Reducing Waste in Research

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Foster Best Practices & Enhanced Standards Research

32. International norms, standards, and guidelines … to govern, manage, and improve the quality of research:

- address inefficiencies
- Promote transparency (planning, ongoing, and completed research)
- Improve access to information

33. New Standards & Norms in line with Priority Setting: Promote Equity in Health Research
11 Interrelated Commitments

- Many related to promotion of research standards
- Many related to transparency and knowledge sharing
- Specific tools: development guidelines, registries, summaries, systematic reviews
- Collaboration with other actors: role international organizations, RECs, Civil Society!
- Concerns for Equity

• Non-publication rates of finished trials: studies report rates of 34 % - 44 %

• Many trials: never finished
  • Become futile after trial started
  • Recruitment problems (due to design or bad estimates)

• Published trials problems:
  • Original outcomes often unreported
  • Manipulation analysis & reporting
  • Results inflated & spin towards favourable conclusions
  • Harms underplayed
For many trials: questions asked, comparisons and outcomes clinically irrelevant

“… irrelevance may be actually the biggest source of waste in randomized controlled trials, although measurement of irrelevance can be subjective. The reasons why all this waste is still acceptable are complex, but largely they reflect the consequences of the current incentive system for performing clinical research.”

“Perhaps we do not need more than 20 000 clinical trials launched each year. We may do well with substantially fewer, if carefully chosen.”
Key Challenges

• Industrial knowledge production process controlled by those with direct financial interest in outcome + other actors (CROs, Commercial IRBs, communication agencies, publication industry, academic research units & authors): interest in maintaining existing data production processes & knowledge distribution

• Limited (regulatory) control on public presentation of data

• Lack of transparency and access to data

• Non-industry funded research: publication incentives academic research do not value careful selection & priority setting
Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

30 Reports of comparative efficacy clinical trials funded by industry

- 90% overall outcome favourable to drug sponsor
- Sources of bias:
  - Dose ranges & escalation schedules: stepwise or faster (efficacy & side-effects)
  - Entry criteria and study population: e.g. treatment resistance: meaning in schizophrenia patients?
- Statistics and Methods
- Reporting and wording of results
- Multiple Publishing (salami-slice publications)

“[S]haring clinical data could … lead to enhanced efficiency and safety of the clinical research process by, for example, reducing unnecessary duplication of effort and the costs of future studies”
Transparency through Rulemaking

- 2007 US FDA Amendment Act, Canada: Vanessa’s Law
- Regulations or guidelines in various PAHO countries (Argentina, Brazil, Cuba, Canada, ...)
- Most advanced model: European Medicines Agency:
  - 2014 Policy on prospective publication CT data
  - New Clinical Trials Regulations 2013
  - Release of 1.9 million pages data between 2011-2013
Restoring invisible and abandoned trials: a call for people to publish the findings

Unpublished and misreported studies make it difficult to determine the true value of a treatment. Peter Doshi and colleagues call for sponsors and investigators of abandoned studies to publish (or republish) and propose a system for independent publishing if sponsors fail to respond.

Peter Doshi postdoctoral fellow\(^1\), Kay Dickersin professor, director\(^2\,3\,4\), David Healy professor of psychiatry\(^5\), S Swaroop Vedula postdoctoral fellow\(^6\), Tom Jefferson researcher\(^7\)
Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

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2Emory University, Atlanta, Georgia, USA
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5Department of Psychiatry, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

ABSTRACT
OBJECTIVES
To reanalyse SmithKline Beecham’s Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The reanalysis under the restoring invisible and abandoned trials (RIAT) initiative was done to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

DESIGN
Double blind randomised placebo controlled trial.

(HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Prespecified secondary outcomes were changes from baseline to endpoint in depression items in K-SADS-L, clinical global impression, autonomous functioning checklist, self-perception profile, and sickness impact scale; predictors of response; and number of patients who relapse during the maintenance phase. Adverse experiences were to be compared primarily by using descriptive statistics. No coding dictionary was prespecified.

RESULTS
The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any prespecified primary or secondary efficacy outcome. HAM-D scores decreased by 10.7

BMJ 2015: correction Keller et al.
International Transparency Initiatives

- **ICMJE**: transparency clearly accepted as norm international scientific publications
  - But: reluctance some science journals to get involved in more forwarding looking initiatives + to withdraw fraudulent publications

- **WHO International Clinical Trials Registry Platform 2006**

- **Declaration of Helsinki**: transparency explicit ethical requirement research: Role of Research Ethics Committees in the region? Need for Strong REC structure and governance
Legal/Regulatory Challenges

Intellectual Property Norms
Privacy Law
Access Challenges Europe: Court challenges 2013/14
Interim Rulings EU GC (May 2013)

- Suspension EMA’s Freedom of Information Regulation access decision 2 drugs: data access on basis of “right to the protection of professional secrets” (commercial secrecy nature of info) framed as fundamental “right to protection of private and family life” ECHR & European Charter

- Overruled in Appeal by Vice-President ECJ

- BUT: EMA allowed redaction of data by companies

- New Court Challenges 2016
(3) Minister may disclose *confidential business information* about a therapeutic product without notification to or consent of person to whose business the information relates, if the purpose of the disclosure is related to the protection or promotion of human health or the safety of the public and the disclosure is to

a) Government  
b) Advisor  
c) Person who carries out function related to public health or public safety
Health Canada confidentiality pact forces doctor to withhold drug data

Dr. Navindra Persaud wants to make public the unpublished clinical trial data on the effectiveness of a morning sickness pill. (CBC)
Pharmaceutical transparency in Canada: Tired of talk

6 Jun, 16 | by BMJ

Health Canada has been talking about improving the transparency of information around pharmaceutical drugs for years. And for years the drug regulator has failed to back up that talk with commitment and action.

The lack of transparency around pharmaceutical drugs continues to undermine patient safety and public health. Unless a drug’s full safety and effectiveness profile is transparent, physicians and patients alike are at best misinformed. At worst, patients could suffer significant harm—even death—after taking a government approved, physician prescribed drug and taxpayers will be left to foot the bill.
<table>
<thead>
<tr>
<th>Institution</th>
<th>Trials Missing Results</th>
<th>Total Registered Trials</th>
</tr>
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<tbody>
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<td>U. of British Columbia</td>
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<td>Ottawa Hospital Research Institute</td>
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Trial Registration Work
PAHO

- Two National trial registries (from Brazil and Cuba) accepted as WHO Primary registries in 2011
- Peru recently applied to become a primary registry; Argentina is developing a research registry
- BIREME/ PAHO developed software OPEN TRIALS to establish Spanish/Portuguese/English language Primary Registries for the Region. “Implementation of the software has been difficult”
# Reporting Standards: PAHO collaboration with Equator

## Enhancing the QUAlity and Transparency Of health Research

### 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.

### Reporting guidelines for main study types

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Guideline</th>
<th>Extensions</th>
<th>Other</th>
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<tbody>
<tr>
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<td>Observational studies</td>
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<td>PRISMA</td>
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<td>Case reports</td>
<td>CARE</td>
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<td>COREQ</td>
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<td>Diagnostic / prognostic studies</td>
<td>STARD</td>
<td>TRIPOD</td>
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<td>Quality improvement studies</td>
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<td>Economic evaluations</td>
<td>CHEERS</td>
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<td>Animal pre-clinical studies</td>
<td>ARRIVE</td>
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<td>Study protocols</td>
<td>SPIRIT</td>
<td>PRISMA-P</td>
<td>Other</td>
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PAHO initiatives RECs

- Development of an open sources software for the processes of ethic committees that include the 20 fields requires for trial registration; The project was developed in cooperation with the PAHO regional Bioethics advisor and the Pontificia Universidad Católica de Paraná de Brasil (PUCPR) from Brazil.

- Monitoring trial registration in the ICTRP


Accomplishments

• Significant success in registration clinical trials

• Increased awareness in the region about importance of registration & data sharing

• Initiatives on results reporting, particularly on standards for reporting: collaboration with Equator

• Less progress on full data sharing: why?
  • resistance from industry & reluctance drug regulatory agencies
  • Other factors?
Where to Go from Here?

1. How to create better awareness of standards of research reporting & international collaboration & improve their use?

2. What can be done to promote better reporting research results & access to data? Can existing governance structure of RECs play a role here?

3. How to stimulate creation governance/regulatory structures in members states that reduce/eliminate regulatory barriers? What partnerships can help here?

4. How to promote equitable priority setting standards in research?