Protocol for Systematic Review of intravenous thrombolysis in acute ischaemic stroke

Background/why this review is needed:
ACEM recognises intravenous thrombolysis (IT) as a potentially beneficial intervention for acute ischaemic stroke (AIS). There is however, conflicting evidence regarding the impact of using IT for AIS, with some trials indicating clear patient benefits and others having been stopped early due to harm. Furthermore, despite a number of systematic reviews having been conducted there continue to be questions over the interpretation of the evidence including the appropriateness of pooling estimates of effect in clinical heterogeneous samples. Thus the administration of stroke thrombolysis by Emergency Department staff remains a controversial area and cannot currently be considered a ‘standard of care.’ The aim of this review is therefore to inform ACEM guidelines regarding the circumstances in which the benefits of administration outweigh the risks.

Objective:
Evaluate the consequence of administering intravenous thrombolysis v. usual care for mortality and morbidity outcomes in acute ischaemic stroke in order to clarify the circumstances in which the benefits of administration outweigh the risks

Research questions to be addressed:
1. Does intravenous thrombolytic therapy alter the risk of death from:
   a. Intracranial haemorrhage:
      i. Within the first 7 days following treatment
      ii. Within the first 30 days following treatment
      iii. 3-6 months post treatment
   b. Other causes
      i. Within the first 7 days following treatment
      ii. Within the first 30 days following treatment
      iii. 3-6 months post treatment
2. Does intravenous thrombolytic therapy alter the risk of symptomatic intracranial haemorrhage:

1 ACEM (2014) STATEMENT ON INTRAVENOUS THROMBOLYSIS FOR ISCHAEMIC STROKE (S126)
a. Within the first 24 hours following treatment

b. Within the first 7 days following treatment

3. Does thrombolytic therapy impact on neurological outcome by:

   a. Altering the proportion of patients who are able to return to independent living after treatment (i.e. moderately severe or severe disability as assessed by measures such as mRs, Barthel index, NIHSS etc) at:
      i. 3 months
      ii. 6 months
      iii. In the longer term (12-18 months, 24 months)

   b. Altering the proportion of patients who are dependent on others for some or all of their activities of daily living (i.e. moderately severe or severe disability as assessed by measures such as mRs, Barthel index, NIHSS etc) at:
      i. 3 months
      ii. 6 months
      iii. In the longer term (12-18 months, 24 months)

4. How does the risk of mortality or morbidity alter depending on:

   a. Patient's age (<65, 65-75, >75)
   b. Sex
   c. Ethnicity
   d. Socioeconomic group
   e. Baseline systolic blood pressure
   f. Timing of administration (90 minutes, 3 hours, 4.5 hours, >6 hours post event)
   g. Drug dose
   h. Co-morbidities (previous stroke/TIA, previous MI, hypertension, diabetes, chronic atrial fibrillation, obesity)
   i. Stroke severity on presentation (NIHSS score)
j. Stroke aetiology or location (e.g. cardioembolic, antherothrombotic, lacunar/small vessel disease, other)

k. Patients currently or previously receiving anticoagulant therapy

l. Patients currently or previously receiving antiplatelet therapy

m. Treatment centre specifics:
   i. Stroke Service
   ii. Stroke Ward
   iii. Allied Health available 24/7
   iv. Presented to Stroke Centre or interhospital transfer to one
   v. Telemedicine

5. Does intravenous thrombolytic therapy provide a cost effective treatment and is cost effectiveness dependent on:
   a. Patient’s age (<65, 65-75, >75)
   b. Sex
   c. Timing of administration (90 minutes, 3 hours, 4.5 hours, >6 hours post event)
   d. Drug dose
   e. Co-morbidities (previous stroke/TIA, previous MI, hypertension, diabetes, chronic atrial fibrillation, obesity)
   f. Stroke severity on presentation (NIHSS score)
   g. Stroke aetiology or location (e.g. cardioembolic, antherothrombotic, lacunar/small vessel disease, other)
   h. Patients currently or previously receiving anticoagulant therapy
   i. Patients currently or previously receiving antiplatelet therapy
   j. Treatment centre specifics:
      i. Stroke Service
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      iii. Allied Health available 24/7
      iv. Presented to Stroke Centre or interhospital transfer to one
      v. Telemedicine
Searches
The following electronic sources will be searched:

- MEDLINE,
- MEDLINE In-Process & Other Non-Indexed Citations,
- EMBASE,
- CDSR,
- CENTRAL (via the Cochrane Library).

Other sources:

- Key conference proceedings and reference lists of included papers will be hand searched.
- Prominent authors/clinicians in the field will be contacted as necessary.

The search strategy will focus on the intravenous administration of thrombolysis in acute ischaemic stroke and its effect on mortality and morbidity (specifically neurological outcomes). Search terms will include:

- Brain ischemia OR cerebrovascular accident OR acute ischemic stroke AND
- Systemic thrombolysis OR thrombolytic therapy OR tPA OR urokinase OR alteplase OR Tenecteplase OR Reteplase OR Streptokinase OR recombinant pro-urokinase OR lumbrokinase OR fibrinolytic agent/therapy OR plasmin/plasminogen

Only studies evaluating intravenous (as opposed to intra-arterial) thrombolysis for adults (aged 18 years and over) will be included in the review. Animal studies will also be excluded.

The search will include studies published in any language in order to determine the extent of the evidence world-wide. However due to time constraints only those published in English will be included in the final review, unless addition of the trials published in non-English journals would significantly boost the sample size available for the analysis.

Types of study to be included

- RCTs
- prospective cohort studies
- single-arm studies
- retrospective reviews of medical records
- case series
- registry studies

Existing systematic reviews will be excluded from the main analysis, but will be assessed for quality and included in the narrative review. In addition we will consider any recent evidence around factors such as clinical decision-making, patient preference, and reasons for patient non-consent to inclusion in trials of thrombolysis in stroke. These findings will provide additional, and alternative insight into the effectiveness of the intervention and inform the report recommendations.

**Condition or domain being studied**
Acute Ischemic Stroke

**Participants/population**
Patients treated for Acute Ischemic Stroke

**Interventions/exposure**
Thrombolysis given intravenously

**Comparator/control**
Usual care or placebo

**Outcomes**
Mortality (+ cause) rate
Rate of symptomatic intracranial haemorrhage
Functional outcome:

- Independent living measured by:
  - mRs score of 0-2
  - Barthel index score of 80-100
  - NIHSS score of 0-4
  - Proportion returning to employment in under 65s
  - Proportion returning to same accommodation type (e.g. own home, low level aged care facility)

- Moderately severe disability measured by:
  - mRs score of 3
  - Barthel index score of 21-79
  - NIHSS score of 5-21
  - Proportion returning to higher level care
Severe disability (dependency) measured by

- mRs score of 4 or 5
- Barthel index score of 0-20
- NIHSS score >22
- Proportion institutionalised

Where available, information on factors such as communication/speech, perception, memory, or concentration will also be extracted.

Treatment costs

Data extraction (selection and coding)
Studies will be screened and outcome data extracted using a standardised data extraction form by one researcher and independently checked by a second. Any disagreements will be resolved through discussion, with involvement of a third reviewer when necessary.

If the data to be extracted is unclear, authors will be contacted for further information.

If there is no response, a further attempt to make contact will be made a fortnight later. If there is no response after a further 4 weeks, the data will be presumed unavailable.

Risk of bias (quality) assessment
All studies will be critically appraised for risk of bias using an appropriate tool, depending on the design of the original study:

- RCT - Cochrane risk of bias$^2$
- Single-arm studies – NICE Methodology Checklist: Prognostic Studies$^3$
- Systematic reviews - AMSTAR tool$^4$.

Any risk of bias arising from potential conflict of interest for authors will also be documented.

The study characteristics and quality assessments will be described narratively and represented in tabular form in the final report.


**Strategy for data synthesis**

Synthesis will be attempted if there is deemed to be sufficient clinical (population characteristics, outcome measures) and methodological (study design) homogeneity of studies. For example, in order to test the reliability of conversion factors for SICH criteria and the groupings for functional outcomes outlined above, separate analyses will be carried out initially depending on the SICH criteria or functional outcome measure used. Studies will then be grouped together and the analysis re-run to enable a comparison of the results generated from separate and grouped studies.

If there is sufficient homogeneity of available data we will combine data from RCTs (using random effects meta-analysis) to provide comparative estimates of treatment efficacy. RCTs and quasi-randomised trials will only be combined if they include similar patients and methods, so as to give an estimate of effect in all studies.

In this case, statistical analyses will include:

- Comparison of intervention by dose, timing of delivery, patient demographics (age, sex ethnicity socioeconomic status), co-morbidities, baseline systolic BP, stroke severity, aetiology/location, anticoagulant or antiplatelet therapy, treatment centre;
- Odds ratios will be calculated for treatment failure within 24 hours, seven days, three, six, 12-18 and 24 months after treatment for each individual study, assessing dose, timing of delivery, patient demographics (age, sex ethnicity socioeconomic status), co-morbidities, baseline systolic BP, stroke severity, aetiology/location, anticoagulant or antiplatelet therapy, treatment centre separately. These odds ratios will then be combined using a random effects model, to cope with (moderate) clinical heterogeneity. Forest plots will be presented for each outcome;
- Weighted mean differences will be calculated for rates of treatment failure, for dose, timing of delivery, patient demographics (age, sex, ethnicity socioeconomic status), co-morbidities, baseline systolic BP, stroke severity, aetiology/location, anticoagulant or antiplatelet therapy, treatment centre;
- Wider exploration of morbidity outcomes will be explored using data derived from single-arm studies and from the individual arms of comparative studies;

Statistical heterogeneity will be examined by visual inspection of forest plots and using the chi-squared test of heterogeneity. The $I^2$ test will be used to quantify the degree of heterogeneity that is not due to chance. The $\tau^2$ statistic will be calculated to assess the between-study variance of true effect.

A cost-consequences analysis will be undertaken to estimate the cost effectiveness of treatment with thrombolysis in acute ischaemic stroke. In this approach the costs of applying each treatment are assessed and matched to the benefits generated. This will allow a comparison to be made to the cost of other treatment options.
(including no treatment) across different contexts, which is both comprehensive and transparent.

**Analysis of subgroups or subsets**

Sub group analysis will include:

- **Treatment factors:**
  - Time after treatment
  - Timing of drug administration
  - Drug dose

- **Patient characteristics**
  - Age
  - Sex
  - Ethnicity
  - Socioeconomic status
  - Co-morbidities
  - Previous or current treatment with anticoagulants
  - Previous or current treatment with antiplatelets

- **Stroke characteristics**
  - Severity on presentation
  - Aetiology or location

- **Treatment centre**
  - Stroke Service
  - Stroke Ward
  - Allied Health available 24/7
  - Presented to Stroke Centre or interhospital transfer to one
  - Telemedicine