

# Research Results Dissemination

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# Research Results Dissemination

- What constitutes responsible reporting of research results? Are clinical trial registries and peer-reviewed publications enough? This presentation will analyze the major issues in disseminating research results.
- This presentation is based on research conducted as part of my masters degree in Health Law at Osgoode Hall Law School of York University.
- I have no financial interests in the outcome of this research.

# Agenda

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- Responsible reporting
- Barriers to dissemination
- Accessibility and transparency
- Is publication enough?
- Open access debate
- Is publication itself a barrier to accessibility?
- Conclusion

# Responsible Reporting

- What is it?
- Social contract w/ participant
- Accountability
  - Author accountability
  - Researcher accountability
  - Manufacturer accountability
- Social contract w/ public

# Social Contract with Participant

- Comply with informed consent
  - SK consent form requirements
    - Benefit to participant
    - Benefit to society
    - Availability of results for participants
  - doctors will learn from the results and future generations will benefit from that knowledge...

A. Caplan, "A public drug registry? It's about time: AMA's efforts to publish results of all studies are long overdue" MSNBC.com (22 June 2004) at para 9-10, online:  
<<http://msnbc.msn.com/id/5269721/print/1/displaymode/1098>>

# Tri-Council Policy Statement

**Additional information that may be required for some projects...**

The ways in which the research results will be published, and how the subjects will be informed of the results of the research.

Table 1, Art. 2.4:

<http://www.pre.ethics.gc.ca/english/policystatement/section2.cfm#2A>

# Tri-Council Policy Statement

## E. Analysis and Dissemination of the Results of Clinical Trials

Researchers and REBs must ensure... that final analysis and interpretation of... data remain with the researchers, whose duty it is to ensure the integrity of their research.

Equally important, though sometimes difficult to achieve, is the researchers' duty to disseminate the analysis and interpretation of their results to the research community. Unfortunately, negative results and outcomes of research frequently are not published or disseminated. Silence on such results may foster inappropriate and potentially harmful clinical practices or needless and wasteful duplication. Researchers and REBs may exert pressure to alleviate this deficiency in the dissemination of research results by resisting publication bans proposed in research protocols, on the basis of ethical obligations of truthfulness and the integrity of research. Research journalists, journal editors, members of editorial peer review boards, sponsors and regulators should address this as an issue of scientific and ethical urgency.

Art. 7.E: <http://www.pre.ethics.gc.ca/english/policystatement/section7.cfm#7A>

# Evidence-based Medicine

“They rightly expect that clinical decisions are based on all available knowledge, not just the biased sample that appears in medical journals”

A. Tonks, “Registering Clinical Trials” (1999) 319 BMJ 1565 online:  
<<http://bmj.bmjournals.com/cgi/content/full/319/7224/1565>> at 1568.

# Evidence-based Medicine

- Too much focus in publication guidelines on getting information to prescribers
- Future research depends on availability of information
- Health research also influences government, medical malpractice & professional governance decisions

# Social Contract with Public

- Public as ultimate consumer of research
  - Research may be publicly funded
  - Members of public may be participants in human subject research
  - Consumers of new products & methods of treatment
  - Affected by funding decisions & other healthcare advancements
  - Rely on research for health & lifestyle decision making

# Responsible Reporting

- Fulfilling a social contract with participants
- Upholding public trust in research & medicine
- Promoting scientific integrity
- Each person/entity involved in research being accountable for its involvement

# Accountability

- Conflict of interest disclosure
- Responsibility to public
  - Author accountability
    - ICMJE guidelines adopted by companies
  - Researcher accountability
    - Social contract with participants & public
    - Contract with funding agencies & companies
    - Ethics guidelines such as TCPS
  - Manufacturer accountability
    - Social contract with participants & public
    - Regulations for marketing drugs/devices
    - Off-market products?

# Accountability

- Phenylpropanolamine (PPA) Example
  - Used in cold & diet remedies
  - Market estimated at \$500 million to \$1 billion annually shared between various pharma companies
  - Safety concerns led to commissioned study
  - Oct 17, 1999: Researchers finalized findings of link with strokes & phoned FDA next day
  - Nov 2000: FDA declared PPA unsafe & requested companies to take it off the market

# Accountability

- “Upon learning that the 1999 study had found a stroke link, the drug makers opened a relentless assault on its methodology and on the integrity of the Yale University researchers who conducted it. They did so despite having paid for the five-year, \$5 million study themselves, approving its protocol and handpicking investigators who had previously expressed skepticism about a link between PPA and stroke... Even now, the industry’s attacks on the study it commissioned are its primary defense against more than 2,500 lawsuits filed by plaintiffs who say they suffered strokes shortly after taking products with PPA”
- Allegations that researchers manipulated data to win promotions and publications in top journals

K. Sack & A. Mundy, “A Dose of Denial: How drug makers sought to keep popular cold and diet remedies on store shelves after their own study linked them to strokes” (28 March 2004) Los Angeles Times A1.



**Who is accountable?**

# Who is accountable?

- Multiple companies point at researchers
- Multiple plaintiffs point at companies
- Regulators waited over a year from receiving findings
- Researchers informed FDA prior to discussing findings with companies
- Study commissioned in the first place due to concerns over safety

# Barriers to Dissemination

- Publication bias
  - Positive results, changing outcomes mid-way through research, study design
  - Role of professional medical writers
- Covert redundant publication
  - Trial identifier
- Lack of access to data
- Lack of access to publications

# Barriers to Dissemination

- Potential harm to
  - Patients
  - Scientific integrity
  - Public trust in research
  - Public trust in medicine & healthcare industry

# Suppression of Negative Results

- NY v. GSK re: anti-depressant drug Paxil

“Specifically, GSK conducted at least five studies on the use of Paxil in children and adolescents. However, GSK only published and disseminated one of these studies, which showed mixed results on efficacy. The lawsuit alleges that the company suppressed the negative results of the other studies, which failed to demonstrate that Paxil is effective and which suggested a possible increased risk of suicidal thinking and acts. GSK is also alleged to have failed to disclose this information in "Medical Information Letters" that it sent to physicians.”

NY State Attorney General Press Release, June 2, 2004:  
[http://www.oag.state.ny.us/press/2004/jun/jun2b\\_04.html](http://www.oag.state.ny.us/press/2004/jun/jun2b_04.html)

# Suppression of Negative Results

- 2 types of dissemination in this example
  - Publication in a journal
  - Direct disclosure to physicians in medical information letters

# Outcome of NY v. GSK

“The world's second largest pharmaceutical company, GlaxoSmithKline, is to publish summaries of the results of all its clinical trials on its website once a product has been launched.”

Gibson, L., BMJ 2004;328:1513 (26 June): <http://www.bmj.com/cgi/content/full/328/7455/1513-a?ck=nck>

# Professional Medical Writers

- Good Publication Practice (GPP)
  - Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. *Current Medical Research & Opinion* 2003;**19**(3):149-154.
  - Available at: <http://www.gpp-guidelines.org/>
    - medical writers should not be hidden
    - guidelines to clarify their role

# Good Publication Practice

- Many companies based their policies on this document
- Endeavor to publish all clinical trials of marketed products
- Apr 5, 2005: UK House of Commons Health Committee recommends companies follow GPP regarding the use of medical writers

# Good Publication Practice

## **The role of professional medical writers**

- The named author(s)/contributors must determine the content of the publication and retain responsibility for it.
- The medical writer should begin drafting the manuscript after consultation and discussion with the named author(s)/contributors. It is often helpful if the author(s)/contributors and the medical writer agree on an outline of the paper before detailed writing begins.
- The named author(s)/contributors should be given adequate time to comment on an early draft of the manuscript.
- The medical writer should remain in close and frequent contact with the author(s)/contributors throughout the development of the manuscript.
- The named author(s)/contributors should approve the final version of the manuscript before it is submitted.
- The lead author should be responsible for submitting the manuscript to the journal and acting as the primary contact for interactions with the journal editor.
- The contribution of the medical writer should be acknowledged.

# Accessibility & Transparency

- Clinical trial registries as a mechanism of transparency
- Transparency – one publicly accessible record of each study from inception to publication
  - Pharmaceutical Research & Manufacturers of America (PhRMA) Guidelines
  - Joint Industry Position (PhRMA along with European, International & Japanese industry associations)
  - ICMJE Guidelines
  - WHO Guidelines

# Is Clinical Trial Registration Enough?

- Are clinical trial registers a solution?
  - Numerous registers
  - Different purposes and standards
  - “Once a product has been launched” – summaries of results (NY v. GSK)
- Which trials to register?
- What information to include?

# Accessibility & Transparency

- Industry
  - Not exploratory trials
  - Results db – results to be posted w/in 1 yr of drug's first approval/commercial availability
- ICMJE
  - Phase 3 must be registered
  - Phase 1 not necessarily
  - Phase 2 up to individual editors
  - Purpose to ensure availability of info on clinical effectiveness and adverse events

# Accessibility & Transparency

- WHO
  - All medical studies that test treatments on humans
  - Including earliest studies
  - Whether patients or healthy volunteers

WHO, May 19, 2006 News Release:

<http://www.who.int/mediacentre/news/releases/2006/pr25/en/index.html>

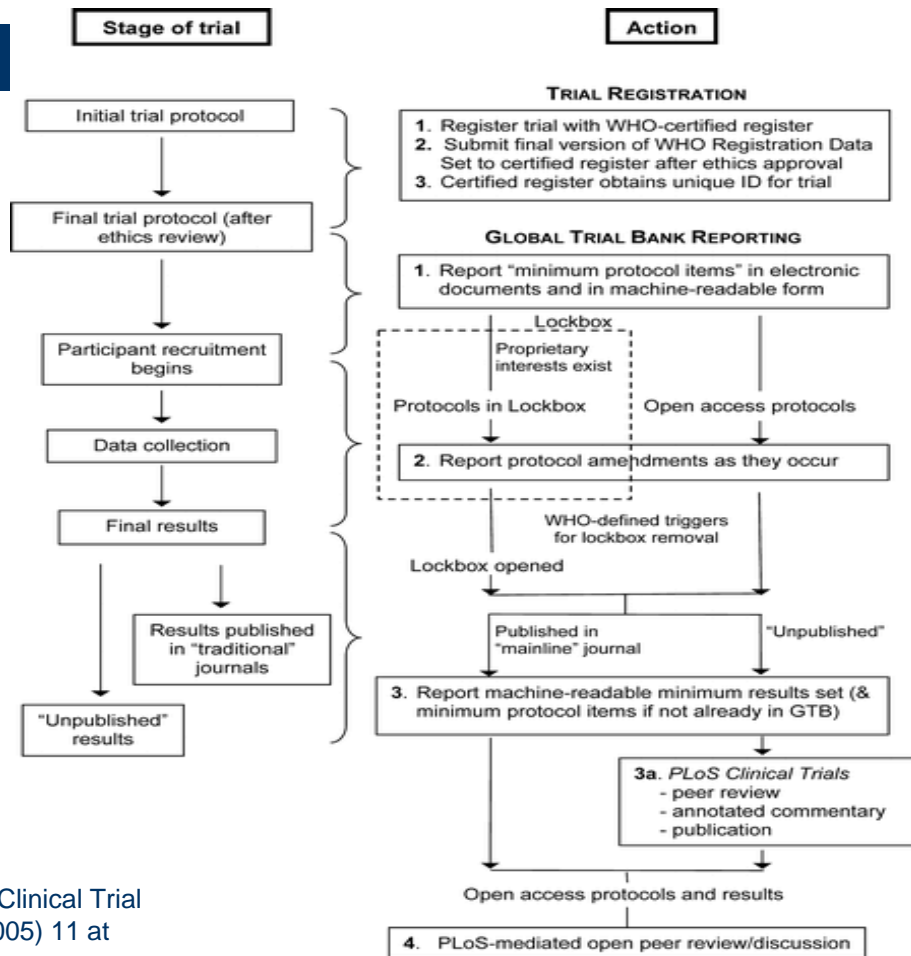
# Barriers to Dissemination

“From our discussion with companies, we soon discovered that this commitment to endeavor to publish the results of all clinical trials was considered a major burden and was probably the reason why so few companies were prepared to publicly endorse the guidelines from the start.”

E. Wager, “‘Good Publication Practice for Pharmaceutical Companies’: Where Are We Now?”, (2005) 7:2 Medscape Gen. Med., online:

<<http://www.medscape.com/viewarticle/501752>>.

# Global Trial Bank



Sim, I. & Detmer, D.E., "Beyond Trial Registration: A Global Trial Bank for Clinical Trial Reporting", *PLoS Medicine* 2 (Nov 2005) 11 at e365.

# Clinical Trial Registries

- Clinical trial registries
  - Information to be included (WHO, ICMJE, PhRMA)
  - Sensitive information at time of registration
- As of October 2006, WHO had not been convinced that there should be any delay of disclosure of any sensitive information in the trial data set and had indicated that it was too complex for the registers to do

Chan, A., “WHO International Clinical Trials Registry Platform: Reducing bias through trial registration and results disclosure” presentation slides Oct 26, 2006 posted at

[http://www.who.int/ictrp/Cochrane\\_parallel\\_26Oct06.pdf](http://www.who.int/ictrp/Cochrane_parallel_26Oct06.pdf).

# WHO International Clinical Trial Registry Platform

- Harmonize register & trial registration standards – global approach
- Raising local awareness in developing and developed countries
- Global trial identification system – unique reference numbers
- Web based search portal – single point of access to numerous registers

# WHO Registry Platform

“Once a trial is registered, full transparency and accountability requires that all of the trial's results be made available to the public without any bias or selectivity in reporting. Although the Registry Platform's current activities are mostly concerned with trial registration, results reporting remains a top concern of the Registry Platform and will be addressed in more detail starting in mid-2006.”

WHO, March 8, 2006: <http://www.who.int/ictrp/results/en/>

# Good Publication Practice

“The GPP guidelines are based on the premise that trials should be reported fully in peer-reviewed journals, and it would be unfortunate if the rush to trial registration (coupled with GlaxoSmithKline's response to the New York case) was to lead companies to concentrate on posting unreviewed summary findings on the Internet at the expense of developing "proper" publications.”

E. Wager, “Good Publication Practice for Pharmaceutical Companies’: Where Are We Now?”, (2005) 7:2 Medscape Gen. Med., online: <http://www.medscape.com/viewarticle/501752>

# Barriers to Readers

- Is peer-reviewed publication enough?
  - Timelines to publication for company funded research
  - Stakeholders and access
  - Open access debate
  - Public archive & library crisis

# Barriers to Readers

- Target audience
  - Stakeholders versus general public
- Accountability rather than a detailed description of research
- Role of media
- Quality concerns

# Target Audience

“Significant segments of the interested community and of the intended audience do not have easy access to this information, including teachers, students, patients and their families, health-related workers, administrators and policy-makers, journalists, and frequently also researchers in institutions without subscriptions to all the relevant literature”

J. Velterop on behalf of BioMed Central Limited, “Submission to the House of Commons Science and Technology Committee’s Inquiry into Scientific Publications” U.K. (6 February 2004) online: <<http://www.biomedcentral.com/openaccess/inquiry/bmcsubmission.pdf>>

# Open Access

- Core of debate centres on free and unrestricted access for reading and personal use
- Can include ability to re-distribute the article or even to use it for commercial purposes
  - e.g. creative commons copyright license

# Open Access

- Public archive
  - Public funding agencies (CIHR, Genome Canada, NIH, Wellcome Trust)
  - NIH example:
    - on basis that public already paid for the research and shouldn't have to pay again to access the results
    - stable archive of research results
  - Public archiving is done
    - through author self-posting or
    - journal automatically posts after specified time period or
    - through open access journal

# Library Crisis

- Library crisis was beginning to open access debate
  - Economic model of journals
    - Subscriber pays vs. author pays
  - License bundling
- Libraries unable to allocate funds to smaller publishers if too much of their budget is directed to larger publishers under license bundling

# Open Access

- Author pays model
  - Author pays
  - Institution pays
  - Granting agency pays
- BioMed Central
  - Charges are specific to each journal
  - Range from £ 250-1200
  - Standard charge is £ 750

# BioMed Central – Author Guidelines for BMC Medical Ethics

- **Article-processing charges**

*BMC Medical Ethics* levies an article-processing charge for every accepted article, to cover the costs incurred by open access publication. In 2007 the article-processing charge is £850 (€1250, US\$1675). Generally, if the submitting author's institution is a BioMed Central member the cost of the article processing charge is covered by the membership, and no further charge is payable. In the case of authors whose institutions are supporter members of BioMed Central, however, a discounted article processing charge is payable by the author. Please click here to check if your institution is a BioMed Central member. We offer a £30 discount for manuscripts formatted with EndNote 5 (or later versions) or Reference Manager 10 or created using Publicon. We routinely waive charges for authors from low-income countries. For further details, see more information about article-processing charges.

# BioMed Central

- BMC lists author charges comparison with other open access journals
  - Compares with immediate open availability & with redistribution/reuse license
- UofT is 1 of 25 BioMed Central members from Canada
- BMC lists granting agencies that allow funds to be used for author payments
  - CIHR and NIH both on this list

# Author Pays Model

- Concerns
  - Reader pays model is more profitable
  - Journals are complementary rather than substitutable
    - Readers want to read 2<sup>nd</sup> and 3<sup>rd</sup> rank journals as well as top rank
    - Author pays model shifts role of consumer to author
    - Choice of journal will depend on competition of author fees
    - Journals become substitutable since author has no reason to publish once in each journal rather than twice in the cheapest journal
    - Greater competition reduces profit margin for journals
    - Publishers will be reluctant to use author pays model

# Author Pays Model

- More concerns
  - Sustainability
    - Costs as much to reject as to accept an article
    - Potential COI for peer-review model
    - Submission charge rather than acceptance charge
  - High producers subsidize low producers
    - Especially if institutions end up paying
    - Research institutes could end up subsidizing pharmaceutical companies

# Accessibility & Transparency

- Economic model of journal publishers is central in the debate
- Subscription based model as barrier to accessibility
- Public archiving
- Timelines to self-posting in public archives
- Alternatives to peer-reviewed publications

# Alternative Forms of Dissemination

- What if
  - Study isn't publishable in a journal?
  - General public doesn't understand scientific jargon?
  - Study participants don't know where to find an article about the study in which they participated?
  - Government policy maker only has access to a limited number of journals and the web?

# Summary

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- Responsible reporting involves multiple accountabilities
- Social contract with public as well as with participant
- Harm not just to current and future patients but also to public trust in medicine and scientific process

# Conclusion

- Preference to peer-reviewed publication
- Role of media in informing general public
- Pharma funded research
  - Results database
  - Concern over jeopardizing publication
- Role of researchers in providing summaries back to participants

# Conclusion

- Multi-party obligations to use as many mechanisms as possible to disseminate research results in order to satisfy responsible reporting, including satisfying the social contract with patient and the general public
- Responsibility goes beyond current guidelines

# Contact Information

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