Completing the published record: a thread of evidence

Daniel Shanahan, Associate Publisher BioMed Central
EQUATOR/REWARD Conference, 28 September 2015
A ‘crisis’ in reproducibility?

• The current over-emphasis on results has led to many problems in the literature:
  • Publication bias
  • Selective reporting of outcomes and analyses
  • HARKing (Hypothesising After the Results and Known)
  • Significance chasing and low statistical power
  • Lack of data sharing and replication
To be sure of hitting the target...
Methods in the madness

• Research only has value if:
  • the hypothesis is relevant
  • the methods are valid
  • the findings are published in a usable form

• The value in science is in the QUESTION it asks and the PROCESSES it uses, not in the OUTCOME observed

• Traditionally, journals offer a précised version of the methods used; this meant that authors often simply cited a previous paper where this technique was used

• Instead we need full, detailed reports of the methods and these need to be evaluated and published **prospectively** to prevent publication bias, selective reporting, HARKing etc.
Completing the published record

Registration is becoming increasingly commonplace, with evidence it helps to reduce publication bias.*

Completing the published record

Evaluating research based on the methods...

This is not new:

• *Trials*, the *BMC series* and others have been calling for the prospective (before recruitment completes) publication of study protocols for almost 15 years

• More recently we have also begun publishing statistical analyses plans

• *Systematic Reviews* calls for the publication of systematic review protocols

• In 2013, the journal *Cortex* launched Registered Reports in clinical psychology

• We even have detailed, expert reporting guidelines for such protocols, which set out the minimum amount of information required to be reported:
...regardless of outcome or significance of findings

• The idea that ‘negative’, non-confirmatory results are valuable and should be published is gaining increasing support:

• ‘Low impact’ publications, such as pilot and feasibility studies, are also increasing recognized as fundamental to research.
Completing the published record

Effect of thrombolytic with alteplase within 6 h of acute ischaemic stroke on long-term outcomes: analysis of the third International Stroke Trial (IST-3): second randomised controlled trial

Abstract

Background and purpose: in acute ischaemic stroke, the Hyperdense Artery Sign for Arterial Occlusion (HAS-O) on computed tomography (CT) angiography is used to select patients for arterial recanalisation. Although improved outcomes among patients with HAS-O have been reported, confirmation of clinical benefit remains lacking. We aimed to determine the effect of thrombolysis in patients with canine arterial occlusion in different functional states based on HAS-O.

Methods: 373 patients were randomised to receive alteplase (100 mg) or placebo with alteplase within 6 h of onset. Of the 373 patients, 363 had HAS-O. The primary outcome was a composite of death, severe disability or dependency at 90 days. We used proportional hazards regression to assess the effect of HAS-O on outcomes.

Results: 363 patients had HAS-O. The median time from symptom onset to treatment was 2.5 h (IQR 1.7-3.9). There were no differences in baseline characteristics between the two groups. The primary outcome occurred in 16.6% of patients in the alteplase group and 20.0% in the placebo group (HR 0.83, 95% CI 0.55-1.27, p=0.38).

Conclusion: HAS-O was not associated with improved outcomes in patients with parallel to thrombolysis. Further studies are needed to determine the role of HAS-O in patient selection for thrombolysis.

Clinical Sciences

Sensitivity and specificity of HAS-O in acute ischemic stroke

Carn B, Mitrović E, Boyd D, MBBS, Francesca M, Campbell, MD, Joana M, Wardlaw, MD, IST-3 Collaborative Group

Pleasant Affiliations

University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU, United Kingdom.

E-mail: joana.wardlaw@ed.ac.uk

Original Contribution

Efficacy and Mechanism Evaluation

VOLUME 1 ISSUE 1 JULY 2016

ISSN 2055-531X

BioMed Central

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Linked publications

**Protocol and updates**

_Update on the third international (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the recruited patients_

Peter Sanderscock, Richard Lindley, Joanna Wardlaw, Martin Dennis, Karen Imrie, David Perry, Vera Soosay, David Buchanan, Graham Versalides, Anna Czlonkowski, Karsten Bruns Slot, Veronica Murray, Andre Pfeeters, Graeme J Hanley, Karl Kisch, Teresa A Cantiani, Gordon Cubilla, Stephen J Phillips, Aria Antoni, Mark Ingold Kane, Erik Lundstrom, and the IST-3 collaborative group

**Abstract**

Background: Intravenous recombinant tissue plasminogen activator (rt-PA) is an approved treatment for patients with acute ischaemic stroke who meet strictly defined criteria. IST-3 sought to evaluate the long-term effects of rt-PA thrombolysis, and to determine whether a wider range of patients might benefit from the treatment.

Design: International, multicentre, prospective, randomised, double-blind, placebo-controlled, parallel-group, placebo-controlled, factorial, 2x2 factorial, study.

Setting: Developing symptoms of acute ischaemic stroke.

Results: The initial trial phase was stopped early due to a significant increase in symptomatic intracranial haemorrhage and brain infarction.

Recruitment began on October 1, 2010, and ended on May 31, 2011.

**Statistical analysis plan**

**Primary results paper**

_The benefits and harms of intravenous recombinant tissue plasminogen activator (rt-PA) for acute ischaemic stroke (the third International Stroke Trial [IST-3]): a randomised controlled trial_ by the IST-3 collaborative group*

**Secondary results papers**

_Observer reliability of CT angiography in the assessment of ischaemic stroke: an update_ by Grant Maclaren, Matthew E Chisholm, Robin J Secher, Mark A. Bignall, Peter A. G. R. Brown, and the IST-3 collaborative group

_Targeting recombinant tissue-type plasminogen activator (rt-PA) for acute stroke: an update_ by E. S. J. R. Brown and Grant Maclaren, on behalf of the IST-3 collaborative group
Identifying related articles
Looking for a needle in a haystack
Completing the published record

Linked publications

Protocol and updates

Update on the third international (IST-3) of thrombolysis for acute is stroke and baseline features of the recruited
Peter Sandeckock1, Richard Lindley2, Joanna Wardlaw1, Martin Dennis1, Karen Irvin1, David Penny1, Vera Sox1, David Buchanan1, Graham Versiels3, Anna Cottinova1, Karsten Bruns2, Veronica Murry2, Andre Peeters4, Graeme J Hanley4, Karl Michels5, Peter H. A. Cantijn1, Gordon Cubillo4, Stephen J. Phillips2, Aine Antonio2, Martin Ingold6, Kim Christensen7, and the IST-3 collaborative group

Abstract
Background: Intravenous recombinant tissue plasminogen activator (tPA) is only efficacious in patients with acute ischaemic stroke who meet strictly defined criteria. IST-3 sought to validate and precision of the estimates of the overall treatment effects on efficacy, safety and efficacy, and to determine whether a wider range of patients could benefit.

Methods: International, multicentre, prospective, randomised, placebo-controlled trial of tPA in acute ischaemic stroke. Suitable patients were randomised to receive tPA or placebo, and to different treatment regimens. The effect of tPA on mortality and disability was evaluated.

Results: The initial trial was shown to be safe and effective. Recruitment began on October 16, 2001.

Conclusion: The study is ongoing.

Statistical analysis plan

Primary results paper

The benefits and harms of intravenous recombinant tissue plasminogen activator (tPA) for acute ischaemic stroke (the third International Stroke Trial [IST-3]): a randomised controlled trial

The IST-3 collaborative group

Summary

Background: Thrombolytic therapy is of net benefit in patients with acute ischaemic stroke and is treated with a variety of drug regimens and a wide range of patients.

Methods: The study was a randomised controlled trial of alteplase tPA, enoxaparin, and placebo in patients with acute ischaemic stroke.

Secondary results papers

Observer reliability of CT angiography in the assessment of ischaemic stroke

Targeting Recombinant Tissue-Type Plasminogen Activator in Acute Ischemic Stroke: an Update
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Linked publications

Trials

Protocol and updates

Update on the third international (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the recruited participants

Primary results paper

The benefits and harms of intravenous recombinant tissue plasminogen activator in acute ischaemic stroke (the third International Stroke Trial [IST-3]): a randomised controlled trial

Secondary results papers

Observer reliability of CT angiography in the assessment of ischaemic stroke

Statistical analysis plan

Special report: Statistical analysis plan for the third International Stroke Trial (IST-3): part of a 'thread' of reports of the trial
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Bringing it all together

**crossref Linked Clinical Trials**

- **Manuscript title**: Peer-led healthy lifestyle program in supportive housing: study protocol for a randomized controlled trial
- **Journal**: Trials journal
- **DOI**: 10.1186/13063-015-0902-z

Create a link to send to the author

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**Clinical Trials**

1. **Clinical Trial Number**: NCT02175641
2. **Trial registry**: ClinicalTrials.gov
3. **Relationship of this paper to the clinical trial**: Pre-results

Approve Awaiting your approval

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Linked reports of clinical trials

Trial registration number

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Wellcome Trust

American Psychological Association
Open Trials
Thank you!

daniel.shanahan@biomedcentral.com