SAG Meeting Objectives

- Develop recommendations for implementation of the Trial Registration Data Set (Version 1.0);
- Provide input into the Primary and Associate Register Criteria;
- Advise on quality assurance policies and mechanisms – compliance oversight, and deduplication;
- Develop recommendation on priorities and strategic approach to results disclosure.
WHO International Clinical Trials Registry Platform

Ida Sim, MD, PhD
Project Coordinator
Department of Research Policy and Cooperation
World Health Organization
Geneva, Switzerland
April 27, 2006
Outline

- Current global overview of trial registration
- Update on Registry Platform administration
- Registry Platform overview
- Disclosure timing
- Summary
Current Global Overview

- International recognition that mis-reporting of clinical trials is unscientific and unethical
- General consensus that “all” clinical trials should be registered
- Registration capacity increasing worldwide (e.g., new national registers)
  - need for regional coordination, quality assurance
- Attention starting to expand to
  - results reporting for all registered trials
  - compliance mechanisms for registration and reporting
WHO Registry Platform

- Registry Platform project is now the acknowledged leading force in trial registration
  - have received support and participation from all relevant stakeholder groups

- Some early accomplishments
  - finalized 20 item Trial Registration Data Set
  - defined a coordinated global "platform" for trial registration

- But much more needs to be done to make trial registration a widespread and routine reality
Outline

- Global overview of trial registration
- Update on Registry Platform administration
- Registry Platform overview
- Disclosure timing
- Summary
Goals and Objectives

Goal
- strengthen public trust in clinical research by promoting transparency and accountability

Objectives
- ensure that all trials worldwide are registered and thus publicly declared and identifiable
- ensure that a minimum set of results are publicly reported for all registered trials
- develop compliance mechanisms to ensure a “level playing field” for all parties
- support use of trial registration information for recruitment, research planning, etc.
Registry Platform Administrative Structure

- **WHO EIP/RPC**
- **International Advisory Board**
  - broad-based, 15 senior leaders
  - advises on strategy/direction
  - leads in communication/advocacy
- **Scientific Advisory Group**
  - 21 experts
  - advises on principles/substantive standards

- **Registry Platform Secretariat**
- **Project Secretariat**
  - 15% offsite coordinator, full-time position posted
  - 1.6 FTEs at HQ + 1 temp secondment
International Advisory Board (IAB)

**Chair**
- **Sir Richard Sykes**, Rector, Imperial College, UK

**Members**
- **Alan Bernstein**, President, Canadian Institutes of Health Research, Canada
- **Jose Carvalheiro**, President, Fiocruz, Brazil
- **Gail Cassell**, Vice President Scientific Affairs, Eli Lilly, USA
- **Iain Chalmers**, Editor, James Lind Library, UK
- **Nirmal K. Ganguly**, Director General, Indian Council for Medical Research, India
- **Victoria Hale**, CEO, One World Health, USA
- **Ching-Li Hu**, Director, Shanghai Research Center for Care for Children, China
- **Ana Langer**, Population Council, Mexico
- **Caroline Loew**, Vice President, Scientific & Regulatory Affairs, PhRMA, USA
- **Pascoal Mocumbi**, European Developing Countries Clinical Trials Partnership, Netherlands
- **Kathy Redmond**, European Cancer Patient Coalition (ECPC), Milan, Italy
- **Joerg Reinhardt**, Head of Development, Novartis, Switzerland
- **Hideo Shinozaki**, President, National Institute of Public Health, Japan
- **Hal Sox**, Editor, Annals of Internal Medicine, USA
Scientific Advisory Group (SAG)

- **(Co-chair) Kay Dickersin**, Johns Hopkins Bloomberg School of Public Health, MD, USA
- **(Co-chair) Richard Horton**, The Lancet, UK
- **Gerd Antes**, Deutsches Cochrane Zentrum, Germany
- **Alan Breier**, Eli Lilly & Co.
- **Chris Chute**, Mayo Clinic, USA
- **Francis P. Crawley**, European Forum for Good Clinical Practice, Belgium
- **Pierre Ducimetiere**, INSERM, France
- **Davina Gherzi**, University of Sydney, Australia
- **Anne Greenwood**, Current Science Group, UK
- **Michael Gropp**, Guidant Corp, Belgium
- **Karmela Krleza-Jeric**, Canadian Institutes of Health Research, Canada
- **Rebecca Kush**, Clinical Data Interchange Standards Consortium, USA
- **David Moher**, Children’s Hospital of Eastern Ontario, Canada
- **Frank Rockhold**, Senior Vice President, GlaxoSmithKline, USA
- **Marc Taylor**, UK Department of Health, UK
- **Toshiro Tango**, National Institute of Public Health, Japan
- **Prathap Tharyan**, Christian Medical College, Velore, India
- **Jimmy Volmink**, University of Cape Town, South Africa
- **Liz Wager**, Sideview Consulting, UK
- **Janet Wale**, Cochrane Consumer Network, Australia
- **Deborah Zarin**, ClinicalTrials.gov, MD, USA

*Yellow = new since last SAG meeting*
Funding

- Department of Health, UK
  - GBP50,000 + GBP5,000 for IAB meeting
- Japanese Ministry of Health
  - US$50,000 for WHO Kobe Center meeting
- Wellcome Trust
  - GBP12,000 for travel support
- Canadian Institutes of Health Research
  - CDN$25,000 for Dr. Chan’s secondment
- Gates Foundation: final decision pending
- In-kind support from IAB, SAG members, etc.
Outline

- Global overview of trial registration
- Update on Registry Platform administration
- Registry Platform overview
- Disclosure timing
- Summary
Registry Platform Overview

WHO Search Portal

CT.gov

ISRCTN

country specific

Registers
Journals
Results
Databases
Which Trials Must Register

- The registration of all interventional trials is a scientific, ethical, and moral responsibility.

- Any research study that prospectively assigns humans or groups of humans to one or more health related interventions to evaluate the effects on health outcomes:
  - all health interventions (e.g., drugs, devices, procedures, etc)
  - early and late phase studies
  - healthy volunteer studies
  - pharmacokinetic studies?
**Responsible Registrant**

- Either the principal investigator (PI) or the primary sponsor
  - primary sponsor ultimately accountable for ensuring that the trial is properly registered
- Should make every reasonable effort to ensure that trial is registered
  - once and only once in any one register
  - in the fewest number of registers necessary to meet applicable regulations
Register Network Structure

- Two-tiered system
  - Primary Registers (relatively few)
    - should be national, regional, or international
      - maximum of one per country
    - submit Registration Data Set directly to WHO
  - Associate Registers (relatively many)
    - serve diverse constituents and objectives
    - must be affiliated with a Primary Register
      - submit Registration Data Set to that register
Register Network and Criteria

- Registers Working Group launched March 06
  - chair Davina Ghersi
  - major national and international registers
    - ClinicalTrials.gov, ISRCTN, Australian Clinical Trials Register, Indian National Register, UMIN (Japan), China, South Africa
  - share best practices, develop standards, etc.

- Aim to launch initial set of Primary Registers May 19 2006 (International Clinical Trials Day)
  - Register Criteria to be discussed this afternoon
Registers and Global Regulatory Capacity

- WHO working to establish regional coordination to ensure fewest number of Primary Registers to meet global needs

- Trial registers may be focal points for developing clinical trial regulatory capacity
  - provide listing of trial activities by country
  - link to ethics review mechanisms, GCP, etc.

- Increasing demand for training and assistance
WHO Trial Registration Data Set

1. Primary Register and Trial ID#
2. Date of Registration in Primary Register
3. Secondary ID#s (e.g., study #, ERB #)
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
9. Public Title
10. Scientific Title
11. Country of Recruitment
12. Health Conditions or Problems Studied
13. Intervention(s)
14. Key Inclusion and Exclusion Criteria
15. Study Type
16. Date of First Enrolment
17. Target Sample Size
18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcome(s)
Coding of Data Fields

- 4 key fields describe the trial’s scientific nature
  - Conditions, Interventions, Primary and Secondary Outcomes

- Should be coded using a standard vocabulary to
  - standardize description of trials
  - support more accurate search

- WHO plans to code Conditions, Interventions, Primary Outcomes in MeSH
  - some registers already code some of these fields
  - assume that most submissions will be in free text
Responsible Registrant

Global Deduplication

UTRN, MeSH Codes

MeSH Coding

Search Portal

WHO Search Database

WHO Central Reference Database

Primary Registers

Associate Registers

WHO Registration Data Set

1. Responsible Registrant

2. Primary Registers

3. Associate Registers

4. WHO Registration Data Set

5. MeSH Coding

6. Global Deduplication

7. UTRN, MeSH Codes
Local and Global Deduplication

- Trials may be registered in more than one register (e.g., to meet regulatory requirements, to promote enrollment)
- Duplicate registrations can falsely inflate the apparent volume of global research activity
- Need to deduplicate trial registrations
  - Local deduplication
    - Individual registers identifying duplicate entries *within* their own register
  - Global deduplication
    - WHO will coordinate the identification of duplicates *across* registers worldwide
Universal Trial Reference Number (UTRN)

- New number to be issued by WHO to each trial deemed unique across registers
  - unique trial: conducted according to a single document (the protocol) that describes the objective(s), design, methodology, statistical considerations, and organization of a trial
  - multi-center trial is conducted according to a single protocol but carried out at more than one site

- UTRN will cross-reference entries for same trial across multiple registers
  - each single, unique trial will have one UTRN
  - each UTRN will relate to a single unique trial worldwide
  - no current trial ID number performs this function
  - promotes integrity of entire system
Open Access One-Stop Search Portal

- Searches all Primary Registers
  - provides gateway to trial information worldwide
  - will have patient and scientist versions
- RFP being reviewed by Legal
Data Interchange Standard

- Working with CDISC to define an XML standard for Registration Data Set interchange
  - an extension of the CDISC Object Data Model (ODM)
  - linked to HL7, BRIDG, caBIG, etc.
  - in very early testing phase
- WHO will provide technical assistance to national or regional registers as needed to use data interchange standard
Registry Platform Overview

WHO Search Portal

CT.gov

ISRCTN

country specific

Registers

Journals

Results

Databases
Outline

- Global overview of trial registration
- Update on Registry Platform administration
- Registry Platform overview
- Disclosure timing
- Summary
WHO considers it in the public interest that all 20 items in the Registration Data Set be publicly disclosed at the time of registration.

Is aware of argument that for some trials:
- public disclosure at the time of registration may threaten academic or commercial competitive advantage.
- competitive advantage could be protected by delaying the public disclosure of one or more registration data items.
Disclosure Timing Discussions

- **April 2005**: Technical Consultation advised WHO that
  - One or more of 5 data items “may be considered sensitive for competitive reasons by the sponsor who may wish to delay release of the information”

- **Nov 2005**: Scientific Advisory Group concluded
  - “critical on scientific grounds, and in the public interest, that all 20 items in the Trial Registration Data Set be fully disclosed at the time of registration”

- **Dec to Jan, and Feb to Mar, 2006**: Open Comments
  - Submissions from community on key disclosure timing topics have further informed Secretariat
Formal Consultation

“Safe harbor” high level consultation yesterday, to inform WHO further
- patients and consumers
- scientists and clinicians
- industry (pharma, devices, biotech)
- medical journal editors
- ethicists, trade law experts, others
Brief Take on General Sentiment

- No compelling case for significant commercial or academic competitive threat from immediate disclosure
- Industry has come a long way
  - delayed disclosure option would allow industry to work through culture change to additional transparency
- Implementation of delayed disclosure could be a “nightmare”
  - external review for delayed disclosure eligibility
  - monitoring and enforcement of triggers for disclosure after delay
- Public trust would be eroded with delayed disclosure
Where We Stand Today (April 27)

<table>
<thead>
<tr>
<th></th>
<th>Potential Risks</th>
<th>Potential Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voluntary Immediate Disclosure</strong></td>
<td>Reduced compliance &amp; participation</td>
<td>Strengthened public trust in all parties</td>
</tr>
<tr>
<td></td>
<td>Unevenly reduced competitive advantage</td>
<td>Informed enrollment</td>
</tr>
<tr>
<td><strong>Delayed Disclosure</strong></td>
<td>Reduced public trust in trial registration</td>
<td>Increased compliance and participation?</td>
</tr>
<tr>
<td></td>
<td>Implementation difficulties</td>
<td>Preserved competitive advantage</td>
</tr>
</tbody>
</table>

☐ Taking everything into account so far, WHO leaning more towards full and immediate disclosure

☐ Final policy to be announced May 19, 2006
Outline

- Global overview of trial registration
- Update on Registry Platform administration
- Registry Platform overview
- Disclosure timing
- Summary
Approximate Project Timeline

Q2 2006
- 2nd Scientific Advisory Group meeting (27-28 Apr)
- Finalize Disclosure Timing Policy (19 May)
- Launch Network of Member Registers

Q3 2006
- First version of assignment of UTRNs to Primary Registers
- Launch Registry Platform Search Portal prototype

Q4 2006
- 1st Annual Registry Platform Meeting: 3rd Scientific Advisory Group, Trial registers (Kobe, Japan)
- Define first version of Results Reporting requirements
- Initiation of training workshops and in-field technical assistance
Conclusions

- Registry Platform is fulfilling charge as stated in WHA58.34

- Key topics for SAG
  - Registers and Register Network
    - Primary and Associate Register Criteria, regional coordination
    - Quality assurance -- compliance monitoring
    - Deduplication
  - Results reporting
  - Compliance enforcement mechanisms
  - Agenda suggestions for SAG meeting in Kobe
WHO Registry Platform Team

- Project Coordinator
  - Ida Sim

- Staff
  - Esther Awit
  - An-Wen Chan
  - Ghassan Karam
  - Patrick Unterlerchner

- Other WHO
  - Metin Gülmezoglu
  - Tikki Pang
  - Luis Gabriel Cuervo (PAHO)

- http://www.who.int/ictrp