Registration of Clinical Trials: Background and Implementation

Ida Sim, MD, PhD
Project Coordinator
Department of Research Policy and Cooperation
World Health Organization
Geneva, Switzerland;
and University of California San Francisco, USA
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Outline

- Background
  - Why register trials?
  - Why WHO project?
- WHO International Clinical Trials Registry Platform
- Intellectual Property Concerns
- Current Work
- Summary
Clinical Trials

- Everyone wants to do evidence-based medicine
  - health care delivery based on best available evidence
- Clinical trials one of the most valuable sources of evidence about
  - whether a health treatment works
  - whether it is safe
- Billions of dollars spent worldwide every year on clinical trials
- Critical that public trusts clinical trial results
Can We Trust Clinical Trials?

“Publication bias”: negative results often not published
- small, negative studies least likely to be published
- negative studies often not submitted to journals
- only ~40% of meeting abstracts published (Scherer, 94)
- of trials submitted to FDA in support of drugs that were eventually approved (Sim, in prep)
  - only 42% published in 3.7 years after drug approved
  - negative trials less likely to be published

Publication bias can mislead clinical practice
- combination chemo for ovarian cancer (Simes, 86)
  - p = 0.02 in published trials
  - p = 0.25 in all registered trials
Can We Trust Clinical Trials? (cont.)

- CLASS trial published in JAMA, 2001
  - 6 month data showed celecoxib caused fewer symptomatic ulcers and ulcer complications than did diclofenac or ibuprofen
  - but trial protocol included 12 month timepoint, which did not show any differences

- Outcomes reporting bias (Chan, 2004)
  - comparing ethics board protocols to publications, 50% of efficacy outcomes not reported
  - positive outcomes more likely to be reported (O.R. 2.4, 95% c.i. 1.4-4.0)
What to Do?

- Problem generally known for over 30 years
- Solution is to register all trials before they start
  - collect key scientific parameters (e.g., outcomes and timepoints)
  - allows tracking of trials to ensure that all trials and all results are published
- But nothing happened until...
Extensive Media Coverage

- **Aug 2004**
  - GSK settles US$20 million suit for fraud in not reporting negative paroxetine results

- **Sept 2004**
  - Merck pulled rofecoxib off the market amid continuing concerns that data was hidden from public
  - estimated tens of thousands of heart attacks happened unnecessarily
Need for Trial Registration

- Public needs and deserves a full and unbiased public record on safety and effectiveness
- Trial registration is necessary to ensure full reporting of trial results
- Global need to restore public trust in clinical trials, avoid drop in participant enrollment
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Current Policies

- As of September 2005, International Committee of Medical Journal Editors (ICMJE) journals accept only registered trials for potential publication
  - many other journals have followed this policy
- Many trial registration laws and policies being proposed worldwide
  - e.g., ~50 laws proposed or adopted in US states and Congress
- Overlapping and conflicting laws will make multi-country trials difficult
Many Registers Worldwide

- Probably around 1000 registers exist worldwide
- Registers vary in their
  - scope: e.g., country, disease, funder
    - many new country registers (India, China, South Africa, Germany, Iran, etc.)
  - purpose: e.g., participant enrollment, administrative tracking, scientific analysis
- Need for global standardization, coordination, and cooperation
Why World Health Organization?

- Global, neutral, independent body with convening capacity (i.e. World Health Assembly resolutions)

- Authoritative; Role in setting norms and standards in research, policy and practice
  - Good Clinical Practice, Ethics guidelines, Classification standards (e.g., ICD)

- Contributes to capacity building (i.e. in developing countries)

- Political legitimacy, accountable to 192 member States

- Commitment to achieving equity in health
Leading up to WHO Registry Platform

- **Oct 2003**
  - WHO Director-General highlighted trial registration in global health research

- **Oct 2004** – Rockefeller Foundation meeting, NY
  - Need for global approach to trial registration
  - WHO should establish formal process on a global approach
Leading up to WHO Registry Platform

- **Nov 2004** – Ministerial Summit on Health Research, Mexico City
  - Ministers of Health and others from 52 countries called on WHO to
    - establish network of clinical trial registers
    - ensure unambiguous identification of trials
    - ensure a single point of access

- **April 2005** – Technical Consultation, Geneva
  - Meeting of diverse stakeholders to build consensus policies

- **May 2005** – 58th World Health Assembly
"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"

Dr J.W. Lee
past WHO Director-General
WHO Registry Platform

- Registry Platform project is now a global leader in trial registration
  - have received support and participation from all relevant stakeholder groups

- Accomplishments to date
  - defined 20 item WHO Trial Registration Data Set
  - called for full disclosure of registration data at time of registration (no “lockbox”)
  - outlined a coordinated global platform for trial registration

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

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

- **Objectives**
  - ensure that all interventional 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 that all parties follow the same rules
  - 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
  - advise on strategy/direction
  - lead in communication/advocacy
- **Scientific Advisory Group**
  - 21 experts
  - advise on principles/substantive standards
  - working groups
    - trial registers
    - results reporting
- **Registry Platform Secretariat**

*Registry Platform*
Funding

- **Internal Support**
  - WHO start-up and operational funds

- **External Support**
  - English Department of Health
  - Japanese Ministry of Health
  - Wellcome Trust
  - Canadian Institutes of Health Research

- **In-kind support from experts and stakeholders**
  - Travel, meetings, consultations
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.
- Includes:
  - all health interventions (e.g., drugs, devices, cells and biological products, procedures, behavioral treatments, care process changes, etc.)
  - early and late phase studies
  - studies on healthy volunteers
  - marketed and not-yet-approved products and indications
  - randomized and non-randomized, etc.
Responsible Registrant

Either the principal investigator (PI) or the primary sponsor, to be decided between them

- primary sponsor is “the individual, organization, group or other legal person taking on responsibility for securing the arrangements to initiate and/or manage a study”
- primary sponsor is ultimately responsible for ensuring that the trial is properly registered
- for multi-centre and multi-sponsor trials, lead PI or lead sponsor is responsible registrant

Should make every reasonable effort to ensure that a trial is registered

- only once in any register
- registered in the fewest number of registers necessary to meet relevent 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
Draft Primary Register Criteria

□ Main requirements
  ■ perform quality assurance and local deduplication
  ■ use Registry Platform data interchange standard
  ■ entries can be in any language, but uploads to WHO must be in English
  ■ open access (free public access to all entries)

□ Encouraged but not required to
  ■ Collect or store protocol document itself
  ■ Collect or store protocol amendments
  ■ Store or link to trial results

□ Should charge no or only minimal registration fees
Registers and Global Regulatory Capacity

- Want the fewest number of registers necessary to serve global needs
  - easier to identify duplicates and assign UTRN
- WHO working with countries to coordinate regional approaches to trial registration
  - Latin America leading in establishing a regional approach
- Trial registers may be focal points for developing clinical trial regulatory capacity
  - national and regional registers listing ongoing trials
  - link to ethics review mechanisms, GCP, etc.
WHO Registration Data Set (1)

1. Primary Register and Trial ID# (e.g., NCT)
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
9. Public Title
10. Scientific Title
WHO Registration Data Set (2)

11. Countries of Recruitment
12. Health Condition(s) or Problem(s) Studied
13. Intervention(s)
14. Key Inclusion & Exclusion Criteria
15. Study Type
16. Date of First Enrollment
17. Target Sample Size
18. Recruitment Status
19. Primary Outcome(s)
20. Key Secondary Outcome(s)
Responsible Registrant

Global Deduplication

MeSH Coding

UTRN, MeSH Codes

Primary Registers

Associate Registers

WHO Central Reference Database

WHO Search Database

WHO Registration Data Set

Search Portal

Responsible Registrant

Other Registers
Local and Global Deduplication

- Trials may be registered in more than one register (e.g., to meet laws, to increase enrollment)
- Registering a trial several times can make it look like there is more research going on than there really is
- Need to deduplicate trial registrations
  - Local deduplication
    - individual registers should identify 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 trial’s objective(s), design, methods, statistical considerations, and organization
  - **multi-center trial**: 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
Search Portal and Interchange Standards

- Search Portal will search all Primary Registers
  - provides gateway to trial information worldwide
  - will have patient and scientist versions
- Data interchange standard in early testing phase
  - an XML standard for Registration Data Set interchange
    - developed with CDISC, industry clinical trial data standards association
Registry Platform Overview

WHO Search Portal

CT.gov

ISRCTN

country specific

Registers

Journals

Results Databases
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“Intellectual Property” Concerns

- Key scientific features of trials
  - intervention, outcomes, condition, and sample size

- Revealing this information publicly at start of enrollment may allow competitors unfair advantage
  - a competitive advantage issue

- To protect competitive advantage, pharma industry (IFPMA, PhRMA) proposed
  - storing registration data privately with 3rd party
  - data to revealed to the public
    - only for products that receive marketing approval
    - within 1 year of product approval in any country
    - if safety concerns, at discretion of company
Issue is Timing of Disclosure

- Issue was not *whether* to register, but when should data be made public
- Question was:
  - does public disclosure of all 20 items (including key scientific datafields) give away competitive advantage?
  - does degree of loss of competitive advantage justify keeping data hidden from the public?
- Many groups strongly against industry proposal
- Had to resolve this issue to move trial registration along
Resolving Disclosure Timing

- **Fall and Winter 2005:** Open Comment Periods
  - web submissions from community on key topics

- **April 2006:** “Safe harbor” discussion session, Geneva
  - high level consultation involving strategic thinkers, key players from all stakeholder groups
    - patients and consumers
    - scientists and clinicians
    - industry (pharma, devices, biotech)
    - medical journal editors
    - ethicists, trade law experts, others
  - discussed balance of transparency vs. protection of competitive advantage
Summary of Disclosure Timing

- Public trust greatest if all 20 items made public before first participant enrolled
- Full and immediate disclosure not a big threat to competitive advantage
  - big differences among companies in what they reveal and when
    - why can one company reveal all outcomes immediately and another none?
  - “intellectual property” information can often be bought from “industry intelligence” sources
  - no convincing evidence that disclosure would harm competition or innovation
    - may even promote innovation
WHO Disclosure Timing Policy

- The benefits of full and immediate disclosure are greater than any potential loss of competitive advantage

- WHO calls for full disclosure of all registration items at time of registration and before recruitment of the first participant
  
  - *Sim et al, Lancet, 2006; 367:1631-3*
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Registers Network

- Want the fewest number of registers necessary to serve global needs
  - easier to identify duplicates and assign UTRN
  - but countries have different needs (e.g., language, research planning, research oversight)

- Current priorities
  - establishing a coordinated regional and international approach to trial registration
    - PAHO/WHO supports Latin American countries, BIREME, and others in plans for a Technical Committee
  - setting, meeting, and monitoring quality, deduplication, and accountability standards
Results Reporting

- Standards currently in development
  - required content being defined
    - must link to trial registration data set, must not have Discussion or Conclusion sections
  - when to report: within 1 year of study completion
  - format: electronic, web-accessible, preferably English
  - availability: open access (all entries free to public)
  - venues: journals, repositories, databases, etc.
    - peer review not required
    - should be linked to trial registers
Ensuring a Fair System

- Everyone should be held to the same rules
  - assures registrants that they will not be at a disadvantage compared to those who do not register

- Promoting and rewarding compliance
  - ICMJE policy
  - requirements by funding agencies (eg CIHR)? universities? countries? regulatory agencies?
  - linking to ethics review?
  - international laws/treaties?
Research

- Need for better evidence to guide registration and reporting policies
- Research topics under consideration
  - registration compliance rates
  - extent of and nature of duplicate registration
  - consequences of duplicate registration
  - patterns of mis-reporting and consequences
  - evidence supporting various recommendations for trial reporting
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WHO Registry Platform...

- Has finalized required registration items
- Is establishing a network of Primary and Associate registers to coordinate registration worldwide
- Will perform global deduplication of trials and issue UTRNs to globally unique trials
- Will launch one-stop search portal of Primary Registers
- Is defining standards for minimum reporting of results
- Is pursuing compliance mechanisms for registration and reporting
Value Added of Registry Platform

- WHO is only neutral body well-placed to define standards
  - Registration Data Set (and disclosure timing policy)
  - results reporting
  - compliance enforcement
- Single international network of high-quality registers
  - simplifies, coordinates where to register
  - global accountability, sharing of best practices
- Duplication checking and unique trial identification (UTRN)
  - enhances global integrity and information quality
- One-stop search portal of registers worldwide
  - "public face," transparency, restore trust/confidence
Conclusion

- Clinical trials transparency and public trust is a global issue.
- WHO taking lead on policy and technical platform for coordinated trial registration and reporting worldwide.
- Overriding principle is to promote scientific and ethical integrity.
- Input from all stakeholders welcome.
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)
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