Research:
Increasing value, reducing waste

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University Medical Center Freiburg

European Society of Clinical Pharmacy
Heidelberg 10 Oct 2017

Conflicts of interest

– Cochrane Germany is a central unit of the University Medical Centre Freiburg

– G. Antes is 100% employed by the University Hospital

– Potential conflict:
Long-lasting commitment to Evidence and Systematic Reviews
Contents

– Evidence to answer the crucial question: What works?
– The global system of knowledge from trials
– Systematic reviews as key technology for knowledge synthesis
– Open Access and Big Data – the new enemies?
– New science or better old science?

What is the optimal decision for the selection of the right diagnostic procedure or the best therapy?
Information from similar persons under same conditions
**Crucial for Trial Quality (Validity)**

Maximal protection against systematic errors (bias)

- Comparison between parallel groups
- Similar groups, only difference in intervention (treatment)
- No influence from expectations of doctors or patients
- High quality scientific analysis

**The path to the truth**

Counterfactual thinking: What would happen if . . .
Two crucial targets

1. Minimization of systematic errors (bias)

2. Control of random errors (play of chance)

Gold standard is
not the randomized controlled trial but
the criteria to control error and to maximize benefit

Transfer of Research into Practice

Answers to medical questions
• Clinical (randomised / controlled) studies
• Epidemiological (observational) studies

• Practicing physicians
• Health authorities, sickness funds, insurances, institutions
• Clinical research
• Patients
Transfer of research results into practice

Patients / healthy persons
Research / studies / data

Literature based synthesis (SR; Cochrane classic)

Individual-patient-based data synthesis (IPD SR)

Access to trial reports (SR from authority data)

Patients / healthy persons
Application / benefit / harm / costs

Trustworthy?

AllTrials: Withholding results costs lives

The results of a 1980 clinical trial on heart drug Lorcaidine were not published until a decade later. Doctors didn’t know that more people died in the trial who were given Lorcanide than who were taking the placebo. It has been estimated that over 100,000 people died avoidably because they were prescribed drugs in the same class. Read about how the researchers were able to get the results of the study published.
WHO calls for increased transparency in medical research

June 2017

14 APRIL 2015 - GENEVA - WHO today issued a public statement calling for the disclosure of results from clinical trials for medical products, whatever the result. The move aims to ensure that decisions related to the safety and efficacy of vaccines, drugs and medical devices for use by populations are supported by the best available evidence.

"Our intention is to promote the sharing of scientific knowledge in order to advance public health," said Dr Marie-Paule Kieny, WHO Assistant Director-General for Health Systems and Innovation. "It underpins the principal goal of medical research: to serve the betterment of humanity."

"Failure to publicly disclose trial results conveys misinformation, leading to skewed priorities for both R&D and public health interventions," said Dr Kieny. "It creates indirect costs for public and private entities, including patients themselves, who pay for suboptimal or harmful treatments."

Unreported trials lead to misinformation

For example, in a study that analyzed reporting from large clinical trials (more than 500 participants) registered on ClinicalTrials.gov and completed by 2009, 23% had no results reported. These unreported trials included nearly 300,000 participants.

Bridging the Data-Sharing Divide
Whose Data Are They Anyway?
Data Authorship as an Incentive to Data Sharing
Advantages of Open-Access Data-Sharing Model
Announcement: Where are the data?

As the research community embraces data sharing, academic journals can do their bit to help. Starting this month, all research papers accepted for publication in Nature and an initial 12 other Nature titles will be required to include information on whether and how others can access the underlying data.

These statements will report the availability of the minimal data set necessary to interpret, replicate and build on the findings reported in the paper. Where applicable, they will include details about publicly archived data sets that have been analysed or generated during the study. Where restrictions on access are in place — for example, in the case of privacy limitations or third-party control — authors will be expected to make this clear.

The new policy details of which are available at [go.nature.com/2ieq9n] builds on our long-standing support for data availability as a condition of publication. It also extends our support for data citation, the practice of citing data sets in reference lists in a similar way to citing papers. Authors are encouraged to cite datasets that have digital object identifiers (DOIs) assigned to them.

The introduction of data-availability statements follows a trial at five Nature journals — Nature Cell Biology, Nature Communications, Nature Geoscience, Nature Neuroscience and Nature Physics — that began in March 2016. The trial confirmed differences in the culture of data sharing and access between different disciplines, and that the task of obvious, public, community repositories
The trial deluge

RCTs (Reports) in Medline
Overall: 436,827

22 Sept 2017
The truth

RCTs (Reports) in Medline (PubMed)
Overall: 436,827

Freiburg Ethics Board
2000-2002:
48% published until 2010
J. Simes (1986)

2.5+ Mio. Patients

22 Sept 2017
Transfer of Research into Practice

Clinical studies (experimental, randomised, controlled, prospective)

Epidemiological studies (observational, retrospective)

Systematic Reviews

EBM

Health Technology Assessment (HTA)

Clinical Guidelines

Patient Information

Disease Management Programs (DMPs)

Clinical Pathways (CPs)
Turner et al. (2008). Selective publication of antidepressant and its influence on apparent efficacy. NEJM.

Overestimation of effectiveness of antidepressive drugs 20% to 50%.
1. Framing the question (PICO)

2. Systematic search for evidence from relevant trials and studies

3. Critical appraisal of trials - inclusion

4. Summary and quantitative synthesis (if possible)

5. Interpreting and putting in context

**Updating!!**

Produce unbiased view of “all” evidence

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**Example**

**Thrombolysis after acute myocardial infarction**

*NEJM 1992*

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**Forest Plot**
Thrombolysis (Streptokinase) after myocardial infarction

Open questions

– No accepted stopping rule

– Have all relevant trials been identified and considered?

Need „all“ (!) relevant, high quality trials:
In 2017 no reliable method and procedure to achieve this
RCTs of aprotinin in cardiac surgery to stop bleeding

Lancet 2005
Clinical Trials 2005

1987

Cited

2002

Finding What Works in Health Care: Standards for Systematic Reviews

Released: March 23, 2011
Type: Consensus Report
Topics: Biomedical and Health Research, Public Health, Quality and Patient Safety
Activity: Standards for Systematic Reviews of Comparative Effectiveness Research
Board: Board on Health Care Services
Excerpt

To improve the effectiveness and value of the care delivered, the nation needs to build its capacity for ongoing study and monitoring of the relative effectiveness of clinical interventions and care processes through expanded trials and studies, systematic reviews, innovative research strategies, and clinical registries, as well as improving its ability to apply what is learned from such study through the translation and provision of information and decision support.
What Works Global Summit

Putting evidence to work for better policies, programmes and practices

The What Works Global Summit 2016
London, 26-28 September 2016

Pre-conference workshops: 24-25 September

We are now accepting submissions!
Submission deadline: 23 April 2016. Find more info here:

The Campbell Collaboration, the Centre for Evidence and Development (Queen’s University Belfast), the International Initiative for Impact Evaluation (IIIEE) and Science with Socio-economic Benefits, announce the first What Works Global Summit this autumn 2016 in London, UK. The event addresses evidence-informed policy globally across all sectors, with active participation from both producers and users of evidence.

To join the conference mailing list, please email www@campbellcollaboration.org with the subject ‘Mailing List’ for information and updates will be posted on Twitter via @IIIEE and @WWS2016.

Further details to follow shortly.

Proceedings
Research in context

Findings? How can we improve the accessibility and usability of research findings, and data availability? And, finally, how can we further raise awareness and continue discussions on the topic of research productivity?

As a first step, we are strengthening our requirement to put research into context. Knowing and rigorously assessing the context and value of research will help editors make decisions about whether to publish a paper, and will help readers to interpret the importance of published research in addressing unanswered questions and building an evidence base. From Jan 1, 2015, all research papers, apart from systematic reviews and meta-analyses, submitted to any journal in The Lancet family must include a Research in context panel with an enhanced structure and subheadings (boxed). Editors will use this information at the first assessment stage and
Leaving things out

Selective reporting =

1. Hiding whole trials (classical publication bias)
2. Hiding (or distorting) information from trials which are published
3. Spin: Interpretations which have nothing to do with the trial results
Is selective reporting really harmful?

Class-I-Antiarrythmic drugs after myocardial infarction

70s: Frequent off-label use, first trials

1980 Trial stopped (commercially not interesting) after 9 / 1 deaths in treatment / control group: not reported!!

1983 Systematic review (14 trials): Failed to show efficacy

1992 CAST Study: Increased mortality in the drug group

1993 Systematic review (JAMA) with 51 randomised trials:
More deaths in treatment group!

80s: 20000 – 70000 per in USA Moore ’93

1993 publication Cowley et al. ’93
The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias

A.J. Cowleya, A. Skeneb, K. Stainera and J.R. Hamptonb

aCardiovascular Medicine, University Hospital, Nottingham, UK and bBritish Heart Foundation Cardiovascular Statistics Group, Nottingham University, Nottingham, UK

(Received 18 January 1993; revision accepted 25 February 1993)

Ninety-five patients with suspected acute myocardial infarction were randomly allocated on admission to hospital on a double blind basis to treatment with lorcainide, a Class IC anti-arrhythmic drug, or matching placebo. Treatment was continued for 6 weeks. Twenty-four-hour ECG tape recordings were made immediately on admission, on the sixth or seventh day after admission, and again just before the end of the treatment period. Lorcainide was shown to be an effective anti-arrhythmic agent. The study was not designed to evaluate the effect of lorcainide on survival, but there were nine deaths among the 49 patients treated with lorcainide compared with only one in the patients given placebo. These findings are consistent with the results of the First and Second Cardiac Arrhythmia Suppression trials (CAST and CAST-II). This study was carried out in 1980 but was not published at the time: it now provides an interesting example of ‘publication bias’.

Off-label use of antiarrythmic drugs after myocardial infarction

Arzneimitteleinsatzes: „The result of this single medical misjudgment about the properties of these drugs produced a death toll larger than the United States’ combat losses in wars as Korea and Vietnam.“ [1]
AllTrials: Withholding results costs lives

On Lorcalcined

Youtube (now)

RESEARCH ARTICLE
Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review

Su Golder¹ *, Yoon K. Loke², Keith Wright³, Gill Norman³

¹ Department of Health Sciences, University of York, York, United Kingdom, 2 Norwich Medical School, University of East Anglia, Norwich, United Kingdom, 3 Centre for Reviews and Dissemination (CRD), University of York, York, United Kingdom. 4 School of Nursing, Midwifery & Social Work, University of Manchester, Manchester, United Kingdom

* su.golder@york.ac.uk

Conclusions
There is strong evidence that much of the information on adverse events remains unpublished and that the number and range of adverse events is higher in unpublished than in published versions of the same study. The inclusion of unpublished data can also reduce the imprecision of pooled effect estimates during meta-analysis of adverse events.
Striving for quality: Trial registration to support and enforce publication

WHO Register Network ICTRP  www.who.int/ictrp

ANZCTR

Clinical Trials.gov

EU Clinical Trials Register

Urology

DRKS
Including ongoing trials into systematic reviews?
Is trial registration leading to higher publication rates?

- Heterogenous registration rates, some very low
- No sanctions, or, if sanctions, they are not applied
- Inconsistent conditions around the world
- Cost effective measure to provide a complete map of currently conducted trials to inform science and practice

Next step towards more complete publication: Results “registration”
Complete picture from minutes to results

Inconsistent conditions around the world

<table>
<thead>
<tr>
<th>Country</th>
<th>Registration</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (2007)</td>
<td>law</td>
<td>law</td>
</tr>
<tr>
<td>Germany (2011)</td>
<td>-</td>
<td>law (drugs)</td>
</tr>
<tr>
<td>Switzerland (2014) (Law for research in humans)</td>
<td>law</td>
<td>-</td>
</tr>
</tbody>
</table>
“Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty...
The Cochrane Collaboration (since 1993)

Trusted evidence. Informed decisions. Better health

Independent network of 36000+ contributors from science and health professions

Systematic Reviews
Leading principle: Minimizing bias

Risk of Bias
Current record count for the Cochrane Library

<table>
<thead>
<tr>
<th>Database</th>
<th>Total Records</th>
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</thead>
<tbody>
<tr>
<td>Cochrane Database of Systematic Reviews</td>
<td>9,967</td>
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<tr>
<td>Cochrane Central Register of Controlled Trials</td>
<td>1,067,170</td>
</tr>
<tr>
<td>Cochrane Methodology Register</td>
<td>25,764</td>
</tr>
<tr>
<td>Database of Abstracts of Reviews of Effect</td>
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<tr>
<td>Health Technology Assessment Database</td>
<td>16,559</td>
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<tr>
<td>NHS Economic Evaluation Database</td>
<td>15,015</td>
</tr>
<tr>
<td>About The Cochrane Collaboration</td>
<td>76</td>
</tr>
<tr>
<td>Cochrane Editorials</td>
<td>119*</td>
</tr>
</tbody>
</table>

Cochrane Library Counts
October 2017

7415 reviews
2572 protocols

Impact Factor 2016: 6.264 (vorläufig)
<20% from Cochrane

The next desaster?

Knowledge accumulation: backfiring?
Systems of wrong incentives, agendas driven by science and scientists' careers, maldevelopment of journals . . .
Open access, data sharing . . .
A new enemy?

Old: The poor can't read
New: The poor can't write
Open-Access

- Author fees are business model for new journals

- Immediate consequence: growth, equivalent to loss of quality in a limited market

Tangled web. The location of a journal’s publisher, editor, and bank account are often continents apart.

John Bohannon Science 2013;342:60-65

Published by AAAS
Predatory journals: Ban predators from the scientific record

Jeffrey Beall

Nature 334, 326 (16 June 2016) doi:10.1038/334326a
Published online 16 June 2016

Subject terms: Publishing - Peer review

Predatory journals are threatening the credibility of science. By faking or neglecting peer review, they pollute the scholarly record with flimsy or junk science and activist research. I suggest that every publishing stakeholder could contribute to reining in these journals.

Universities and colleges should stop using the quantity of published articles as a measure of academic performance. Researchers and respectable journals should not cite articles from predatory journals, and academic library databases should exclude metadata for such publications.

Open-Access Mega-Journals: A Bibliometric Profile

Simon Watanabe*, Peter Willott, Claire Crease, Jenny Fei, Stephen Pichl, Valeria Spera

Abstract

In this paper we present the first comprehensive bibliometric analysis of eleven open-access mega-journals (OAMJs). OAMJs are a relatively new phenomenon, and have been characterised as having four key characteristics: large size, broad disciplinary scope, a Gold OA business model, and a poor review policy, that seeks to determine only the scientific soundness of the research rather than evaluate the novelty or significance of the work. Our investi...
Current Incentives for Scientists Lead to Underpowered Studies with Erroneous Conclusions

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* a.higginson@exeter.ac.uk (ADH), m.munafo@bristol.ac.uk (MRM)

Abstract

We can regard the wider incentive structures that operate across science, such as the priority given to novel findings, as an ecosystem within which academics strive to maximise their fitness (i.e., publication record and career success). Here, we develop an optimality model that predicts the most rational research strategy, in terms of the proportion of research effort spent on seeking novel results rather than on confirmatory studies, and the amount of research effort per exploratory study. We show that, for parameter values derived from the scientific literature, researchers acting to maximise their fitness should spend most of their effort seeking novel results and conduct small studies that have only 10%–40% statistical power. As a result, half of the studies they publish will report erroneous conclusions. Current incentive structures are in conflict with maximising the scientific value of research; we suggest ways that the scientific ecosystem could be improved.

Medical and scientific publishers have lost their moral voice. Do they have the courage to reclaim it? There is little sign of it as yet.

Today's medical/scientific publishing industry operates in a moral vacuum. It has betrayed its Enlightenment values. Time to remoralise.

Richard Horton, Editor of The Lancet
Jan 2017
A further obstacle: The language
Transfer of Research into Practice

Answers to medical questions
- Clinical (randomised / controlled) studies
- Epidemiological (observational) studies

Knowledge Translation

- English language
- 5% of world population anglophone

Implementation: local/national languages

1000+ lay language summaries in German

Most frequently visited SRs:
- ...
The biggest challenge: Updating

Updating of systematic reviews is generally more efficient than starting all over again when new evidence emerges, but to date there has been no clear guidance on how to do this. This guidance helps authors of systematic reviews, commissioners, and editors decide when to update a systematic review, and then how to go about updating the review.

The solution? Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap
The new competitor:
Big data, innovation, personalized medicine . . .

Big Data:
A Revolution That Will Transform How We Live, Work and Think

Kenneth Cukier
Viktor Mayer-Schönberger
Big Data Hype: The Mantras

Big Data

– can analyze unstructured data
– can easily solve every problem by using more data
– needs ownership moving from owner to user
– cannot reproduce results because everything is changing every second: real-time results
– The era of causality is over, now is the era of correlation (enabled by unlimited access to data)

Chris Anderson
16/2007 Wired Magazine:

The End of Theory. The Data Deluge Makes the Scientific Method Obsolete

Science in megalomania

Neue Züricher Zeitung 11 Jan. 2015
How Big Data makes us and our life predictable

The End of Randomness

Transfer of research results into practice

- Knowledge Systems
  - Literature based synthesis (SR;
  - Cochrane
  - classical)
  - Individual-data-based synthesis (IPD SR)
- Artificial Intelligence
- Deep learning system
- Data drilling
- Big data
- Machine learning
- Access to trial data or trial reports from authority data

patients / healthy persons
Research / studies / data

patients / healthy persons
application / benefit
Investment from MD Anderson: $62 million

Large amounts of electronic patient records . . . will help to avoid any wrong diagnosis and treatment.
Golden future or empty promises?

Solutions?
Lack of transparency in medical research: many victims, many culprits

Who is guilty? – The axis of evil

- Industry
- Researchers and scientists
- Universities and faculties
- Ethics boards
- Doctors
- Journals and publishers
- Funders
- Regulators
- HTA agencies, guidelines groups etc.
- WHO
- Parliaments and governments
- Patients
Research: increasing value, reducing waste
Published January 8, 2014

Executive summary

The Lancet presents a series of five papers about research. In the first report, Iain Chalmers et al. discuss how decisions about which research to fund should be based on issues relevant to users of research. Next, John Ioannidis et al. consider improvements in the appropriateness of research design, methods, and analysis. Rustam Al-Shahri et al. then turn to issues of efficient research regulation and management. Next, An-Wen Chan et al. examine the role of fully accessible research information. Finally, Paul Glasziou et al. discuss the importance of unbiased and usable research reports. These papers set out some of the most pressing issues, recommend how to increase value and reduce waste in biomedical research, and propose metrics for stakeholders to monitor the implementation of these recommendations.

Comments

How should medical science change?
Sabine Kleinert, Richard Horton

The Reward Alliance
Increasing Research, Reducing Waste
http://researchwaste.net/

Jährlich für biomedizinische Forschung (2010):

240 Milliarden U$ für Lebenswissenschaften
Summary

- Enormous progress to use knowledge from trials and studies: Global knowledge – local implementation

- Systematic Reviews key technology for knowledge synthesis and translation

- Deep insight into knowledge process – only limited success to solve them

- Evidence in environment which does work, could work or doesn’t work
May 2013 in German
(English: Testing Treatments)

downloadable and free on
de.testingtreatments.org

- www.cochrane.de
- www.cochrane.org
- www.thecochranelibrary.com