Global opportunities and challenges for trial registration:
Update from the WHO Registry Platform

October 26, 2006

An-Wen Chan, MD DPhil
Scientist
World Health Organization, Geneva
“All great truths begin as blasphemies.”

George Bernard Shaw
Glaxo faces drug fraud lawsuit
Firm accused of keeping back negative trial results

Trials Under Fire

UK News
Horror Drug Trial 'Shouldn't Have Happened'
Friday, 13th October 2006, 07:22

Cracking down on medical trials
Doctors need to have unbiased data on effectiveness of new drugs,
ethicist Arthur Schafer
EDITORIALS

Managing allegations of scientific misconduct and fraud: lessons from the “Hall affair”

If we can learn from this, it will have made a contribution to the pursuit of integrity in research

COMMENTARY

Scientists behaving badly

To protect the integrity of science, we must look beyond falsification, fabrication and plagiarism, to a wider range of questionable research practices, argue Brian C. Martinson, Melissa S. Anderson and Raymond de Vries.

Annals of Internal Medicine

Research Misconduct, Retraction, and Cleansing the Medical Literature: Lessons from the Poehlman Case

Harold C. Sox, MD, and Drummond Rennie, MD
Outline

- Background and overview
- Global challenges
- Global opportunities
Ethical obligations to participants

Knowledge

Risk
"The design of all studies should be publicly available."

"Negative as well as positive results should be published or otherwise publicly available."
Access to trial information

Trial 1
Publication
Selective outcome reporting

Trial 2
Publication
Outcomes
Systematic reviews

Trial 3
Selective study publication
Why is WHO involved?

- Global, neutral, independent body
- Authoritative role
- Capacity building
- Political legitimacy
- Commitment to global equity
Ministerial Summit on Health Research

Mexico City, November 2004

52 health ministers decided that WHO should:

- establish a network of trial registers
- ensure identification of all trials
- ensure a single website for access
"We are ready to move forward with an international Clinical Trials Registry. This will do much to strengthen the research process and its ability to win public trust"
WHO International Clinical Trials Registry Platform

- Established in August 2005
- Will NOT create a WHO register
- Define a coordinated global network for trial registration and results reporting
Goal and objectives

**Overall Goal**
- Strengthen public trust in clinical trials by promoting transparency & accountability

**Objectives**
- Registration of all clinical trials worldwide
- Disclosure of minimum set of results
WHO Registry Platform overview

CT.gov, ISRCTN, ACTR

Registers
WHO Registry Platform overview

Registers

CT.gov, ISRCTN, ACTR

Journals
WHO Registry Platform overview

CT.gov, ISRCTN, ACTR

Registers

Journals

Results databases
WHO Registry Platform overview

CT.gov, ISRCTN, ACTR

Registers
Journals
Results databases
Outline

- Background and overview
- Global challenges
- Global opportunities
Challenge 1:
Coordination of multiple stakeholders

- Trial registration
- Trial participants
- Governments
- Ethics boards
- Registers
- Journals
- Industry/Funders
- Researchers
Challenge 1: ...with multiple interests

- Patient care
- Trial registration
- Commercial success
- Academic success
- Journal success
- Create new knowledge
- Political gain
A BILL

To amend the Public Health Service Act to expand the clinical trials drug data bank.

1 Be it enacted by the Senate and House of Representa-

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial
Challenge 2: Establishing global standards

- Trial registration
  - Which trials
  - What data
  - When

- Results disclosure
Which trials to register?

- Any prospective research study that
  - Assigns humans to an intervention
  - Measures effects of the intervention on health outcomes
Why register early ‘Phase 1’ trials?

- Ethical responsibilities to participants
- Informed enrollment
- Dangers of hidden knowledge
  - Preliminary indication of adverse effects
  - Inform future or ongoing research
- Intellectual property protected by patents

“The rights of trial participants hold primacy over commercial and career interests”

Nuremburg Code (1947)
What data to register?
WHO Registration Data Set (1.0)

Trial administration
1. Primary register and Trial ID#
2. Date of registration in Primary Register
3. Secondary ID#s
4. Source(s) of monetary or material support
5. Primary sponsor
6. Secondary sponsor(s)
7. Contact for public queries
8. Contact for scientific queries
**What data to register?**
***WHO Registration Data Set (1.0)***

<table>
<thead>
<tr>
<th>Category</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial recruitment</strong></td>
<td>9. Key Inclusion/Exclusion Criteria</td>
</tr>
<tr>
<td></td>
<td>10. Countries of Recruitment</td>
</tr>
<tr>
<td></td>
<td>11. Date of First Enrollment</td>
</tr>
<tr>
<td></td>
<td>12. Recruitment Status</td>
</tr>
<tr>
<td><strong>Trial topic</strong></td>
<td>13. Public title</td>
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<tr>
<td></td>
<td>14. Scientific title</td>
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<tr>
<td></td>
<td>15. Health condition(s)/problem(s)</td>
</tr>
<tr>
<td></td>
<td>16. Intervention(s)</td>
</tr>
<tr>
<td><strong>Basic methodology</strong></td>
<td>17. Study type</td>
</tr>
<tr>
<td></td>
<td>18. Target sample size</td>
</tr>
<tr>
<td></td>
<td>19. Primary outcome(s)</td>
</tr>
<tr>
<td></td>
<td>20. Key secondary outcome(s)</td>
</tr>
</tbody>
</table>
When to register and publicly disclose?

- Before recruiting the first trial participant
- Full public disclosure upon registration
‘Commercially sensitive’ items

- Intervention
- Scientific title
- Primary outcomes
- Key secondary outcomes
- Planned sample size
No delayed disclosure

- Patents protect intellectual property
- No evidence that disclosure threatens competition and hence innovation
  - Large variation in disclosure practices
  - ‘Sensitive’ information is available
- Who decides what information is ‘sensitive’

Results reporting

- Timing
- Venue
- Content
- Relation to journal publication (if any)
Challenge 3: Capacity building

- Increasing number of trials in lower income countries:
  
  **Non-US trials submitted to FDA**
  
  - 271 in 1990 → 4,458 in 1999
    
    (US Dept of Health & Human Services)
  
  **% in Latin America**
  
  - 2.1% in 1993 → 7.5% in 2000
    
    (IMS Health)
“Clinical trials remain a major concern for us. South Africa is overwhelmed and our people are exposed to too many trials. Regulation, coordination and better access to information on which trials are going on are essential to protect the people.”

Manto Tshabalala Msimang
Minister of Health, South Africa
Challenge 4: Global coordination of registers

- >400 listed on TrialsCentral™

- Highly variable:
  - Purpose
  - Scope
  - Content
  - Quality
  - Accessibility
WHO Registers Network

Primary Registers

Associate Registers

Researcher/Sponsor
Challenge 5:
Compliance with registering trials

- Only 2/3 of US prostate/colon cancer trials of new drugs were publicly registered despite legislation

Manheimer E & Anderson D, *BMJ* 2002
Challenge 5: Compliance with Data Set items

- ClinicalTrials.gov fields:

<table>
<thead>
<tr>
<th>Industry trials</th>
<th>Blank</th>
<th>Useless</th>
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</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td>Intervention name</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

- All non-industry trials had full information

Challenge 5:
Compliance with Data Set items

- Review of information recorded in 21 registers in 2005
  - 12 of 20 WHO Data Set items

Moja L et al, *submitted*
Compliance mechanisms

- World Health Assembly resolution
- Legislation
- Journal editors
- Funding agencies
- Research ethics committees
- Register policies
Outline

- Background and overview
- Global challenges
- Global opportunities
Global opportunities

Ethics
- Transparency
- Accountability
- Informed enrollment

Practice
- Informed policy
- Research efficiency
  - Ethics review
  - Grant review
  - Trial recruitment
  - Collaboration
- Systematic reviews
- Methodological research

Improved public trust
How can Cochrane contribute?

- Advocacy and promotion
- Methodological research
- Participation in ongoing discussions
Conclusions

- Strong rationale for public disclosure
- WHO is leading a coordinated, global network for trial registration & reporting
- Policies will be monitored and re-visited

Overriding principle:
To promote ethical & scientific integrity
WHO Registry Platform Team

- **Staff**
  - Davina Ghersi (coordinator)
  - Esther Awit
  - An-Wen Chan
  - Ghassan Karam
  - Ida Sim
  - Patrick Unterlerchner

- **Other WHO**
  - Metin Gülmezoglu
  - Luis Gabriel Cuervo (PAHO)
  - Tikki Pang
“The difference between what we do and what we are capable of doing would suffice to solve most of the world's problems.

Mahatma Gandhi