Pragmatic Ischaemic Stroke Thrombectomy Evaluation: PISTE

Running title:	**PISTE**
Protocol Version:	**1.5**
Date:	**1st September 2014**
REC Reference Number:	**Scotland A REC 12/SS/0059** **NRES Committee North East- Newcastle & North Tyneside 2 12-NE-0315**
Sponsor's Protocol Number:	**GN11NE257**
Sponsor:	**NHS Greater Glasgow & Clyde**
Funder:	**The Stroke Association**

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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This clinical trial is sponsored by NHS Greater Glasgow & Clyde.

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ABBREVIATIONS

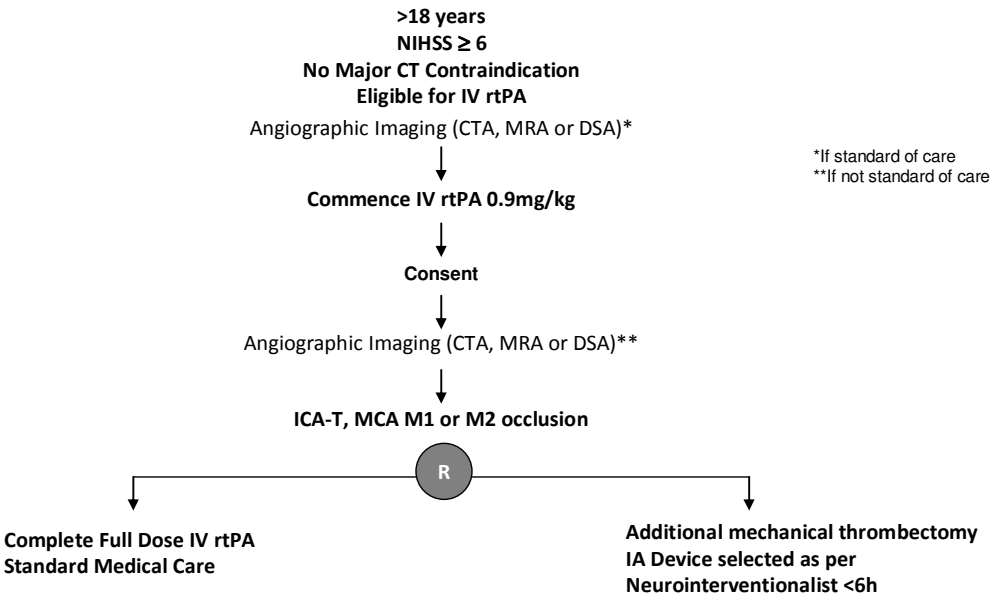
AE	Adverse event
CI	Chief Investigator
CNS	Central Nervous System
eCRF	Electronic Case Report Form
CRN	Clinical Research Network
CT	Computed Tomography
CTA	Computed Tomography Angiogram
CTP	Computed Tomography Perfusion
CV	Curriculum Vitae
DSA	Digital Subtraction Angiography
ECASS	European Cooperative Acute Stroke Study
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
GP	General Practitioner
HI	Hemorrhagic Infarct
IA	Intra-arterial
ICA	Internal Carotid Artery
ICH	Intracerebral Haemorrhage
ICH GCP	International Conference on Harmonization of Good Clinical Practice
IDMC	Independent Data Monitoring Committee
I.V.	Intravenous
IVRS	Interactive Voice Recognition System
MCA	Middle Cerebral Artery
MI	Myocardial Infarction
MRA	Magnetic resonance angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
mRS-RFA	Modified Rankin Scale - Rankin Focussed Assessment
NIHSS	National Institute of Health Stroke Scale
PH	Parenchymal Haemorrhage
PHr	Parenchymal Haemorrhage remote
r-TPA	Recombinant Tissue Plasminogen activator
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RFA	Rankin Focussed Assessment
SAE	Serious adverse event
SICH	Symptomatic intracranial haemorrhage
SRN	Stroke Research Network
SOP	Standard Operating Procedure
TSC	Trial Steering Committee

STUDY SYNOPSIS

Title of Study:	**Pragmatic Ischaemic Stroke Thrombectomy Evaluation: PISTE**
Study Centre:	Multicentre UK Trial
Duration of Study:	2 years
Primary Objective:	To determine if endovascular thrombectomy in addition to IV thrombolysis improves the proportion of patients with favourable functional 3 month outcome (defined by modified Rankin 0-2) in patients with acute ischaemic stroke due to occlusion of the middle cerebral or intracranial internal carotid artery.
Secondary Objective:	To determine the safety.
Primary Endpoint:	The proportion with favourable functional outcome at 90 (±7) days based on the modified Rankin scale. This will be assessed by use of the Rankin Focused Assessment tool (RFA).
Rationale:	Use of mechanical thrombectomy devices in acute ischaemic stroke is associated with higher rates of recanalisation in large artery occlusions (such as the middle cerebral artery main segment or intracranial internal carotid artery) compared to historical data for intravenous thrombolysis, the current standard of care for eligible patients. However, thrombectomy takes significantly longer than IV thrombolysis, and may have higher haemorrhagic complications. Registry data and studies using historical controls do not support any improvement in outcome over routine medical care for thrombectomy, but are confounded by the patient group having much more severe strokes than would be enrolled in IV thrombolysis trials. No randomised controlled trial has yet evaluated whether thrombectomy is associated with improved clinical outcome.
Methodology:	Prospective, randomised, controlled, parallel group study with blinded outcome evaluation (PROBE).
Sample Size:	800
Screening:	Patients with acute ischaemic stroke eligible for IV thrombolysis will be identified prospectively at participating centres.
Registration/Randomisation:	Randomisation via IVRS to additional mechanical thrombectomy or routine medical care.
Inclusion Criteria:	• Clinical diagnosis of supratentorial acute ischaemic stroke • Male or non-pregnant female ≥18 years of age • Clinically significant neurological deficit and NIHSS score ≥6 • Eligible for IV rtPA according to standard guidelines and able to be commenced on IV treatment <4.5h after symptom onset (<3h after symptom onset for patients >80 years of age) • Enrolment, randomisation and procedure commencement (groin puncture) possible within 90 minutes of the start of IV rtPA treatment (maximum 5.5h after stroke onset) • Occlusion of the main middle cerebral artery (MCA) trunk, MCA bifurcation or intracranial internal carotid artery (carotid-T, M1 or single proximal M2 branch) demonstrated on CTA, MRA, or DSA • Interventional device delivery (guide catheter placed beyond aortic arch and angio obtained) can be achieved within 6 hours of onset of the stroke • Consent of patient or representative • Independent prior to the stroke (estimated mRS 0-2) • Expected to be able to be followed up at 3 months
Exclusion Criteria:	• CT evidence of intracranial haemorrhage, or evidence of extensive established hypodensity on CT

	• Clinical history suggestive of subarachnoid haemorrhage even if CT normal • Known vascular access contraindications e.g. femoral bypass surgery, tight ipsilateral carotid stenosis, unsuitable proximal vascular anatomy likely to render endovascular catheterisation difficult or impossible • Extracranial ICA exclusion or basilar artery occlusion • Alternative intracranial pathology potentially responsible for the new symptoms • Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (e.g. severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy) • Known allergy to radiological contrast
Product, Dose, Modes of Administration:	Patients within 4.5 hours of stroke onset (within 3 hours for patients >80 years of age) who are eligible for IV thrombolysis and have evidence of anterior circulation large artery occlusion on angiographic imaging (affecting the intracranial internal carotid artery [carotid T], middle cerebral artery M1 or single M2 branch) < 30 minutes after commencing thrombolysis to additional mechanical thrombectomy or no additional interventional treatment. Mechanical thrombectomy may be undertaken within a maximum of 90 minutes of the start of the rtPA infusion using any approved thrombectomy device, at the discretion of the interventional neuroradiologist.
Duration of Treatment:	A single neurointerventional procedure will be undertaken, commencing a maximum of 6h after stroke onset. Involvement in the trial will entail follow-up (clinical and radiological) for up to 90 days.
Statistical Analysis:	The Robertson Centre for Biostatistics will manage and analyse trial data. All statistical analyses will be conducted according to Statistical Analysis Plan, which will be authored by the Trial Statistician and agreed by the Trial Steering Committee. This is the start-up phase of a definitive trial and will be intended to show a 10% increase in the proportion of patients with mRS 0-2 at 3 months.

STUDY FLOW CHART



Primary Outcome:	**mRS 0-2 at 3m**		
Secondary Outcomes:	**22-36h Recanalisation**	**Full recovery (mRS 0-1)**	**Immediate recanalisation**
	Early major neurological improvement (≥8 points or NIHSS 0-1 at 72h)	**Mortality**	
Safety Outcomes	**SICH (SITS-MOST) confirmed on 22-36h CT or MRI**	**Extracranial bleeding**	
	Any ICH on 22-36h CT or MRI		

SCHEDULE OF ASSESSMENTS

Study Procedure	Pre- Randomisation	Randomisation	Procedure	0-24h	24h	72 h	Day 7 (±2)	Day 30 (±5)	Day 90 (±7)
Obtain Consent	X								
Review Inclusion/Exclusion Criteria	X								
CT brain	*				X				
CT Angiography (or MRA or DSA)	X				X				
Vital Signs (temperature, blood pressure, heart rate)	*				X	X	X		
Post-thrombolysis observations (BP, pulse)			X	*[1]					
Physical Examination- NIHSS	*				X	X	X	X	X
Weight	*								
Haematology and Coagulation	X								
Bloods - Biochemistry	*				X	X			
IVRS		X							
Pregnancy Test (female patients of child bearing potential)	X								
mRS - RFA								X	X
Adverse Events Evaluation			X	X	X	X	X	X	X
Home time evaluation									X

X study-specific procedure; *clinically routine procedure (data captured for study); ×procedure clinically routine in some patients

[1] BP and pulse monitored more frequently after starting IV thrombolysis, hourly recordings will be documented for study purposes

1. INTRODUCTION

1.1 Background

After arterial occlusion, brain tissue undergoes infarction over a period of minutes to hours depending upon the severity of the reduction in cerebral perfusion.[1] Restoration of blood flow by recanalisation of the occluded artery limits the extent of damage. Reperfusion may occur spontaneously due to endogenous clot breakdown, but therapeutic intervention using thrombolytic drugs increases the chances of reperfusion[2] and is therefore associated with increased probability of favourable outcome if delivered promptly after symptom onset. Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) significantly increases the proportion of patients achieving independence 3 months after ischaemic stroke when delivered within a maximum of 4.5h after onset of symptoms.[3-5] Since stroke has not been regarded as a medical emergency in the past, large-scale reconfiguration of health care systems has been necessary to deliver rtPA to patients, and although the proportion of patients undergoing IV thrombolysis is small globally, there has been a rapid expansion in the numbers treated in the UK and elsewhere in recent years.

However, IV thrombolysis results in recanalisation of the occluded artery in only just over 50% of patients,[6] and the probability of successful recanalisation is least with occlusions in large arteries, reflecting the larger volume of clot.[7,8] Patients with large artery occlusion also have the most severe clinical presentations and poorest outcomes.[9,10] Recanalisation rates for occlusions of the terminal internal carotid artery (ICA) or main middle cerebral artery (MCA M1) are reported to be only 9% and 33% respectively, compared to 66% in smaller MCA branches (M2 or distal).[7] The speed of recanalisation is also important, with more rapid recanalisation being associated with higher probability of early neurological improvement and independence at 90 days.[6]

The intra-arterial (IA) delivery of thrombolytic agents directly into the occluded vessel via microcatheter injection offers hypothetical advantages in terms of thrombolytic dose titration, but only two randomised controlled trials (RCTs) have evaluated IA thrombolytic drug delivery,[11,12] and in addition to inconsistent clinical efficacy (benefit in one trial,[11] but not in the other[12]) and control groups that did not receive what would now be regarded as best medical care, the specific agents employed in these trials (urokinase and pro-urokinase) are no longer available. A combined IV+IA thrombolytic drug approach was evaluated in the first open label Interventional Management of Stroke (IMS) trial, [13] and in a prospective registry study,[6] with superior rates of recanalisation compared to IV rtPA alone, but also somewhat higher risks of symptomatic intracranial haemorrhage (SICH) that likely reflect procedural risks of trauma to vessels from microcatheter or guidewire, and also later delivery of treatment.

The use of IA thrombolytic drugs has been superseded by the development in recent years of a wide range of mechanical devices which can directly revascularise occluded cerebral vessels. However, evidence of efficacy for devices has been limited to case series and prospective observational studies, mostly designed simply to establish the mechanical characteristics and performance of a device with respect to the limited end-point of recanalisation of intracranial vessels, which is all that is currently required for licensing by regulatory authorities. Recanalisation rates are higher than expected for IV thrombolysis compared with historical controls, in some instances very considerably so.[14-18] However, despite these high rates of recanalisation, clinical outcomes have in some cases been poorer than would be expected based on historical controls given IV thrombolytic treatment. Relevant factors that may increase risk of IA thrombectomy include higher reported risks of SICH (around 9% compared to 2-4% for IV thrombolysis), and longer procedure duration, leading to more prolonged onset-to-treatment time; a marked reduction in the probability of favourable outcome with IV thrombolytic therapy over the first 4.5h after onset is well documented[3] and reflects a combination of reducing volumes of salvageable tissue over time as well as increased bleeding risk. The additional time incurred in IA delivery – often up to 6 hours after symptom onset before microcatheter deployment even in experienced centres[19] - may offset any benefit from improved recanalisation rates, since reperfusion of non-viable brain tissue carries no clinical benefit and may increase bleeding risks. On the other hand, patients selected for IA treatment usually have more severe strokes, successful recanalisation is uncommon with IV treatment alone, and favourable outcomes in registry studies are more frequent than expected for IV treatment in groups of equivalent clinical severity with definite arterial occlusion. In order to define the overall role for mechanical thrombectomy, evaluation in a RCT is necessary. To date no RCT of IA mechanical reperfusion has been published. Several trials are either ongoing or are at an early stage of development. (Table)

Trial	IMS 3	MR CLEAN	SYNTHESIS expansion	THRACE
Country	USA, selected European Centres	Netherlands	Italy	France
Time window	5h	6h	3h (IV) / 6h (IA)	3h
Arms	IV rtPA v IV rtPA (2/3 dose) + IA rtPA ± mechanical thrombectomy	Standard medical care (including IV rtPA if indicated) v IA rtPA, mechanical thrombectomy or both	IV rtPA v IA rtPA ± mechanical thrombectomy	IV rtPA v IV rtPA+ mechanical thrombectomy
Patients	18-80 years NIHSS ≥ 10	>18 years NIHSS ≥ 2	18-80 years	18-80 years NIHSS ≥ 10 and <25
Angiographic Inclusion criteria	ICA, M1, M2, basilar or vertebral arteries	Intracranial ICA, M1, M2, A1 or A2 occlusion	Not specified	ICA, MCA M1 or distal BA
Imaging Modalities	DSA	CTA, MRA, DSA or TCD	Not specified	
Devices	Merci retriever, EKOS, Penumbra	Investigator discretion	Investigator discretion	Merci, Penumbra, Catch, Solitaire
IA lytic drug allowed	Yes (rtPA, max 22mg)	Yes (UK, rtPA)	50% randomised to IA rtPA	
IV lytic drug pre-intervention	Mandatory (IV rtPA <3h), full or reduced dose	Allowed (IV rtPA <4.5h), not mandatory	Not in intervention arm	

The IMS III trial has already taken many years to enrol only two-thirds of the required sample size (in large part a reflection of a move to interventional treatment in North America that is based on reimbursement rather than clinical evidence), with attendant risks that practice will have drifted during the course of the trial and that the assumptions that informed the design may no longer pertain. The devices that IMS III permits no longer reflect state of the art designs and it will therefore not be possible to judge the generalised efficacy or safety of IA device revascularisation. The SYNTHESIS Expansion in Italy has now randomised 200 patients; the MR CLEAN trial in the Netherlands is just commencing; and THRACE has not yet commenced. The clinical trial designs differ somewhat in standard medical care arms, including a mixture of IV rtPA-eligible and ineligible patients, age restrictions, time windows (<3h or <4.5h), and policies on inclusion of strokes involving the basilar artery, that have a different natural history and clinical picture from anterior circulation events; the main investigational arm in several is IA rtPA, with adjunctive thrombectomy permitted in a non-randomised manner; and the majority select only patients with very severe strokes. Interventional procedures are currently undertaken in an *ad hoc* manner in the UK, with most

individual centre experience being limited. Case selection includes a mixture of patients, with many proceeding to IA therapy because of a perceived contraindication to IV thrombolytic therapy (eg recent surgery, anticoagulation, outwith 4.5h time window, very high NIHSS), or because of more widely available non-invasive angiographic information from CT angiography (CTA) or MR angiography (MRA) coupled with the knowledge of poor recanalisation rates in large artery occlusion despite IV thrombolysis. A randomised controlled trial that compares IV rtPA with IV rtPA and adjunctive thrombectomy using current state of the art devices and in patients eligible for IV rtPA is needed in order to establish whether the greater recanalisation rates that can be achieved with IA devices translate into superior clinical outcomes. In the absence of RCT data, it is highly probable that there will be an increasing number of these procedures, which carry high cost and entail substantial service reorganisation but with the risk that they may mainly deliver futile recanalisation.

1.2 Study rationale – hypothesis

We hypothesise that mechanical thrombectomy will be associated with an improved chance of favourable functional recovery in patients with significant anterior circulation stroke and major artery occlusion compared to standard medical care with intravenous rtPA, to be assessed by functional outcome on the modified Rankin Scale at day 90.

2. STUDY OBJECTIVES

This is the start-up phase of a pragmatic randomised, controlled clinical trial using a Prospective Randomised Open Blinded End-point (PROBE) design.

Primary Endpoint

- Proportion of subjects with favourable outcome at 90 (±7) days based on the modified Rankin scale. This will be assessed by use of the Rankin Focused Assessment tool (RFA). Independence being defined by a dichotomous mRS score (0-2 versus 3-6).

Secondary endpoints

- Full neurological recovery (mRS 0-1 versus 2-6)
- Mortality
- Change in distribution of mRS scores adjusted by baseline variables
- Early major neurological improvement of 8 or more points, or return to NIHSS total score of 0 or 1, at 72 hours (or discharge if earlier)
- Angiographic patency at 22-36 hours (Core lab assessed), using CTA or MRA
- Immediate (i.e. end of procedure) recanalisation rates in subjects undergoing interventional procedures (core lab assessed)
- Days spent at home between stroke at day 90±7

Safety Outcomes

- Symptomatic intracranial haemorrhage rates defined as local or remote parenchymal haemorrhage type 2 (PH2 or PHr2 ICH by ECASS 2 definition) on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death (SITS-MOST definition)
- Any intracranial haemorrhage on 22-36h CT or MRI
- Extracranial bleeding, groin haematoma requiring evacuation / surgery or transfusion
- Other extracranial haemorrhage

3. STUDY DESIGN

This study (PROBE design) will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

Blinding will be ensured by conduct of outcome assessment by a suitably trained healthcare professional not involved in the patient's initial treatment. Secondary imaging end-points will be evaluated blind to treatment allocation where possible.

3.1 Study Population

The study will recruit male and female patients aged ≥18 years with acute ischaemic stroke deemed eligible for IV thrombolysis.

Patients eligible for IV rtPA will have treatment initiated as per standard practice, up to 4.5h after symptom onset (<3h after symptom onset for patients >80 years of age). After ascertaining that mechanical revascularisation is feasible within the trial timescale (randomization, enrolment, and procedure commencement (groin puncture) within 90 minutes of *starting* IV rtPA treatment, and placement of a guide wire beyond the aortic arch within 6 hours of stroke onset), consent for the trial will be sought from patients or their legal representatives. Eligible patients must have vascular imaging evidence of a relevant arterial occlusion (anticipated to be determined by CTA in the majority, although MRA or DSA are allowable). If vascular imaging is the standard of care at a centre, then this may be acquired prior to consent.

Routine procedures conducted in accordance with standard medical care for stroke will be accepted measures to assess entry criteria.

3.2 Main inclusion criteria

- Clinical diagnosis of supratentorial acute ischaemic stroke
- Male or non-pregnant female ≥18 years of age
- Clinically significant neurological deficit and NIHSS score ≥6
- Eligible for IV rtPA according to standard guidelines and able to be commenced on IV treatment <4.5h after symptom onset (<3h after symptom onset for patients >80 years of age)
- Enrolment, randomisation and procedure commencement (groin puncture) possible within 90 minutes of the start of IV rtPA treatment (maximum 5.5h after stroke onset)
- Occlusion of the MCA trunk, MCA bifurcation or intracranial internal carotid artery (carotid-T, M1 or single proximal M2 branch) demonstrated on CTA, MRA, or DSA
- Interventional device delivery (guide catheter placed beyond aortic arch and angio obtained) can be achieved within 6 hours of onset of the stroke
- Consent of patient or representative

- Independent prior to the stroke (estimated mRS 0-2)
- Expected to be able to be followed up at 3 months.

3.3 Main exclusion criteria

- CT evidence of ICH, or evidence of extensive established hypodensity on CT.
- Clinical history suggestive of subarachnoid haemorrhage even if CT normal.
- Vascular access contraindications e.g. femoral bypass surgery, tight ipsilateral carotid stenosis, unsuitable proximal vascular anatomy likely to render endovascular catheterisation difficult or impossible.
- Extracranial ICA exclusion or basilar artery occlusion.
- Alternative intracranial pathology potentially responsible for the new symptoms.
- Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (eg severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy).
- Known allergy to radiological contrast.

3.4 Centre Qualification

An accreditation committee [Prof Brown, Dr Clifton, Dr White] will review data provided by centres to ensure adequate experience by the interventional team and documentation of protocols for intra-arterial management of acute stroke. There is a recognition that the service configuration for neurovascular services differs between European countries and therefore different approaches to credentialing may be required.

Each centre must have a hyperacute stroke team including consultant stroke physicians or neurologist(s) with an on call system for delivery of IV thrombolysis for ischaemic stroke. They must also have a team of interventionists (2 or more) undertaking regular cerebral endovascular interventional procedures including thrombectomy for stroke.
Local protocols for advanced stroke imaging techniques (including CTA and/or CT Perfusion (CTP), or MRI techniques including DWI/MRP/MRA) should be in place.

Intra-arterial thrombectomy procedures will be carried out by designated consultant interventionists with expertise in cerebral interventional endovascular procedures and the techniques required for stroke thrombectomy. Good collaboration between the hyperacute stroke team and interventionists is essential and centres should have regular neurovascular meetings.

Centres will be required to submit documentation of detailed local protocols for both the intravenous and intra arterial treatment of acute stroke. Prospective centres will need to provide documentary evidence being kept of angiographic and clinical outcomes for their acute ischaemic stroke interventions (e.g. audits of recent results for both IVT and their IA experience). Attendance by personnel from prospective centres at training session(s) in stroke thrombectomy will be encouraged prior to participation.

As a guide, UK centres configured on a large volume regional neuroscience centre basis with specialist INR services, will have treated ≥10 patients with hyperacute ischaemic stroke using intra-arterial thrombectomy within the preceding 18 months. In addition a much larger experience in cerebral endovascular interventional procedures will need to be documented. Centres must provide documentation that they have performed >120 cerebral vascular interventional procedures per annum for at least the last 3 years. Individual interventional consultants will all need to document considerable personal experience of intracranial vascular interventional procedures (>120 each, of which at least 60 were undertaken in preceding 18 months) plus evidence of deployment of devices other than coils intracranially (e.g. stents) [for any indication] in at least 25 cases over the last 3 years. Centres where there is little or no experience of thrombectomy for ischaemic stroke will not be able to join PISTE during the start up phase but may join later. Such centres will be expected to meet the above minimum experience of ten thrombectomy procedures within 18 months etc. required to join the trial.

Non UK centres with a different service configuration for neurovascular services will be required to have an interventional radiology team with ample experience of intra-arterial interventions for cerebrovascular disease (carotid stenting or aneurysm coiling) and peripheral artery disease and/or coronary artery disease. As a guide, centres will have treated ≥10 patients with hyperacute ischaemic stroke using intra-arterial thrombectomy within the preceding 18 months. In addition a larger experience in cerebral endovascular interventional procedures will need to be documented. Centres must provide documentation that they have performed ≥50 cerebral vascular interventional procedures (including thrombus extraction) along with at least a further 80 peripheral, coronary or other vascular interventions in the last 18 months. Individual interventional consultants will all need to document large personal experience of vascular interventional procedures (>100 each, of which at least 50 were undertaken in the preceding 18 months).

3.5 Identification of participants and consent

Potential participants will be identified on referral to participating acute stroke services and will be screened by the clinical inclusion and exclusion criteria listed in sections 3.2 and 3.3.

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). Arrangements for consent in incapacitated patients will reflect the legal framework in the different countries of the UK:

- In Scotland, consent will be sought from their next of kin or legal representative;
- In England and Wales, consent will be sought from a consultee;
- In Northern Ireland, assent will be sought from their next of kin.

Consent will be sought prior to study specific investigations, but may occur after initial clinically routine imaging, which will vary according to standard local practice at different sites (usually CT alone, but this may include CT and CTA, or in some cases MRI and MRA, or DSA). Consent may be required before vascular imaging in centres where this imaging is not the routine standard of care.

Patients will be randomised to additional IA thrombectomy using a regulatory-approved device (choice at the discretion of the interventionalist), or to continue standard medical management. Randomisation will be achieved by a telephone call to an interactive voice response system (IVRS) telephony system or by web access. The randomisation algorithm will be based on a minimisation algorithm incorporating a small probability of completely randomised allocation. Minimisation will be achieved using categories based on age (<81, >80 years), NIHSS score (6-12, 13-19, >19), onset to treatment with rtPA time (<3h, 3-4.5h), and centre. Participants will be assigned a unique number based on site identifier number and consecutive recruitment number at each site.

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

3.6 Study schedule

Clinical evaluations will include standard neurological impairment and outcome scales as outlined in the study flow chart. In addition, day 90±7 outcome will include home time, an objective index of functional outcome that also contributes health economic data.

Visit 1: Pre Randomisation / Randomisation visit

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

- Medical history, including symptom onset time, past history, medication, level of function or disability
- CT brain (or MRI)
- Blood samples for biochemistry (including eGFR and blood glucose/ capillary glucose) and haematology (including coagulation)

- Blood pressure, heart rate and temperature
- Weight
- Physical examination including NIHSS (see appendix C)

Study specific procedures will take place following informed consent, these include:

- CT angiography or other angiographic imaging (unless standard of care at the site, in which case may precede consent)
- Pregnancy test for females of childbearing potential
- Randomisation using IVRS
- Allocation of patient unique study number
- Completion of electronic Case Report Form (eCRF)

Visit 2: Procedure

General anaesthesia or sedation may be used for the procedure as locally required.

Intra-arterial mechanical thrombectomy will be undertaken using an approved device at the discretion of the interventional neuroradiologist. The procedure should commence (i.e. groin puncture) within 90 minutes of the start of the IV rtPA infusion and a guide catheter should be placed beyond the aortic arch within a maximum of 6 hours of stroke onset.

Procedure documentation will include drug administration (including anaesthesia or sedation), total duration, device used, number of passes, AEs.

Post-treatment monitoring: will be documented on a study worksheet for transcription into the eCRF. This includes the following items that are collected routinely in patients treated with IV thrombolysis:

- Blood pressure hourly for 24 hours, then four hourly for 24 hours

Visit 3: 24 hours (22-36h) post treatment (or hospital discharge if earlier):

- Brain imaging will include repeat CT and CTA or alternatively MRI and MRA
- Vital signs
- NIHSS
- Blood samples for biochemistry
- Adverse event assessment
- Completion of eCRF

Visit 4: 72±8 hours post treatment (or hospital discharge if earlier):

- Vital signs

- NIHSS
- Blood samples for biochemistry
- Adverse event assessment
- Completion of eCRF

Visit 5: 7 (±2) **days post treatment (or hospital discharge if earlier):**

- Vital signs
- NIHSS
- Adverse event assessment
- Completion of eCRF

Visit 6: 30 days (±5)

- NIHSS
- mRS
- Adverse event assessment
- Completion of eCRF

Visit 7: 90 days (±7)

- NIHSS
- mRS
- Adverse event assessment
- Completion of eCRF
- Study completion
- Home time evaluation.

3.7 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 interview. Raters will have undergone training in administration of the scale. mRS will be assessed by use of the Rankin Focused Assessment tool (RFA).

3.8 Imaging

Routine brain imaging in acute stroke consists of brain CT, an X-ray based examination involving ionizing radiation. This identifies stroke caused by ICH with very high sensitivity and specificity, and may additionally show areas of established ischaemic damage that define eligibility for treatment. In

some centres, the standard of care may include additional vascular imaging (usually CTA), or may use magnetic resonance imaging (MRI), including MRA, as an alternative. Consent may take place after vascular imaging, or may precede vascular imaging if this is not the standard of care. Randomisation will occur after vascular imaging confirms eligibility.

CT angiography acquires thin axial sections during the first arterial passage of approximately 50ml of an iodinated contrast agent delivered via an IV cannula sited in a large forearm vein, delivered at a controlled rate (usually 6 ml/second) by a power injector. CTA acquisition that covers the arch of the aorta to the circle of Willis is recommended. Alternative vascular imaging is permitted (MRA or DSA).

Follow-up imaging at 24 (22-36) hours in patients treated with IV thrombolysis usually includes CT brain to define infarct size, haemorrhagic complications and brain swelling. Additional trial-specific imaging will be repeat CTA to define vessel recanalisation. Alternatively, follow-up imaging may be with MRI brain and MRA.

3.8.1 Image Processing and Analysis

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 site and study number. Imaging studies will be uploaded to or forwarded on removable media to the University of Edinburgh Systematic Image Review System (SIRS) for central review.

3.9 Blood testing / venepuncture

Additional blood testing for trial purposes is not required. Blood results relevant to acute stroke with thrombolytic treatment will be reviewed for trial purposes and routinely include the following:

Biochemistry – blood glucose/ capillary blood glucose, urea and creatinine (and calculated estimated Glomerular Filtration Rate, eGFR).

Haematology – platelet count and coagulation studies (including prothrombin time, INR and activated partial thromboplastin time).

Because of the emergency nature of stroke treatment and the potential for patients to have been transferred from other hospitals for care, lab results may be derived from a number of different hospitals. Any NHS hospital laboratory will be acceptable as the source of pre-treatment blood results.

4. INVESTIGATIONAL DEVICE INFORMATION

Neurointerventionalists may elect to use any CE-marked device approved for thrombectomy. Devices will be those available as clinical routine at a site, and will not be supplied as part of the trial. The device make and model that is used for a procedure will be documented in trial documentation. All devices should be used in accordance with the manufacturer's Instructions for Use (IFU).

Devices with CE mark and approval for thrombectomy are the following:

- MERCI retriever
- Covidien ev3 Solitaire
- Phenox BONNET
- Phenox pRESET
- PENUMBRA
- Concentric Trevo
- Acandis Aperio
- Codman Micrus ReVive
- Penumbra Direct Aspiration System
- ERIC Retrieval Device

Other devices will be approved for trial use by the Steering Committee after review of the relevant IFU.

5. SAFETY REPORTING

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 Definition of Serious Adverse Event

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. Details of SAEs will be reported to the pharmacovigilance office and followed until resolution. The relationship with the study procedures will be assessed for all SAEs. All 'related' SAEs will be forwarded to the CI for assessment of the expectedness. All 'possibly' or 'definitely' related, unexpected SAEs will be reported to the REC as detailed below.

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 SmPCs.

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

- Systemic bleeding

AEs related to thrombectomy devices:

- Intracranial haemorrhage (symptomatic and asymptomatic), including subarachnoid haemorrhage
- Arterial wall damage including arterial puncture and dissection
- Puncture site haematoma or haemorrhage
- Device fracture
- Failure to withdraw device successfully

5.5 Reporting to sponsor (Pharmacovigilance (PV) Office)

All SAEs arising during the study will be reported by the Principal Investigator (or designee) to sponsor (PV Office) 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.

SAEs should be reported using a paper SAE form (non-CTIMP) which 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). A copy of the complete form should be placed in the Study Site File.

If necessary a verbal report can be given by contacting the PV Office on +44 (0)141 330 4870/ +44 (0)141 330 4744. This must be followed up as soon as possible with a written report.

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

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

The study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be authored by the Trial Statistician and agreed by the Trial Steering Committee (TSC) before any unblinded data is seen.

6.2 General considerations

6.3 Primary efficacy variable

The mRS score at day 90 (±7) will be treated as a dichotomous variable with scores of 0-2 defining favourable, and 3-6 unfavourable, outcome.

6.4 Secondary efficacy analysis

6.5 Safety analysis

The safety data (adverse events) – both numbers of subjects and events – will be summarised by randomised group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified.

6.6 Software and statistical analysis

The statistical software to be used will be specified in the Statistical Analysis Plan. It is likely to be SAS 9.2 for Windows, Cary, NC, USA.

6.7 Sample size

It is intended that the start-up phase of the trial will gather data on event rates that will inform and refine sample size calculations prior to commencing the main phase of the trial. We intend to recruit approximately 70 patients in the start-up phase of the trial.

It is estimated that 45% of patients with an occluded MCA M1 or supra-clinoid ICA may be independent at 3 months with current best medical treatment. If revascularisation can be achieved in patients, then retrospective data[6] suggest that the proportion achieving independence may be increased to approximately 60% of patients. Using exact figures from a previous retrospective study in a comparable population of 44% and 57% achieving mRS 0-2 with combined IV and endovascular versus IV treatment alone yields a sample size of approximately 200 subjects per group for 80% power, p=0.05 for the full study. A more conservative 10% absolute increase in independent recovery at day 90 would be regarded as clinically valuable. Given the major implications for resource utilization and service redesign, a smaller absolute benefit than 10% is unlikely to justify change in

routine clinical practice. The sample size for a 10% improvement (from 45% to 55%) in independent recovery is approximately 400 subjects per group.

6.8 Management and delivery

The Robertson Centre for Biostatistics, functional unit of the Glasgow Clinical Trials Unit, a fully registered UK CRN Clinical Trials Unit, will manage and analyse trial data. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

7. TRIAL CLOSURE / DEFINITION OF END OF TRIAL

The trial will end when the TSC agrees that one or more of the following situations applies:

i. The planned sample size has been achieved;

ii. The Independent Data Monitoring Committee (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 (see below);

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.

The safety aspects of the trial will be overseen by an IDMC consisting of an independent stroke physician, medical statistician, and interventionist. The progress of the study will be assessed at regular intervals determined by the IDMC. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including SAEs believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the IDMC, along with any other analyses that the Committee may request. In the light of these, the IDMC will advise the chairman of the TSC if, in their view, the randomised comparisons have provided both (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely.

The end of the trial is defined as the last participant who has completed the 90 day follow up visit.

8. DATA HANDLING

8.1 Randomisation

A central randomisation facility (IVRS) will allocate the randomised therapy per patient. The IVRS, based at the Data Centre, will be available by telephone. A central unblinding facility based at Data Centre will also be available by telephone. Notification of any unblinding will be sent to the CI.

8.2 Case Report Forms / Electronic Data Record

An electronic case report form (eCRF) will be used to collect study data. The eCRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow 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 Record Retention

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 by a Trial Management Group that will include those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, project manager, and data manager. The role of the group is to 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 should:

- agree the trial protocol and any protocol amendments
- provide advice to the investigators on all aspects of the trial
- have members who are independent of the investigators, in particular an independent chairperson.

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 the 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 and will be the only body that has access to unblinded data. It will make recommendations to the TSC.

10. STUDY MONITORING AND AUDITING

Study monitoring visits will be conducted by NHS Greater Glasgow and Clyde Monitors. The level of monitoring will be based on the outcome of the completed monitoring risk assessment, and will be clearly documented in the Monitoring Plan which will be approved by the NHS GG&C Research Governance Manager. As standard, Monitoring Visit(s) will cover Site File review, review of Informed Consent Forms (ICFs), Source Data Verification (SDV) and Serious Adverse Event (SAE) review.

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 any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor. The CI and the TSC will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor's representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC, and participating site Research and Development (R&D) office.

12. ETHICAL CONSIDERATIONS

12.1 Ethical conduct of the study

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

Favourable ethical opinion will be sought from the relevant REC before patients are entered into this clinical trial. Patients will only be allowed to enter the study once wither they have provided written informed consent or their next of kin have provided written informed assent.

The CI will be responsible for updating the REC 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 a proxy as as required by each participating country. In England & Wales, a consultee will give an opinion on whether the patient would have wished to participate. In Northern Ireland, the next of kin of potential participants who are unable to consent for themselves will be approached for assent as to whether the participants should be included in the study. A clinical 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 PISTE trial is sponsored by NHS Greater Glasgow & Clyde. 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 study, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

14. FUNDING

The PISTE study start-up phase is funded by The Stroke Association grant, reference TSA 2011/06

15. SPONSOR RESPONSIBILITIES

The Sponsor of this clinical study is NHS Greater Glasgow and Clyde. Sponsor responsibilities undertaken by NHS Greater Glasgow and Clyde will be as defined in the Research Governance Framework for Health and Community Care (Second edition, February 2006).

A Clinical Study Agreement will be put in place between NHS Greater Glasgow and Clyde and each of the participating sites. This agreement outlines the responsibilities of each party in the running of the study.

16. 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, regulatory authority and sponsor with the first submitted one year after the date that all trial related approvals are in place.

17. DISSEMINATION OF FINDINGS

The original protocol was developed by members of the Acute Studies group of the NIHR Stroke Research Network (SRN). The trial will be submitted for adoption by the SRN.

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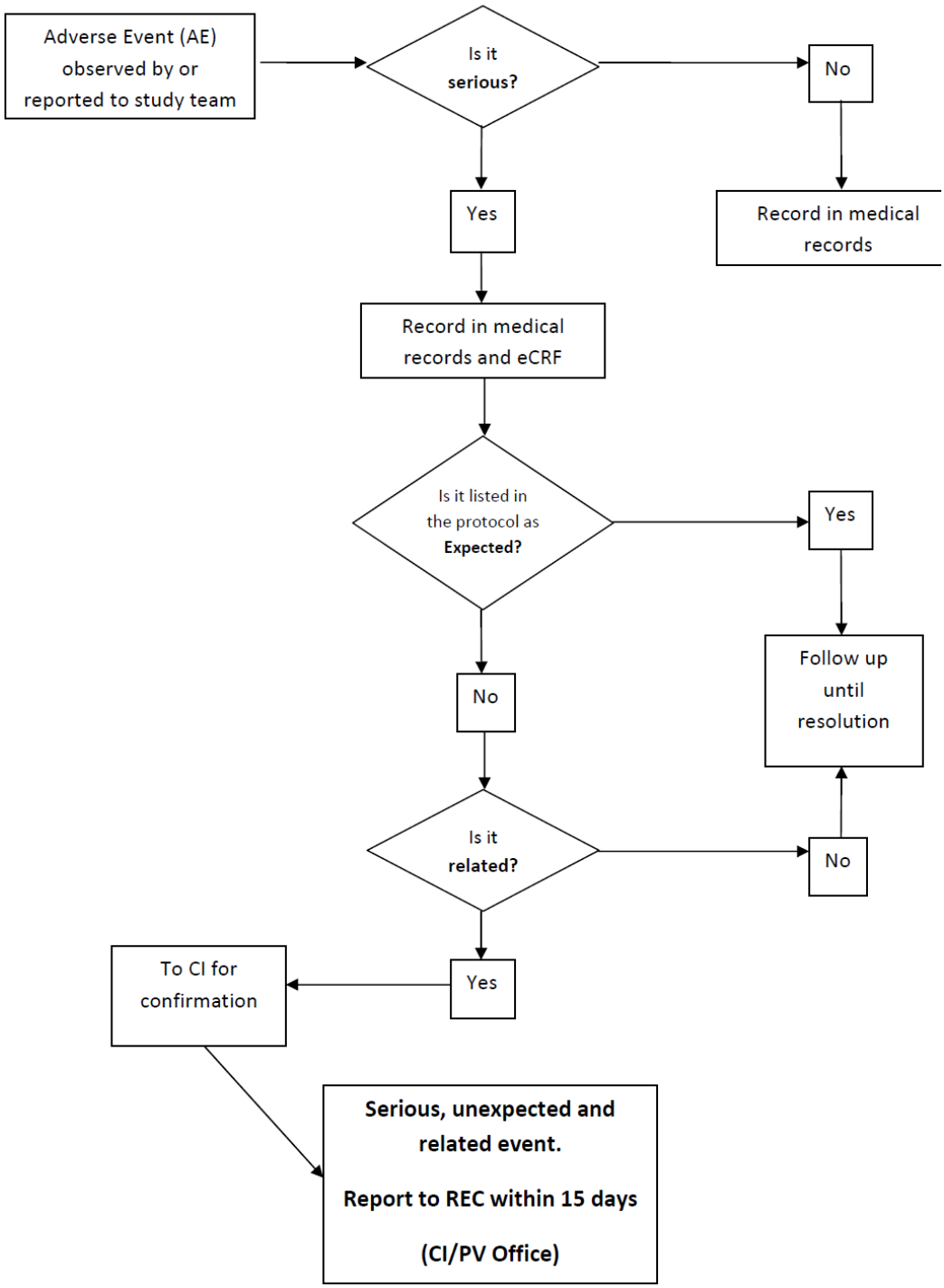
APPENDIX A: Flowchart for Assessing and Reporting Adverse Events



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

NIHSS page 1

NIH 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.	_____

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NIH 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**	_____

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NIH 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:_____	_____

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NIH 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.	_____

_____

_____

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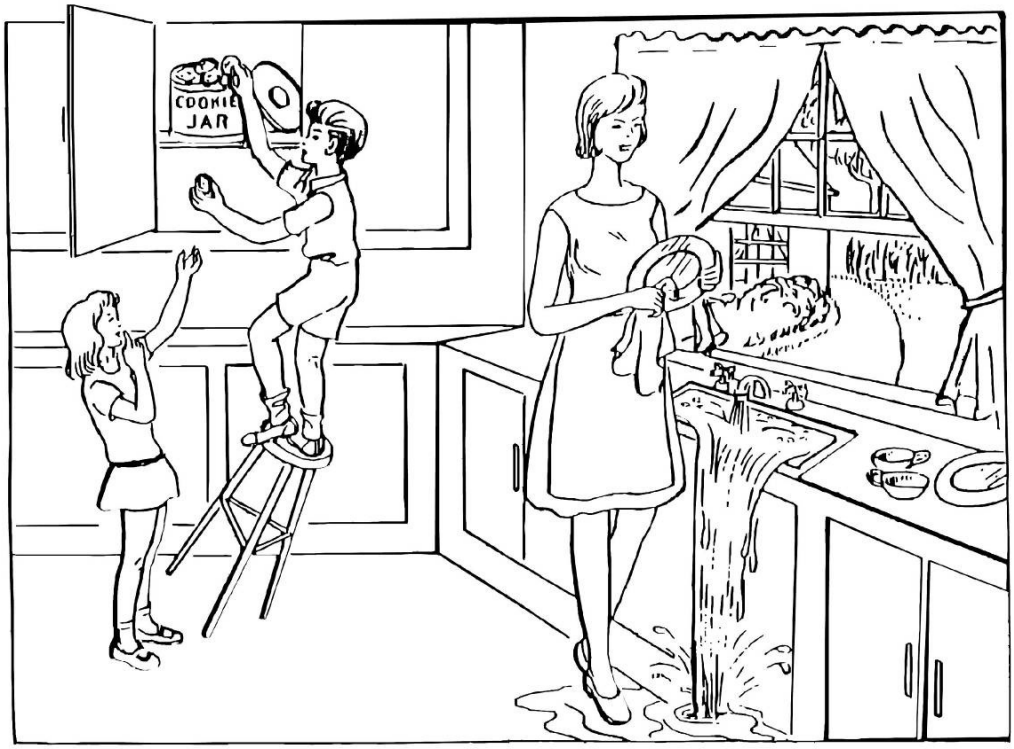


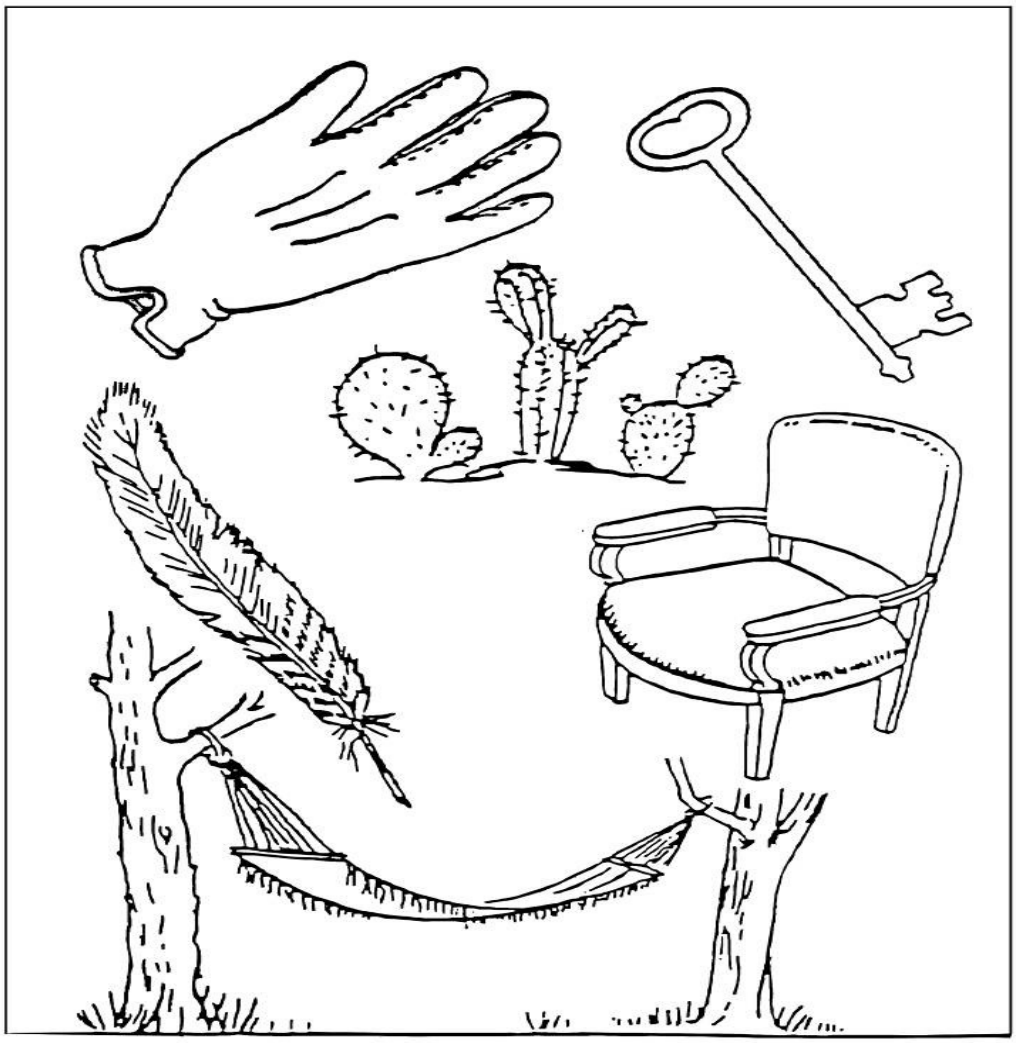
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix D: Modified Rankin Scale (mRS)

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

MODIFIED RANKIN SCALE (mRS)

Study ID: _____

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.

Appendix E: Rating Form Prestroke Rankin Focused Assessment (RFA) *Provided by UCLA Stroke Center*

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

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:
_____
_____

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 (1) □ No

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

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

_____

_____

_____

Rankin Grade = ☐

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Appendix F: Rating Form Rankin Focussed Assessment (RFA) *Provided by UCLA Stroke Center*

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

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: _____ Subject 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:
_____
_____

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