



strokefoundation

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29 May 2015

Dr. Andrew Gosbell
Director of Policy & Research
Australasian College for Emergency Medicine
34 Jeffcott St
West Melbourne VIC 3003

Sent via email andrew.gosbell@acem.org.au

Dear Dr. Gosbell,

Re: Call for submissions on evaluation of the evidence for administration of thrombolytic therapy in acute ischaemic stroke

Thank you for the opportunity to submit information for the evaluation. As you know, the National Stroke Foundation (NSF) is a not for profit organisation that works with stroke survivors, carers, health professionals, the public, and government to reduce the impact of stroke on the Australian community.

The NSF Clinical Council have provided the following information that we hope will help to inform your Review Team and Expert Advisory Panel.

- The NSF supports evidence based practice and is supportive of this review as we are cognisant that the clinical guidelines were reviewed several years ago now.
- The interventions listed in the search string include multiple thrombolytics, not just alteplase. Alteplase is currently the only agent used (or approved) clinically, outside of a clinical trial. Pooling results from other thrombolytic trials will only obscure the question of thrombolytic effectiveness. For example, including streptokinase will be misleading as this agent was specifically discontinued due to ICH risk. Analysis confined to the agent used in practice worldwide is recommended to make the review more efficient and meaningful. Given the stated concerns regarding heterogeneity in the data, exclusion of thrombolytics other than alteplase is also a logical step to reduce heterogeneity. On this note, the criteria for what is or is not acceptable heterogeneity for pooling should be pre-specified.
- The reviewers are strongly encouraged to include the individual patient pooled meta-analysis published last year by an independent statistical group (Emberson et al The Lancet). We believe this paper utilizes optimal methodology and the results will answer several of the questions proposed in the review which will not be possible without the insights from this individual patient pooled dataset.



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- We note the decision to exclude all systematic reviews from the review. We recommend that this decision be reviewed. The proposed inclusion of lower levels of evidence in the evaluation (e.g. single arm studies, retrospective audit and case series) would be generally be inappropriate given the availability of large RCTs. Large registries such as SITS may assist with answering some of the subgroup questions although we would emphasize the difference between prognosis and treatment effect (the latter requiring a control group). We suggest excluding non-randomised studies from the evaluation (or include only in narrative review if necessary).
- Regarding question 1 (mortality), the timeframe for assessing fatal SICH should be 7 days as any later SICH would be unrelated to treatment (and generally not reported). We also note that the available outcome measure for mortality (and other outcomes) is a proportion (and not a 'rate').
- Regarding question 2 (symptomatic ICH), we suggest that the question of how to categorise symptomatic ICH is not straightforward and should be pre-specified in the protocol. We recommend the use of SITS-MOST or ECASS-III definitions (several definitions were used across the studies but the 2014 Emberson meta-analysis reports some harmonized data for all patients). We recommend against out-of-date methods such as the NINDS definition of haemorrhage which has been found to overestimate the rate of true symptomatic ICH. "Conversion" between definitions as suggested on page 7 is not appropriate.
- Regarding question 3 (neurological outcome), the NIHSS is listed as a possible outcome at 3/6/12 months. The NIHSS, a neurological impairment measure, bears very little relationship to functional status at these time points and is not useful as an outcome measure. Furthermore, given that mRS 0-1 is the primary outcome of most published RCTs, it is not clear why this is not being assessed (and 0-2 is used instead). mRS 1 versus 2 is a meaningful difference for patients and we recommend that this is one of the specified outcomes at the onset.
- The protocol places heavy emphasis on death and hemorrhagic complications rather than focusing on reduction in disability when this is the main aim of treatment and is the outcome most relevant to patients. In this regard we would strongly support the inclusion of patient preferences within the review as there is useful published literature on this topic. The term "treatment failure" is introduced on page 7 without definition – this will be a key determinant of the validity of the findings and should be pre-specified. The timing of assessment for primary outcome accepted throughout the stroke field is 3 months as this captures the majority of stroke recovery.
- We note that "reasons for non-consent" is listed as a topic for analysis. It would be very difficult to find data on reason for non-consent as researchers are not allowed to ask this question.
- There are several other questions, mainly related to subgroups, which may be challenging in the absence of individual patient data (e.g. age strata of <65, 65-75 and >75 have not generally been reported).



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- We recommend that the appropriate parameter to examine effects of time is “onset to treatment time” – not “time after treatment” or “timing of drug administration”. Also, no trial has followed patients to 24 months (only IST-3 followed beyond 3 months), no trial has examined tPA beyond 6h from onset, and mortality at 90 days has been reported but not the proposed 30 days. Thus, there is no value in including these outcomes in the proposed review protocol. The feasibility of the proposed stratifications and time cut-points should be reviewed before finalization of the protocol.
- As outcome from stroke is strongly associated with initial severity, we recommend pre-specifying inclusion of NIHSS strata for severity subgroups.

Our sincere thanks for the invitation to comment on the evaluation and we welcome the opportunity to discuss our comments with you in more detail should you require further clarification.

Yours sincerely

Bruce C.V. Campbell

Dr Bruce Campbell
Chair
Clinical Council