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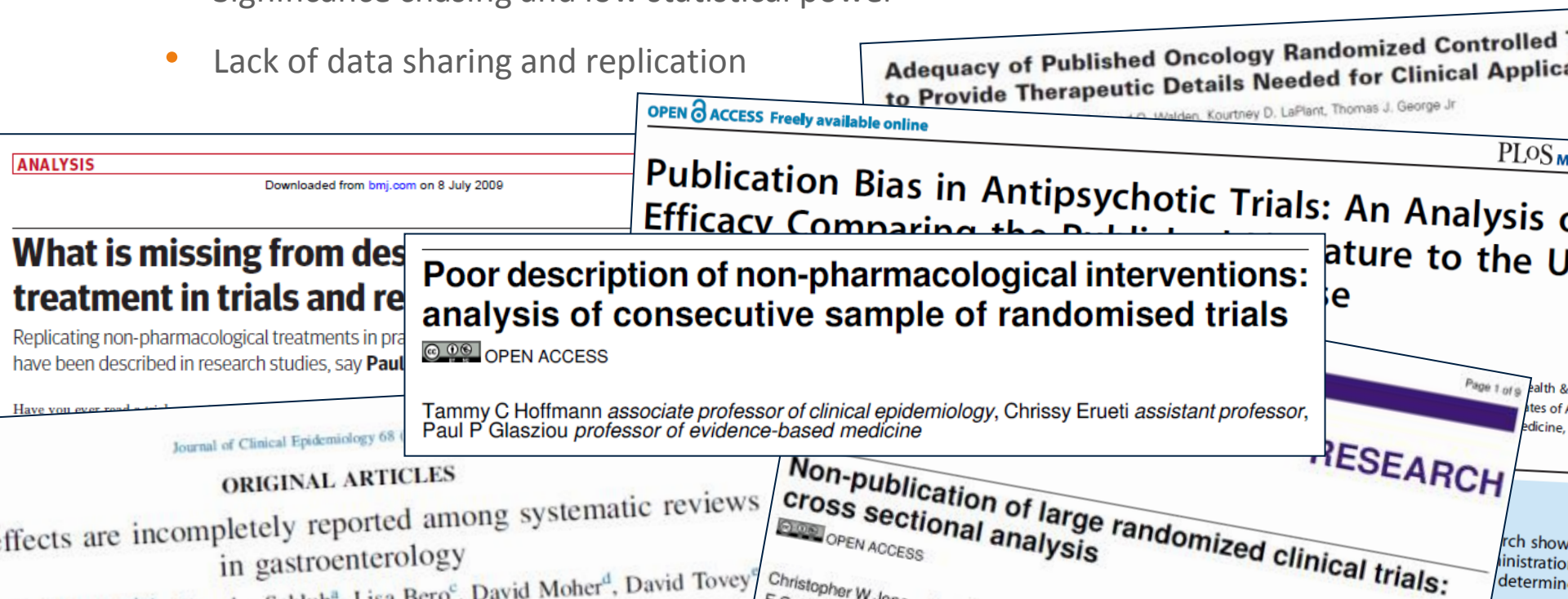
Completing the published record: a thread of evidence

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

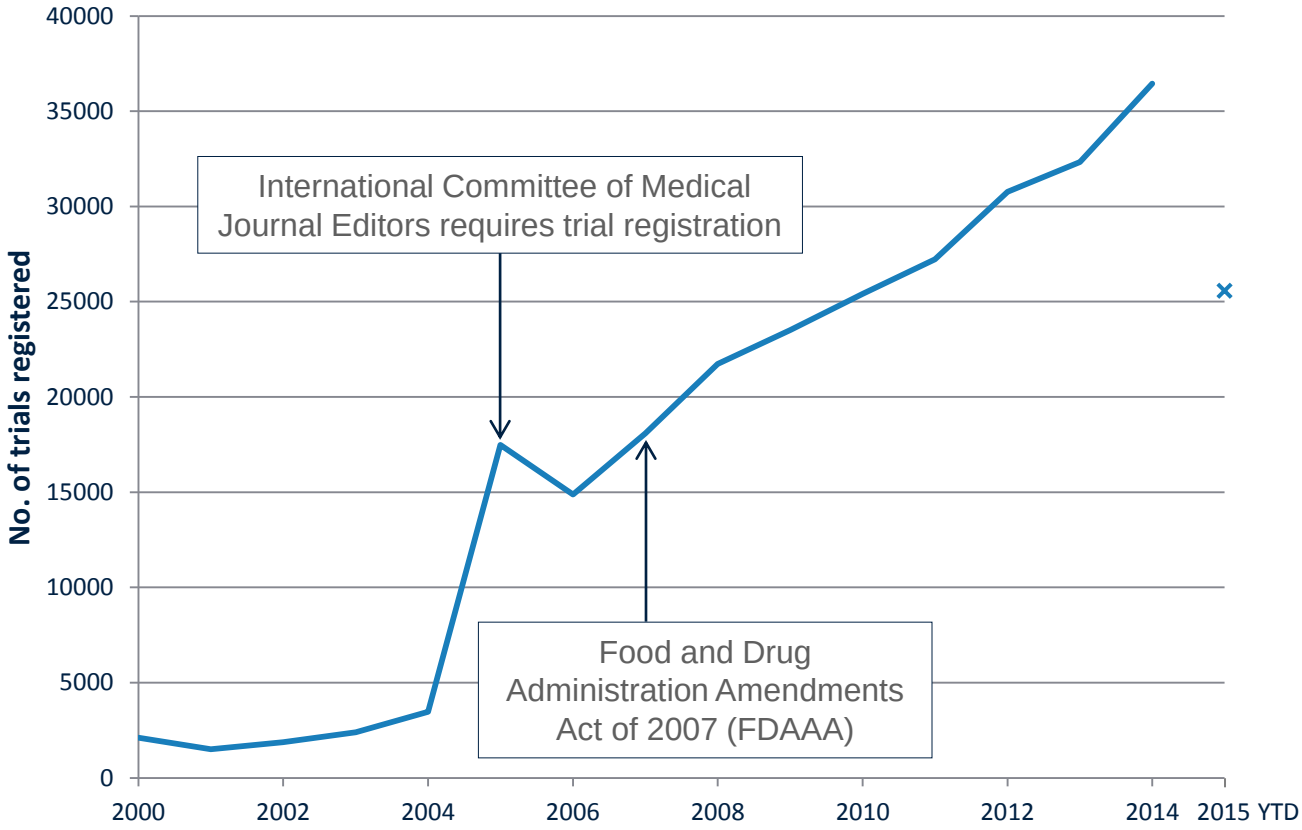
- Research only has value if:
  - the hypothesis is relevant
  - the methods are valid
  - the findings are published in a usable form

This is where we come in

- 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.

Prospective study registration

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



*Emdin *et al. JAMA Intern Med.* 2015;175(2):304-307.

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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:

RESEARCH AND REPORTING METHO

SPIRIT 2013 Statement: Defining Standa
Clinical Trials

An-Wen Chan, MD, DPhil; Jennifer M. Tetzlaff, MSc; Douglas G. Altman, DSc;
Karmela Krleža-Jerić, MD, DSc; Asbjørn Hróbjartsson, PhD; Howard Mann, MD
Caroline J. Doré, BSc; Wendy R. Parulekar, MD; William S.M. Summerskill, M
Harold C. Sox, MD; Frank W. Rockhold, PhD; Drummond Rennie, MD; and D

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality.

Moher et al. Systematic Reviews 2015, 4:1
http://www.systematicreviewsjournal.com/content/4/1/1

SYSTEMATIC REVIEWS

RESEARCH Open Access

Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement

David Moher[1*], Larissa Shamseer[1], Mike Clarke[2], Davina Ghersi[3], Alessandro Liberati[4], Mark Petticrew[4], Paul Shekelle[5], Lesley A Stewart[6] and PRISMA-P Group

Abstract

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…regardless of outcome or significance of findings

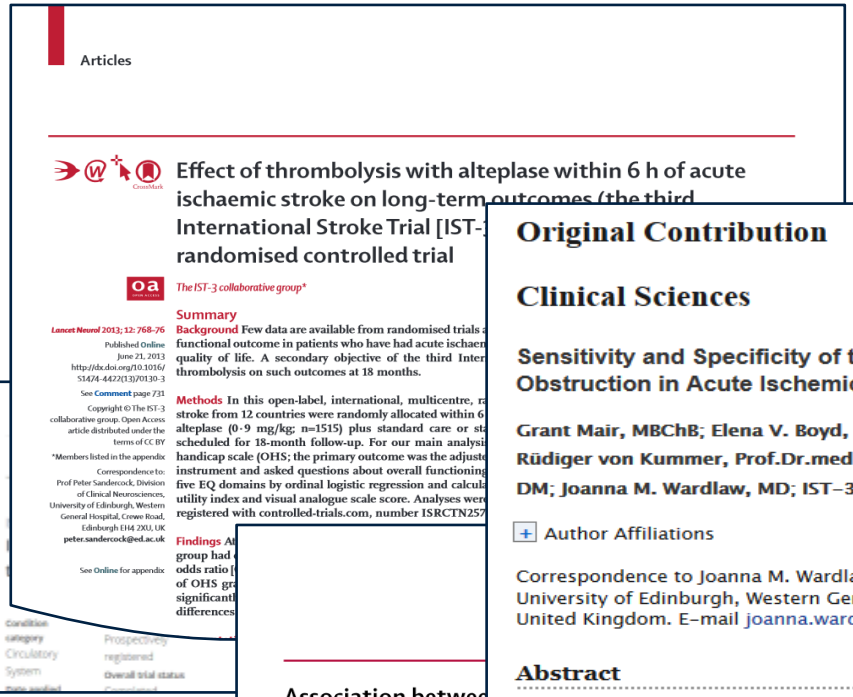
- The idea that 'negative', non-confirmatory results are valuable and should be published is gaining increasing support:

JOURNAL OF NEGATIVE RESULTS IN BIOMEDICINE

BILL & MELINDA GATES foundation

NHS
Health Research Authority

- 'Low impact' publications, such as pilot and feasibility studies, are also increasing recognized as fundamental to research.



Articles

Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-] randomised controlled trial

The IST-3 collaborative group*

Summary

Background Few data are available from randomised trials a functional outcome in patients who have had acute ischaem quality of life. A secondary objective of the third Inter thrombolysis on such outcomes at 18 months.

Methods In this open-label, international, multicentre, r stroke from 12 countries were randomly allocated within 6 alteplase (0·9 mg/kg; n=1515) plus standard care or st scheduled for 18-month follow-up. For our main analysi handicap scale (OHS; the primary outcome was the adjust instrument and asked questions about overall functioning five EQ domains by ordinal logistic regression and calcul utility index and visual analogue scale score. Analyses wer registered with controlled-trials.com, number ISRCTN257

Findings A group had odds ratio [of OHS gr significant differences

Lancet Neurol 2013; 12: 768–76
Published Online June 21, 2013 http://dx.doi.org/10.1016/S1474-4422(13)70130-3

See Comment page 731

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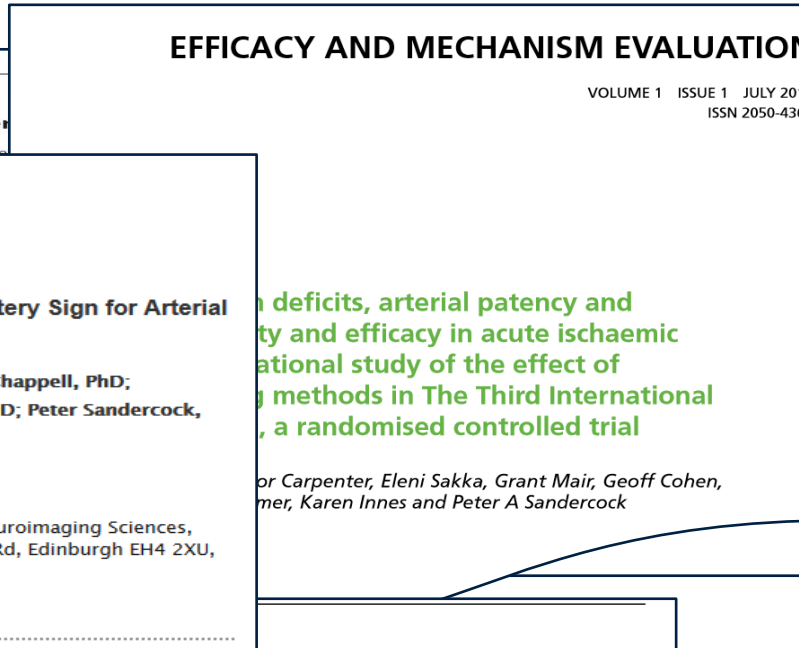
*Members listed in the appendix

Correspondence to: Prof Peter Sandercock, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK peter.sandercock@ed.ac.uk

See Online for appendix

Third Inter

William Whitele



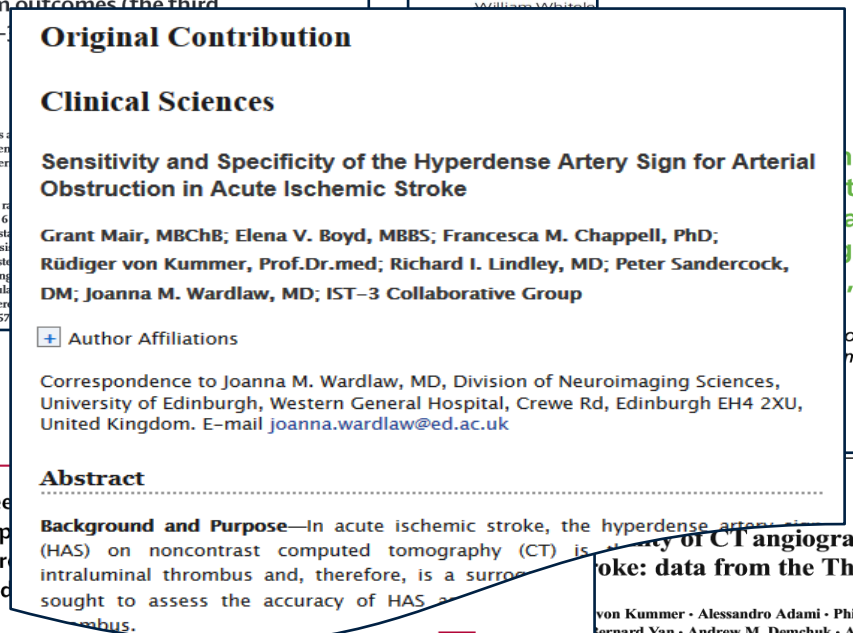
EFFICACY AND MECHANISM EVALUATION

VOLUME 1 ISSUE 1 JULY 20

ISSN 2050-43

deficits, arterial patency and
ty and efficacy in acute ischaemic
ational study of the effect of
methods in The Third International
, a randomised controlled trial

or Carpenter, Eleni Sakka, Grant Mair, Geoff Cohen,
mer, Karen Innes and Peter A Sandercock



Original Contribution

Clinical Sciences

Sensitivity and Specificity of the Hyperdense Artery Sign for Arterial Obstruction in Acute Ischemic Stroke

Grant Mair, MBChB; Elena V. Boyd, MBBS; Francesca M. Chappell, PhD; Rüdiger von Kummer, Prof.Dr.med; Richard I. Lindley, MD; Peter Sandercock, DM; Joanna M. Wardlaw, MD; IST–3 Collaborative Group

Author Affiliations

Correspondence to Joanna M. Wardlaw, MD, Division of Neuroimaging Sciences, University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU, United Kingdom. E-mail joanna.wardlaw@ed.ac.uk

Abstract

Background and Purpose—In acute ischemic stroke, the hyperdense artery sign (HAS) on noncontrast computed tomography (CT) is a marker of intraluminal thrombus and, therefore, is a surrogate sought to assess the accuracy of HAS a mbus.

Association betwee
outcomes, and resp
acute ischaemic str
Trial (IST-3): second
controlled trial

The IST-3 collaborative group*

Summary

Background Brain scans are essential to exclude haemorrhage in patients with suspected acute ischaemic stroke before treatment with alteplase. However, patients with early ischaemic signs could be at increased risk of haemorrhage after alteplase treatment, and little information is available about whether pre-existing structural signs, which are common in older patients, affect response to alteplase. We aimed to investigate the association between imaging signs on brain CT and outcomes after alteplase.

Methods IST-3 was a multicentre, randomised controlled trial of intravenous alteplase (0·9 mg/kg) versus control within 6 h of acute ischaemic stroke. The primary outcome was independence at 6 months (defined as an Oxford Handicap Scale [OHS] score of 0–2). 3035 patients were enrolled to IST-3 and underwent prerandomisation brain CT. Experts who were unaware of the random allocation assessed scans for early signs of ischaemia (tissue hypoattenuation, infarct extent, swelling, and hyperattenuated artery) and pre-existing signs (old infarct, leukoaraiosis, and atrophy). In this prespecified analysis, we assessed interactions between these imaging signs, symptomatic intracranial haemorrhage (a secondary outcome in IST-3) and independence at 6 months, and alteplase, adjusting for Institutes of Health Stroke Scale (NIHSS) score, and time to randomisation. This trial is registered number ISRCTN25765518.

Findings 3017 patients were assessed in this analysis, of whom use, Onset to stroke Treatment Time, NIHSS [DRAGON]; Totaled Prognosed control. A reduction in independence was predict model; and a model with National Institutes of Health Stroke Scale and age) had similar (0·51, 0·38–0·68) receiver operator characteristic curves (AUROCC) to predict sICH (*P* for difference >0.05). The simplest model (with covariates National Institutes of Health Stroke Scale and age) predicted both sICH (AUROCC, 0.63; 95% CI, 0.58–0.68) and poststroke poor functional outcome (AUROCC, 0.80; 95% CI, 0.77–0.82) similarly to complex models. There was no evidence that the effect of r-tPA in patients at high predicted risk of sICH or poor functional outcome after stroke was less than in those at

Conclusions—There is a clinically relevant net positive effect of r-tPA in patients with acute of sICH or poor functional outcome.

Lancet Neurol 2015; 14: 485–96
Published Online March 27, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00012-5

See Comment page 458

*Collaborators are listed in the appendix pp 2–5

Correspondence to: Prof J M Wardlaw, Brain Research Imaging Centre, Centre for Clinical Brain Sciences, Univ

Targeting Rec
Activator in Acu
Intracranial Hem
An Analysis

William N. Whiteley, Geoff Cohen, MA; Ri Peter Sandercock,

Background and Purpose—Intravenous symptomatic intracranial hemorrhage models could identify patients least lik

Methods—We used the Third Internation randomized trial of 0.9 mg/kg r-tPA discrimination and calibration of pre developed a new model using variables of death or dependency with r-tPA in pa

Results—Prediction models for sICH or p Dense Artery, Age, National Institutes Severity [GRASPS]; Stroke Thrombo Treatment Time, NIHSS [DRAGON]; Totaled with National Institutes of Health Stroke Scale and age) had similar (0·51, 0·38–0·68) receiver operator characteristic curves (AUROCC) to predict sICH (*P* for difference >0.05). The simplest model (with covariates National Institutes of Health Stroke Scale and age) predicted both sICH (AUROCC, 0.63; 95% CI, 0.58–0.68) and poststroke poor functional outcome (AUROCC, 0.80; 95% CI, 0.77–0.82) similarly to complex models. There was no evidence that the effect of r-tPA in patients at high predicted risk of sICH or poor functional outcome after stroke was less than in those at

Conclusions—There is a clinically relevant net positive effect of r-tPA in patients with acute of sICH or poor functional outcome.

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Richard I. Lindley, Geoff Cohe

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versus control given wi
ratios (ORs) and 95% CI
atients treated up to 6 h

f stroke significantly in
low-up (1611/3483 [46·
19–66) per 1000 peop
00. The benefit of rt-P
1·53, 1·26–1·86, p<0·
vs 202/883 [22·9%], 1·
within 7 days were incr
llow-up the excess w
0·33). Symptomatic i
accounted for most o
years or younger

ography in the assessment of acute
oke: data from the Third International Stroke Trial

von Kummer · Alessandro Adami · Philip M. White · Gernard Yan · Andrew M. Demchuk · Andrew J. Farrall · h Ramaswamy · Daisy Mollison · Elena V. Boyd · Karim Samji · Andrew J. Baird · Geoff Cohen · ner · David Perry · Richard Lindley · k · Joanna M. Wardlaw · The IST-3 Collaborative Group

Accepted: 22 September 2014 / Published online: 7 October 2014 eidelberg 2014

ography (CTA) is often used for assessing patients with acute ischaemic stroke. Only limited observer reliability data exist. We tested inter- and intra-observer reliability for the assessment of CTA in acute ischaemic stroke.

Methods We selected 15 cases from the Third International Stroke Trial (IST-3, ISRCTN25765518) with various degrees of arterial obstruction in different intracranial locations on CTA. To assess inter-observer reliability, seven members of the IST-3 expert image reading panel (>5 years experience reading CTA) and seven radiology trainees (<2 years experience) rated all 15 scans independently and blind to clinical data for: presence (versus absence) of any intracranial arterial abnormality (stenosis or occlusion), severity of arterial abnormality using relevant scales (IST-3 angiography score, Thrombolysis in Cerebral Infarction (TICI) score, Clot Burden Score), collateral supply and visibility of a perfusion defect on CTA source images (CTA-SI). Intra-observer reliability was assessed using independently repeated expert pan el scan ratings. We assessed ol Krippendorff's-alpha O ience indicates that intravenous rt-PA incr come and alive and independent at final follo ly as possible after acute ischaemic stroke, alt

Electronic supplementary material The online version of this article

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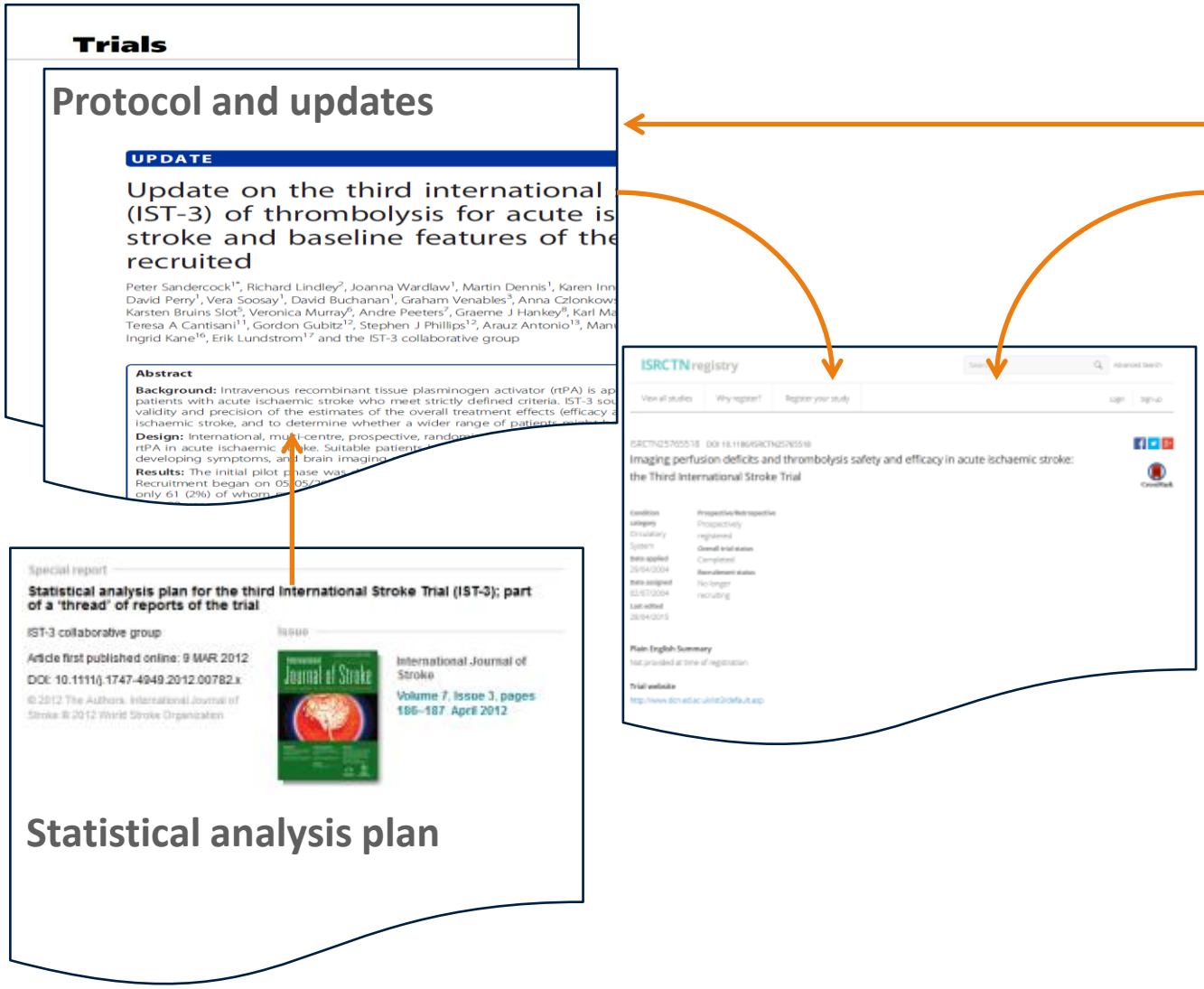
Linked publications



~~Identifying related articles~~

Looking for a needle in a haystack

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Linked publications

Trials

Protocol and updates

UPDATE

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

Peter Sandercock[1*], Richard Lindley[2], Joanna Wardlaw[1], Martin Dennis[1], Karen Inn David Perry[1], Vera Soosay[1], David Buchanan[1], Graham Venables[3], Anna Czlonkows Karsten Bruins Slot[5], Veronica Murray[6], Andre Peeters[7], Graeme J Hankey[8], Karl Ma Teresa A Cantisani[11], Gordon Gubitz[12], Stephen J Phillips[12], Arauz Antonio[13], Mani Ingrid Kane[16], Erik Lundstrom[17] and the IST-3 collaborative group

Abstract

Background: Intravenous recombinant tissue plasminogen activator (rtPA) is ap patients with acute ischaemic stroke who meet strictly defined criteria. IST-3 sou validity and precision of the estimates of the overall treatment effects (efficacy s ischaemic stroke, and to determine whether a wider range of patients might ben

Design: International, multi-centre, prospective, randomi rtPA in acute ischaemic stroke. Suitable patients developing symptoms, and brain imaging

Results: The initial pilot phase was Recruitment began on 05/05/2 only 61 (2%) of whom

Special report

Statistical analysis plan for the third International Stroke Trial (IST-3); part of a 'thread' of reports of the trial

IST-3 collaborative group

Article first published online: 9 MAR 2012

DOI: 10.1111/j.1747-4949.2012.00782.x

International Journal of Stroke

Volume 7, Issue 3, pages 186–187, April 2012

Statistical analysis plan

ISRCTN registry

Imaging perfusion deficits and thrombolysis safety and efficacy in acute ischaemic stroke: the Third International Stroke Trial

Primary results paper

The benefits and harms of intrav recombinant tissue plasminoger acute ischaemic stroke (the third [IST-3]): a randomised controlled

*The IST-3 collaborative group**

Summary

Lancet 2012; 379: 2352-63

Published Online May 23, 2012

DOI:10.1016/S0140-6736(12)60768-5

Background Thrombolysis is of net benefit in patients with age and are treated with in 4·5 h of onset. It wider range of patients might ben

Methods In this

Secondary results papers

DIAGNOSTIC NEURORADIOLOGY

Observer reliability of CT angiography in the assess ischaem

Grant Mair, Matthew E. Robin J. Se Mark A. Ro Eleni Sakka Peter A. G.

Received: 19 A

Abstract

Introductio

assessing pa

Targeting Recombinant Tissue-Ty

Articles

Recombinar stroke: an up

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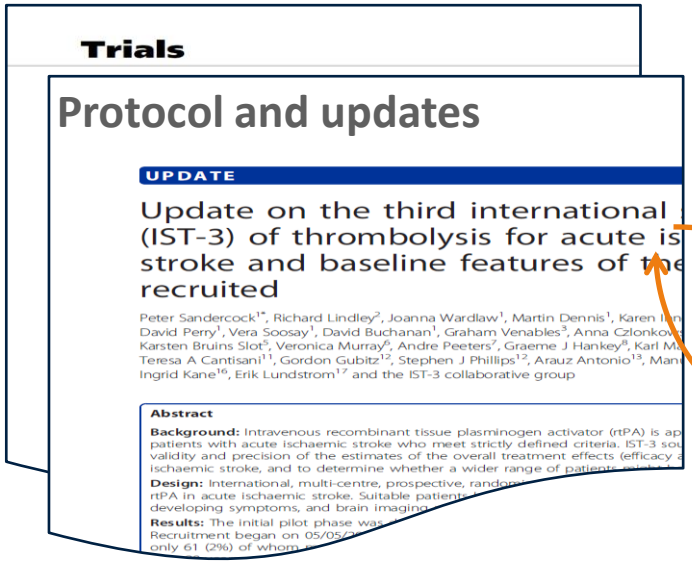
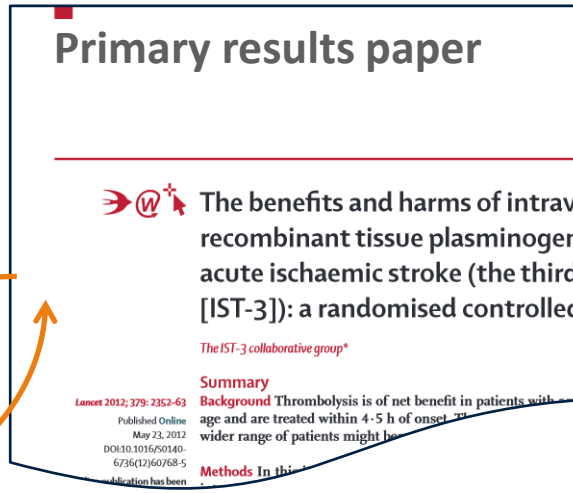
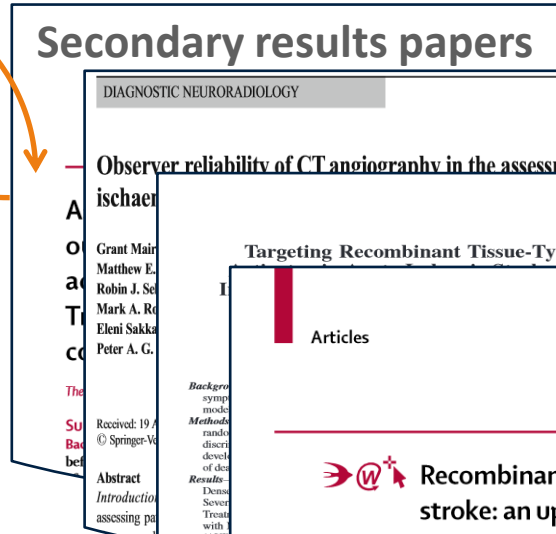
Linked publications

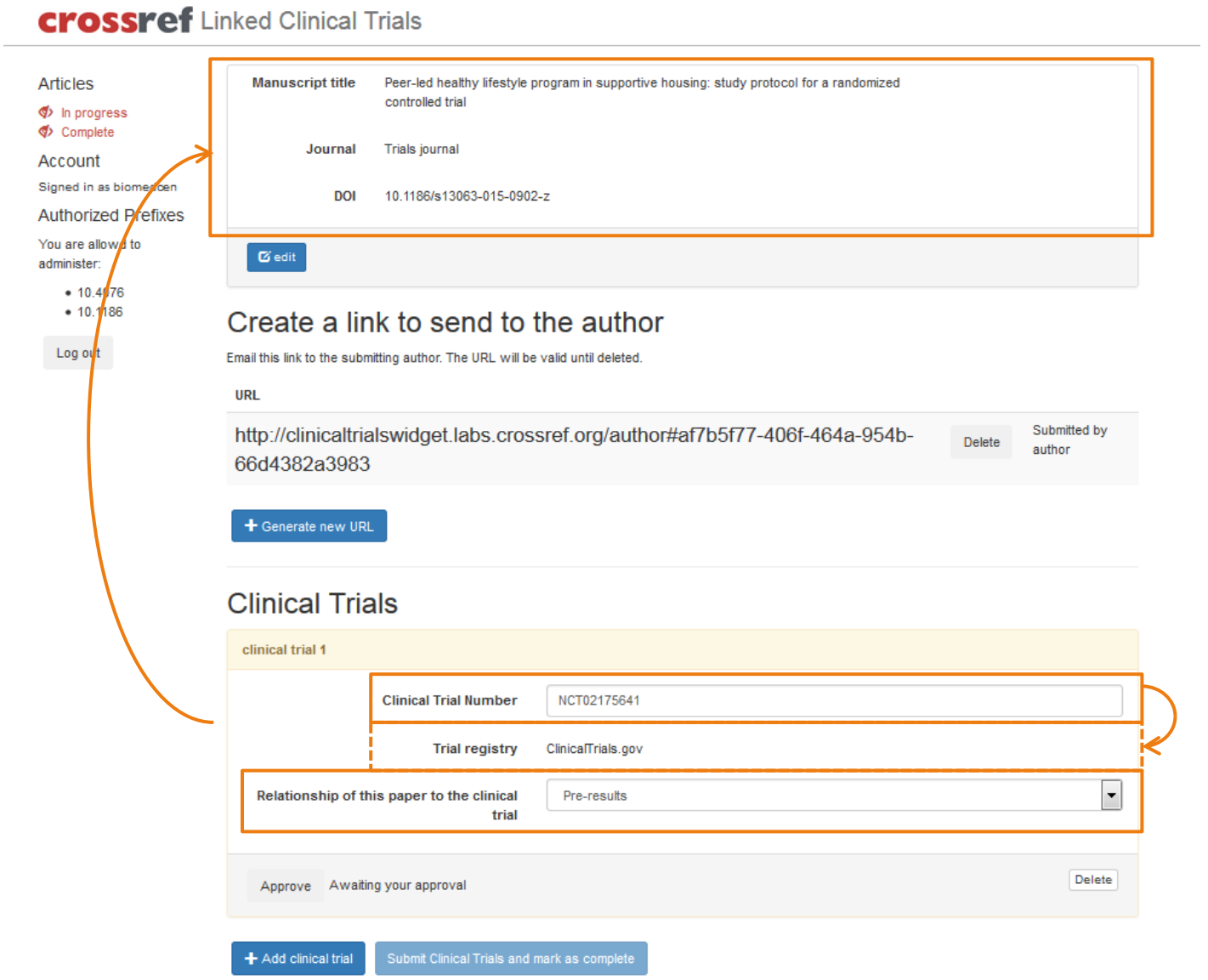




Trial registration number



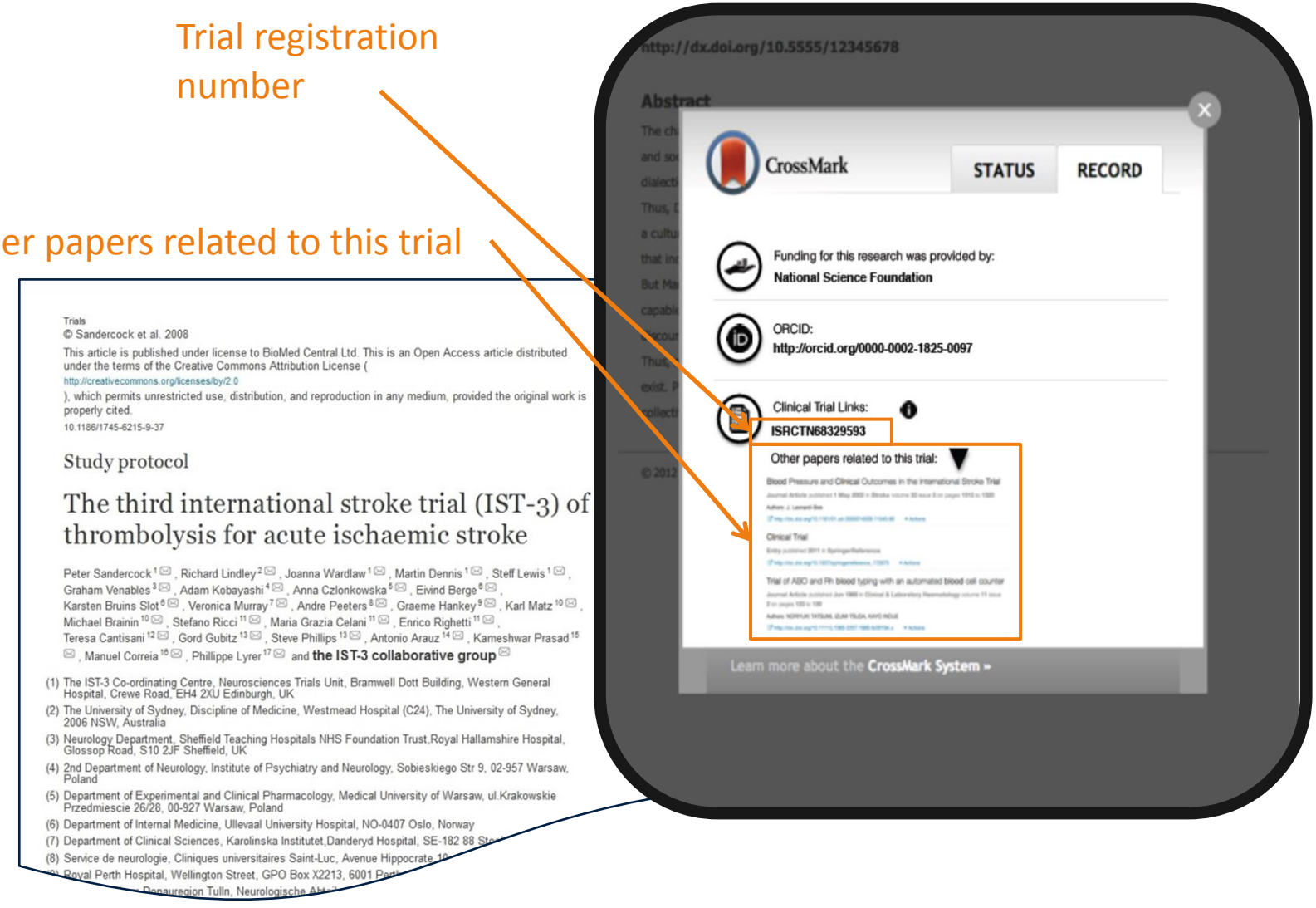
Bringing it all together



Linked reports of clinical trials

Trial registration number

Other papers related to this trial



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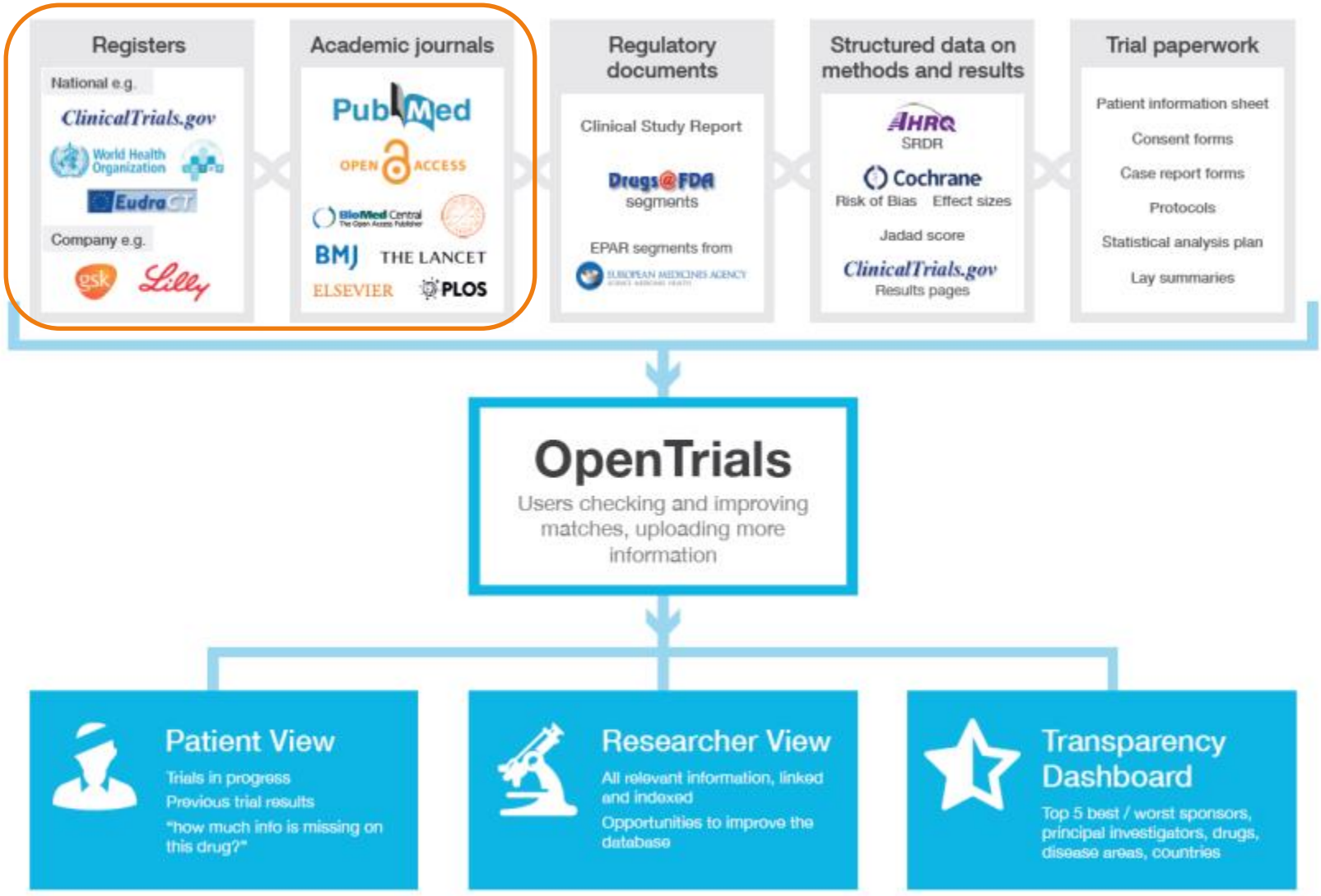
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Thank you!

daniel.shanahan@biomedcentral.com