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

Ioannidis: Clinical Trials: What a waste? BMJ 2014

- 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

Ioannidis: What a Waste

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)

Am. J. Psych. 2006: 163(2): 185-194

Remedy: Transparency

Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk

ISBN
978-0-309-31629-3

280 pages
6 x 9
PAPERBACK (2015)

Committee on Strategies for Responsible Sharing of Clinical Trial Data; Board on Health Sciences Policy; Institute of Medicine

"[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

Role Independent Scientists, Science Journals & Civil Society

Restoring invisible and abandoned trials: a call for people to publish the findings


OPEN ACCESS

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]

BMJ 2015: correction Keller et al.

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

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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

International Transparency Initiatives

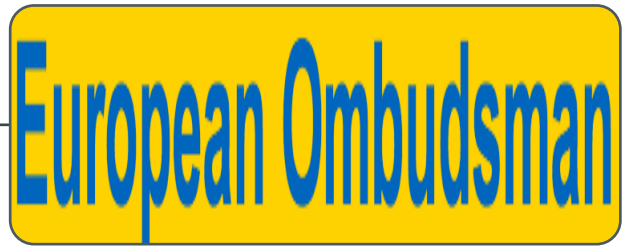
- **ICMJE** : transparency clearly accepted as norm international scientific publications
  - But: reluctance some science journals to get involved in more forwarding looking initiatives + to withdraw fraudulent publications
- **WHO International Clinical Trials Registry Platform 2006**
- **Declaration 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

Council of Canadian Academies, 2015) 219 p. (online at: http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/health-data/healthdatafullreporten.pdf

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

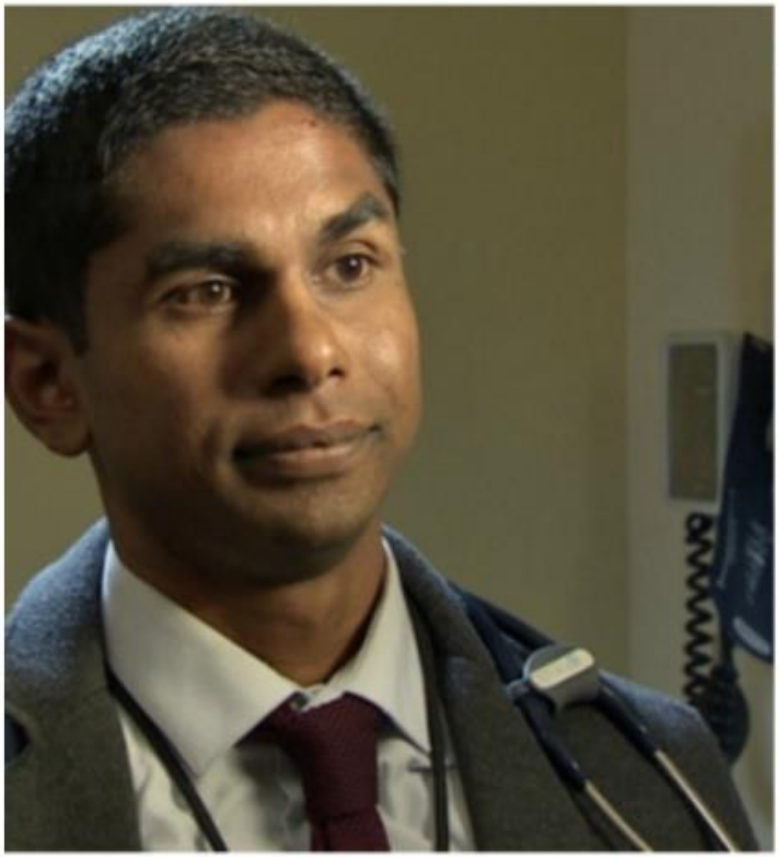
Vanessa's Law: New S.21.1 FDA

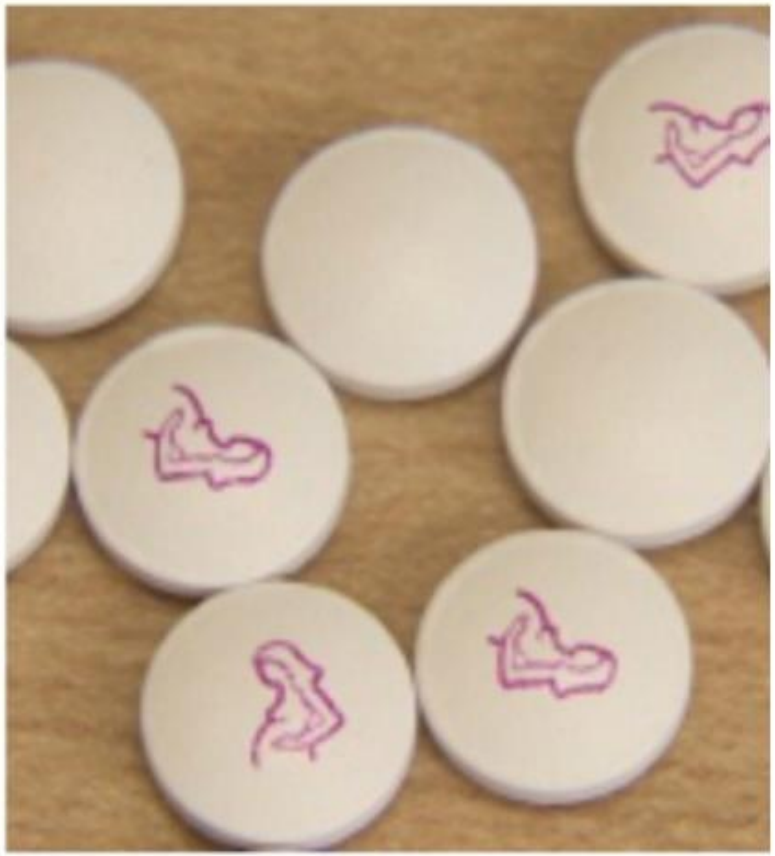
(3) Minister may disclose *confidential business information* about a therapeutic product without notification to or consent of person to whose business the information relates, if the purpose of the disclosure is related to the protection or promotion of human health or the safety of the public and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

a) Government
b) Advisor
c) Person who carries out function related to public health or public safety

Wednesday October 14, 2015

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)

thebmj

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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 coul suffer significant harm—even death—after taking a government approved, physician prescribed drug and taxpayers will be left to foot the bill.

Canadian universities and institutions with the most **missing results**

	Trials **Missing** Results	Total **Registered** Trials
U. of British Columbia	126	174
U. Health Network	106	139
Hospital for Sick Children	59	95
U. of Calgary	50	66
U. of Alberta	48	72
U. of Manitoba	43	64
Queen's University	40	57
U. of Toronto	38	58
Ottawa Hospital Research Institute	37	58

trialstracker.ebmdatalab.net

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

equator network

Enhancing the QUAlity and Transparency Of health Research

EQUATOR resources in Portuguese | Spanish

Home | Library | Toolkits | Courses & events | News | Blog | Librarian Network | About us | Contact

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
- Not sure which reporting guideline to use?
- Reporting guidelines under development
- Visit the library for more resources

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 studies	SQUIRE		Other
Economic evaluations	CHEERS		Other
Animal pre-clinical studies	ARRIVE		Other
Study protocols	SPIRIT	PRISMA-P	Other

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

Publications PAHO

1. Khanoyan C, Cuervo LG. Registration of Observational Studies: Influence Research and its Impact (Editorial Process)

2. Lee B, Cuervo LG, Rodríguez-Feria P, Luciani S. Analysis of registered cancer clinical trials in Latin America and the Caribbean, 2007–2013. Rev Panam Salud Publica. 39(2):115–21.

3. Rodríguez Feria PA, Cuervo LG. Progress in trial registration in Latin America and the Caribbean, 2007-2013. In print.

4. Reveiz L, Bonfill X, Glujovsky D, Pinzon CE, Asenjo-Lobos C, Cortes M, Canon M, Bardach A, Comandé D, Cardona AF. Trial registration in Latin America and the Caribbean's: study of randomized trials published in 2010. J Clin Epidemiol. 2012 May;65(5):482-7.

5. White L, Ortiz Z, Cuervo LG, Reveiz L. Clinical trial regulation in Argentina: overview and analysis of regulatory framework, use of existing tools, and researchers' perspectives to identify potential barriers. Rev Panam Salud Publica. 2011;30(5):445-52.

6. Reveiz L, Saenz C, Murasaki RT, Cuervo LG, Ramalho L. Progress and challenges of clinical trials registration in Latin America and the Caribbean's. Rev Peru Med Exp Salud Publica. 2011;28(4):676-81.

7. Krleža-Jerić K, Lemmens T, Reveiz L, Cuervo LG, Bero LA. Prospective registration and results disclosure of clinical trials in the Americas: a roadmap toward transparency. Rev Panam Salud Publica. 2011;30(1):87-96

Promoting Common Good practices Research Priorities

Reveiz L, Elias V, Terry RF, Alger J, Becerra-Posada F. **Comparison of national health research priority-setting methods and characteristics in Latin America and the Caribbean, 2002 - 2012**. Rev Panam Salud Publica [Internet]. 2013 July [cited 2016 Nov 25] ; 34(1): 1-13.

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?