Title: Penumbra and Re-canalisation Acute Computed Tomography in Ischaemic Stroke Evaluation: PRACTISE study protocol

Cover title: PRACTISE study protocol

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Abstract:

Rationale:

Multimodal imaging, including CT angiography (CTA) and CT perfusion (CTP) imaging, yields additional information on intracranial vessels and brain perfusion, and can differentiate between ischaemic core and penumbra which may affect patient selection for intravenous thrombolysis.

Hypothesis:

The use of multimodal imaging will increase the number of patients receiving IV thrombolysis, and lead to better treatment outcomes.

Sample size: 400 patients

Methods and Design:

PRACTISE is a prospective, multicentre, randomised, controlled trial (RCT) in which patients presenting within 4.5 hours of symptom onset are randomised to either the current evidence-based imaging (NCCT alone) or additional multi-modal CT imaging (NCCT + CTA + CTP). Clinical decisions on IV rtPA are documented. Total imaging time in both arms and time to initiation of treatment delivery in those treated with IV rtPA, is recorded. Follow up will include brain imaging at 24h to document infarct size, presence of oedema and the presence of intra-cerebral haemorrhage. Clinical evaluations include NIHSS score at baseline, 24 hrs and day 7+/-2, and mRS at day 90 to define functional outcomes.

Study outcomes:

The primary outcome is the proportion of patients receiving IV rtPA. Secondary end-points evaluate times to decision making, comparison of different image processing software and clinical outcomes at 3 months.

Discussion:

Multimodal CT is a widely available tool for patient selection for revascularization therapy, but it is currently unknown whether the use of additional imaging in all stroke patients is beneficial. The study opened for recruitment in March 2015 and will provide data on the value of multimodal imaging in treatment decisions for acute stroke.

Introduction and Rationale

Intravenous recombinant tissue plasminogen activator (IV rtPA) remains under-utilised, being given to less than 10% of all stroke patients(1) and in only 20-40% of patients with acute ischaemic stroke (AIS) presenting to hospital within the appropriate time window(2-4). The utilization rate of IV rtPA remains low despite thrombolysis in an expanded time window of 4.5 hours in centres outside the USA, treatment of more patients above the age of 80 (5) and several non-randomised studies showing safety of treatment in other clinical situations initially excluded from licensed usage based on clinical trial exclusion criteria(6-8).

Brain imaging is an essential component of diagnosis in patients with suspected acute stroke, and at present relies on non-contrast computed tomography (NCCT). The specificity is high but the sensitivity of NCCT to early ischaemic changes is low, with early ischaemic changes (EIC) seen in less than 60% of patients scanned within 6 hours of symptom onset, meaning that treatment decisions are often made on the basis of clinical presentation and negative imaging. Magnetic resonance imaging (MRI) is sensitive to cytotoxic oedema and thus has greater diagnostic sensitivity than NCCT,(9) but its use in acute stroke is subject to practical difficulties related to availability, time required for imaging and inability to image certain patients (eg those with pacemakers or metallic implants) (10, 11). Multimodal imaging, including CT angiography (CTA) and CT perfusion (CTP) imaging, yields information on intracranial vessels and brain perfusion, and can differentiate between ischaemic core and penumbra(12). The potential value of multimodal imaging in patient selection for IV thrombolysis has been suggested by observational studies(13-15) that demonstrate significantly greater diagnostic sensitivity, especially among those with less severe stroke, and in a few randomised controlled studies of treatment in an extended time window or with agents other than alteplase(16). Multimodal imaging was an integral part of patient selection in several recently published positive endovascular therapy trials that showed this treatment modality to improve outcome among selected patients compared to best medical care,(17) and may have a role in stroke pathways that offer this treatment option (18). Multimodal imaging, however, comes with the risk of delayed treatment, exposure to radiological contrast, and higher radiation dose, as well as increased financial costs. It is currently unclear whether multimodal imaging in all patients is beneficial. To date there has been no prospective, randomised study specifically designed to evaluate the role of

multimodal imaging in defining individual patient treatment decisions in acute stroke within the current time window and with currently approved treatment options.

Methods

Design

PRACTISE is a prospective, multicentre, randomised, controlled trial (RCT) comparing the current evidence-based imaging (control, NCCT alone) with additional multimodal CT imaging (NCCT + CTA + CTP). Patients who are clinically eligible for IV rtPA, and who have no contraindications for CTP or CTA are randomised to NCCT alone or NCCT+CTP+CTA. Patients will be excluded from the study if the initial NCCT identifies specific contraindications to IV thrombolysis such as intracranial haemorrhage or non-stroke pathology consistent with the presenting neurological deficit.

The decision on IV rtPA treatment based on allocated imaging will be documented on a structured case record form that asks clinicians to assess the independent contributions of CTA and CTP. The clinician may reach a treatment decision using as many or as few imaging studies as they wish. Total imaging time in both arms (acquisition, processing, review and clinical interpretation), and time to initiation of treatment delivery in those treated with IV rtPA, will be recorded. If patients do not receive treatment, the reason is recorded.

Follow up structural brain imaging in all randomised patients with ischaemic stroke at approximately 24h (22-26h window) will document infarct size, presence of brain swelling, and the presence of intra-cerebral haemorrhage (ICH). MRI is permissible as an alternative to NCCT. Clinical evaluations will include National Institutes of Health Stroke Scale (NIHSS)(19) score at baseline, 24 hrs, and day 7 (or hospital discharge if earlier). Functional outcome will be determined by the modified Rankin Scale (mRS)(20)using the Rankin Focused Assessment (RFA)(21) tool at day 90 evaluated by central telephone follow-up, supplemented by local site follow-up if required.

Technical details of CT scanners, CTP and CTA acquisition and post-processing will be obtained for each centre. Central data analysis will be undertaken to investigate i) inter-observer agreement on interpretation of CTA and CTP, and ii) whether CTP processing using manufacturer-independent software significantly influences interpretation of CTP. Locally-processed CTP and CTA will be uploaded to the Systematic Image Review System 2 (SIRS2, www.neuroimage.co.uk/sirs) hosted by the University of Edinburgh.

Central CTP processing will use commercial stand-alone analysis software to generate perfusion maps of all major parameters (cerebral blood flow, cerebral blood volume, mean transit time and time to peak) and in addition will produce thresholded maps of penumbra and infarct core. Centrally processed CTP maps will be uploaded to SIRS for deferred review by readers, including the clinicians at the randomising centre, in order to determine inter-observer agreement and compare interpretation of images with manufacturer-specific output with respect to thrombolysis decisions.

Patient Population

This study aims to recruit a total of 400 patients (200 in each arm), male and female, aged 18 or more presenting in stroke centres offering thrombolysis in the UK, within 4.5 hours of symptoms onset and clinically eligible for thrombolysis based on current guidelines. Patients requiring CTA on clinical grounds, including those meeting local criteria for endovascular treatment should not be randomised into the trial.

Inclusion and Exclusion Criteria

- Inclusion Criteria
  - Clinical diagnosis of stroke
  - Written informed consent from patient, legal representative or consultee
  - Male or female ≥18 years of age
  - Within 4.5 hours of onset as defined by time since last known well
- Exclusion Criteria
  - Contraindications to thrombolytic drug treatment for stroke
  - Pregnancy
  - Known impaired renal function precluding CT contrast administration
  - Known allergy to radiological contrast
  - Severe concurrent medical condition that would prevent participation in study procedures or with life expectancy ≤ 3 months.

Randomisation

Patients will be randomised to NCCT alone or NCCT+CTP+CTA an interactive voice response (IVRS) telephone system. Randomization can be done prior to scanning or at latest immediately after NCCT, provided that any additional trial imaging can be acquired at the same examination and without delay. The randomisation system will allocate patients using a mixed minimisation

and randomisation system. Patients will be randomized in blocks of 10, in which 8 patients are allocated by minimisation on study centre, stroke severity and hemispheric lateralisation, and 2 are allocated at random. In cases where the minimisation algorithm favours neither therapy, the allocation will be made at random; for the 8 patients allocated by minimisation within each block of 10, there will be 4 potential random allocations to each therapy

Treatment or Intervention

Routine brain imaging in most UK centres is currently NCCT. If the patient is randomised to undergo multimodal imaging further imaging will be conducted in the same scanner with minimal delay. The order in which these examinations are acquired may differ from one individual to another. CT workstations at local sites will be used to undertake interpretation of NCCT, CTA and post processing of CTP with whatever software is used locally (first post processing) and this information will be available to inform a decision on thrombolysis (with or without thrombectomy) in patients randomised to multimodal CT.

Central "core lab" post-processing of CTP will be undertaken using an independent dedicated analysis package (Apollo Medical Imaging Technology, Melbourne, VIC, Australia) to generate maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and delay time (DT). The volume of ischaemic penumbra will be defined according to thresholds identified in previous studies(22). Ischaemic core is defined as tissue with relative delay time >2 s and cerebral blood flow <40% relative to contra lateral hemisphere, while penumbra volume is defined as tissue with relative delay time >2 s and relative cerebral blood flow 40% or greater than contra lateral hemisphere (23) Processed CTP along with NCCT and CTA will be uploaded to SIRS2 for distributed, non-acute review by readers, including the clinicians at the randomising centre, in order to investigate inter-observer agreement and compare interpretation of images with manufacturer-specific output with respect to thrombolysis decisions.

Primary Outcomes

The primary outcome is the proportion of patients receiving IV rtPA. We hypothesise that the additional diagnostic information will increase the proportion of patients treated, principally by increasing treatment rates among those with clinically mild or improving symptoms. We hypothesise that a smaller number of subjects will be excluded from treatment due to identification of features signifying high risk or minimal benefit of treatment (e.g. large ischemic core or no visible ischemic penumbra).

Secondary Outcomes

Secondary outcomes will include time to decision and initiation of treatment, diagnostic accuracy, neurological and functional status. Early change in neurological status will be determined by the 24h NIHSS, and functional status will be determined by the mRS at 3 months. Secondary outcomes will include both a comparison of the distributions across all mRS disability categories, as well as the odds of achieving independence (dichotomised as mRS 0-1 or 0-2). Additional secondary outcomes include assessing inter-observer agreement for rtPA eligibility between local and centrally processed CTP/CTA. To achieve this central reading of trial scans will be performed to determine extent of ischaemic lesion on NCCT, any perfusion lesion, and angiographic occlusion, using validated visual rating as developed for IST-3 and MASIS (http://www.bric.ed.ac.uk/research/imageanalysis.html).

Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will review patient safety and may recommend early stopping of the study because of clinically and statistically relevant differences between randomised groups. Trial progress will be reviewed by a Trial Steering Committee (TSC). Premature discontinuation of the trial will be considered in the event of evolving safety issues being identified; or feasibility issues due to under-recruitment.

Sample Size Estimates

The trial will evaluate whether multimodal CT leads to an increase in the proportion of patients given IV rtPA. An increase in the proportion treated from 25% to 40% of ischaemic stroke patients evaluated within the 4.5h time window can be detected with 80% power at p=0.05 with 152 subjects per group. Literature identifies 27% of ischaemic stroke patients within 3h of onset being given IV rtPA while 31% were excluded primarily because of a mild or improving clinical deficit.(24) Allowing for randomisation before initial NCCT, and a diagnosis of non-ischaemic stroke pathology in 15% of patients, and allowing also for data acquisition and analysis problems yielding uninterpretable imaging of 10% in the multimodal imaging group, a total of 200 subjects per group would be initially recruited.

Statistical Analysis

The proportions of patients treated with IV rtPA in the two groups will be compared using logistic regression analysis adjusting for randomised treatment group and randomisation

minimisation variables. Odds ratios for the treatment effect will be estimated along with 95% confidence intervals and p-values. Exploratory analyses will also adjust for baseline factors predictive of treatment with rtPA.

Time to treatment decision will be analysed using a stratified Wilcoxon rank sum test and time to treatment administration using a stratified log-rank test to account for censored outcomes. Diagnostic sensitivity and specificity will be analysed. To provide a provisional assessment of the impact of the different strategies on outcome the analyses of the mRS will use an ordinal analysis approach to seek evidence of differences between the two randomised groups in distributions across the entire scale of the mRS. Odds ratios and 95% confidence intervals will be calculated from ordinal logistic regression analysis adjusting for randomisation minimisation variables. Inter observer agreement will be assessed using Kappa statistics and Krippendorff's alpha

Study Organization and Funding

The study is funded by the Efficacy and Mechanism Evaluation (EME) programme of the UK National Institute for Health Research (NIHR).

The study opened for recruitment in March 2015.

Discussion

Advanced imaging is increasingly used to guide thrombolysis decisions, with about 40% of patients in the United States undergoing some form of additional imaging in the acute stage(25). Perfusion imaging selection was also deployed in several recent trials of mechanical thrombectomy. However, there is no consensus on the equivalence of competing advanced imaging protocols, technical capabilities vary widely across sites, and observer interpretation differs significantly from either automated or consensus review in multicentre studies(26, 27) Critically, clinical trials of IV thrombolysis all used NCCT alone in patient selection, and whether reported gains in diagnostic accuracy or safety outcomes by additional advanced imaging selection translate into better clinical outcomes has not been evaluated(28, 29). By delaying institution of IV rtPA, the additional time required for advanced imaging acquisition, processing and interpretation may negate any benefits from improved patient selection.

NCCT is the currently recommended first line imaging modality for AIS (30). NCCT has the advantages of being fast, widely available and sensitive for identification of acute intracranial haemorrhage. However, early ischaemic changes reflecting cytotoxic oedema are detected in only 60% of all patients with moderate to severe stroke scanned within the first 6 hours after

symptom onset,(31) and a far lower proportion of patients with less severe symptoms(32). NCCT has limited ability to differentiate between ischaemic core and penumbra. Areas of hypo-attenuation are thought to reflect the ischaemic core while areas of swelling or gyral effacement without hypoattenuation are thought broadly to reflect penumbra, but sensitivity and inter-observer agreement for identification of these areas requires experience and, whilst good amongst experienced observers, is lower amongst non-experts, limiting clinical utility(33, 34). While extensive EIC (for example, defined as an area of more than one third of the MCA territory, or more quantitatively as lower Alberta Stroke Programme Early NCCT (ASPECT) or more extensive IST-3 score) correlate with poor clinical or imaging outcomes, (35, 36) there is no interaction between lesion extent and IV thrombolysis effect (37, 38), and therefore exclusion from treatment on the basis of early infarct signs extent alone is not justified. Finally, NCCT scans have limited ability to identify patients with intracranial vessel occlusion. The hyper dense artery sign, a marker of intracranial vessel obstruction, was reported to have a high specificity but sensitivity of about 52% in a large clinical sample, and its detection is related to scan quality, slice thickness, and clot burden. (39, 40)

Multimodal imaging provides additional information that can guide treatment decisions. CTA is 83% sensitive and 95% specific for detection of intracranial occlusion in AIS(41) with potential consideration of adjunctive thrombectomy as a treatment option in large artery occlusion.(42, 43) The overall diagnostic sensitivity of CTP among patients with suspected stroke is reported to be as high as 80%, with a lower sensitivity for patients with NIHSS <7.(15) Interpretation of CTP is confounded by variation in scan acquisition and analysis parameters(44). Different CTP selection criteria have been used in endovascular trials (45-50). Observational studies suggest an improved outcome when multimodal imaging is used for patient selection(13) with one centre reporting a threefold increase in thrombolysis rate(52). Some experienced centres using routine multimodal CT report feasibility and safety, with no major delays in door to needle times.(15, 52) This, however, might reflect improved efficiency in other aspects of the stroke pathway compensating for a typical 10-15 minutes of extra scanning (52, 57, 77, 78).. Additional imaging may, however, delay treatment initiation and evidence that CTA or CTP features modify treatment effect is so far lacking(55-57), and clinicians may find the interpretation of multimodal imaging difficult(58). It is possible that multimodal imaging should be utilised in specific subgroups (55, 58, 79), but these are not currently possible to specify. There is also no consensus

on whether multimodal imaging should include both CTA and CTP, or be limited to only one modality. CTP features did not modify treatment effect in recent endovascular thrombectomy trials.(59)

Minor or rapidly improving symptoms are a common cause for exclusion of patients from IV rtPA, despite lack of consensus on the definition of these terms, and poor outcome has been reported in up to one third of patients initially considered "too mild to treat"(60-62). Presence of an intracranial arterial occlusion is associated with poor outcome in patients presenting with transient ischaemic attacks or minor stroke(63-65), which suggests that CTA would be useful in this situation. The use of CTP had an additional value in predicting patients with TIA or minor stroke with a poor outcome, compared to CTA results or admission NIHSS alone(66).

In more severe stroke, especially in patients presenting towards the end of the therapeutic window, there may be concerns about increased risk of haemorrhage and whether there is enough salvageable tissue to warrant treatment. Higher ischaemic core volume is associated with poor clinical outcomes, but some studies specifically suggest adverse interaction with IV thrombolysis in this group of patients, with higher risk of ICH among those with core volume more than 100 ml (67) (68). Presence of a "target mismatch" profile has also been reported to be a good prognostic factor (13, 68). However, a recent analysis failed to identify a relationship between any perfusion pattern and response to IV rtPA(69). The benefit of treatment in patients with a small perfusion deficit has been recently questioned (51)

Multimodal imaging may increase clinician confidence in the diagnosis and might avoid thrombolysis in patients with stroke mimics. Between 5 and 30% of all patients treated with acute thrombolysis may have an alternative diagnosis on discharge(70, 71). Although the risk of IV rtPA associated haemorrhage in this group of patients appears very low (estimated at about 0.5%)(72), treatment is associated with increased direct and indirect costs, mainly related to prolonged hospital stay and acute care(70). Hypo- or hyper- perfusion on CTP that does not respect vascular territory has been described infrequently in cases of migraine and seizure, (73-75) and may assist in diagnosis of stroke mimics(15). Potential benefits of multimodal imaging need to be balanced against safety, cost and potential treatment delays. Additional radiation exposure risk (with once only investigation) and incidence of contrast induced nephropathy (2-3%) are low but still relevant. The greater concern is that any added value in patient selection

will be overshadowed by delays in treatment. The benefit of revascularization therapy is strongly time dependent, with the best results obtained within the 90 minutes of stroke.(76) Additional scans will delay treatment, but the clinical effect of this delay is currently not known.

The impact of evolving endovascular mechanical thrombectomy services on care pathways on the trial will be evaluated but this is not currently widespread at participating centres. Altered patient selection for endovascular treatment is another potential outcome of relevance.

Summary and Conclusions

Multimodal CT is a widely available tool for patient selection for revascularization therapy, but it is currently unknown whether the use of additional imaging in all stroke patients is beneficial or cost effective. This study will provide important data the effect of multimodal imaging on treatment of acute stroke.

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Independent Data Monitoring Committee (IDMC)

Andrew Demchuk (chair), Jean Claude Baron, Alan Montgomery

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