discontinued after a futility analysis.
Clinical trials that have investigated intra-arterial (IA) reperfusion treatments, either as an adjunct to IV rtPA[22] or as a direct alternative, have been based on NCCT alone and have found no additional benefit from IA therapies. A single trial investigating imaging-based selection for “rescue” IA treatment, MR RESCUE[23], could not identify any interaction of treatment and MRI criteria for penumbra, but the sample size was small, intervention late, and the patients recruited were unusually severe, so generalisability is doubtful.

CTP uses serial scanning during an IV iodinated contrast bolus to calculate a number of perfusion parameters that may distinguish penumbra from irreversibly damaged tissue (infarct core). Discriminating penumbra from non-viable infarct core depends on defining combinations of perfusion thresholds. Studies to validate the thresholds for tissue viability and penumbra have been small (all fewer than 100 patients) and used widely varying definitions of lesion core and at risk tissue, [24]compounded by significant differences between scanner manufacturers with respect to both the methodology for image acquisition, post-processing of perfusion parameters[25], and derivation of tissue thresholds, resulting in conflicting thresholds (e.g. irreversible damage signified by cerebral blood volume <2.0ml/100g on Philips scanners,[26] but <0.82ml/100g on Siemens scanners; and signified by a different parameter, cerebral blood flow in independent studies[27]).

Systematic review of CT and MRI perfusion studies identified 69 papers (49 MRI and 20 CTP) that defined thresholds for tissue viability. The total number of patients included in all CT studies was 266. Six different thresholds to discriminate viable from non-viable tissue were identified, and four-fold variation in some commonly used perfusion parameter thresholds. Worse heterogeneity was present in MRI studies.[28] The extent of mismatch between viable and non-viable tissue that might help stratify patients for thrombolytic treatment, if indeed there is one, is not established. The observational DEFUSE study, identified increased differential treatment effects with an increasing ratio of the volume of at risk:core tissue.[29] However, all patients in DEFUSE received IV rtPA, and were treated beyond the current licence time window (3-6h after onset).

1.2 EXISTING RESEARCH (cont.)

Further systematic reviews of CTP studies identified three key sources of variability that significantly affect the visual appearance of perfusion maps, and influence the estimated volume of tissue at risk:[30] data acquisition, post-processing, and display parameters. Implementation of different approaches, especially to post-processing and display output, makes results appear very different among different scan manufacturers' software.[31] Similar large discrepancies in the proportion of patients with any perfusion lesion and consequently with "mismatch" (the discrepancy between volumes of viable and non-viable tissue), between none and 70%, were identified simply by processing the same MRI perfusion dataset to produce ten different but commonly used perfusion parameters.[32] Only30 one clinical trial to date (DIAS-2) allowed recruitment selection based on CTP findings, and marked variability in CTP interpretation across centres and scanners contributed to failure of the trial.[33]

All other published series have made assumptions about the interpretation of CTP and CTA to support thrombolysis decisions, and are essentially descriptions of local practice that extrapolate imaging selection criteria from pathophysiological assumptions or data that relate predominantly to later time windows. CTA provides high-resolution vascular imaging during a first arterial passage of IV iodinated contrast. Although in general it is well established from observational studies and randomised trials of reperfusion therapies that recanalisation of the occluded artery yields better clinical outcomes than does persistent occlusion,[34] the impact of pre-treatment CTA on decision-making for IV rtPA is not yet known, although data from the DIAS 3 and 4 studies will help address this issue, albeit predominantly in the specific environment of randomised trials of drugs or as a selection criterion for interventional revascularisation techniques. Several studies indicate that vascular imaging has independent prognostic value, including one recent CTA/CTP based study that identified leptomeningeal collateral vessels as an independent prognostic marker for favourable outcome after IV thrombolysis.[3135] Intracranial vascular occlusion is an independent marker of deterioration or recurrent stroke in patients with minor stroke or TIA, which may be particularly relevant in the selection of patients currently excluded from IV rtPA treatment.[4,36] Significant technical issues with CTP include limited brain coverage by most current scanners (typically 2-4cm blocks, depending upon the detector size, therefore covering 50% or less of typical brain volume and requiring clinicians to predict lesion location); manufacturer-specific software post-processing that uses different, often opaque, methods and thresholds to define tissue viability, all based on very small studies; a range of clinical situations that may lead to technically inadequate scans that may produce misleading results (e.g. severe extra-cranial stenosis, poor cardiac output; mistimed or failed contrast injection); significant radiation dose compared with NCCT; and lack of standards for interpretation of vascular or perfusion imaging.

Why not use alternative imaging (e.g. MRI)? Diffusion weighted MRI is more sensitive than NCCT for ischaemic stroke and when combined with perfusion imaging is able to define tissue viability, with the same hypothesised advantages in patient stratification. However, several surveys have shown that MRI is poorly available in the emergency situation,[37,38] and is not feasible in up to 40% of acutely ill stroke patients mostly due to medical instability or ferromagnetic implants,[39,40,41] a problem borne out by slow recruitment rates to trials that require MRI at randomisation, practical experience in observational studies even in well-equipped centres with research-dedicated MR scanners [Ref Wardlaw JNNP Wyeth MASS], and the extremely low use (only 2%) of MRI to support randomisation in the multicentre IST-3 thrombolytic trial. CT, on the other hand, is universally available in the UK for acute stroke assessment, and most hospitals have multidetector systems capable of multimodal CT imaging.

1.3 RATIONALE

Diagnostic imaging is expensive, labour-intensive, adds to time to treatment and a scarce resource within the NHS and worldwide, yet its utility is, in general, poorly evaluated in properly controlled studies. More complex imaging in acute stroke is widely hypothesised to be valuable, but this remains unproven, and to date there has been no prospective, randomised study evaluating the role of multimodal imaging in defining individual patient treatment decisions in acute stroke, especially within the current time window for routine IV rtPA use.

Multidetector CT scanners capable of multimodal CT are widely available in the NHS, but adoption of CTP and CTA into clinical management has varied widely among centres, with no standardisation. It is not known whether benefits from potentially improved patient selection will outweigh the disadvantages of additional resource utilisation, radiation and contrast exposure, and treatment delay.

It is also possible that in order to realise benefit from better patient selection, post-processing will require to be standardised, since there is well-documented variation in processing methods and data presentation for diagnostic decisions across equipment manufacturers.

The utility of multimodal CT in patients who are clinically eligible for IV rtPA will not be addressed by other ongoing trials that incorporate complex imaging. Other trials are either explicitly concerned with extending treatment to patients ineligible under current strict licences for IV rtPA, or use imaging criteria to enrich populations in clinical trials that are primarily designed to test the efficacy of a medical treatment (e.g. angiographic occlusion on CTA in the evaluation of a novel thrombolytic drug in a later time window in the recently stopped DIAS-4, MRI-based mismatch to select patients for late rtPA in ECASS-4 and EXTEND, IA therapy based on combinations of CTA occlusion and clinical features). However the value of additional imaging is not being tested in any current trial.

If additional diagnostic testing identifies a subgroup of patients that are more or less likely to respond to treatment and hence influences treatment decisions favourably, then these should be adopted as standard practice, but would require substantial changes to clinical services. An additional question to be addressed is whether the different processing approaches used in different scanners are equivalent, and whether a unified processing approach improves diagnostic accuracy.

1.4 STUDY HYPOTHESES

- The net effect of additional imaging will be to increase the proportion of clinically eligible patients who are treated with IV rtPA
- Multimodal imaging improves the diagnostic certainty in acute stroke
- Unified post processing of multimodal imaging is better than using different approaches in different hospitals

2 STUDY OBJECTIVES

- To evaluate the utility of additional multimodal CT imaging in acute ischaemic stroke patients considered clinically eligible for IV rtPA, compared to standard clinical imaging (NCCT). This will be based on the proportion of patients treated with IV rtPA in the two groups. Secondary end-points include diagnostic accuracy and clinical outcomes at 3 months.
- To compare diagnostic interpretation of CTP processed by individual scanners at local centres with diagnostic interpretation of CTP processed by a uniform analysis independent of a specific manufacturer.
- Evaluate the sample size requirements, feasibility, and optimal design of a larger study to test the effect of different diagnostic imaging strategies on functional outcome after stroke.

2.1 PRIMARY ENDPOINT

- The primary endpoint is the proportion of patients receiving IV rtPA

2.2 SECONDARY ENDPOINTS

- Time to treatment a) decision and b) administration
- 3 month modified Rankin Scale (mRS), by intention to treat, using a Cochran- Mantel-Haenszel (CMH) distribution analysis
- Safety – SICH and major infarct swelling rates
- Diagnostic sensitivity and specificity
- 3 month mRS distribution in patients i) selected for IV rtPA and ii) excluded from IV rtPA
- Comparisons of efficacy & safety outcomes in Target Population (imaged as per randomised allocation and per protocol)
- Inter-observer Agreement for rtPA eligibility between local and centrally processed CTP/CTA

3 STUDY DESIGN

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006). Central Image reading and interpretation will be conducted by an experienced team blinded to the patient's details. Multiple image readers at different centres are also blinded when testing the inter-observer variability.

The study will be a prospective, multicentre, randomised, controlled trial (RCT) comparing the current evidence-based imaging (control, NCCT) with additional multimodal CT imaging (CT + CTA + CTP).

Technical details of CT scanners, CTP and CTA acquisition and post-processing will be obtained for each centre. Modification to ensure adherence to minimum standards identified in the Stroke Research Imaging roadmap[42] will be undertaken if necessary. The purpose of the trial is not to standardise radiological procedures at individual sites, but to evaluate multimodal CT as employed in clinical practice, with the assumption that technical parameters will be dictated by scanner manufacturers' software and hardware capabilities (which may also vary over time). A key question is whether the utility of CTP is influenced by post-processing, which will involve comparison of interpretation of locally and centrally-processed scans.

The trial will recruit patients with acute stroke within 4.5 hours of symptom onset, in whom treatment decisions regarding use of IV thrombolysis are required. Patients who are eligible for rtPA without contraindications to CT/CTA/CTP, will be randomised to NCCT alone or CT+CTP+CTA. Randomisation and imaging strategy allocation will be undertaken using an interactive voice response (IVRS) telephone system run by the Robertson Centre for Biostatistics, University of Glasgow, either prior to scanning or at latest immediately after NCCT provided that any additional trial imaging can be acquired at the same examination and without delay. The randomisation system will allocate patients using a mixed minimisation and randomisation system, in which 80% of patients are allocated by minimisation on study centre, stroke severity and hemispheric lateralisation, and 20% are allocated at random.

Initial NCCT may identify specific contraindications to IV thrombolysis: these are categorised as

- Intracranial haemorrhage
- Non-stroke pathology consistent with neurological deficit (e.g. brain tumour)
- Established ischaemic damage not consistent with onset <4.5h earlier

Patients within these categories will be excluded and no further study imaging or procedures undertaken.

In patients with clinical and imaging diagnosis of ischaemic stroke and no contraindication to rt-PA, the decision on IV rtPA based on allocated imaging will be documented on a structured case record form. In those randomised to multimodal CT, the treatment decision following further imaging will be recorded after local processing and interpretation. The structured form will ask clinicians to assess the independent contributions of CTA and CTP. It is at the discretion of the treating clinician to determine how to use the additional imaging: it is not mandatory for the clinician to review all additional imaging studies before making a treatment decision – the study asks the clinician to state the perceived contributions of CTP and CTA separately. If a clear treatment decision has been reached after reviewing only one of the additional modalities, then that is acceptable. Total imaging time in both arms (acquisition, processing, review and clinical interpretation), and time to initiation of treatment delivery in those treated with IV rtPA, will be recorded.

3 STUDY DESIGN (cont.)

Follow up structural brain imaging in all randomised patients with ischaemic stroke at approximately 24h (22-26h window) will document infarct size, presence of brain swelling, and the presence of intra-cerebral haemorrhage (defined using ECASS 2 categorisation). MRI is permissible as an alternative to NCCT.

Clinical evaluations will include National Institutes of Health Stroke Scale (NIHSS) score at baseline, 24 hrs, then day 7 (or hospital discharge if earlier). Functional outcome will be determined by the mRS using the Rankin Focused Assessment (RFA) tool at day 90 using a central telephone follow-up, supplemented by local site follow-up if required.

Data will be entered by study sites onto the InferMed MACRO eCRF system, to be designed and maintained by the King's Clinical Trials Unit. Clinically significant changes in renal function will be identified through adverse event reporting.

An Independent Data Monitoring Committee (IDMC) constituted as per EME guidance will review patient safety. This committee will have the right to recommend early stopping of the study because of safety concerns. Trial progress will be reviewed by a Trial Steering Committee (TSC). Premature discontinuation of the trial will be considered in the event of evolving safety issues being identified; or feasibility issues due to under recruitment. The latter is possible if recruitment rate declines during the course of the study due to drift of clinical practice in favour of additional imaging, and if no alternative trial centres can be identified to make up recruitment; or if centres fail to adhere to allocated imaging strategy and there is an excessive crossover rate that cannot be made up from additional centres becoming involved.

Central data analysis will be undertaken to investigate i) inter-observer agreement on interpretation of CTA and CTP, and ii) whether CTP processing using manufacturer-independent software significantly influences interpretation of CTP. Locally-processed CTP and CTA will be uploaded to the Systematic Image Review System 2 (SIRS2, www.neuroimage.co.uk/sirs) hosted by the University of Edinburgh. This has been developed and successfully employed in >6000 scans for the multicentre IST-3 trial, studies of intra-cranial vascular malformations (SIVM) and large observer reliability studies such as ACCESS[43.44] for EME-funded study CT and MR angiography in IST-3 including of their observer reliability [ref EME report: Wardlaw et al ACCESS[43,44], volume 1, number 1] and enables web-based review of uploaded scans by multiple independent readers blind to clinical treatment details.

Central CTP processing will use commercial stand-alone analysis software to generate perfusion maps of all major parameters (cerebral blood flow, cerebral blood volume, mean transit time and time to peak) and in addition will produce thresholded maps of penumbra and infarct core. Centrally processed CTP maps will be uploaded to SIRS for review by readers, including the clinicians at the randomising centre, in order to determine inter-observer agreement and compare interpretation of images with manufacturer-specific output with respect to thrombolysis decisions. SIRS (www.neuroimage.co.uk/sirs) has undergone development as part of the MRC Methodology Hub, Edinburgh, to include colour images and linear and volume measurement tools.

3.1 STUDY POPULATION

This study will recruit a total of 400 patients (200 in each arm) with acute ischemic stroke presenting in hyperacute stroke centres in the UK, within 4.5 hours of symptoms onset and eligible for thrombolysis based on current guidelines.

Male and female patients aged ≥18 years who present with symptoms of stroke will be evaluated according to the stroke unit's standard of care for stroke and the clinical judgement of the attending medical staff. Routine procedures conducted in accordance with standard medical care for stroke will be accepted measures to assess entry criteria. Eligible patients will be randomised (1:1) to undergo either a NCCT or multimodal imaging before a decision on thrombolysis is made.

3.2 INCLUSION CRITERIA

- Clinical diagnosis of stroke
- Written informed consent from patient, legal representative or consultee
- Male or non-pregnant female ≥18 years of age
- Within 4.5 hours of onset as defined by time since last known well

3.3 EXCLUSION CRITERIA

- Contraindications to thrombolytic drug treatment for stroke
    - Evidence of intracranial haemorrhage or significant non-stroke intracranial pathology (including CNS neoplasm, aneurysm or AVM) on pre-treatment CT
    - Established hypodensity on pre-treatment brain CT of more than one third of the MCA territory or ASPECT score <4 (sulcal effacement or loss of greywhite differentiation in cortical territories alone are not counted towards ASPECT score)
    - o Hypodensity consistent with recent cerebral ischaemia likely to predate the presenting event
    - o Very severe stroke (eg NIHSS>25)
    - systolic blood pressure> 185 or diastolic BP> 110 mm Hg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
    - If on warfarin, INR <1.7
    - Current prescription of non-warfarin oral anticoagulant drugs
    - Significant abnormality of coagulation parameters pre-treatment (prolonged INR or APTT, or platelet count <100,000/mm^3)
    - administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory, or use of therapeutic dose low molecular weight heparin within 48h
    - Clinical history suggestive of subarachnoid haemorrhage even if no blood is evident on CT
    - Risk of bleeding (Major surgery within previous 1 month; intracranial or spinal surgery; recent trauma to the head or cranium; prolonged cardiopulmonary resuscitation (> 2minutes) within the past 2 weeks; acute pericarditis and/or subacute bacterial endocarditis; acute pancreatitis; severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis; active peptic ulceration; any known history of haemorrhagic stroke or stroke of unknown origin; arterial aneurysm and known arteriovenous malformation)
    - Dependent (mRS 3-5) pre-stroke
    - Blood glucose <2 mmol/l or >18 mmol/l
    - Seizure at onset of symptoms unless brain imaging identifies positive evidence of significant brain ischaemia (eg CTA confirmed arterial occlusion, early ischaemic change on plain CT, hypoperfusion on CTP)
    - Pregnancy
- Known impaired renal function precluding CT contrast administration
- Known allergy to radiological contrast
- Severe concurrent medical condition that would prevent participation in study procedures or with life expectancy ≤ 3 months.

3.4 IDENTIFICATION OF PARTICIPANTS AND CONSENT

Potential participants will be identified on referral to the acute stroke service and will be screened by the clinical inclusion and exclusion criteria listed above. These are identical to criteria for routine use of IV alteplase, with the exception of renal function assessment which is relevant only to contrast administration, but is part of the routine pre-treatment biochemistry work-up.

If patients fulfil clinical criteria, a clinician familiar with the study will seek consent for participation in the trial from the patient themselves (if deemed to have capacity). Many patients will lack capacity due to the acute stroke, and arrangements for recruitment of adults with incapacity will follow legal requirements appropriate to the country, seeking consent from: in Scotland, their legal representative; in England & Wales, a consultee (including an independent clinician in the event that no representative is available). Consent will be sought prior to randomisation procedure using IVRS to allocate either a NCCT or multimodal imaging.

Data collected for routine clinical care will be used for clinical trial documentation (e.g. blood results, NIHSS score, imaging findings, ECG). Consent will specifically include the use of clinically routine data for study purposes.

Informed consent by the patient or consent/assent from the next of kin or opinion of personal/nominated consultee will be obtained by local investigators or delegated research staff, after the patient has been evaluated for study participation. Following written consent or assent, each signature will be dated by the signatory, the original retained in the site file, a copy provided to the patient/relative and a copy inserted into the patient medical notes.

3.5 WITHDRAWAL OF SUBJECTS

Participants or their legal representative or consultee may withdraw a patient at any stage of follow-up, but data acquired up to the point of withdrawal will be retained in the analysis. Crossovers (where allocated imaging was not adhered to) will be recorded as a tertiary end-point relevant to study feasibility, but main analyses will be on an intention to treat (ITT) basis.

4 TRIAL PROCEDURES

4.1 STUDY SCHEDULE

4.1.1 VISIT 1: PRE-RANDOMISATION

Procedures that are part of routine patient care for assessment of eligibility for treatment of thrombolysis will be documented for study purposes, these include:

- Medical history
- Biochemistry results (eGFR and blood glucose)
- Blood pressure
- Physical examination including NIHSS score

4.1.2 VISIT 2: RANDOMISATION AND INVESTIGATIONS

- Randomisation is done using IVRS
- Randomisation will allocate either a NCCT or Multimodal Imaging (CT+CTP+CTA)
- Once imaging is done, the clinician will interpret the images
- The treatment decision for IV thrombolysis will be documented,and reasons will be detailed in a structured form completed by the treating clinician, including the contribution of different imaging modalities in the group undergoing multimodal CT

4.1.3 VISIT 3: TREATMENT WITH ALTEPLASE

In patients deemed appropriate for treatment with IV thrombolysis, standard IV alteplase will be reconstituted and administered as quickly as practical once a treatment decision is made. All other participants will receive best medical care excluding thrombolytic drug administration.

4.1.4 VISIT 4: 24 H (22 – 36 H) POST-TREATMENT

- CT brain (or MRI Brain)
- NIHSS
- Adverse event assessment

4.1.5 VISIT 5: 7 DAYS (±2) POST-TREATMENT (OR HOSPITAL DISCHARGE IF EARLIER)

- NIHSS
- Adverse event assessment
- Blood pressure

4.1.6 VISIT 6: DAY 90 (±7)

- mRS using telephone assessment by the RFA tool
- Adverse event assessment

MODIFIED RANKIN SCALE

The mRS is a hierarchical ordinal scale used to assess disability in stroke trials, with seven discrete levels that range from No Symptoms (mRS=0) to death (mRS=6). Inter-observer agreement is significantly enhanced by use of a standardised structured approach. All investigators undertaking outcome assessment will undergo both standard mRS certification (via American Stroke Association online training) and training in the RFA method.

IMAGING

Routine brain imaging in acute stroke consists of brain CT, an X-ray based examination involving ionizing radiation. This identifies stroke caused by intra-cerebral haemorrhage with very high sensitivity and specificity, and may additionally show areas of established ischaemic damag The examination is undertaken in a radiology department and can be acquired rapidly (typically in <2 minutes including localiser views). If the patient is randomised to undergo multimodal Imaging in addition to plain CT; further imaging in the same scanner with CTP and CTA will be done with minimal (ideally no) delay.

Both CTP and CTA scans require intravenous administration of an iodinated contrast agent via an IV cannula sited in a large forearm vein, delivered at a controlled rate (usually 6 ml/second) by a power injector. Two doses of contrast, each of approximately 50 ml, are required for acquisition of CTP and CTA. Some scanners can acquire CTA and CTP simultaneously from a single IV contrast administration. Staff of participating departments will have familiarity with acquisition of both CTA and CTP, equipment for contrast administration, and processes for contrast use.

CTP acquires a time series of brain images during the first pass of contrast through the arterial system by scanning repeatedly through the same anatomical levels. The enhancement of brain tissue is plotted to derive a time-density curve for each voxel and this is mathematically processed to derive parameters that reflect brain perfusion, plotted on colour coded maps. Applying threshold values to these maps allows definition of ischaemic core (tissue that will inevitably infarct) and penumbra (tissue at risk that may be salvageable if re-perfused promptly), although there is currently limited agreement on these thresholds.

CTA acquires thin axial sections during the first arterial passage of contrast to permit reconstruction that defines intra- and extracranial arterial anatomy. CTA typically covers aortic arch to vertex, and in many stroke services is part of routine care for vascular imaging, although not necessarily undertaken at the acute stage.

The order in which these examinations are acquired may differ from one individual to another.

IMAGE PROCESSING AND ANALYSIS

CT workstations at local sites will be used to undertake interpretation of NCCT, CTA and post processing with whatever software is typically used (first post processing) and this information will be available to inform a decision on thrombolysis in patients randomised to multimodal CT. Locally processed CTP and CTA will be uploaded to the Systematic Image Review System (SIRS, www.neuroimage.co.uk/sirs) hosted by the University of Edinburgh. Trial imaging studies will be transferred from clinical scanners or radiology archives after removal of individual identifiers from the DICOM file (patient name, date of birth, Community Health Index or similar unique identifier) which will be replaced with the study number.

Second Post processing of CTP maps will be undertaken on a central PC workstation using an independent dedicated analysis package, MiStar. The CTP scans will be processed to generate maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). The volume of ischaemic penumbra will be defined according to the optimal thresholds which will be confirmed based on previous studies. Delay correction algorithms or delay-independent analyses will be applied to remove any effect of extra-cranial occlusion on contrast bolus arrival. Processed CTP along with CT, CTA will be uploaded to SIRS2 for review by readers, including the clinicians at the randomising centre, in order to determine inter-observer agreement and compare interpretation of images with manufacturer-specific output with respect to thrombolysis decisions.

4.2 STUDY OUTCOME MEASURES

All outcomes will be compared in the control (NCCT) group and the multimodal CT (CT+CTA+CTP) group:

4.2.1 PRIMARY OUTCOME MEASURE

The primary outcome is the proportion of patients receiving IV rtPA. We hypothesise that the additional diagnostic information will increase the proportion of patients treated, principally by increasing treatment rates among those with clinically mild or improving symptoms. A smaller number of subjects may be excluded from treatment due to identification of features signifying high risk of treatment. Treatment rates will be known immediately to the clinician at each centre since rtPA must be initiated as soon as possible after initial imaging, and will be documented in medical notes. Data will be prospectively recorded by SRN-supported research staff at each participating site and uploaded to an electronic case record form (eCRF).

4.2.2 SECONDARY OUTCOME MEASURE

Secondary outcomes will include time to decision and initiation of treatment, diagnostic accuracy, neurological and functional status. It is anticipated that a future, larger scale trial will be based on change in functional outcome. Early change in neurological status will be determined by the NIHSS, a standard scale of neurological impairment[45] administered by trained local staff. Functional status atday 90 will be determined by the modified Rankin Scale (mRS), a hierarchical ordinal, scale with seven categories ranging from no symptoms (mRS 0) to death (mRS 6),[46,4746] that is standard in stroke trials. A structured interview (the Rankin Focused Assessment, RFA) and online training will be employed to minimise inter-observer variability[48,49]. Analysis of the primary outcome will involve comparison of the proportion treated in the two groups. Analysis of secondary outcomes will employ both a test for shift in the distribution of patients across all mRS disability categories using the CMH approach, as well as the odds of achieving independence (dichotomised as mRS 0-1 or 0-2) adjusting for baseline variables of prognostic significance. Central reading of trial scans to determine extent of ischaemic lesion on NCCT, any perfusion lesion, and angiographic occlusion etc, using validated visual rating as developed for IST-3 and MASIS ([50]http://www.bric.ed.ac.uk/research/imageanalysis.html) under CT perfusion and angiography studies reading form); comparison of local processed images with central processing and reading.

Secondary Outcomes:

- Time to treatment a) decision and b) administration
- 3 month mRS, by intention to treat, using a CMH distribution analysis
- Safety – symptomatic ICH and major infarct swelling rates
- Diagnostic sensitivity and specificity
- 3 month mRS distribution in patients i) selected for IV rtPA and ii) excluded from IV rtPA
- Comparisons of efficacy & safety outcomes in Target Population (imaged as per randomised allocation and per protocol)
- Inter-observer Agreement for rtPA eligibility between local and centrally processed CTP/CTA

Inter-observer agreement in interpretation of locally-processed CTP scans

4.3 LABORATORY TESTS

No laboratory tests are required as part of the trial. Baseline routine laboratory tests will be recorded since relevant to safety assessments (calculated eGFR and/or creatinine) or as a covariate predictor of outcome (blood glucose).

Change in renal function after the acute stage will be reported as an adverse event. No additional blood tests beyond those required for clinical care are required.

5 ASSESSMENT OF SAFETY

This study is a non-CTIMP

5.1 DEFINITIONS OF ADVERSE EVENTS

Adverse Event (AE) - any unfavourable and unintended sign, symptom or disease temporally associated with participation in the research project.

5.2 DEFINITIONS OF SERIOUS ADVERSE EVENTS

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

a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is otherwise considered medically significant by the investigator

5.3 RECORDING AND REPORTING OF ADVERSE EVENTS

AEs will be identified by observation and /or enquiry at study visits. AEs that do not meet criteria for seriousness will be recorded in the medical notes only.

The trial is not assessing the safety or efficacy of a treatment, but of an imaging strategy. However, modification of the imaging strategy may alter the safety profile of the treatment and therefore relevant details will be recorded and reviewed. The nature of SAEs related to stroke, thrombolytic drug treatment, and radiological investigation, are all well documented, and relevant safety parameters are those that occur within the early time frame after treatment. Details of all SAEs that occur up to visit 4 (day 7 or discharge) will therefore be recorded in the eCRF. Thereafter, only fatal or unexpected SAEs up to the final visit (day 90) will be recorded.

Expected SAEs are listed below.

The relationship with the study procedures will be assessed for any *unexpected* SAEs: if possibly or definitely related, SAEs deemed unexpected in the opinion of the reporting site will be communicated to the Chief Investigator (CI) for review and final determination of expectedness, and will be reported to the REC as detailed below. Unrelated and unexpected SAEs will be followed until resolution.

5.4 EXPECTED ADVERSE EVENTS

The following AEs are considered to be expected:

AEs related to acute stroke:

- Brain swelling / brain oedema (including brain herniation, raised intracranial pressure, mass effect, "malignant oedema")
- Haemorrhagic transformation of the infarct (symptomatic and asymptomatic)
- Neurological deterioration
- Infections, including pneumonia, urinary tract infection
- Complications of immobility (deep vein thrombosis, pulmonary embolism, falls, fractures, spasticity, joint immobility or pain)

AEs related to thrombolytic drug administration:

These are detailed in relevant Summary of Product Characteristics (SmPC).

- Intracranial haemorrhage (symptomatic and asymptomatic)
- Angio-oedema
- Anaphylactoid reaction
- Hypotension
- Systemic bleeding

AEs related to co-morbid medical conditions:

- Myocardial infarction, angina, coronary interventions
- Carotid revascularization procedures (endarterectomy or stenting)
- Systemic embolism
- Peripheral arterial disease (including claudication, peripheral artery occlusion, revascularization procedures)

AEs related to radiological contrast agents

Allergic reactions including anaphylaxis

- Impaired renal function
- Tissue injury related to extravasation
- Lacticacidosis in patients concomitantly treated with metformin

The clinical judgement of the Chief Investigator will ultimately determine expectedness.

5.5 REPORTING TO SPONSOR (PHARMACOVIGILANCE (PV) OFFICE)

All reportable SAEs arising during the study will be reported by the Principal Investigator (PI) (or designee) to sponsor (PV Office) by entering the details into the eCRF as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any follow up information should also be reported.

If reporting via the eCRF is not possible a paper SAE form (non-CTIMP) can be downloaded from the Glasgow Clinical Trials Unit website: www.glasgowctu.org. This should be completed and faxed to the PV Office. (Fax No: +44 (0) 141 357 5588)

If necessary a verbal report can be given by contacting the PV Office on +44 (0)141 330 4744. This must be followed up as soon as possible with an electronic or written report.

If a report of a "related" and "unexpected" SAE is received at the PV Office an email alert will be sent to the CI for confirmation.

5.6 REPORTING TO THE RESEARCH ETHICS COMMITTEE (REC)

Any SAE occurring to a research participant will be reported to the main REC (i.e. the REC that gave a favourable opinion of the study) where in the opinion of the Chief Investigator (CI), the event was:
• "Related" – that is, it resulted from administration of any of the research procedures, **and**
• "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted to the REC **within 15 days** of CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the National Research Ethics Service (NRES) website.

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

The form should be completed in typescript and signed by the CI (or designee). The PV Office will assist in the preparation and submission of the report.

The co-ordinator of the main REC will acknowledge receipt of safety reports within 30 days.

5.7 ANNUAL PROGRESS REPORT

The CI is also responsible for providing an annual progress report to the REC using an NRES "Annual Progress Report form for all other research". This form is available at:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

A section on the safety of participants is included in this report. The PV Office will assist in the collation of the safety information required for the report.

5.8 REPORTING TO LOCAL RESEARCH AND DEVELOPMENT (R&D) DEPARTMENTS

The Principal Investigator at each site is responsible for the provision of reports to their local R&D department per the conditions of Management approval.

6 STATISTICS AND DATA ANALYSIS

6.1 STATISTICAL ANALYSIS PLAN

A full statistical analysis plan will be developed and signed off before database lock. Classification of images using different approaches will be compared using methods for the analysis of paired categorical variables. To provide a provisional assessment of the impact of the different strategies on outcome the analyses of the mRS will use a CMH test to seek evidence differences between the two randomised groups in distributions across the entire scale of the mRS.

6.2 PRIMARY EFFICACY ANALYSIS

The proportions of patients treated with IV rtPA in the two groups will be compared using logistic regression analysis adjusting for randomised treatment group and randomisation minimisation variables. Odds ratios for the treatment effect will be estimated along with 95% confidence intervals and p-values. Exploratory analyses will also adjust for baseline factors predictive of treatment with rtPA.

6.3 SECONDARY EFFICACY ANALYSIS

Time to treatment decision will be analysed using a stratified Wilcoxon rank sum test and time to treatment administration using stratified logrank test to account for censored outcomes. Diagnostic sensitivity and specificity will be analysed. To provide a provisional assessment of the impact of the different strategies on outcome the analyses of the mRS will use the van Elteren test to seek evidence of differences between the two randomised groups in distributions across the entire scale of the mRS. Inter observer agreement will be assessed using Kappa statistics.

6.4 SAFETY ANALYSIS

Safety outcomes will be summarised in tabular form but will not be analysed formally. The Robertson Centre for Biostatistics will prepare unblinded reports for review by the IDMC and blinded reports for the Steering Committee. Incidence of intra-cerebral haemorrhage will utilise different classifications of symptomatic haemorrhage (defined as per criteria in SITS-MOST, ECASS-2, ECASS-3 and NINDS trials).

6.5 SAMPLE SIZE

The trial will evaluate whether multimodal CT leads to an increase in the proportion of patients given IV rtPA. An increase in the proportion treated from 25% to 40% of ischaemic stroke patients evaluated within the 4.5h time window can be detected with 80% power at p=0.05 with 152 subjects per group. Literature identifies 27% of ischaemic stroke patients within 3h of onset being given IV rtPA while 31% were excluded primarily because of a mild or improving clinical deficit.[2] Allowing for randomisation before initial NCCT, and a diagnosis of non-ischaemic stroke pathology in 15% of patients, and allowing also for data acquisition and analysis problems yielding uninterpretable imaging of 10% in the multimodal imaging group, a total of 200 subjects per group would be initially recruited.

7 STUDY CLOSURE / DEFINITION OF END OF TRIAL

The study will end when the steering committee agrees that one or more of the following situations applies:

- Last patient last study visit;

OR

i. The planned sample size has been achieved;
ii. The IDMC has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatment arms;
iii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
iv. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial;
v. Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

8 DATA HANDLING

8.1 RANDOMISATION

A central randomisation facility (IVRS) will allocate the randomised therapy per patient, using a mixed minimisation and randomisation method. Using the method of randomised permuted blocks, for every 10 patients, 8 will be allocated using a minimisation algorithm, to ensure balance with respect to study centre, stroke severity (NIHSS 0-6, 7-16, 17-25) and hemispheric lateralisation (right, left, bilateral), whilst 2 will be allocated at random, one to each therapy. In cases where the minimisation algorithm favours neither therapy, the allocation will be made at random; for the 8 patients allocated by minimisation within each block of 10, there will be 4 potential random allocations to each therapy. stratifying by treatment centre and key prognostic variables. The IVRS, based at the Robertson Centre for Biostatistics, will be available by telephone.

8.2 CASE REPORT FORMS / ELECTRONIC DATA RECORD

An eCRF will be used to collect study data. The eCRF will be developed by the Robertson Centre for Biostatistics and access to the eCRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the eCRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change)

8.3 CENTRAL FOLLOW-UP

Local investigators will provide contact details for each patient by entering contact details via a section of the eCRF that will be encrypted and will be accessible only to members of the research team in Glasgow responsible for Day 90 review. This will include GP, patient and patient representative contact details (telephone number and address).

Follow-up at Day 90 will be undertaken by telephone interview from the study centre in Glasgow. A member of the research team trained in the used of the mRS (and specifically the Rankin Focussed Assessment RFA instrument to derive the mRS) will first contact the patient's GP to determine the patient's status. If a patient has died, then details of cause of death will be requested from the GP and followed up with the local investigators. If a patient is alive, the contact number provided will be used to contact the patient or their representative to ascertain outcome. If telephone contact is not successful, then a letter will be send requesting updated contact information and a further telephone review requested. If all contact from the central research team is unsuccessful, then local investigators will be asked to undertake follow-up.

In the event that no follow-up information is available, access to linked health records to determine vital status will be undertaken.

8.4 RECORD RENTENTION

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP , local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

9 TRIAL MANAGEMENT

9.1 ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP

The trial will be coordinated from the University of Glasgow by a Trial Management Group. The Trial Management Group will include individuals responsible for the day-to-day management of the trial, (CI, statistician, trial manager, research fellow). The group will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

9.2 TRIAL STEERING COMMITTEE (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will conform to the EME guidelines and should:

- agree the trial protocol and any protocol amendments
- provide advice to the investigators on all aspects of the trial
- include at least members who are independent of the investigators, in particular an independent chairperson
- include a patient or carer representative

Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

9.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The role of iDMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will be independent of both the investigators and the funder/sponsor. It will make recommendations to the TSC. The composition of the IDMC will conform to Efficacy and Mechanism Evaluation (EME) guidelines.

10 STUDY MONITORING

This study will be monitored by NHS Greater Glasgow & Clyde Research Governance. A risk assessment and monitoring plan will be devised and approved by the Governance Manager. The monitoring will specifically target subject eligibility and data quality; the latter focussing mainly on adverse event reporting. Each site will receive one monitoring visit after the first subjects have been enrolled into the study. The first few recruiting sites will be monitored at an early stage, typically within 3 months of the first randomisation. Other sites will be recruited at a stage largely influenced by the outcomes of the earlier visits. Ideally however, some sites will be visited at a later stage of the study, to ensure consistency of trial conduct and compliance with amendments where applicable.

11 PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and Sponsor and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI and the TSC will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and office(s).

12 ETHICAL CONSIDERATIONS

12.1 ETHICAL CONDUCT OF STUDY

The study will be carried on accordance with the World Medical Association Declaration of Helsinki (1964) and it revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. Relevant procedures for recruitment of incapacitated adults in an emergency situation will be followed according to specific country requirements.

The CI will be responsible for updating the Ethics committee of any new information related to the study.

12.2 INFORMED CONSENT

Written informed consent should be obtained from each trial participant, alternatively, if the patient is unable to consent for themselves, then written informed consent should be provided by the appropriate person designated according to legislation relating to adults with incapacity. The Research Nurse or investigator will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. This will include the known side-effects that may be experienced, and the risks of participating in this clinical trial. Trial participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

In the case of patients who were unable to consent at the start of the study, written informed consent will be sought once they regain capacity.

13 INSURANCE AND INDEMNITY

The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

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

As this is a clinician-led study there are no arrangements for no-fault compensation.

14 FUNDING

The study is funded by the EME programme of the National Institute for Health Research (NIHR). Funding is awarded starting from June 2013.

15 ANNUAL REPORTS

A biannual progress report will be submitted to the funder, the first being submitted 6 months from the date that all trial related approvals are in place. Annual reports will be submitted to the ethics committee and sponsor with the first submitted one year after the date that all trial related approvals are in place.

16 DISSEMINATION OF FINDINGS

The final report of the project will be published on EME website. Findings will be disseminated through presentation of results in major stroke conferences such as the European stroke conference and the publication of final results in peer reviewed journals.

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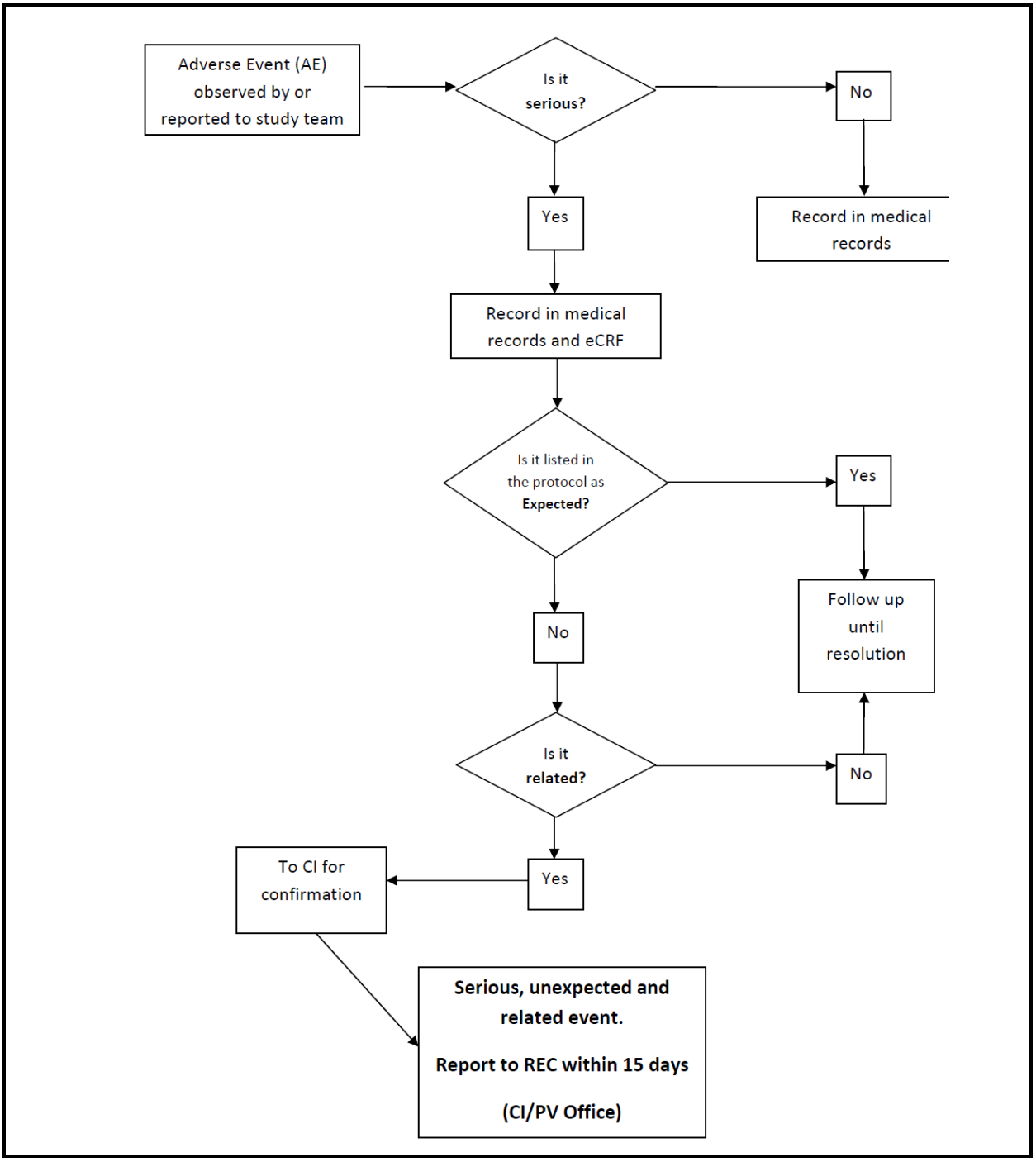
APPENDIX A.

FLOWCHART FOR ASSESSING AND REPORTING ADVERSE EVENTS



APPENDIX B.

DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for

research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX C.

NIH STROKE SCALE

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy**; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation**, or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Rev 10/1/2003

NIH STROKE SCALE (cont.)

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

Rev 10/1/2003

NIH STROKE SCALE (cont.)

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	____

Rev 10/1/2003

NIH STROKE SCALE (cont.)

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

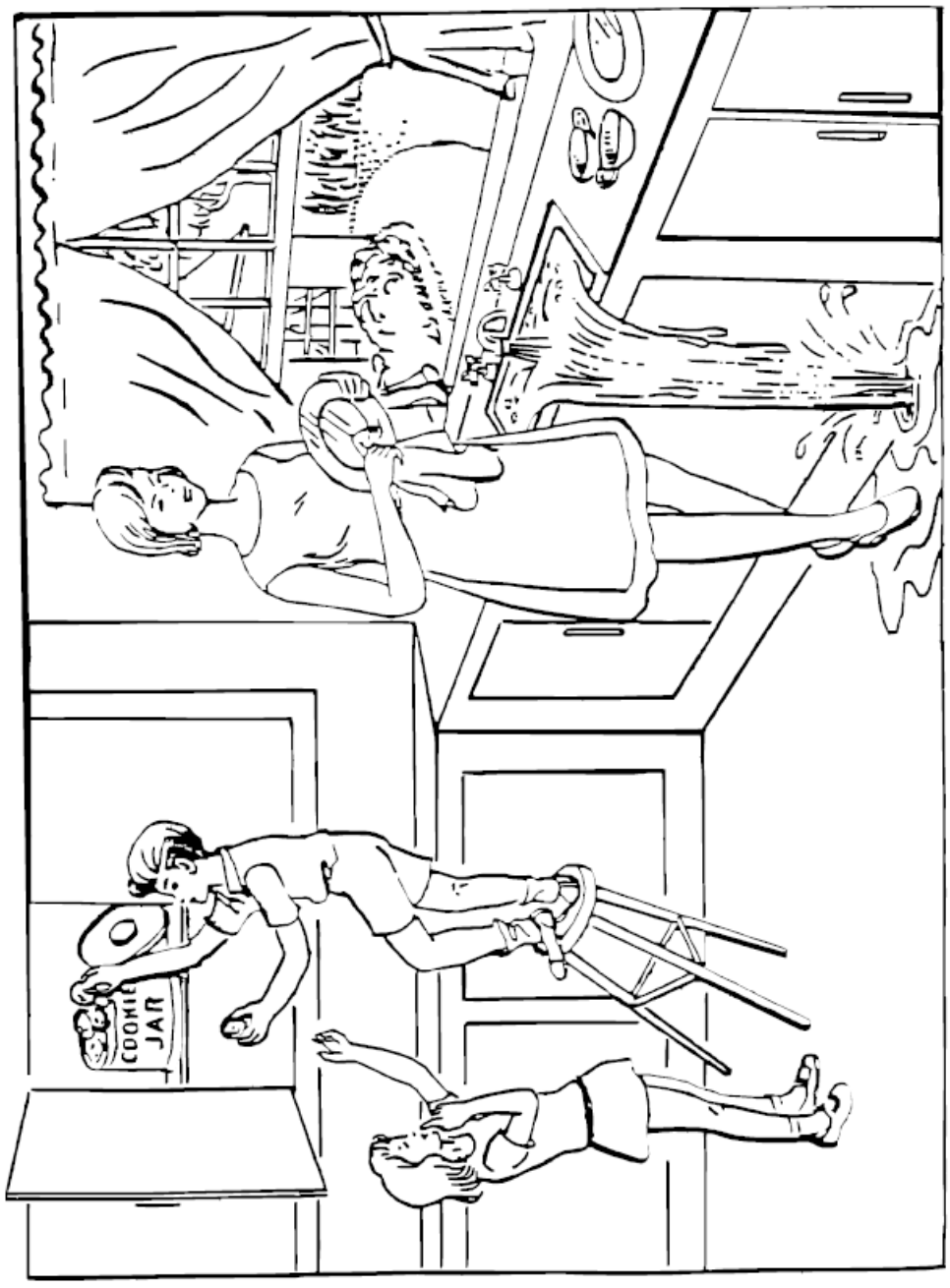
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

_____

_____

Rev 10/1/2003

NIH STROKE SCALE (cont.)



NIH STROKE SCALE (cont.)

You know how.

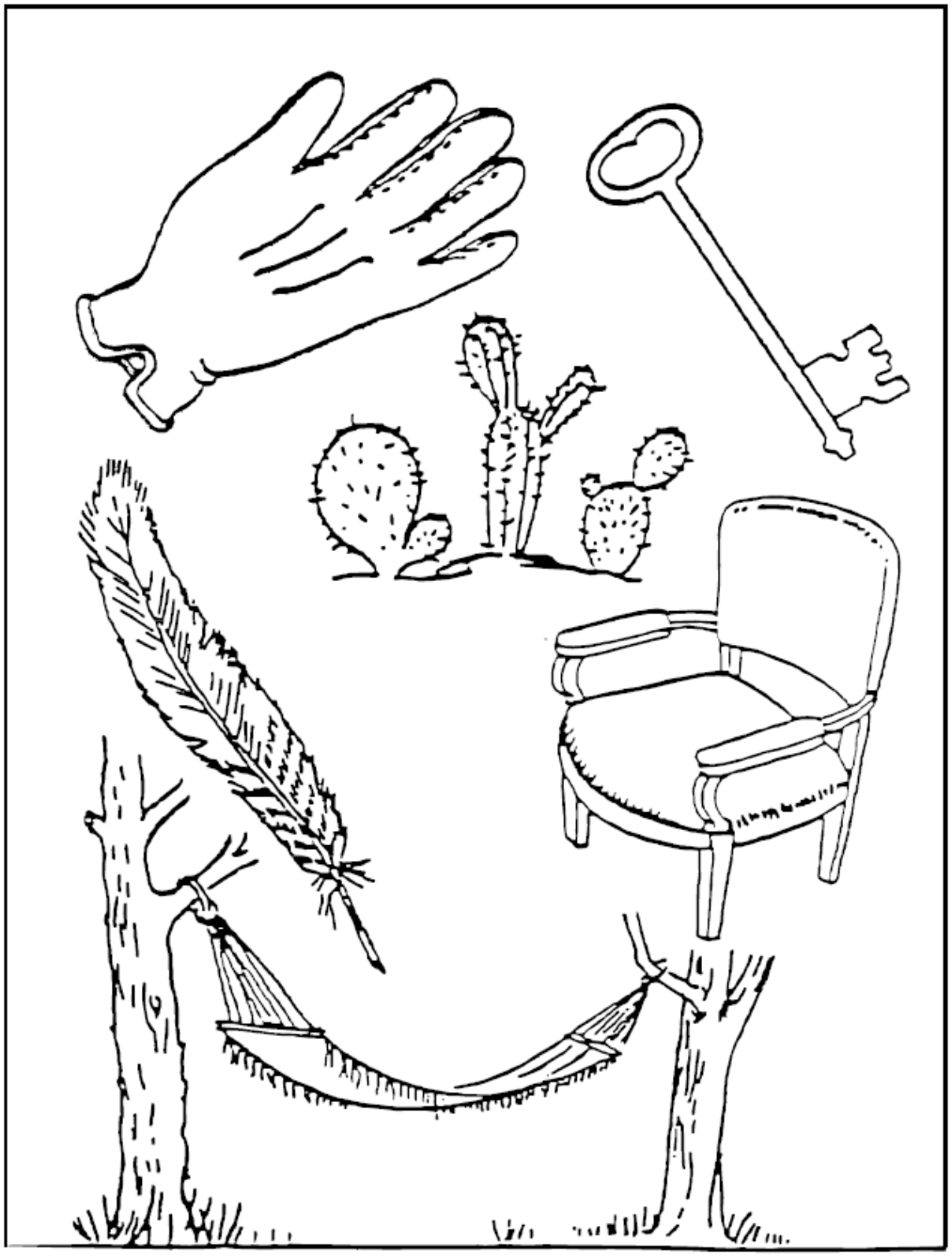
Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

NIH STROKE SCALE (cont.)



NIH STROKE SCALE (cont.)

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

APPENDIX D.

MODIFIED RANKIN SCALE (MRS)

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

References

Rankin J. "Cerebral vascular accidents in patients over the age of 60."
Scott Med J 1957;2:200-15

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke."
Stroke **1988 Dec;19(12):1497-1500**

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients."
Stroke **1988;19(5):604-7**

Provided by the Internet Stroke Center — www.strokecenter.org

APPENDIX E.

RATING FORM PRESTROKE RANKIN FOCUSED ASSESSMENT (RFA)

PROVIDED BY UCLA STROKE CENTRE (see following pages)

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

Rating Form
Prestroke Rankin Focused Assessment (RFA)

Name of rater performing assessment: _____

Information for completing this form was obtained from (check all that apply):

[ ] Patient
[ ] Spouse
[ ] Son
[ ] Daughter
[ ] Father
[ ] Mother
[ ] Physical therapist
[ ] Speech therapist
[ ] Medical record
[ ] Other individual, specify role: _____
[ ] Sister
[ ] Brother
[ ] Other relative, specify relationship:_____
[ ] Friend
[ ] Nurse
[ ] Home health aide
[ ] Occupational therapist
[ ] Physician

Please mark (X) in the appropriate box. Please record responses to all questions (unless otherwise indicated in the text). Please answer questions based on the patient's status BEFORE the current stroke. Answers should reflect how all the medical/physical conditions the patient had before the current stroke affected their daily functioning before the current stroke. Please see instruction sheets for further information.

5	**BEDRIDDEN**	
5.1	**Is the person bedridden?** The patient is unable to walk even with another person's assistance. (if placed in a wheelchair, unable to self-propel effectively). May frequently be incontinent. Will usually require nearly constant care – someone needs to be available at nearly all times. Care may be provided by either a trained or untrained caregiver.	□ Yes □ No (5)

If yes, explain:

_____
_____

4	**ASSISTANCE TO WALK**	
4.1	**Is another person's assistance essential for walking?** Requiring another person's assistance means needed another person to be always present when walking indoors around house or ward, to provide physical help, verbal instruction, or supervision. (Patients who use physical aids to walk, e.g. stick/cane, walking frame/walker, but do not require another person's help, are NOT rated as requiring assistance to walk). (For patients who use wheelchairs, patient needs another person's assistance to transfer into and out of chair, but can self-propel effectively without assistance.)	□ Yes □ No (4)

If yes, explain:

_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

3	**ASSISTANCE TO LOOK AFTER OWN AFFAIRS**	
	Assistance includes physical assistance, or verbal instruction, or supervision by another person. Central issue--Could the patient live alone for 1 week if he/she absolutely had to?	
3.1	**Is assistance ABSOLUTELY essential for preparing a simple meal?** (For example, able to prepare breakfast or a snack)	□ Yes □ No (3)
3.2	**Is assistance ABSOLUTELY essential for basic household chores?** (For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.)	□ Yes □ No (3)
3.3	**Is assistance ABSOLUTELY essential for looking after household expenses?**	□ Yes □ No (3)
3.4	**Is assistance ABSOLUTELY essential for local travel?** (Patients may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.)	□ Yes □ No (3)
3.5	**Is assistance ABSOLUTELY essential for local shopping?** (Local shopping: at least able to buy a single item)	□ Yes □ No (3)

If yes to any of the above, explain:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

2. USUAL DUTIES AND ACTIVITIES. The next sets of questions are about how the patient usually spends his/her day.

2.1 Work

2.1	**Does a medical/physical condition substantially reduce the person's ability to work (or, for a student, study)?** e.g. change from full-time to part-time, change in level of responsibility, or unable to work at all. If patient is not working or is retired, is that because of a medical/physical condition?	□ Yes □ No (2)

If yes, explain:

_____
_____
_____

2.2 Family responsibilities

2.2	**Does a medical/physical condition substantially reduce the person's ability to look after family at home?**	□ Yes □ No (2)

If yes, explain:

_____
_____
_____

2.3 Social & leisure activities

(Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. Activities outside the home: going to the coffee shop, bar, restaurant, club, church, cinema, visiting friends, going for walks. Activities at home: involving "active" participation including knitting, sewing, painting, games, reading books, home improvements).

2.3	**Does a medical/physical condition substantially reduce the person's regular free-time activities by more than one half as often?**	□ Yes □ No (2)

If yes, explain:

_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

1. SYMPTOMS AS A RESULT OF A PRIOR STROKE
(Can be any symptoms or problems reported by the patient).

1.1 SPONTANEOUSLY REPORTED SYMPTOMS

1.1	**Does the patient have any symptoms resulting from a prior stroke?**	□ Yes □ No (1)

If yes, record symptoms here:

_____

_____

1.2. SYMPTOM CHECKLIST

1.2.1	**Does the person have difficulty reading or writing as a result of a prior stroke?**	□ Yes □ No (1)
1.2.2	**Does the person have difficulty speaking or finding the right word as a result of a prior stroke?**	□ Yes □ No (1)
1.2.3	**Does the person have problems with balance or coordination as a result of a prior stroke?**	□ Yes □ No (1)
1.2.4	**Does the person have visual problems as a result of a prior stroke?**	□ Yes □ No (1)
1.2.5	**Does the person have numbness (face, arms, legs, hands, feet) as a result of a prior stroke?**	□ Yes □ No (1)
1.2.6	**Does the person have weakness or loss of movement (face, arms, legs, hands, feet) as a result of a prior stroke?**	□ Yes □ No (1)
1.2.7	**Does the person have difficulty with swallowing as a result of a prior stroke?**	□ Yes □ No (1)
1.2.8	**Does the person have any other symptoms related to a prior stroke?**	□ Yes □ No (1)

Details supporting any "Yes" checked boxes in Section 1:

_____

_____

_____

Rankin Grade = ☐

APPENDIX F.

RATING FORM RANKIN FOCUSED ASSESSMENT (RFA)

PROVIDED BY UCLA STROKE CENTRE (see following pages)

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

Rating Form
Rankin Focused Assessment (RFA)

Name of rater performing assessment: _____

Information for completing this form was obtained from (check all that apply):

[ ] Patient
[ ] Spouse
[ ] Son
[ ] Daughter
[ ] Father
[ ] Mother
[ ] Physical therapist
[ ] Speech therapist
[ ] Medical record
[ ] Other individual, specify role: _____
[ ] Sister
[ ] Brother
[ ] Other relative, specify relationship: _____
[ ] Friend
[ ] Nurse
[ ] Home health aide
[ ] Occupational therapist
[ ] Physician

Please mark (X) in the appropriate box. Please record responses to all questions (unless otherwise indicated in the text). Please see instruction sheets for further information.

5	**BEDRIDDEN**	
5.1	**Is the person bedridden?** The patient is unable to walk even with another person's assistance. (If placed in a wheelchair, unable to self-propel effectively). May frequently be incontinent. Will usually require nearly constant care - someone needs to be available at nearly all times. Care may be provided by either a trained or untrained caregiver.	□ Yes □ No (5)

If yes, explain:

_____
_____
_____
_____

4	**ASSISTANCE TO WALK**	
4.1	**Is another person's assistance essential for walking?** Requiring another person's assistance means needing another person to be always present when walking, including indoors around house or ward, to provide physical help, verbal instruction, or supervision. (Patients who use physical aids to walk, e.g. stick/cane, walking frame/walker, but do not require another person's help, are NOT rated as requiring assistance to walk). (For patients who use wheelchairs, patient needs another person's assistance to transfer into and out of chair, but can self-propel effectively without assistance.)	□ Yes □ No (4)

If yes, explain:

_____
_____
_____
_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

3	**ASSISTANCE TO LOOK AFTER OWN AFFAIRS**	
	Assistance includes physical assistance, or verbal instruction, or supervision by another person. Central issue--Could the patient live alone for 1 week if he/she absolutely had to?	
3.1	**Is assistance ABSOLUTELY essential for preparing a simple meal?** (For example, able to prepare breakfast or a snack)	□ Yes □ No (3)
3.2	**Is assistance ABSOLUTELY essential for basic household chores?** (For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.)	□ Yes □ No (3)
3.3	**Is assistance ABSOLUTELY essential for looking after household expenses?**	□ Yes □ No (3)
3.4	**Is assistance ABSOLUTELY essential for local travel?** (Patients may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.)	□ Yes □ No (3)
3.5	**Is assistance ABSOLUTELY essential for local shopping?** (Local shopping: at least able to buy a single item)	□ Yes □ No (3)

If yes to any of the above, explain:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___ / ___ /____

2. USUAL DUTIES AND ACTIVITIES. The next sets of questions are about how the patient usually spends his/her day.

2.1 Work

2.1	**Has the new stroke substantially reduced (compared to prestroke status) the person's ability to work (or, for a student, study)?** e.g. change from full-time to part-time, change in level of responsibility, or unable to work at all.	□ Yes □ No (2)

If yes, explain:

_____
_____
_____

2.2 Family responsibilities

2.2	**Has the new stroke substantially reduced (compared to prestroke status) the person's ability to look after family at home?**	□ Yes □ No (2)

If yes, explain:

_____
_____
_____

2.3 Social & leisure activities

(Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. Activities outside the home: going to the coffee shop, bar, restaurant, club, church, cinema, visiting friends, going for walks. Activities at home: involving "active" participation including knitting, sewing, painting, games, reading books, home improvements).

2.3	**Has the new stroke reduced (compared to prestroke status) the person's regular free-time activities by more than one half as often?**	□ Yes □ No (2)

If yes, explain:

_____
_____
_____

2.4 Other physical/medical condition

2.4	**Are the patient's work, family, and/or social/leisure activities substantially reduced by a physical/medical condition other than the stroke that led to trial enrollment?**	□ Yes □ No (2)

Provide explanation if 1) answer is yes, but prestroke assessment section 2 answers were all no, or 2) answer is no, but any prestroke assessment 2 section answer was yes:

_____
_____
_____

Study Number: __ __ __ - __ __ __ __ Initials: __ __ __ Date of Visit: ___ / ___ /____

1. SYMPTOMS AS A RESULT OF THE STROKE
(Can be any symptoms or problems reported by the patient).

1.1 SPONTANEOUSLY REPORTED SYMPTOMS

1.1	**Does the patient have any symptoms resulting from the new stroke?**	□ Yes □ No (1)

If yes, record symptoms here:

_____
_____
_____

1.2. SYMPTOM CHECKLIST

1.2.1	**Does the person have difficulty reading or writing as a result of the new stroke?**	□ Yes □ No (1)
1.2.2	**Does the person have difficulty speaking or finding the right word as a result of the new stroke?**	□ Yes □ No (1)
1.2.3	**Does the person have problems with balance or coordination as a result of the new stroke?**	□ Yes □ No (1)
1.2.4	**Does the person have visual problems as a result of stroke?**	□ Yes □ No (1)
1.2.5	**Does the person have numbness (face, arms, legs, hands, feet) as a result of the new stroke?**	□ Yes □ No (1)
1.2.6	**Does the person have weakness or loss of movement (face, arms, legs, hands, feet) as a result of the new stroke?**	□ Yes □ No (1)
1.2.7	**Does the person have difficulty with swallowing as a result of the new stroke?**	□ Yes □ No (1)
1.2.8	**Does the person have any other symptoms related to the new stroke?**	□ Yes □ No (1)

Details supporting any "Yes" checked boxes in Section 1:

_____
_____
_____

Rankin Grade = ☐

Is this Rankin Grade score lower (better) than the prestroke Rankin Grade? □ Yes □ No
If yes, explain why:

_____
_____

Rankin Focussed Assessment (RFA) references

- Rankin J. Cerebral vascular accidents in patients over the age of 60, II: prognosis. Scott Med J 1957;2:200-215.
- Wilson JTL, Hareendran A, Grant M, *et al* Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the modified Rankin scale. Stroke 2002;33:2243-2246.
- Quinn TJ, Lees KR, Hardemark HG, Dawson J, Walters MR. Initial experience of a digital training resource for modified Rankin scale assessment in clinical trials. Stroke 2007;38:2257-2261.
- Saver JL. Novel end point analytic techniques and interpreting shifts across the entire range of outcome scales in acute stroke trials. Stroke 2007;38:3055-3062.
- Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007;38:1091-1096.
- Lai SM, Duncan PW. Stroke recovery profile and the modified Rankin assessment. Neuroepidemiology 2001;20:26-30.