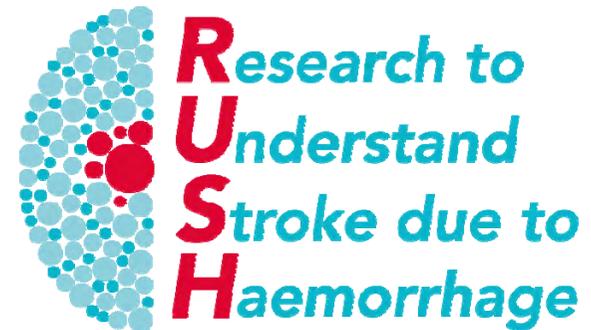


Increasing value and reducing waste in clinical research

Rustam Al-Shahi Salman
*professor of clinical neurology
& honorary consultant neurologist*



THE UNIVERSITY *of* EDINBURGH



My competing interests

Salary



Editorial boards



Research grants



GE Healthcare



Endorsements



<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

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

85% wasted



x 240

The REduce research Waste And REward Diligence (REWARD) Alliance...

2009

2



2013

42



2015

236



2016

2 meetings



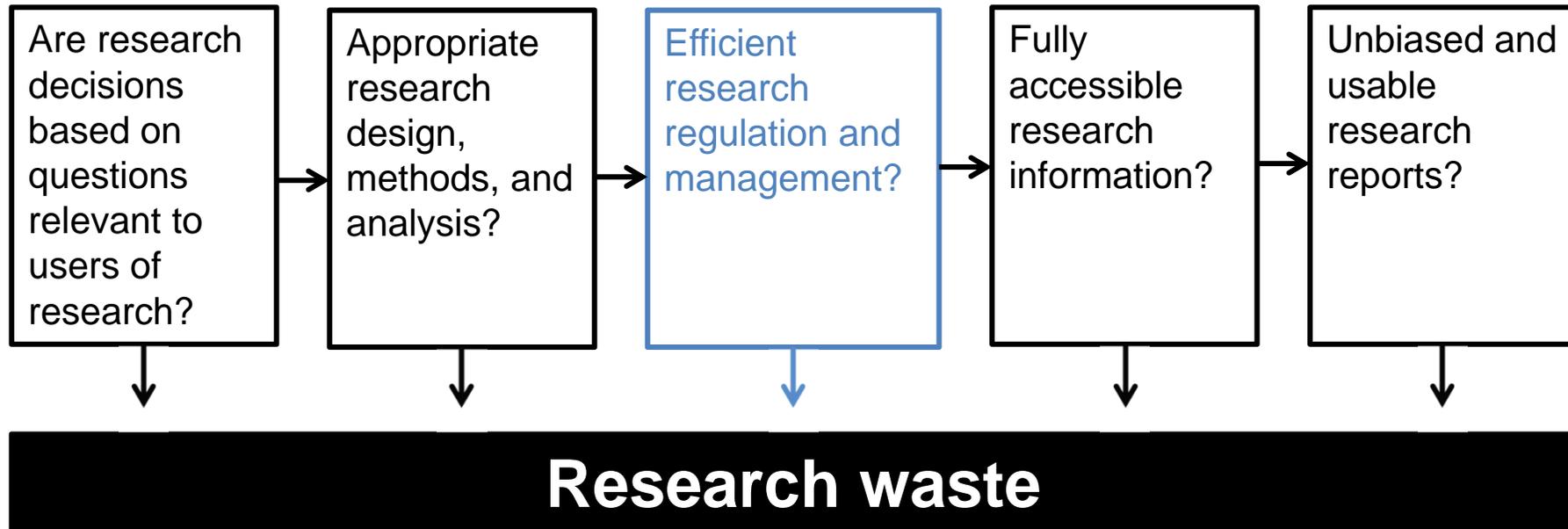
THE LANCET
Neurology



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And Reward Diligence

How does waste arise?



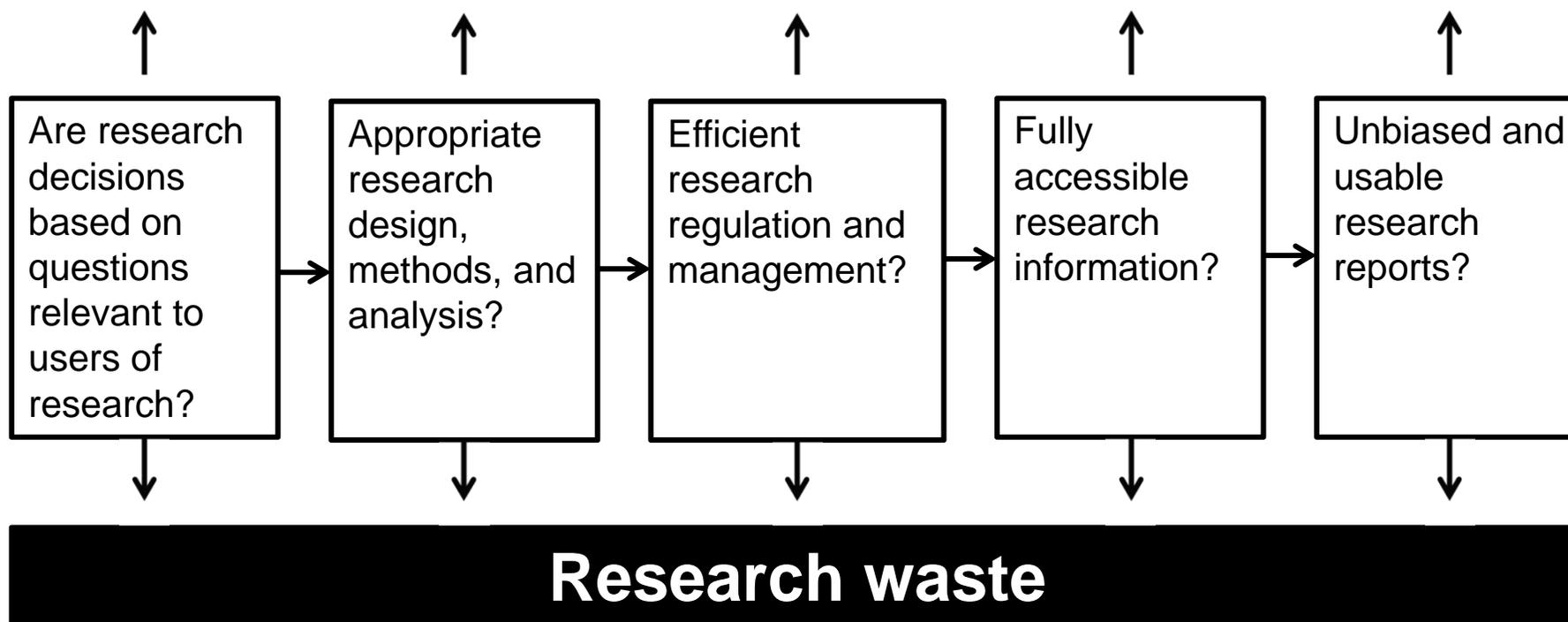
Lancet 2009;374:86–9 → *Lancet* 2014;383:101–4



REWARD

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17 recommendations, and how to monitor progress



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



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REduce research Waste
And Reward Diligence

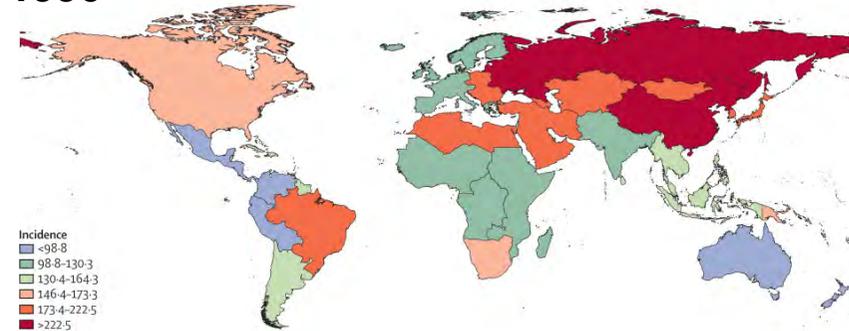
17 recommendations, and how to monitor progress



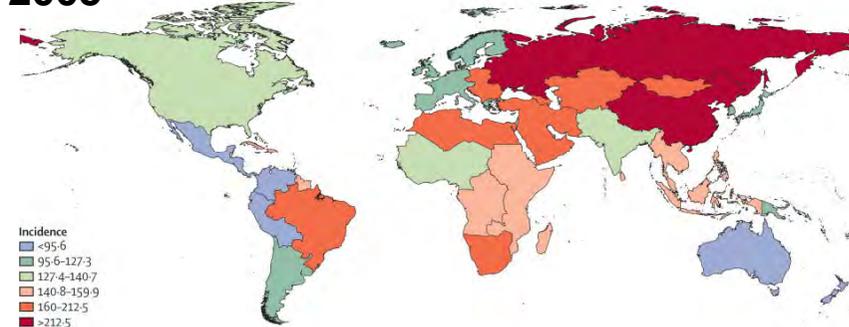
Stroke: increase value, reduce waste... decrease burden?

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

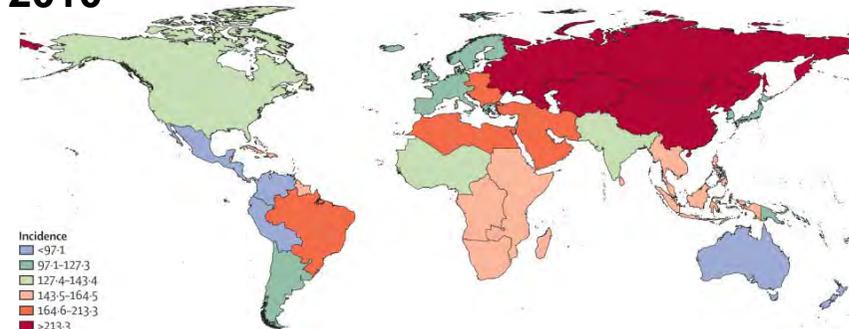
1990



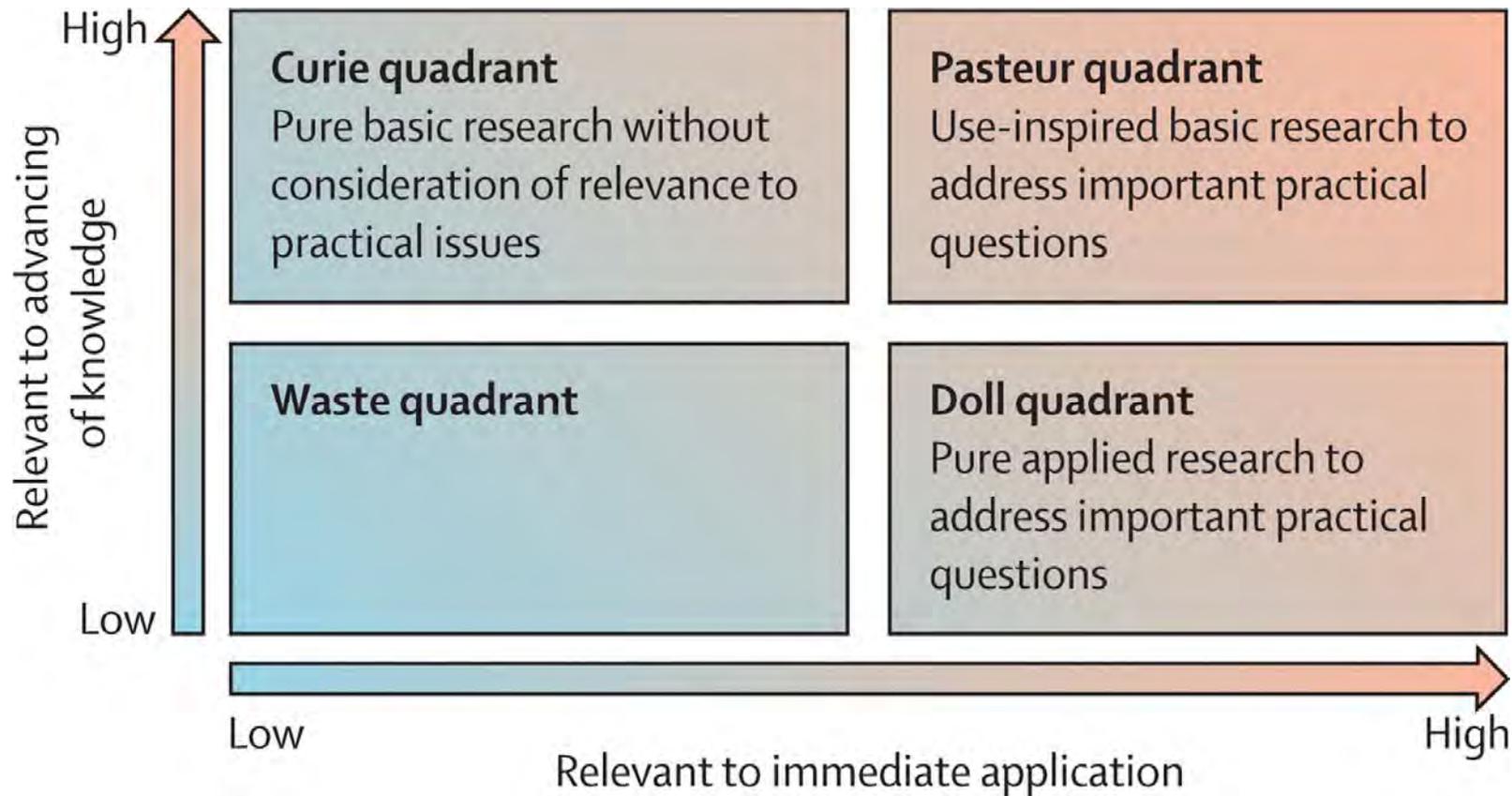
2005



2010



1. Setting research priorities



Lancet 2014;383:156–65



1. Setting research priorities

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

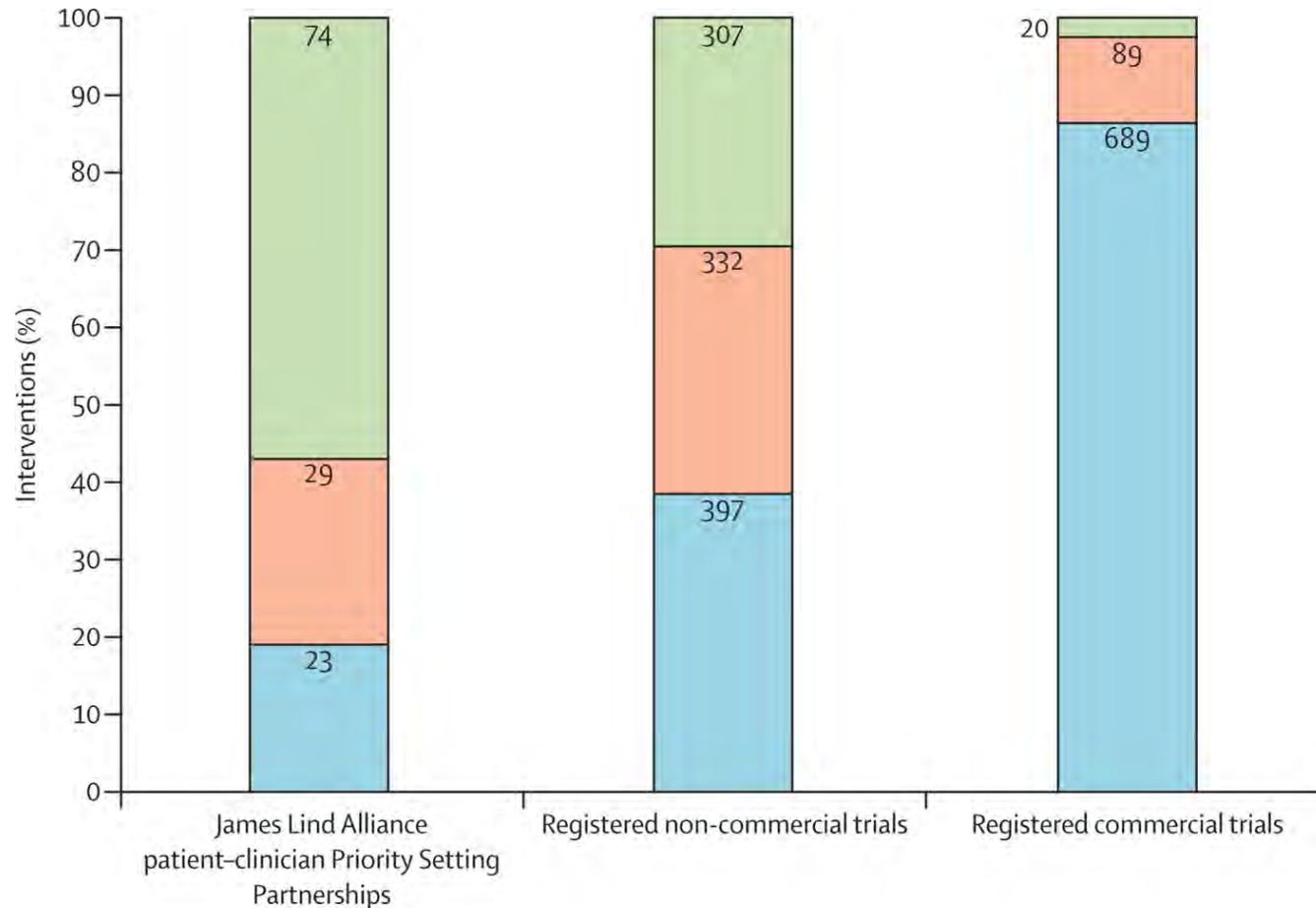


1. Setting research priorities

- 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**



1. Setting research priorities: whose?



- Education and training, service delivery, psychological interventions, physical interventions, exercise, complementary interventions, diet, and other
- Radiotherapy, surgery and perioperative interventions, devices, and diagnostic interventions
- Drugs, vaccines, and biologicals

Lancet 2014;383:156–65



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REduce research Waste
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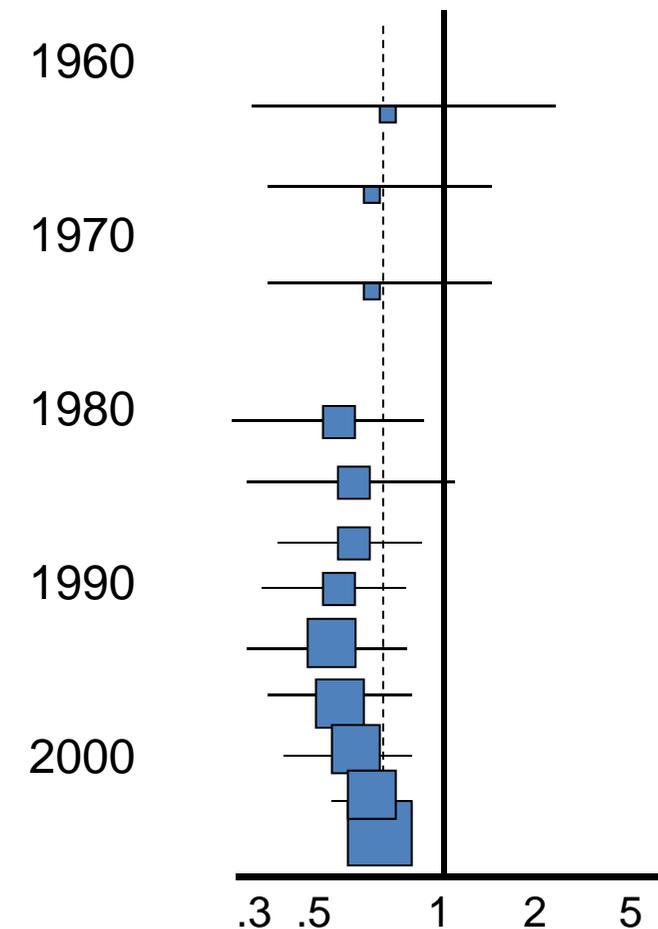
1. Recommendations

- 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



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



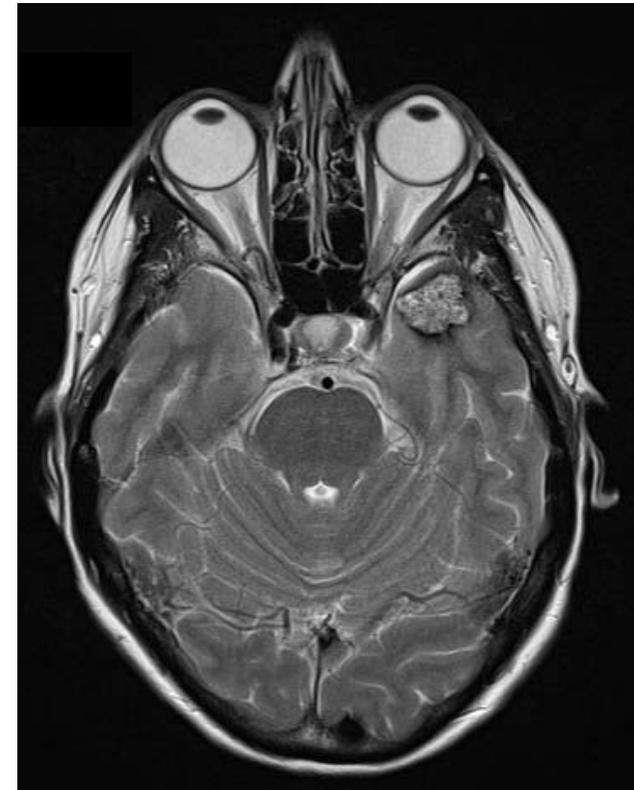
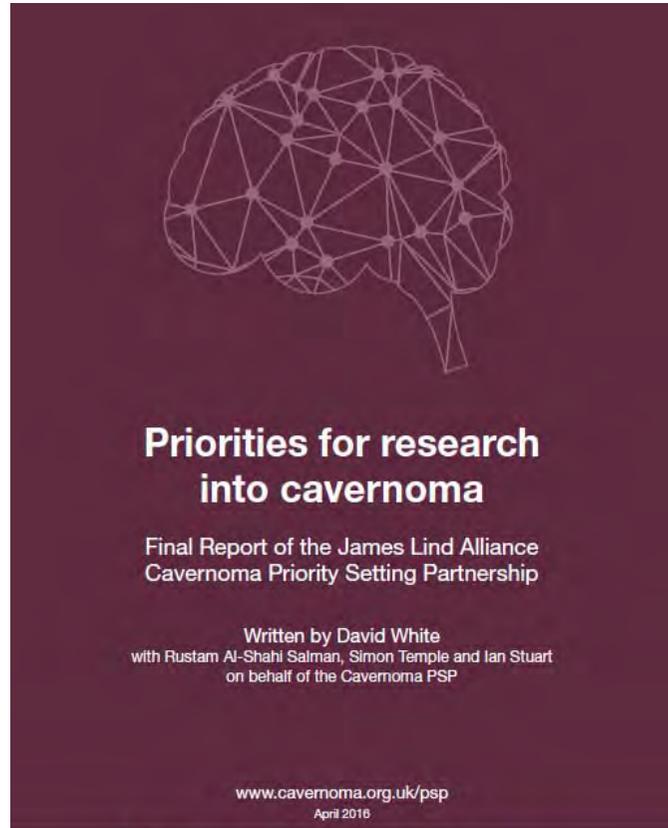
← Acute stroke unit better (death/dependence)

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

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





Lancet Neurology 2016;15:354-5



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?

2. Design, conduct and analysis

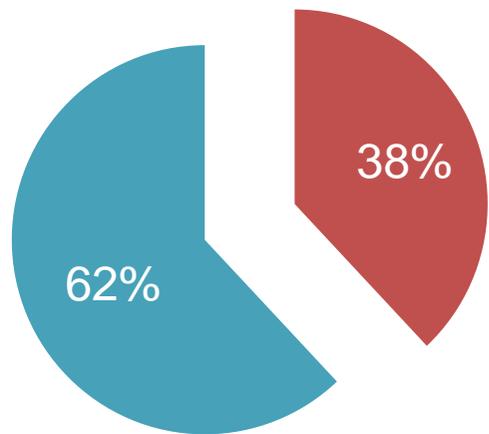


“To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of.”

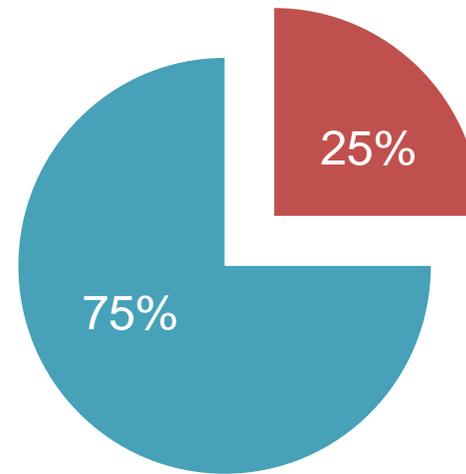
Sir Ronald Fisher
(1890–1962)

2. Design, conduct and analysis

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



nature



BMJ



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

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.)

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.”

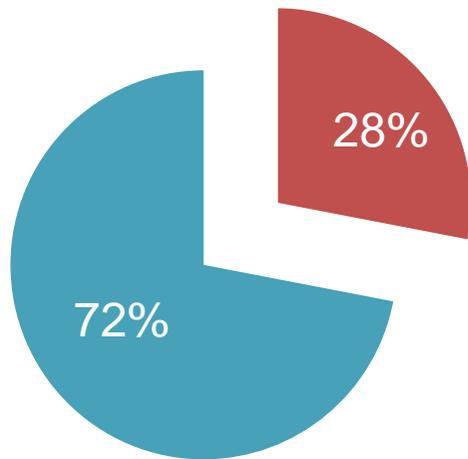
Richard Smithells (1924-2002)

Lancet 1990;336:846–7

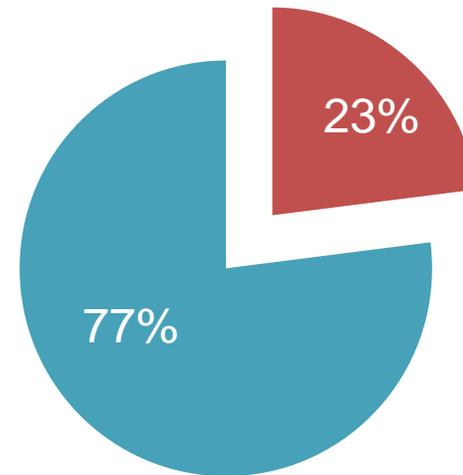


3. Regulation and management

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



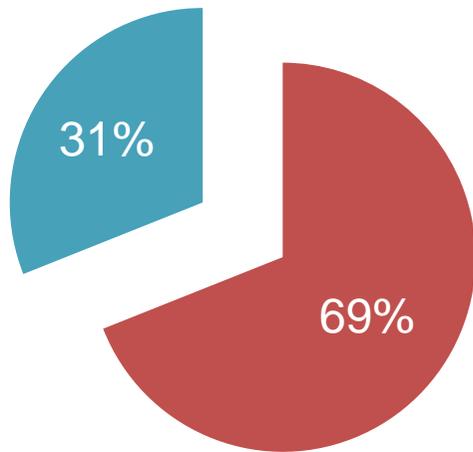
UK National Cancer Registry including postcode, name and address, and sending a letter inviting them to a research study



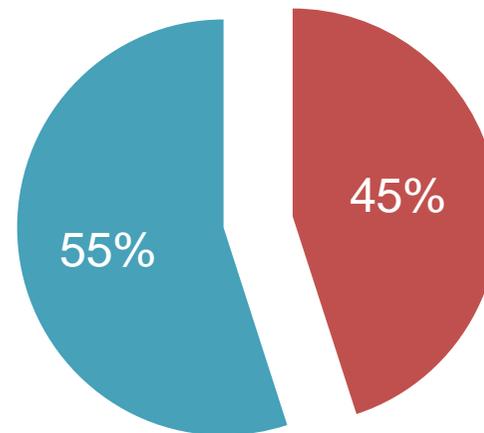
Finland national biobank of existing diagnostic and research samples

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

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)

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)

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**

3. Regulation and management

Regulatory enforcement


Health Research Authority

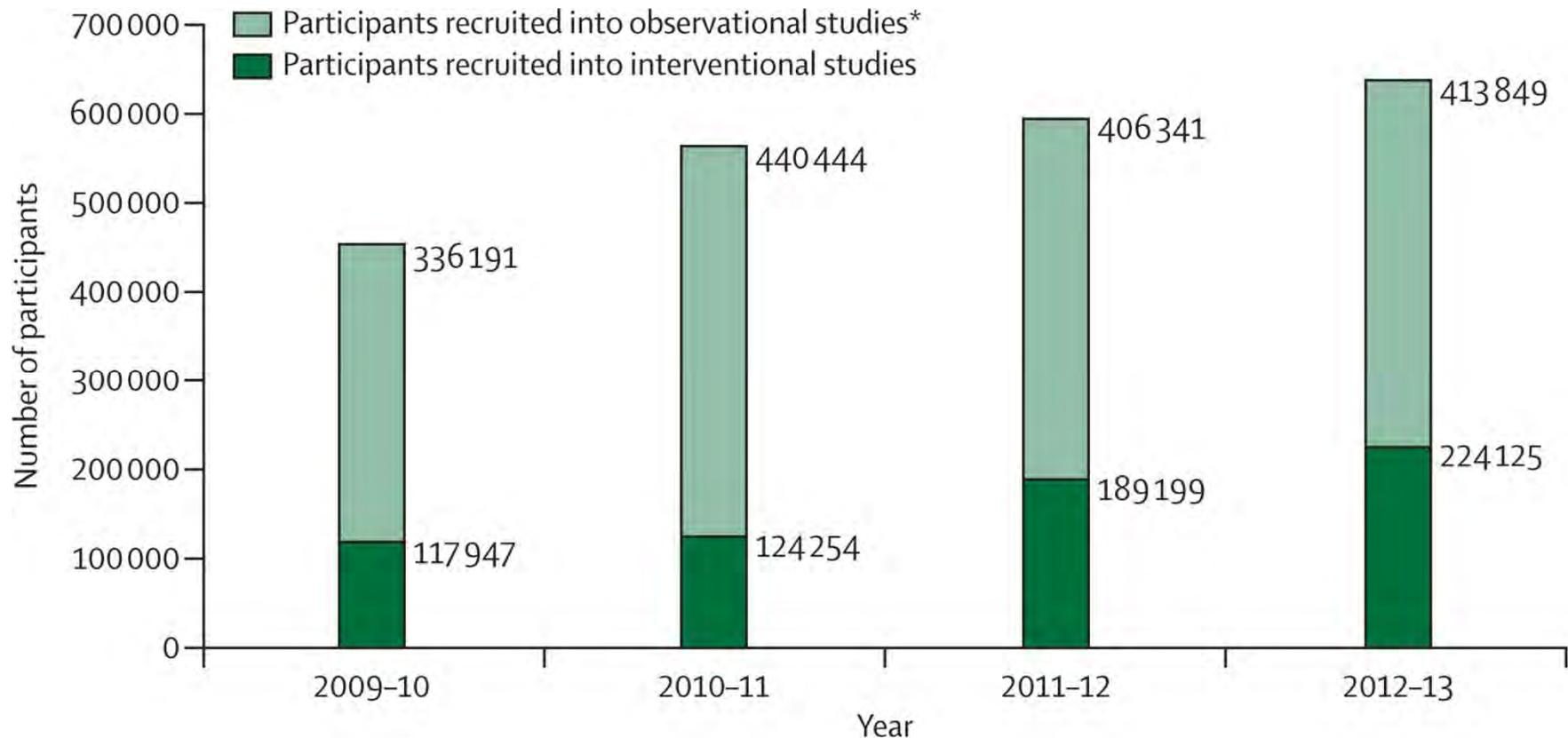


- All randomised trials should be registered
- Proportionate approaches to:
 - application
 - patient information leaflets

 **REWARD**
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And Reward Diligence

3. Regulation and management

Better recruitment after UK clinical research networks



Lancet 2014;383:176–85



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And Reward Diligence

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

STUDY PROTOCOL Open Access

Promoting Recruitment using Information Management Efficiently (PRIME): study protocol for a randomised controlled trial



UPDATE Open Access

Promoting Recruitment using Information Management Efficiently (PRIME): statistical analysis plan for a stepped wedge cluster randomised trial within the REstart or STOP Antithrombotics Randomised Trial (RESTART)

Amy E. Maxwell¹, Maureen A. O'Connell¹ and Rustam Al-Shahi Salman²



Richard A. Parker^{1*}, Christopher J. Weir¹, Amy E. Maxwell² and Rustam Al-Shahi Salman²

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



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)

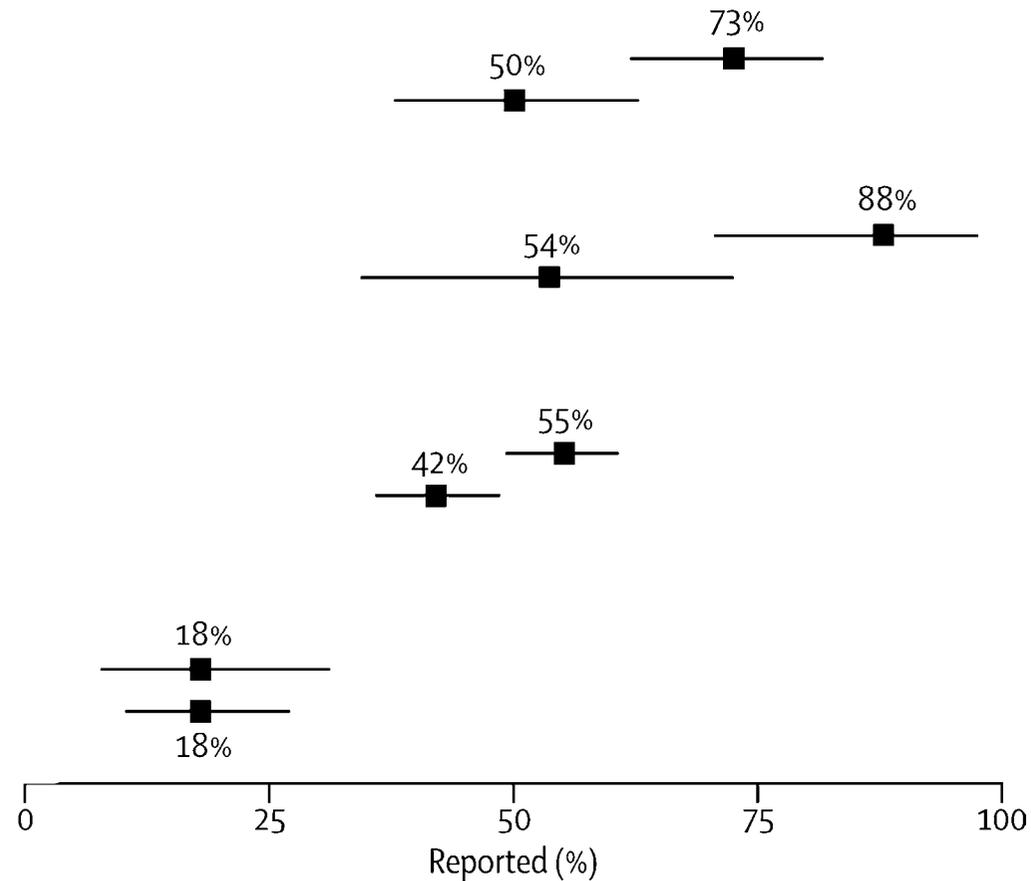
OR 1.7 (1.4-2.0)

Manuscripts submitted to journals (4 cohorts)

Positive studies (n=1869)

Null or negative studies (n=767)

OR 1.1 (0.8-1.4)



Lancet 2014;383:257-66

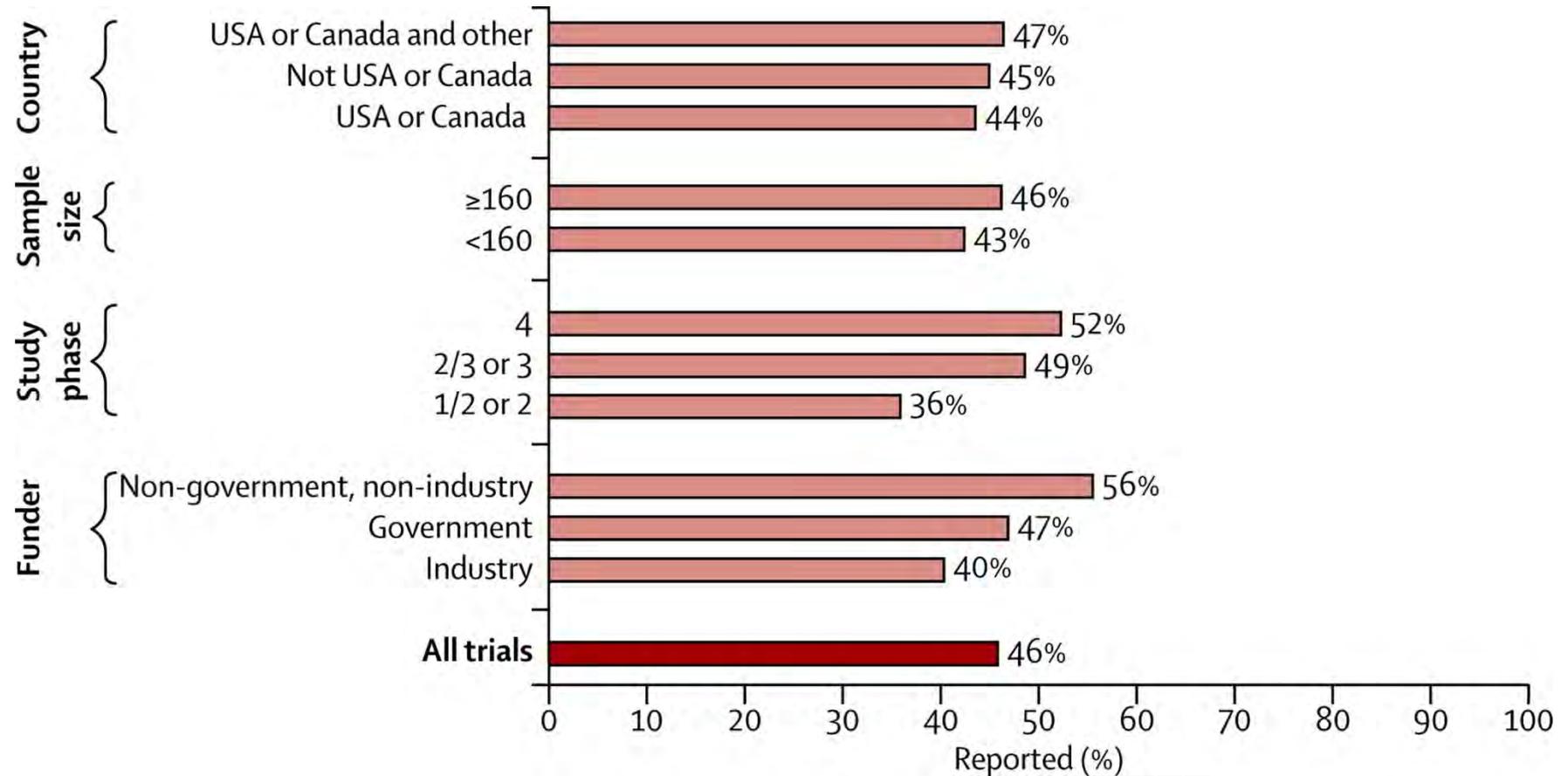


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4. Accessible reporting

Associations with reporting



Lancet 2014;383:257–66

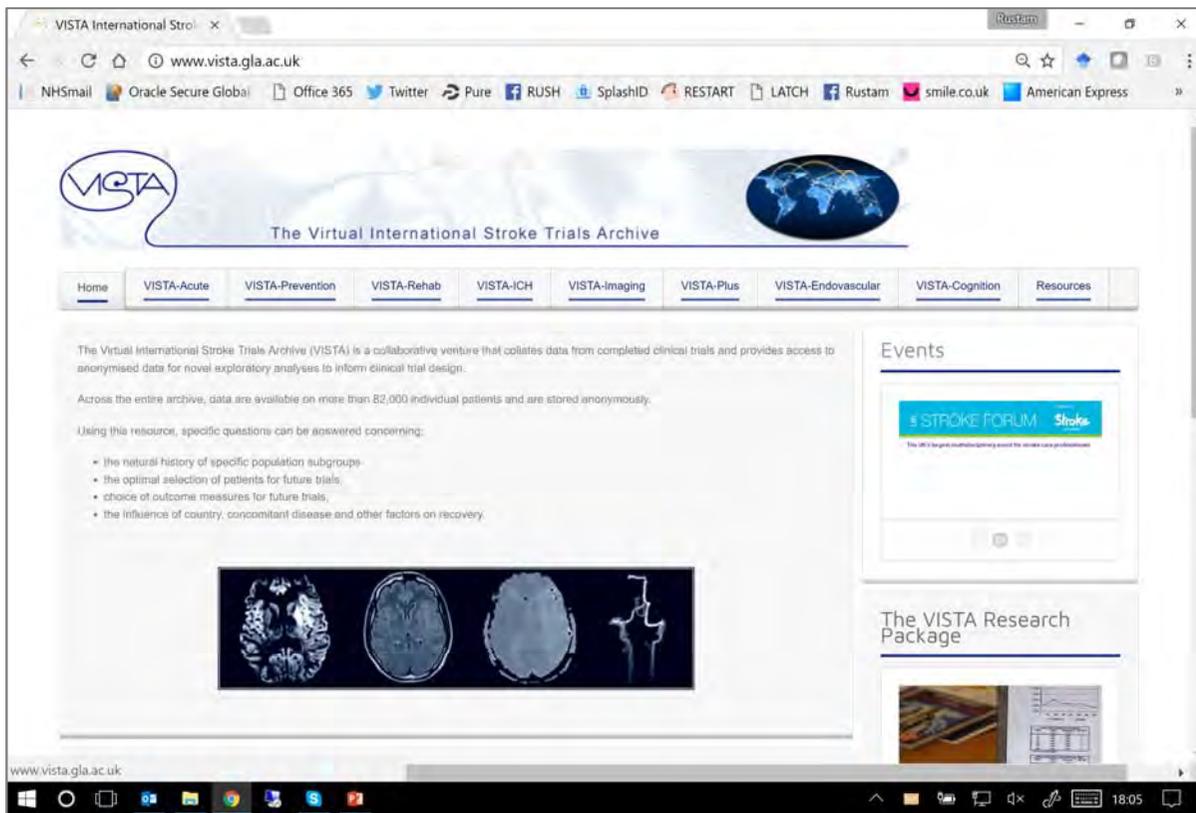


4. Recommendations

- 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

4. Accessible reporting

Stroke RCT IPD repository: VISTA



www.vista.gla.ac.uk



4. Accessible reporting



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



RESEARCH **Open Access**

The International Stroke Trial database

Peter AG Sandercock^{1*}, Maciej Niewada^{2,3}, Anna Czlonkowska^{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.

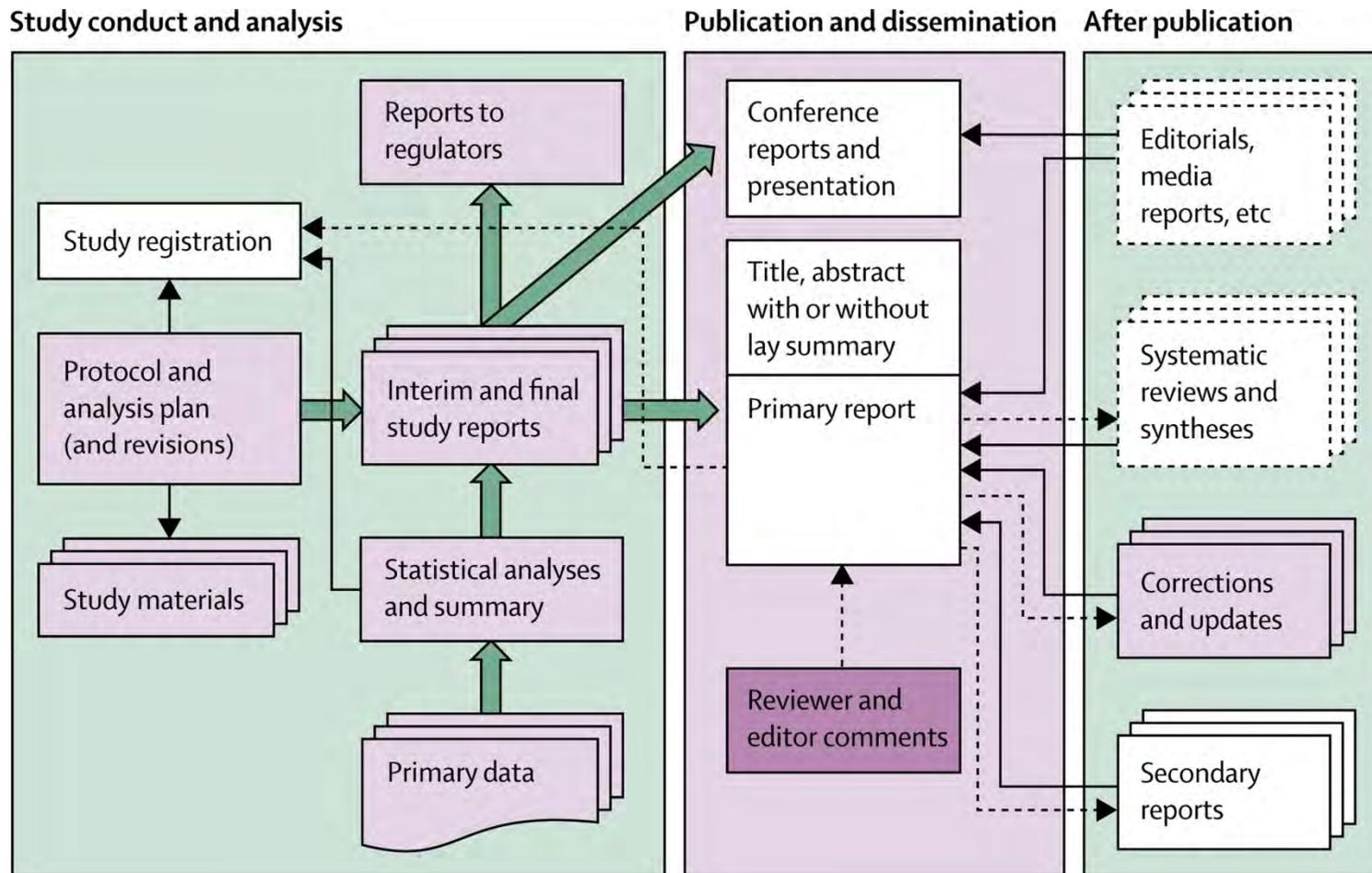


Open Data Award 2012

Trials 2011;12:101



5. Complete & usable reporting



Lancet 2014;383:267–76



5. Complete & usable reporting

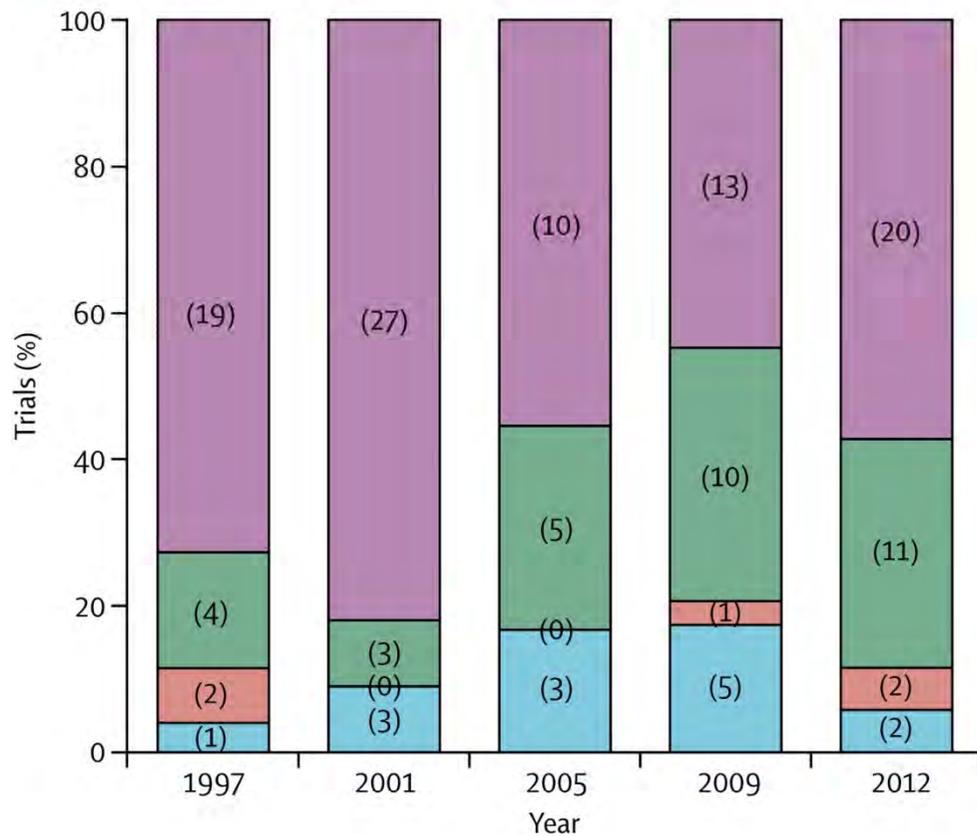
<p style="text-align: center;">Abstract</p> <p>Trials: missing effect size and confidence interval (38%); no mention of adverse effects (49%)⁷²</p>
<p style="text-align: center;">Methods</p> <p>Trials: 40–89% inadequate treatment descriptions^{11, 13} fMRI studies: 33% missing number of trials and durations³ Survey questions: 65% missing survey or core questions²⁵ Figures: 31% graphs ambiguous⁴⁵</p>
<p style="text-align: center;">Results</p> <p>Clinical trials: outcomes missing: 50% efficacy and 65% harm outcomes per trial incompletely reported⁶ Animal studies: number of animals and raw data missing¹⁷ (54%, 92%); age and weight missing (24%) Diagnostic studies: missing age and sex (40%)¹⁵</p>
<p style="text-align: center;">Discussion</p> <p>Trials: no systematic attempt to set new results in context of previous trials (50%)⁶⁹</p>
<p style="text-align: center;">Data</p> <p>Trials: most data never made available; author-held data lost at about 7% per year</p>

Lancet 2014;383:267–76



5. Complete & usable reporting

- No apparent systematic attempt to set results in the context of other trials
- Discussed a previous review but did not attempt to integrate findings
- Contained an updated systematic review integrating the new results
- First trial addressing the question



Lancet 2014;383:267–76



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

5. Complete & usable reporting

Reporting guidelines

equator network Enhancing the **QUALITY and Transparency Of health Research**

EQUATOR resources in [Portuguese](#) | [Spanish](#)

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Your one-stop-shop for writing and publishing high-impact health research
 find reporting guidelines | improve your writing | join our courses | run your own training course | enhance your peer review | implement guidelines

Library for health research reporting

The Library contains a comprehensive searchable database of reporting guidelines and also links to other resources relevant to research reporting.

[Search for reporting guidelines](#)

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions	Other
Observational studies	STROBE	Extensions	Other
Systematic reviews	PRISMA	Extensions	Other
Case reports	CARE	Extensions	Other
Qualitative research	SRQR	COREQ	Other
Diagnostic / prognostic studies	STARD	TRIPOD	Other
Quality improvement	SQUIRE		Other

Science reporting guidelines by specialty

Visit our new browse reporting guidelines by specialty page

www.equator-network.org



5. Complete & usable reporting

The Lancet's Research in Context panel

The image shows a screenshot of a journal article with a 'Research in Context' panel overlaid. The panel is divided into three sections: 'Evidence before this study', 'Added value of this study', and 'Implications of all the available evidence'. A separate callout box explains the 'Interpretation' section. The background text is partially obscured by the 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 in context

Systematic Review
This section should describe all the studies searched for all the outcomes that they assessed, the quality of the studies selected and how the results were synthesized.

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

Putting c
May 20, 2005, s
trials day,' celebr
the concept of
biomedical resea
between the r
Biomedical resea
children every d
However, biome
Part of the d
avoidable: some
ments will be fo
alternative and s
risk is underlined
paid for the altr
More troubling
avoidable but in
As societal aware
medical research
that bad research
inappropriately,
which is done b
which is publish
existence or its
recently been the
of clinical trial at,
But what of unnecessary and badly presented research:
Dean Fergusson and colleagues⁵ 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
that although 64 trials investigated the effectiveness of
meta-analysis does not exist, authors are encouraged to
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
injure volunteers and patients, or crush or squelch other

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



5. Complete & usable reporting

TIDieR checklist

TIDieR

**Template for Intervention
Description and Replication**

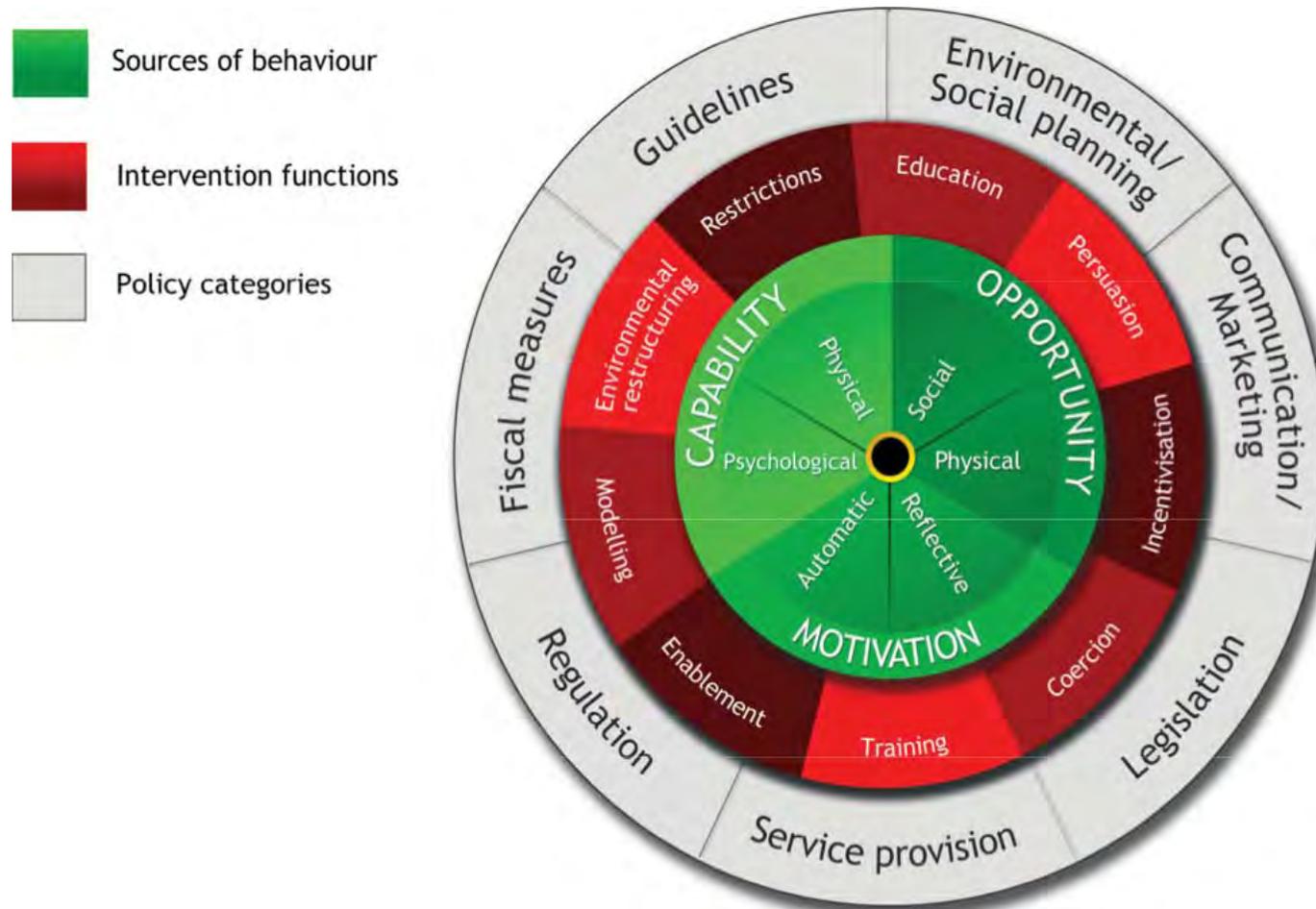


BMJ 2014;348:g1687

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

How can, and will, we change?!



Implementation Science 2011;6:42



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Funders and regulators are key change agents

The screenshot shows the NHS National Institute for Health Research website. The page title is 'Adding Value in Research'. The NHS logo is in the top right corner. The page content includes a navigation menu on the left, a main text area with a list of bullet points, a blue callout box, and a search bar on the right. The search bar indicates that project search is no longer available and suggests searching via the NIHR Journals Library. There are also links for a website survey, NIHR Journals Library, and a mailing list sign-up.

NHS
National Institute for
Health Research

Evaluation, Trials and Studies

You are here: [Home](#) > [About us and our approach](#) > [Adding Value in Research](#)

- Research programmes
- Funding opportunities
- Project portfolio
- Resources for researchers
- Become a reviewer
- Identifying research questions
- Public and patient involvement
- About us and our approach**
- Adding Value in Research**
- Public health
- International work
- Needs-led, science-added

Adding Value in Research

The NIHR is committed to Adding Value in Research to maximise the potential impact of research that it funds for patients and the public. This means ensuring that it answers the right questions, delivers the research efficiently and publishes the results in full in an accessible and unbiased report.

Adding Value in Research ensures that NIHR funded research:

- answers **questions** relevant to clinicians, patients and the public;
- uses appropriate **design and methods**;
- is **delivered** efficiently;
- results in accessible full **publication**; and
- produces unbiased and usable **reports**.

Maximising the potential impact for patients and the public from money spent on health research

Adding Value in Research is the positive response to the work of Sir Iain Chalmers and Professor Paul Glasziou in 2009*. We use their stages in the research cycle to assess our research management processes and identify where we can add value in research.

Search

Project search no longer available. Search via the NIHR Journals Library

We'd like your views

Help us improve your experience of our website by participating in a short survey.

[Website survey](#)

NIHR Journals Library

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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>



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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>

The screenshot shows the top of the The Lancet website. The navigation bar includes links for Home, Journals, Specialties, The Lancet Clinic, Global Health, Multimedia, Campaigns, More, Information for, and Submit a Paper. The main header features the 'THE LANCET' logo and a search bar. Below the header, there is a section for the REWARD campaign with a video player and a list of partner logos. The video player shows a title 'REWARD' and a description: 'The Lancet REWARD (Reduce research Waste And Reward Diligence) Campaign invites everyone involved in biomedical research to critically examine the way they work to reduce waste and maximise efficiency. Read the REWARD statement and join the campaign.' The list of partners includes logos for REWARD, Oxford, BioMed Central, NHS, Cochrane, equator network, SPIRIT, gsk, TRIALFORGE, CERF, OXFORD, Wessex Institute Southampton, European Association of Science Editors, science in transition, nature, METRICS, VUmc, The World Health Organisation, CONSORT, TMF, GIMBE, NRI, National Institute for Health Research, UMC Utrecht, UK Dermatology Clinical Trial Network, CMAJ, CMAJ OPEN, HerpeZ, UNZA-UCLMS, SONG, UNIVERSITY OF BIRMINGHAM, Hartstichting, EbM, v>e, and Radboud umc.

Look out for REWARD symposia...



Rustam Al-Shahi Salman



Malcolm Macleod



Iain Chalmers



Paul Glasziou



An-Wen Chan



John Ioannidis



Iveta Simera



Doug Altman



Ana Marušić



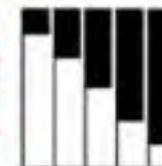
Philippe Ravaud



David Moher



Gerd Antes



REWARD

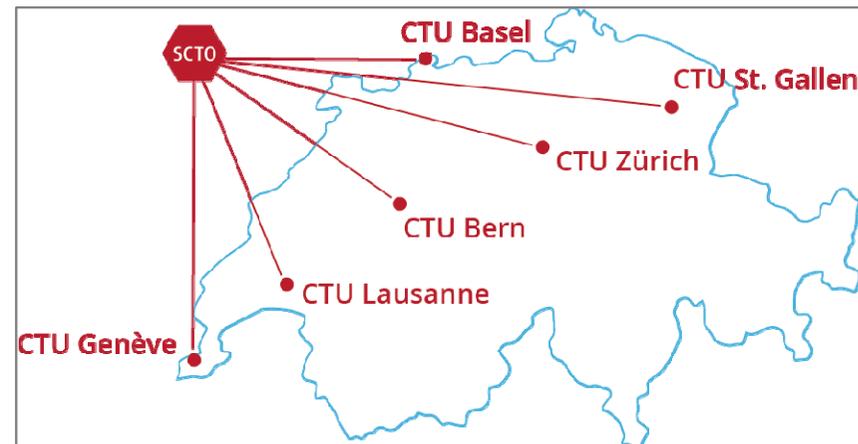
REduce research Waste
And Reward Diligence

www.wcri2017.org

www.scto.ch



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



REWARD

REduce research Waste
And Reward Diligence

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