Increasing value and reducing waste in clinical research

Rustam Al-Shahi Salman

professor of clinical neurology

& honorary consultant neurologist

Research to Understand Stroke due to Haemorrhage

THE UNIVERSITY of EDINBURGH

NHS Lothian

www.RUSH.ed.ac.uk @BleedingStroke …/bleedingstroke

My competing interests

Salary

Editorial boards

Research grants

Endorsements

REWARD
REduce research Waste And Reward Diligence

@rewardalliance

http://rewardalliance.net/

www.whopaysthisdoctor.org

Do you suffer from any of these diseases?

Significosis	*an inordinate focus on statistically significant results*
Neophilia	*an excessive appreciation for novelty*
Theorrhea	*a mania for new theory*
Arigorium	*a deficiency of rigor in theoretical and empirical work*
Disjunctivitis	*a proclivity to produce large quantities of redundant, trivial, and incoherent works*

The Leadership Quarterly 2017;28:5-21 (John Antonakis, Lausanne)

Life sciences research in 2010:
US$ 240,000,000,000

85% wasted

x 240

Lancet 2013;382:1286-307 and *Lancet* 2009;374:86–9

The REduce research Waste And Reward Diligence (REWARD) Alliance…

2009

2013

2015

2016

CTaD

ESOC 2016
10-12 May, Barcelona

THE LANCET
Neurology

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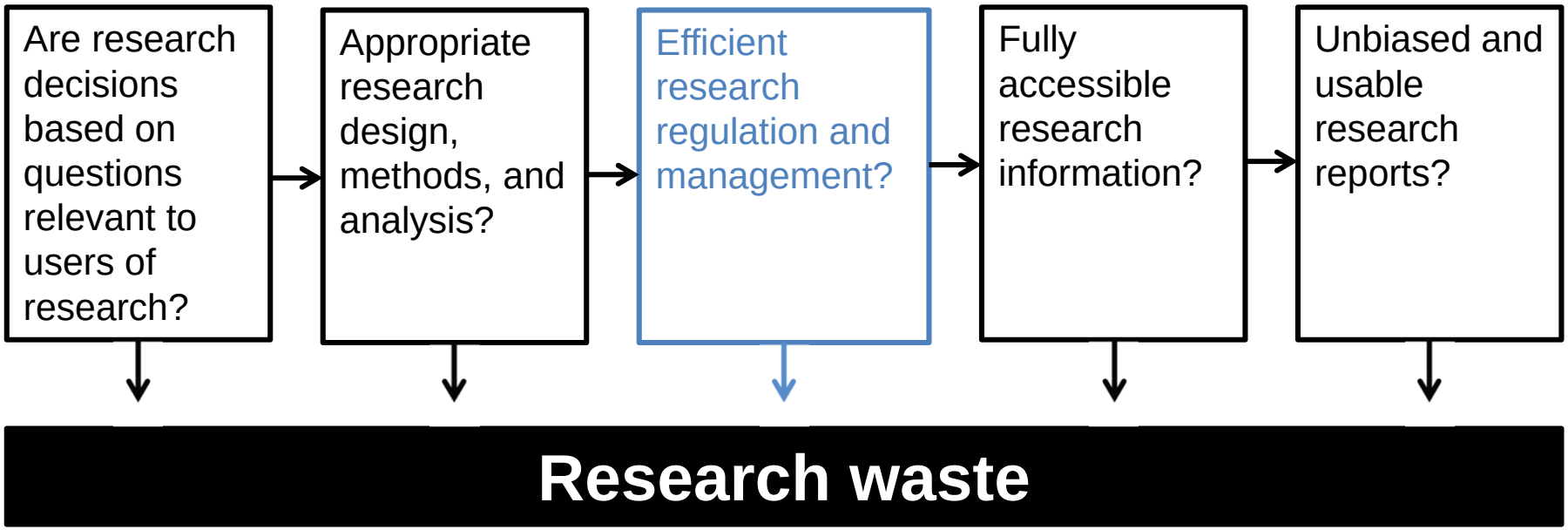
How does waste arise?



Lancet 2009;374:86–9 ➔ *Lancet* 2014;383:101–4

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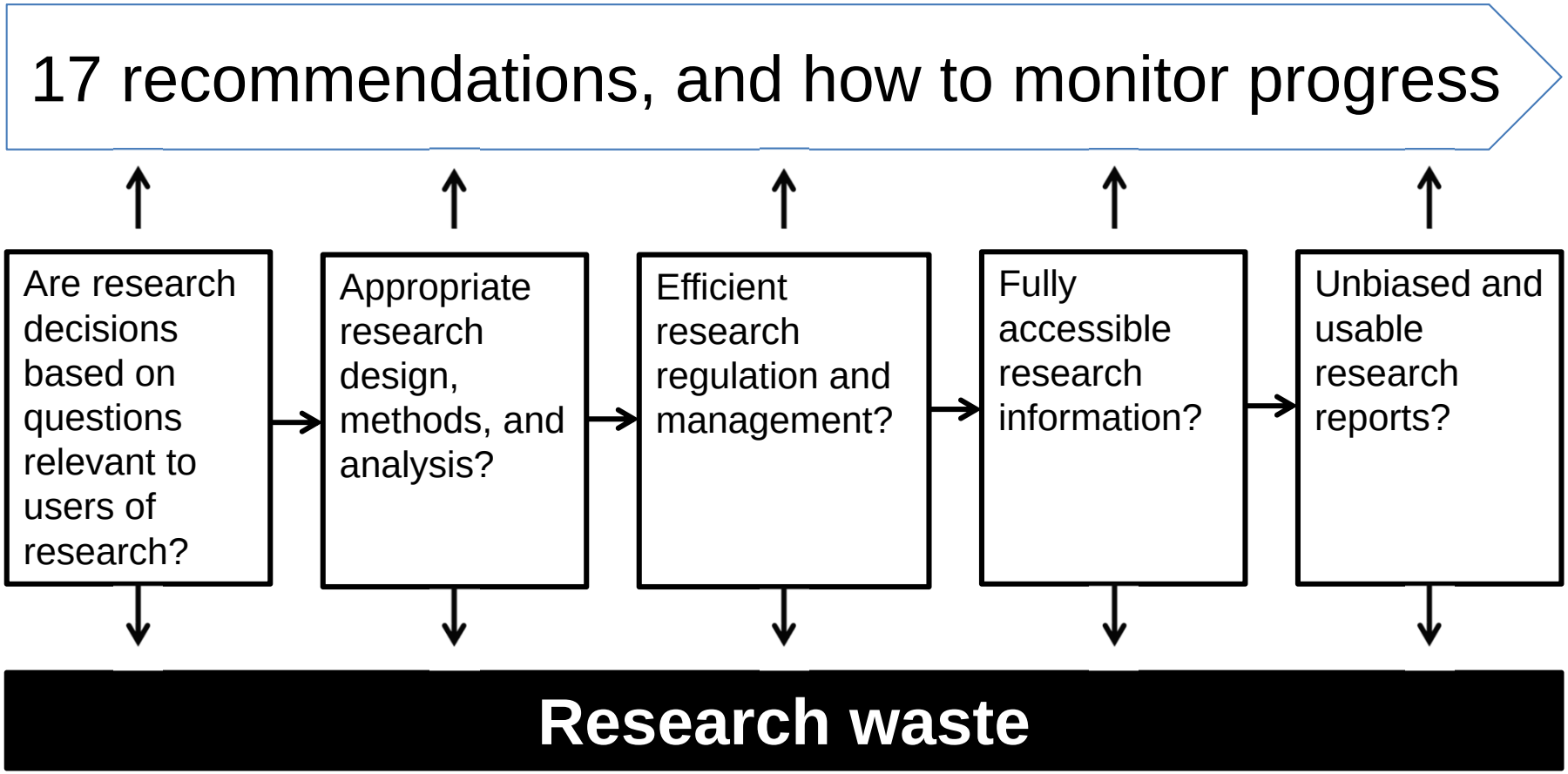

Lancet 2009;374:86–9 ➔ *Lancet* 2014;383:101–4

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17 recommendations, and how to monitor progress

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Stroke: increase value, reduce waste… decrease burden?

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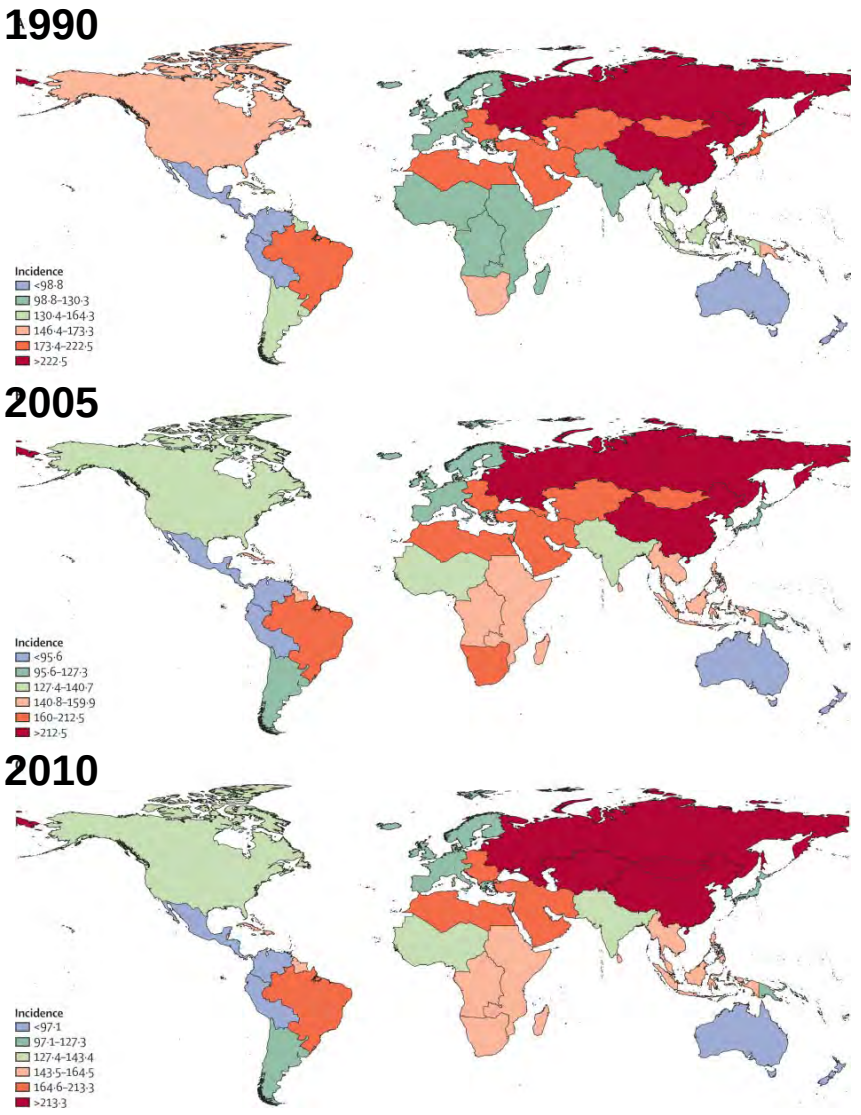
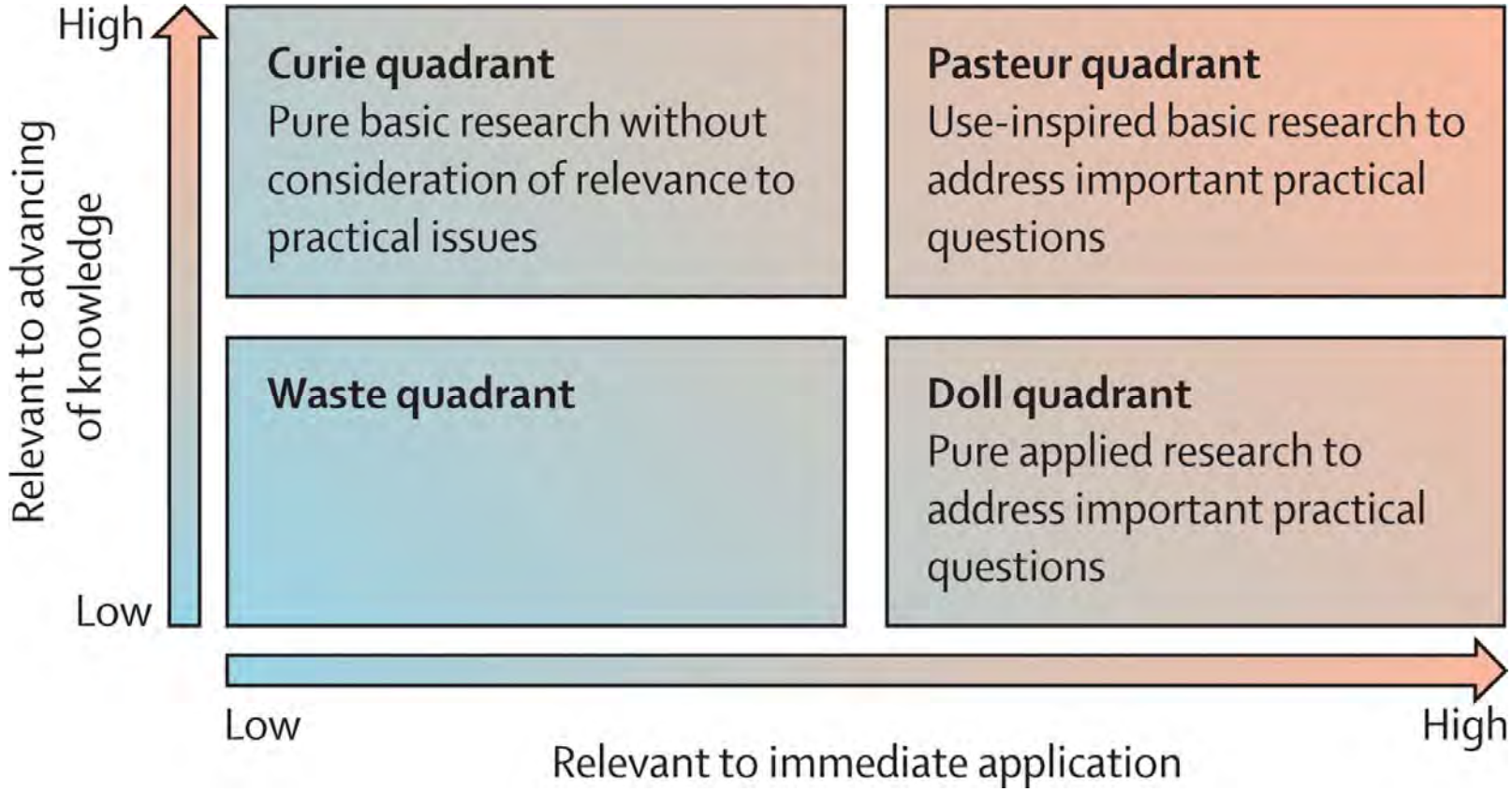
- Leading cause of disability in adults
- Second leading cause of death
- Costs ~€64.1 billion in Europe/year
- Burden is projected to increase



Lancet Global Health 2013;1:e259-81

1. Setting research priorities



Lancet 2014;383:156–65

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1. Setting research priorities

- James Lind (1716-1794)
- Tackling treatment uncertainties together
- Finding out what research is important to:
  - Patients
  - Carers
  - Clinicians / healthcare professionals

NHS
National Institute for Health Research

www.jla.nihr.ac.uk

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1. Setting research priorities

- Priority Setting Partnerships
- Gather uncertainties
- Check existing evidence
- Interim prioritisation
  - relevant individuals and stakeholder groups
  - identify the priorities
- Final consensus meeting to reach agreement on the **top ten research priorities**

NHS
National Institute for Health Research

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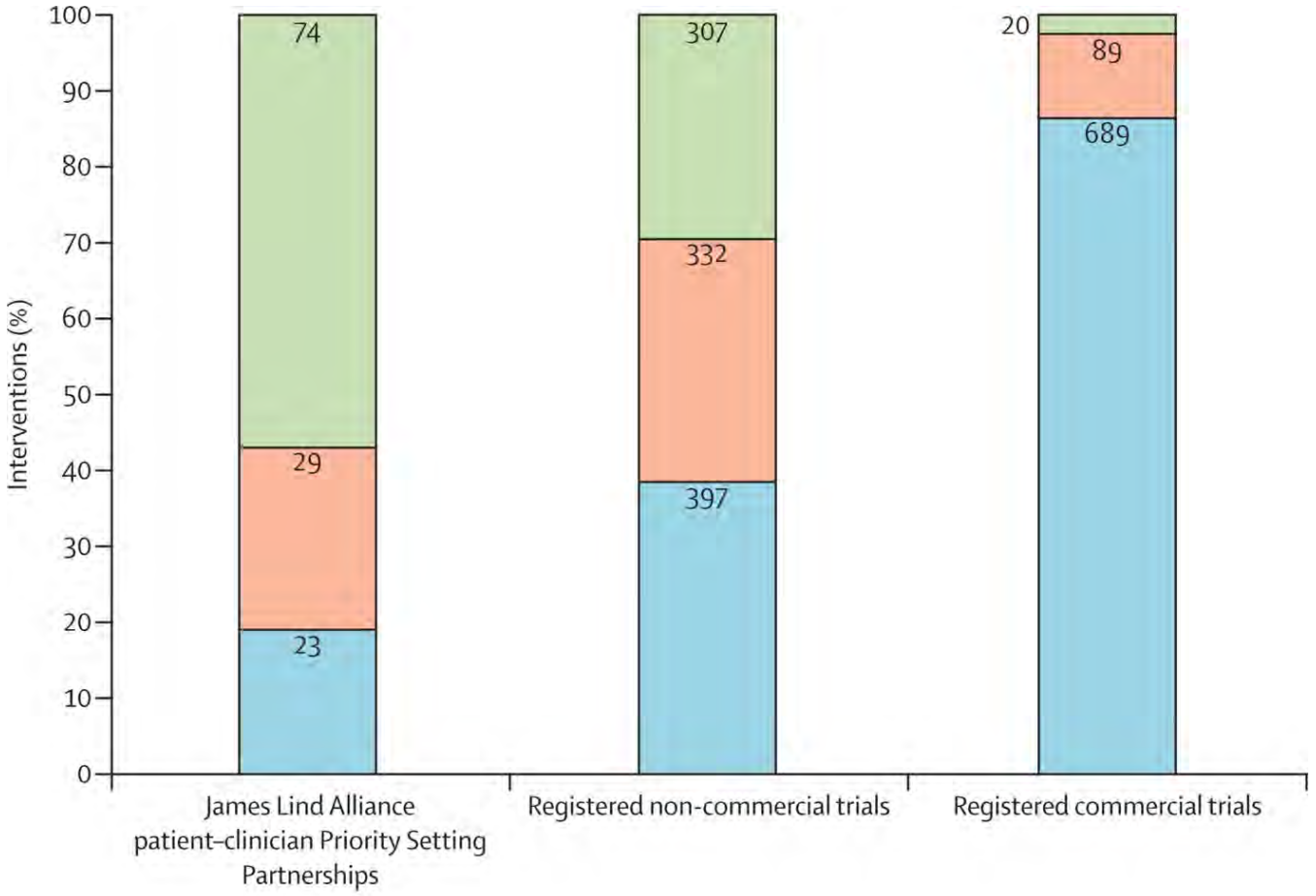
www.jla.nihr.ac.uk

1. Setting research priorities: whose?



Lancet 2014;383:156–65

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1. Recommendations

- Research on research: factors associated with successful replication of basic research and translation to application in health care, and most productive ratio of basic to applied research
- Research funders should make information available about how they decide what research to support
- Research funders and regulators should fund, and ensure that proposals for additional primary research are justified by, systematic reviews
- Research funders and research regulators should strengthen sources of information about research in progress, insist on publication of protocols at study inception, and encourage collaboration

Lancet 2014;383:156–65

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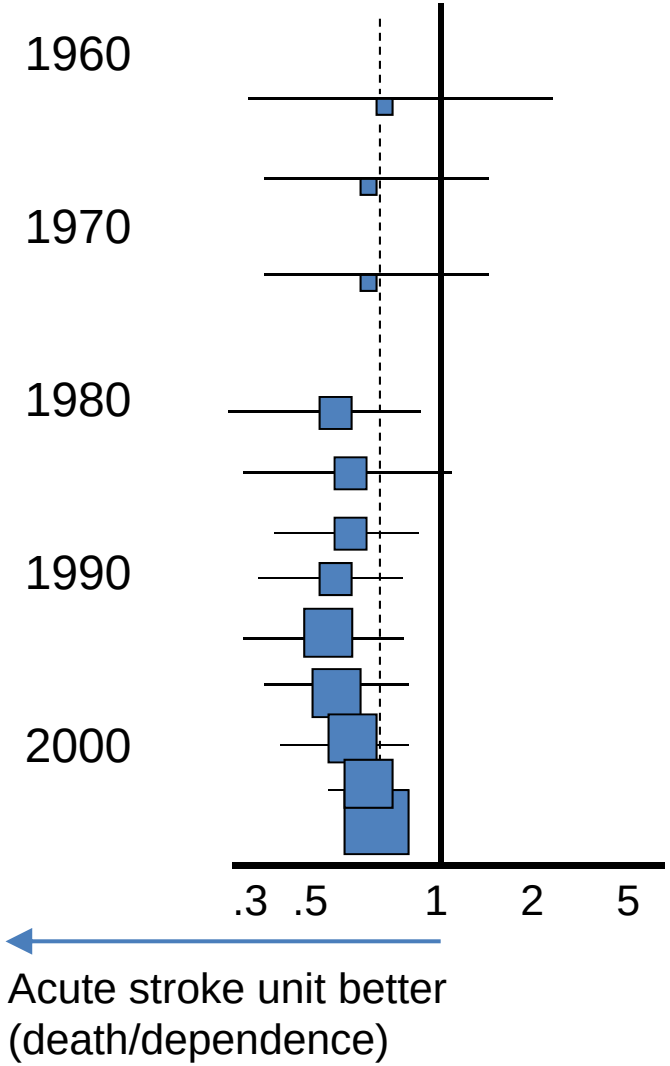
1. Does an up-to-date systematic review confirm the stroke priority?



- Cumulative meta-analysis of acute stroke unit RCTs
- Meta-analysis published 1993

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1. Does an up-to-date systematic review confirm the stroke priority?

- Guidelines, systematic reviews and RCTs
- Ongoing research
- Priorities for future research
- 25,472 references to 9,764 RCTs and 1,379 systematic reviews

www.askdoris.org

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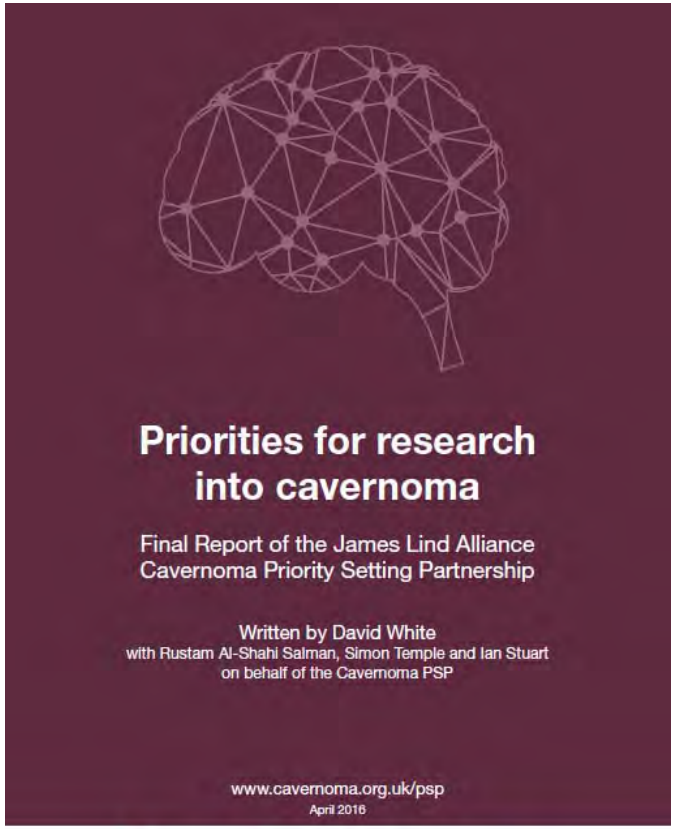
10 For Ten Years

Celebrate with CAUK

www.cavernoma.org.uk

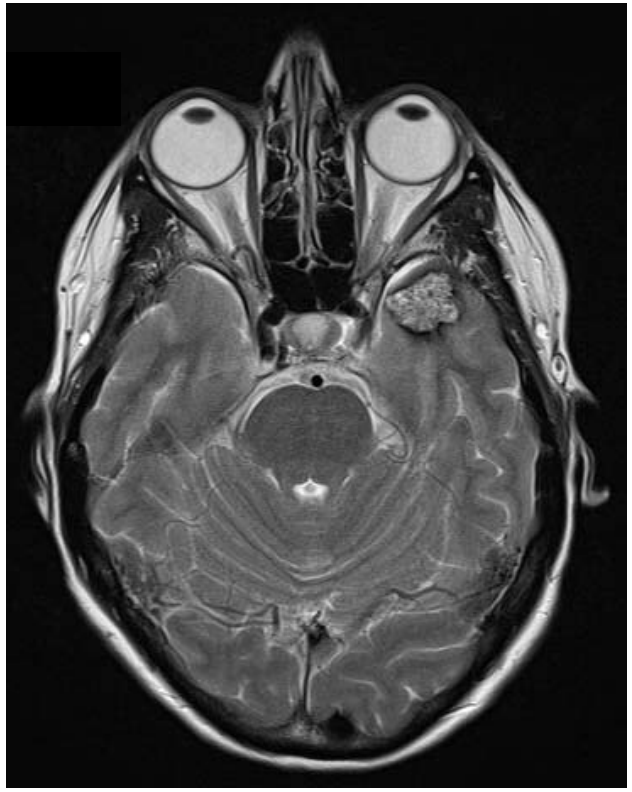
Cavernoma Alliance UK

Helping the Cavernoma Community



James Lind Alliance NHS

National Institute for Health Research



Cavernoma Alliance UK
Helping the Cavernoma Community

James Lind Alliance
Priority Setting Partnerships

Brain & Spine Foundation

Lancet Neurology 2016;15:354-5

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The PSP's top 10 cavernoma uncertainties

1. Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?
2. How do brain or spine cavernomas start and develop?
3. What is the risk of brain/spine cavernomas bleeding for the first and subsequent times?
4. Could drugs targeted at cavernomas improve outcome for people with brain or spine cavernomas compared to no drug treatment?
5. What mechanisms trigger bleeding or epileptic seizures in people with brain or spine cavernomas?
6. Are any features of brain or spine cavernoma on imaging associated with a higher or lower risk of bleeding?
7. Does the use of anticoagulant drugs increase the risk of bleeding from brain or spine cavernoma?
8. Does regular monitoring of brain or spine cavernoma improve outcome compared to no monitoring?
9. What features of brain cavernoma lead to the development of epilepsy, or influence the severity of existing epilepsy?
10. Do any specific activities undertaken by people with brain or spine cavernomas provoke bleeds or other symptoms?

Lancet Neurology 2016;15:354-5

2. Design, conduct and analysis

"To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of."

Sir Ronald Fisher (1890–1962)

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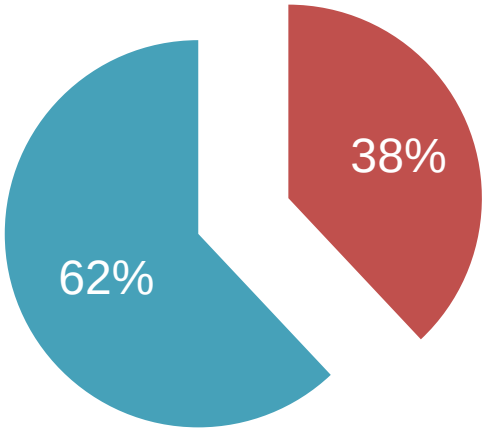
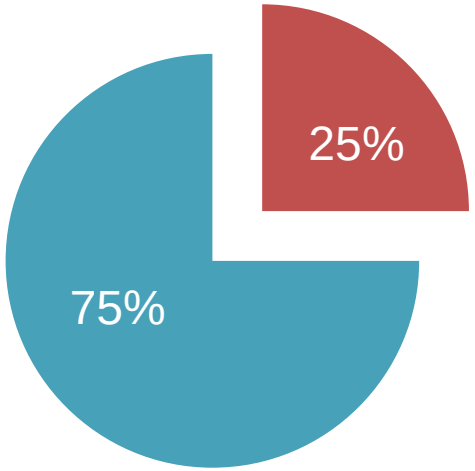
Lancet 2014;383:166–75

2. Design, conduct and analysis

Incongruent statistical findings in publications in 2001 (rounding, transcription, or type-setting errors)



nature



BMJ

BMC Med Res Methodology 2004;4:13

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2. Recommendations

- Make publicly available the full protocols, analysis plans or sequence of analytical choices, and raw data
- Maximise the effect-to-bias ratio in research through high standards of design and conduct, methodologists, and training
- Reward reproducibility practices and reproducible research, and enable an efficient culture for replication of research

Lancet 2014;383:166–75

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2. Design, conduct and analysis

Statistical Analysis of the Primary Outcome in Acute Stroke Trials

Philip M.W. Bath, FRCP, FESO; Kennedy R. Lees, FRCP, FESO;
Peter D. Schellinger, MD, FESO; Hernan Altman, BSc, MBA; Martin Bland, PhD; Cheryl Hogg, MSc;
George Howard, PhD; Jeffrey L. Saver, MD, FAHA; on behalf of the European Stroke Organisation Outcomes Working Group†

Abstract—Common outcome scales in acute stroke trials are ordered categorical or pseudocontinuous in structure but most have been analyzed as binary measures. The use of fixed dichotomous analysis of ordered categorical outcomes after stroke (such as the modified Rankin Scale) is rarely the most statistically efficient approach and usually requires a larger sample size to demonstrate efficacy than other approaches. Preferred statistical approaches include sliding dichotomous, ordinal, or continuous analyses. Because there is no best approach that will work for all acute stroke trials, it is vital that studies are designed with a full understanding of the type of patients to be enrolled (in particular their case mix, which will be critically dependent on their age and severity), the potential mechanism by which the intervention works (ie, will it tend to move all patients somewhat, or some patients a lot, and is a common hazard present), a realistic assessment of the likely effect size, and therefore the necessary sample size, and an understanding of what the intervention will cost if implemented in clinical practice. If these approaches are followed, then the risk of missing useful treatment effects for acute stroke will diminish. (*Stroke*. 2012;43:1171-1178.)

Stroke 2012;43(4):1163-70

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3. Regulation and management

"…the clinician who is convinced that a certain treatment works will almost never find an ethicist in his path, whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them."

Richard Smithells (1924-2002)

Lancet 1990;336:846–7

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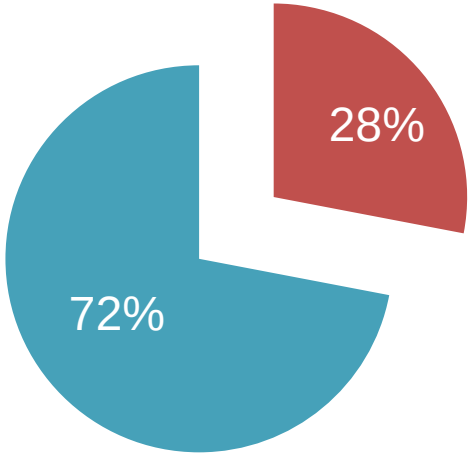
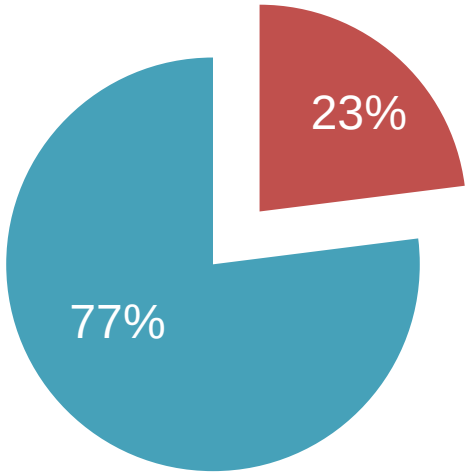
3. Regulation and management

Is regulation proportionate, when the (large) majority of the public approves?



UK National Cancer Registry including postcode, name and address, and sending a letter inviting them to a research study



Finland national biobank of existing diagnostic and research samples

Lancet 2014;383:176–85

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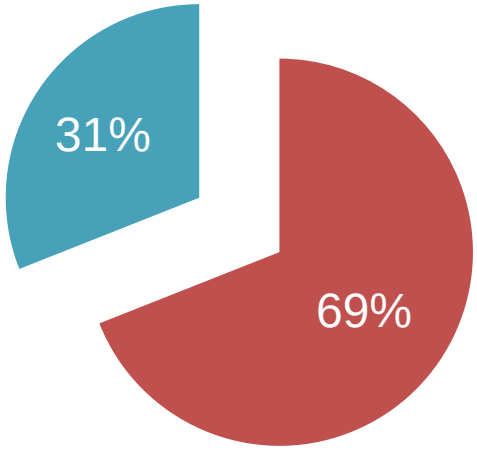
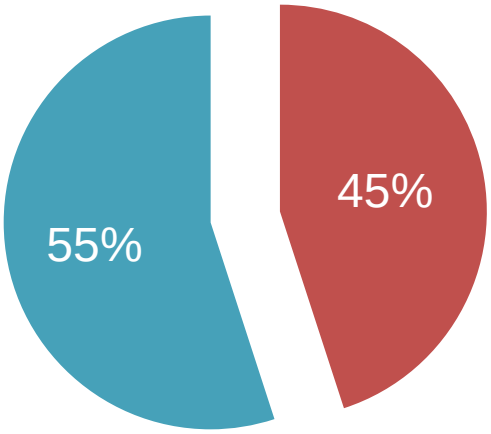
3. Regulation and management

RCTs recruited pre-specified sample size



114 RCTs funded by MRC or HTA in the UK in 1994-2003



73 RCTs funded by MRC or HTA in the UK in 2002-2008

Lancet 2014;383:176–85

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3. Regulation and management

Methods to improve RCT recruitment

- Systematic review
- 45 studies within a trial (SWATs)
- 43,000 participants
- 46 interventions!

- Effective strategies:
  1. Telephone reminders to non-respondents (RR 1.7, 95%CI 1.0-2.5)
  2. Opt-out contact (RR 1.4, 95%CI 1.1-1.8)
  3. Open trial design (RR 1.2, 95%CI 1.1-1.4)

BMJ Open 2013;3:e002360

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3. Regulation and management

Methods to improve RCT retention

- Systematic review
- 38 SWATs
- 24,304 participants

- Effective strategies for MCQ response:
  1. Monetary incentive (RR 1.2, 95%CI 1.1-1.3)
  2. Recorded delivery (RR 2.1, 95%CI 1.1-3.9)
  3. Open trial design (RR 1.4, 95%CI 1.2-1.6)

BMJ Open 2014;4:e003821

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3. Recommendations

- Regulators should facilitate reduction of other causes of waste and inefficiency
- Streamline, harmonise and make proportionate the laws, regulations, guidelines, and processes that govern whether and how research can be done
- Increase the efficiency of recruitment, retention, data monitoring, and data sharing in research, and do additional research to learn how efficiency can be increased
- Improve the efficiency of clinical research by promoting integration of research in everyday clinical practice

Lancet 2014;383:176–85

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3. Regulation and management

Regulatory enforcement

NHS
Health Research Authority

- All randomised trials should be registered
- Proportionate approaches to:
  - application
  - patient information leaflets

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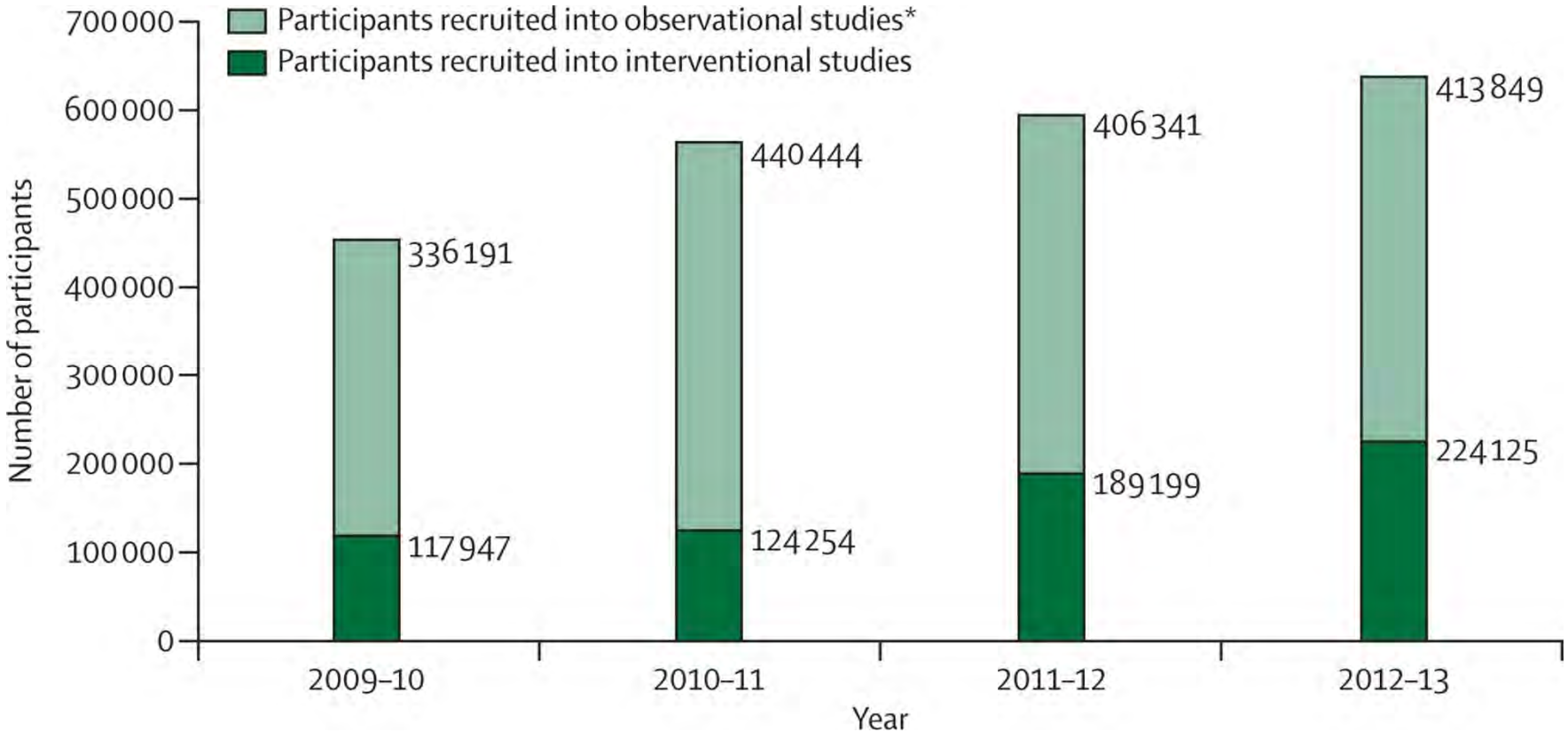
3. Regulation and management

Better recruitment after UK clinical research networks



Lancet 2014;383:176–85

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3. Regulation and management

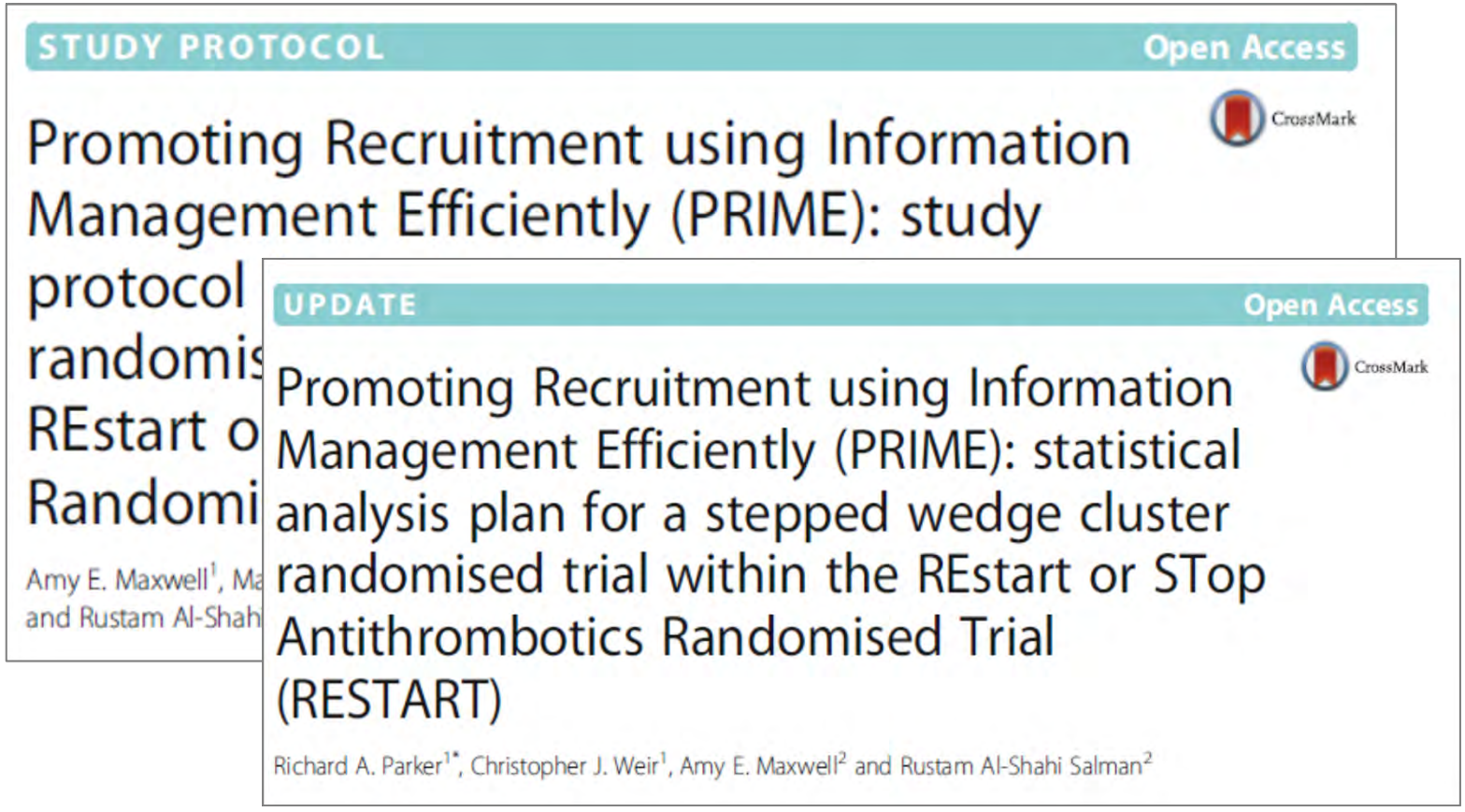
Integration of research in everyday clinical practice

- Oral Anticoagulant Therapy in Acute Ischaemic Stroke With Atrial Fibrillation
  - Start <4 days vs. start 5-10 days after stroke onset
- Registry-based RCT in the Swedish Stroke Register

NCT02961348 www.riksstroke.org

3. Regulation and management

Recruitment to prevention RCTs after stroke



Trials 2017;18:22 and *Trials* 2017;18:94

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4. Accessible reporting

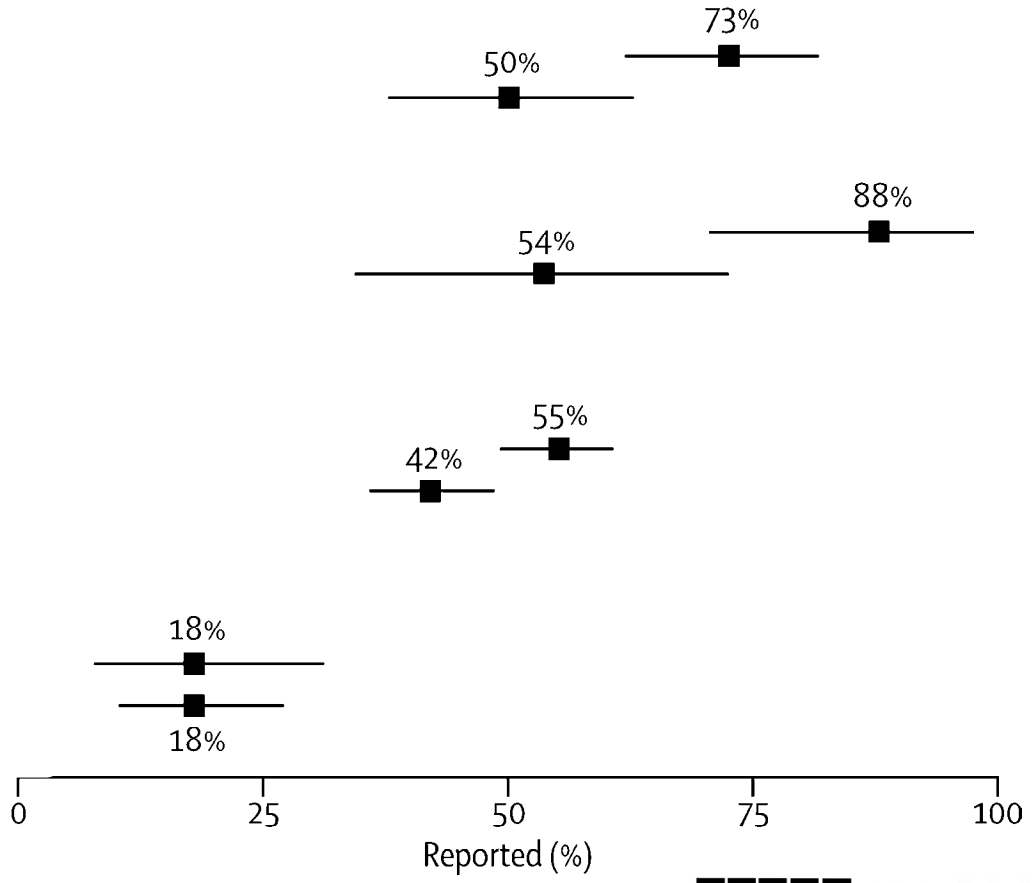
Reporting is selective

Time of inception (12 cohorts)
Positive studies (n=1555)
Null or negative studies (n=976)
OR 2·9 (95% CI 2·4–3·5)

Regulatory submissions (4 cohorts)
Positive studies (n=615)
Null or negative studies (n=240)
OR 5·0 (95% CI 2·0–12·5)

Abstract presentation at conference (27 cohorts)
Positive studies (n=6109)
Null or negative studies (n=4180)
OR 1·7 (1·4–2·0)

Manuscripts submitted to journals (4 cohorts)
Positive studies (n=1869)
Null or negative studies (n=767)
OR 1·1 (0·8–1·4)



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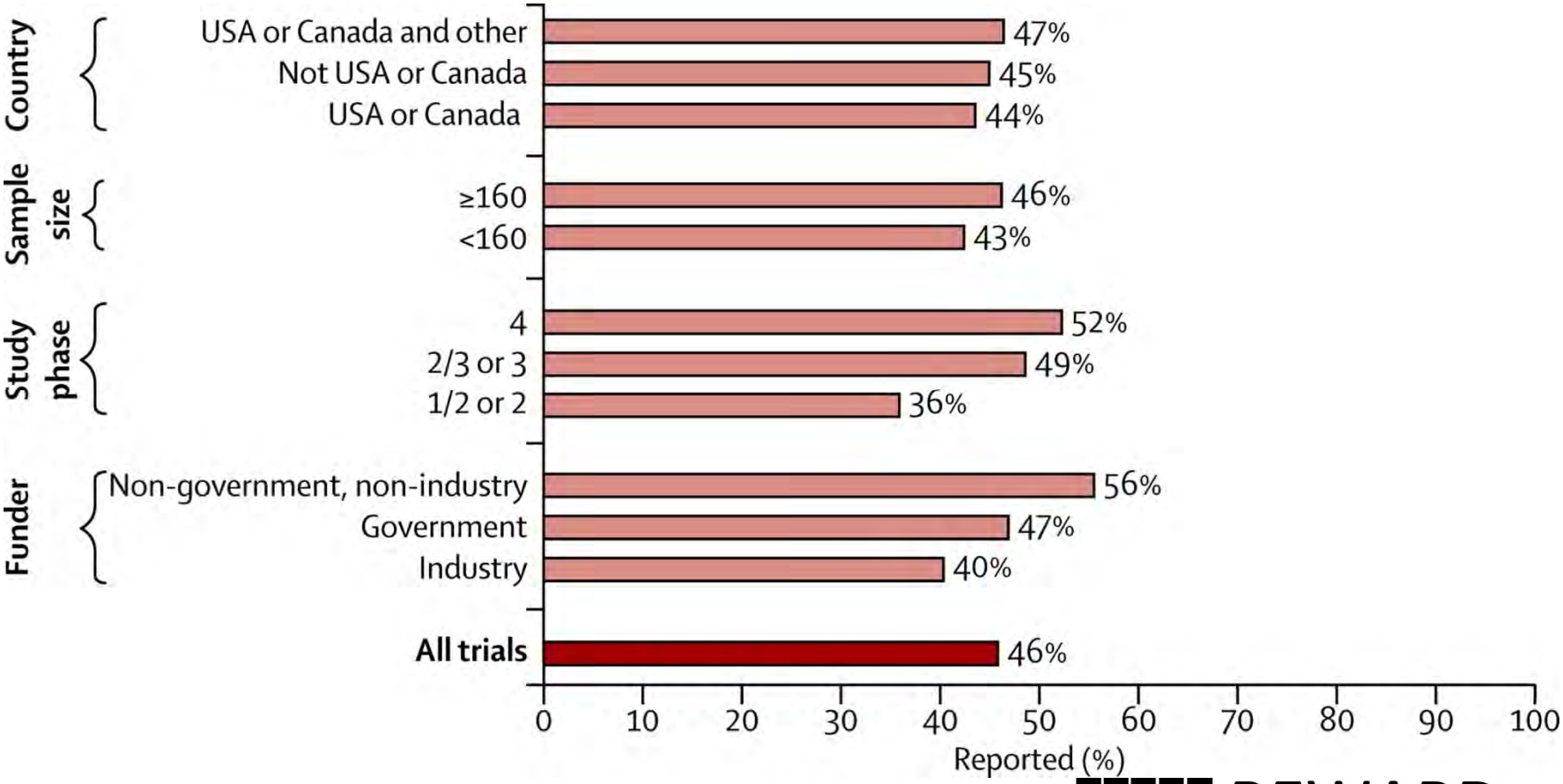
Lancet 2014;383:257–66

4. Accessible reporting

Associations with reporting



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Lancet 2014;383:257–66

4. Recommendations

- Performance metrics that recognise full dissemination of research and reuse of original datasets by others
- Develop and adopt standards for the content of study protocols and full study reports, and for data sharing
- Endorse and enforce study registration policies, wide availability of full study information, and sharing of participant-level data

Lancet 2014;383:257–66

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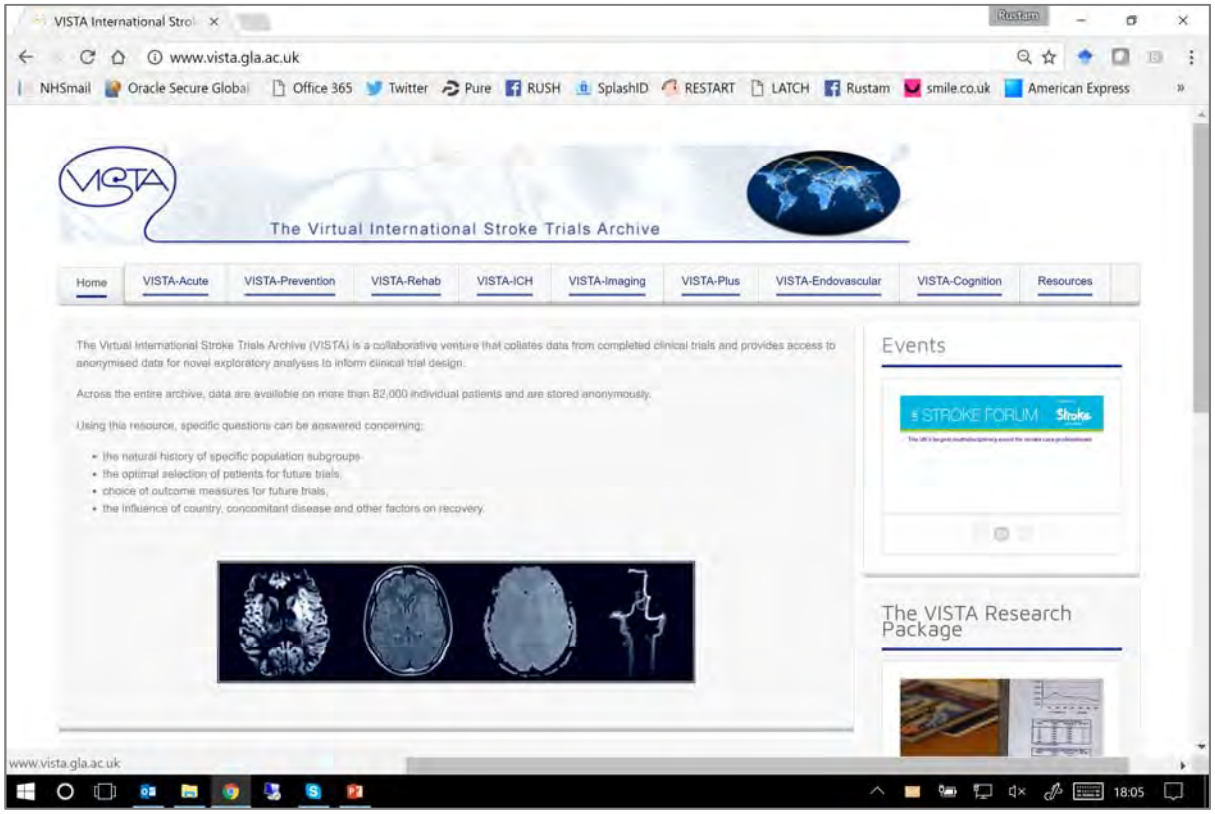
4. Accessible reporting

Stroke RCT IPD repository: VISTA



www.vista.gla.ac.uk

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4. Accessible reporting

Sandercock *et al. Trials* 2011, **12**:101
http://www.trialsjournal.com/content/12/1/101

TRIALS

RESEARCH **Open Access**

The International Stroke Trial database

Peter AG Sandercock[1*], Maciej Niewada[2,3], Anna Członkowska[2,3] and for the International Stroke Trial Collaborative Group

Abstract

Background: We aimed to make individual patient data from the International Stroke Trial (IST), one of the largest randomised trials ever conducted in acute stroke, available for public use, to facilitate the planning of future trials and to permit additional secondary analyses.

Methods: For each randomised patient, we have extracted data on the variables assessed at randomisation, at the early outcome point (14-days after randomisation or prior discharge) and at 6-months and provide them as an analysable database.

Results: The IST dataset includes data on 19 435 patients with acute stroke, with 99% complete follow-up. Over 26.4% patients were aged over 80 years at study entry. Background stroke care was limited and none of the patients received thrombolytic therapy.

Conclusions: The IST dataset provides a source of primary data which could be used for planning further trials, for sample size calculations and for novel secondary analyses. Given the age distribution and nature of the background treatment given, the data may be of value in planning trials in older patients and in resource-poor settings.

BioMed Central 7th Annual Research Awards

BioMed Central

Open Data Award 2012

Trials 2011;12:101

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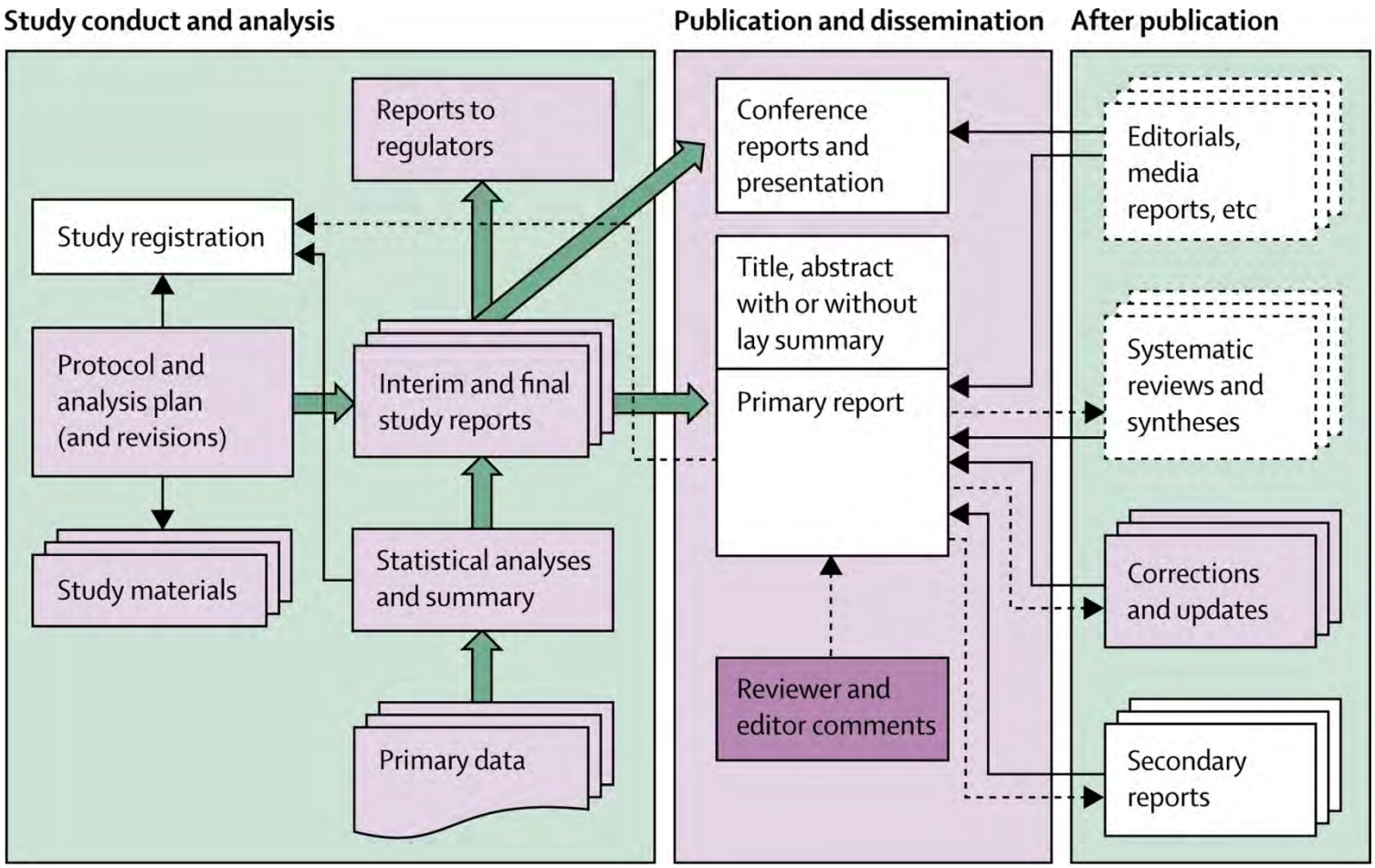
5. Complete & usable reporting



Lancet 2014;383:267–76

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5. Complete & usable reporting

Abstract
Trials: missing effect size and confidence interval (38%); no mention of adverse effects (49%)[72]
Methods
Trials: 40–89% inadequate treatment descriptions[11, 13] **fMRI studies:** 33% missing number of trials and durations[3] **Survey questions:** 65% missing survey or core questions[25] **Figures:** 31% graphs ambiguous[45]
Results
Clinical trials: outcomes missing: 50% efficacy and 65% harm outcomes per trial incompletely reported[6] **Animal studies:** number of animals and raw data missing[17] (54%, 92%); age and weight missing (24%) **Diagnostic studies:** missing age and sex (40%)[15]
Discussion
Trials: no systematic attempt to set new results in context of previous trials (50%)[69]
Data
Trials: most data never made available; author-held data lost at about 7% per year

Lancet 2014;383:267–76

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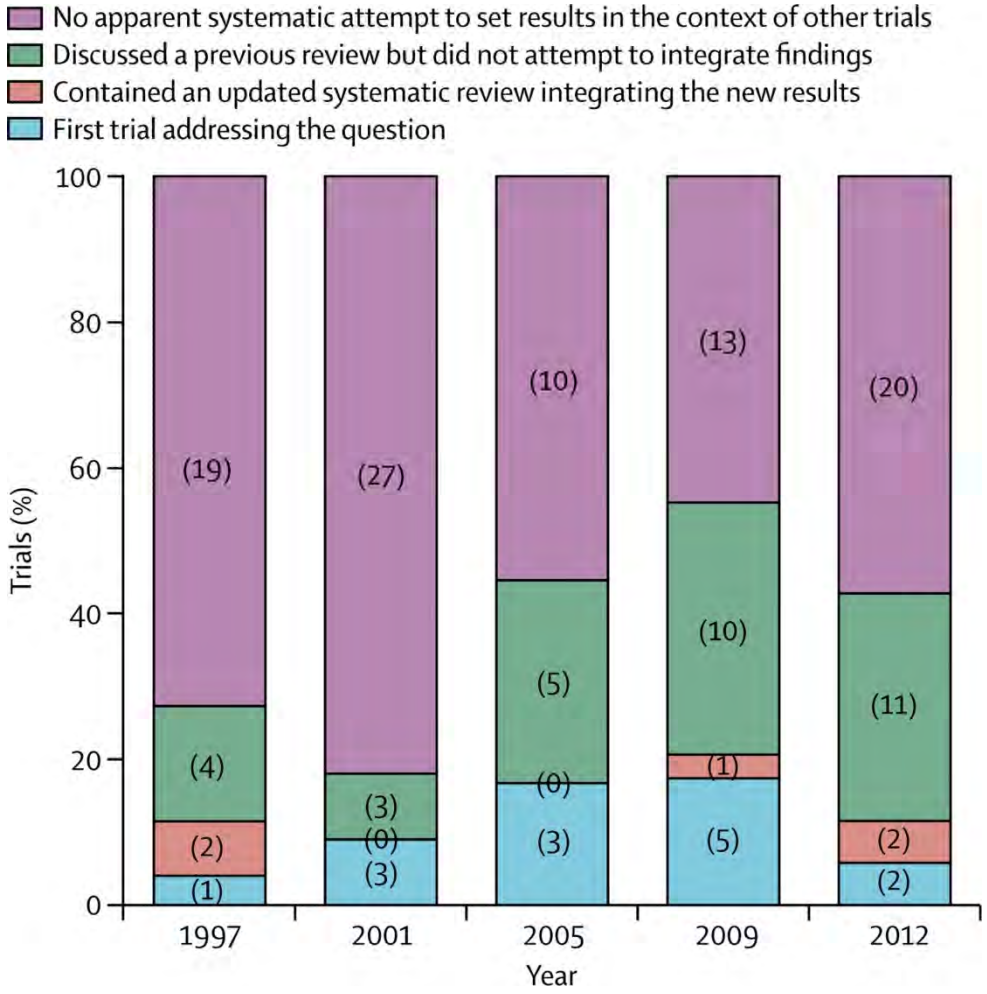
5. Complete & usable reporting



Lancet 2014;383:267–76

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5. Recommendations

- Funders and research institutions must shift research regulations and rewards to align with better and more complete reporting
- Research funders should take responsibility for reporting infrastructure that supports good reporting and archiving
- Funders, institutions, and publishers should improve the capability and capacity of authors and reviewers in high-quality and complete reporting

Lancet 2014;383:267–76

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5. Complete & usable reporting

Reporting guidelines

www.equator-network.org

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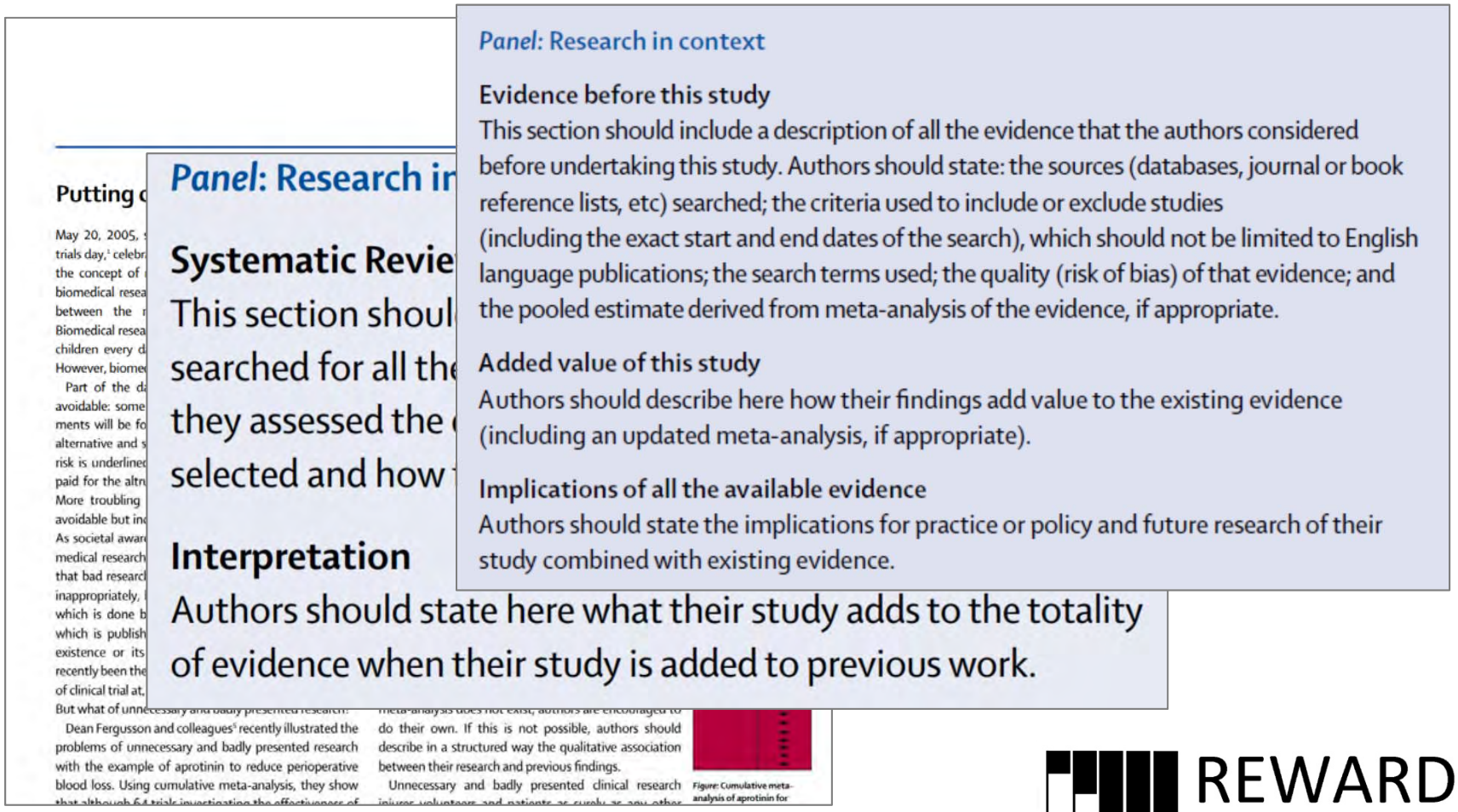
5. Complete & usable reporting

The Lancet's Research in Context panel



Panel: Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence (including an updated meta-analysis, if appropriate).

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Panel: Research ir

Systematic Revie

This section shoul
searched for all the
they assessed the
selected and how

Interpretation

Authors should state here what their study adds to the totality of evidence when their study is added to previous work.

Putting

May 20, 2005, trials day,[1] celebr the concept of biomedical resea between the Biomedical resea children every d However, biome Part of the d avoidable: some ments will be fo alternative and risk is underline paid for the altr More troubling avoidable but in As societal awar medical research that bad researc inappropriately, which is done b which is publish existence or its recently been the of clinical trial at, But what of unn

Dean Fergusson and colleagues[5] recently illustrated the problems of unnecessary and badly presented research with the example of aprotinin to reduce perioperative blood loss. Using cumulative meta-analysis, they show

do their own. If this is not possible, authors should describe in a structured way the qualitative association between their research and previous findings.

Unnecessary and badly presented clinical research

Figure: Cumulative meta-analysis of aprotinin for

Lancet 2005;366:107-8, 2010;376:10-1, 2014;384:2176-7

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5. Complete & usable reporting

Reporting guidelines

- 28 rehabilitation and disability journals joined together in a collaborative initiative to enhance research reporting standards through adoption of reporting guidelines
- 

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5. Complete & usable reporting

TIDieR checklist

TIDieR

Template for Intervention Description and Replication

BMJ 2014;348:g1687

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Issues for discussion…

- Evidence of waste
  - Shortage of ‘research on research’
  - Especially in low-middle income countries
  - It can change systems
- Evidence supporting solutions
  - Shortage of ‘research in research’
- Much of this is very obvious, but change is needed

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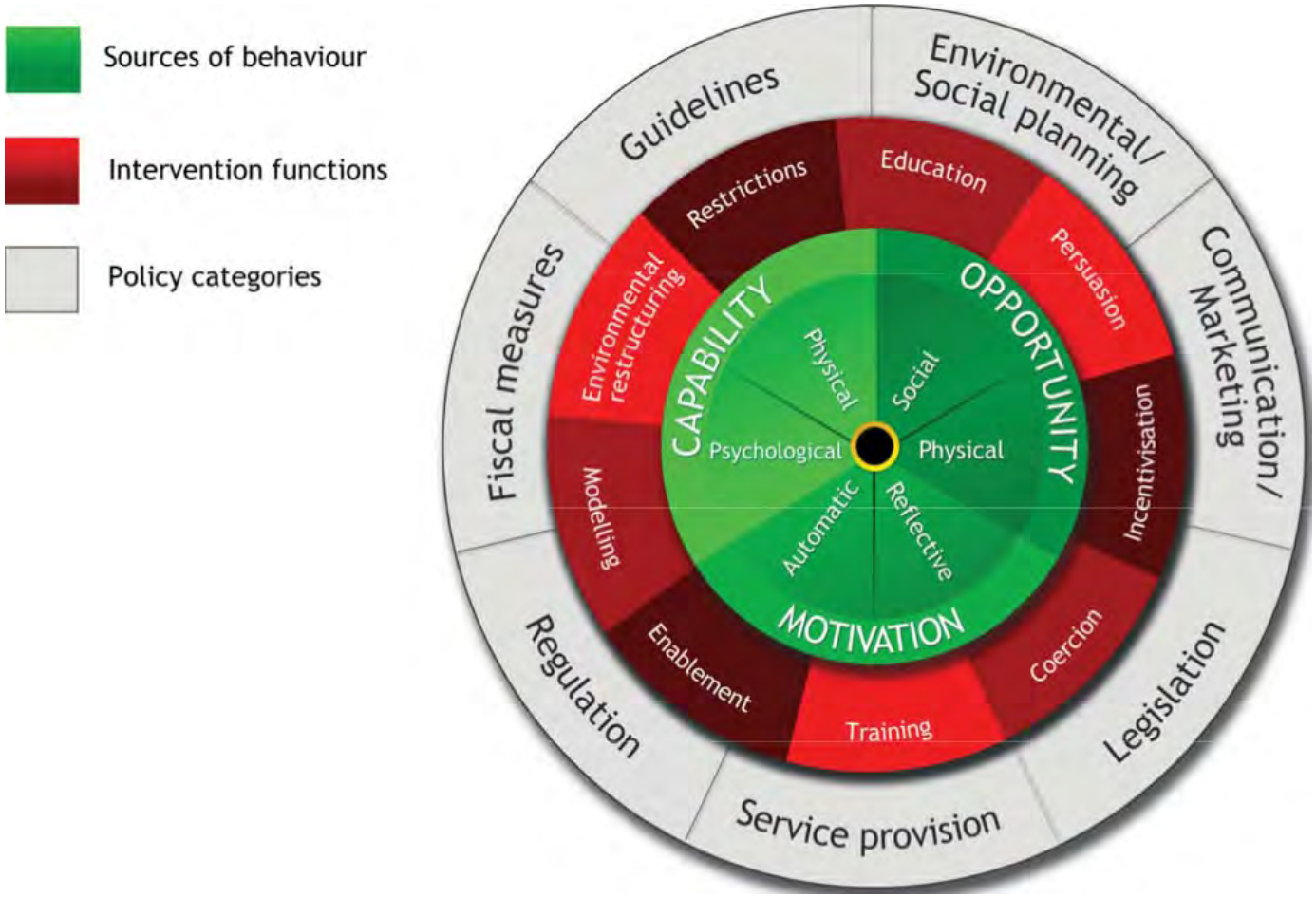
And Reward Diligence

How can, and will, we change?!



Implementation Science 2011;6:42

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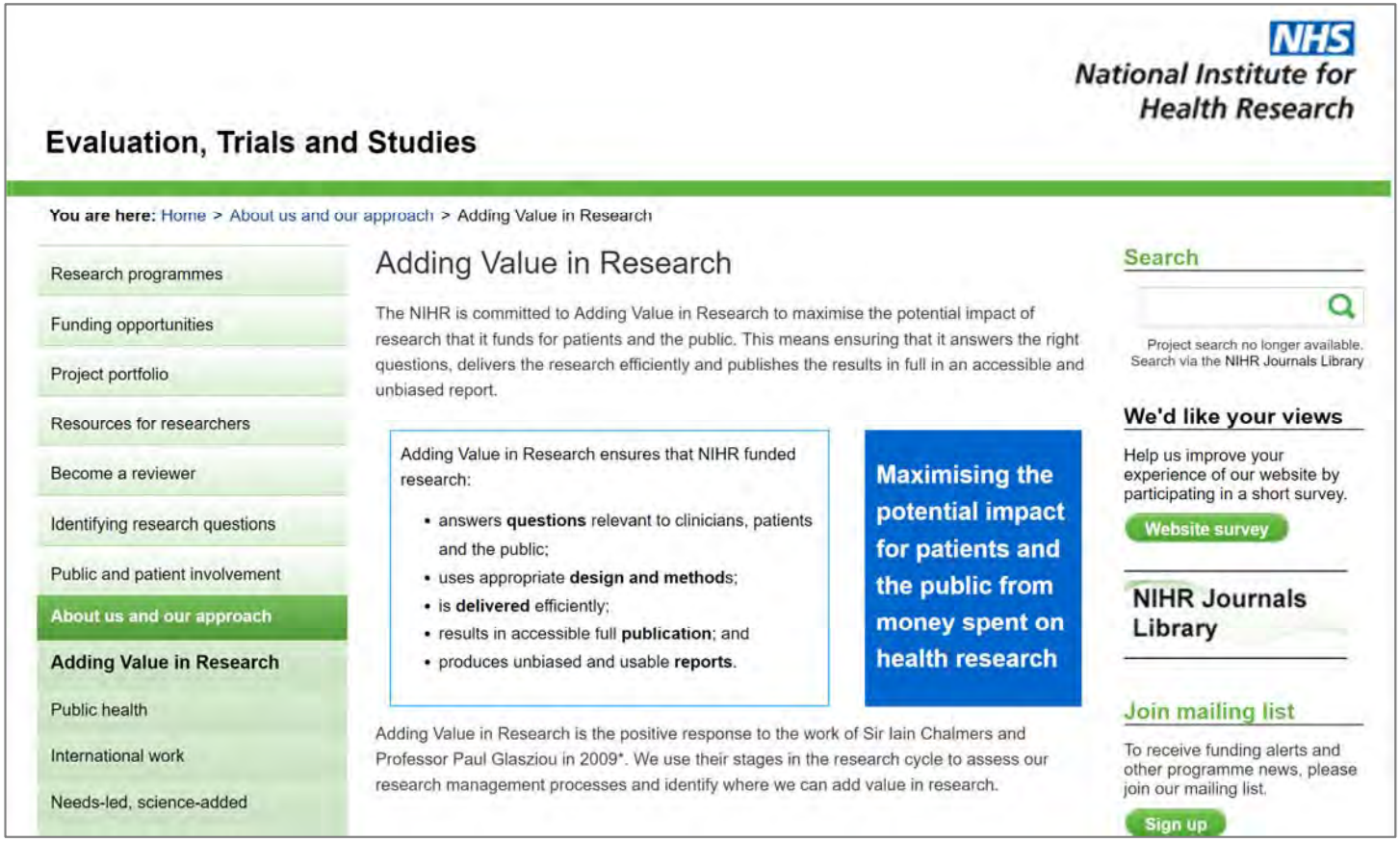
Funders and regulators are key change agents



www.nets.nihr.ac.uk/about/adding-value-in-research

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Endorse the REWARD statement

"We recognise that, while we strive for excellence in research, there is much that needs to be done to reduce waste and increase the value of our contributions. We maximise our research potential when:

- *we set the right research priorities*
- *we use robust research design, conduct and analysis*
- *regulation and management are proportionate to risks*
- *all information on research methods and findings are accessible*
- *reports of research are complete and usable*

We believe we have a responsibility not just to seek to advance knowledge, but also to advance the practice of research itself. This will contribute to improvement in the health and lives of all peoples, everywhere. As funders, regulators, commercial organisations, publishers, editors, researchers, research users and others – we commit to playing our part in increasing value and reducing waste in research."

via http://rewardalliance.net

rewardalliance

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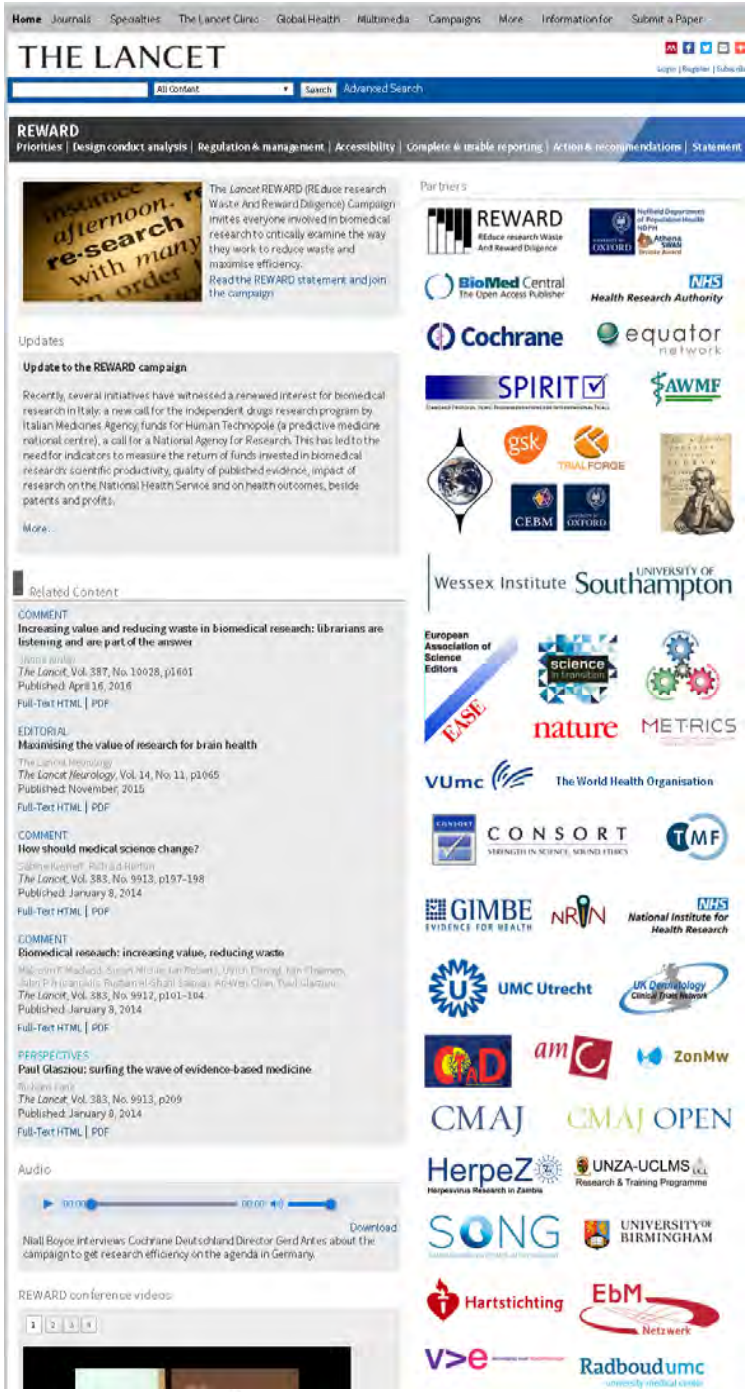
Partner *The Lancet*'s REWARD campaign!

- Priorities
- Design, conduct, analysis
- Regulation and management
- Accessibility
- Complete and usable reporting
- Action and recommendations
- Statement

http://www.thelancet.com/campaigns/efficiency



Look out for REWARD symposia...

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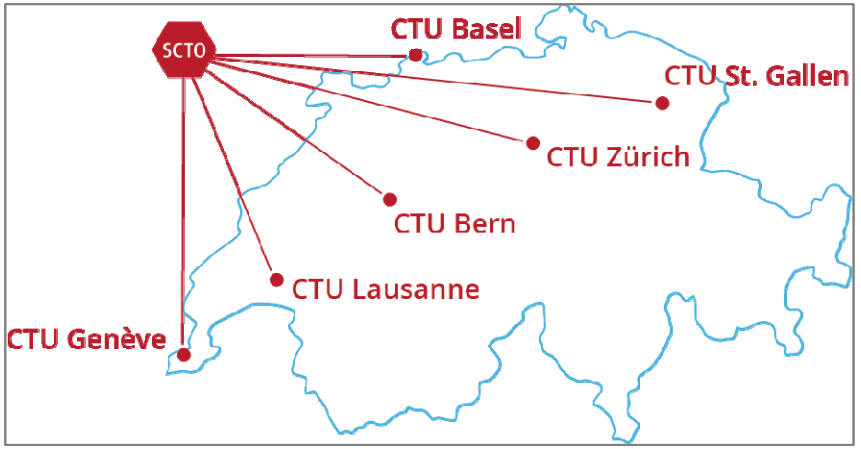
www.wcri2017.org

www.scto.ch

5th World Conference on Research Integrity

«Adding value in clinical research: what's been achieved and how do we manage new challenges?»
1 June 2017



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Issues for discussion…

- Evidence of waste
  - Shortage of ‘research on research’
  - Especially in low-middle income countries
  - It can change systems
- Evidence supporting solutions
  - Shortage of ‘research in research’
- Much of this is very obvious, but change is needed

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