Registration of clinical trials

Davina Ghersi
Coordinator, International Clinical Trials Registry Platform
Department of Research Policy and Cooperation (RPC/EIR)
World Health Organization

Training Course in Reproductive Health/Sexual Health Research 2008

Why register trials?

"Registration of all interventional trials is a scientific, ethical and moral responsibility"

WHO ICTRP Secretariat, Nov 2005

A trial is any research study that prospectively assigns humans or groups of humans to health-related interventions

- *Includes Phase I to Phase IV trials*

Why register trials

- An ethical responsibility
- Publication bias
- Transparency and accountability
- Identifying gaps

An ethical responsibility

" Medical research involving human subjects must … be based on a thorough knowledge of the scientific literature, other relevant sources of information…."

" Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others…. The design of all studies should be publicly available."

Declaration of Helsinki

Publication bias

Publication bias

> “Where the likelihood of publication is influenced by the direction or strength of the trial results” (Dickersin 1990)

Selective publication

> “Different conclusions may be reached by selecting trials from the published literature or from a clinical trials registry” (Simes 1986)

Selective reporting

> Incomplete reporting of trial outcomes associated with statistical significance (Chan 2005)

Registered v Published studies

OVARIAN CANCER CHEMOTHERAPY: SINGLE V COMBINED

	Published	Registered
No. studies	16	13
Survival ratio	1.16	1.05
95% CI	1.06-1.27	0.98-1.12
P-Value	0.02	0.25

Simes, J. Clin Oncol, 86, p1529

Other research in publication bias

- Follow-up of 737 studies at Johns Hopkins (Dickersin, JAMA, 1992)
  - Positive SUBMITTED more than negative (2.5 times)

Public (mis)trust

In a recent survey, only a quarter of Americans said the (pharmaceutical) industry was doing a good job, putting it on a par with the tobacco industry. When your customers see you as "manipulative, dark, menacing," you could be said to be losing the battle for hearts and minds… drug companies are under increasing pressure to prove value for money, where "value" is about more than just the effectiveness of their drugs.

Fiona Godlee: BMJ 2005;330 (28 May)
doi:10.1136/bmj.330.7502.0-g

Enhancing public trust

Two initiatives … could help improve the industry's image or help individual drug companies stand out from the crowd. The first is trial registration. …. Drug companies have been closely involved in recent negotiations and should now, for their own sake as much as the public's, embrace this opportunity to show their commitment to greater transparency.

Fiona Godlee: BMJ 2005;330 (28 May)
doi:10.1136/bmj.330.7502.0-g

Other reasons to register

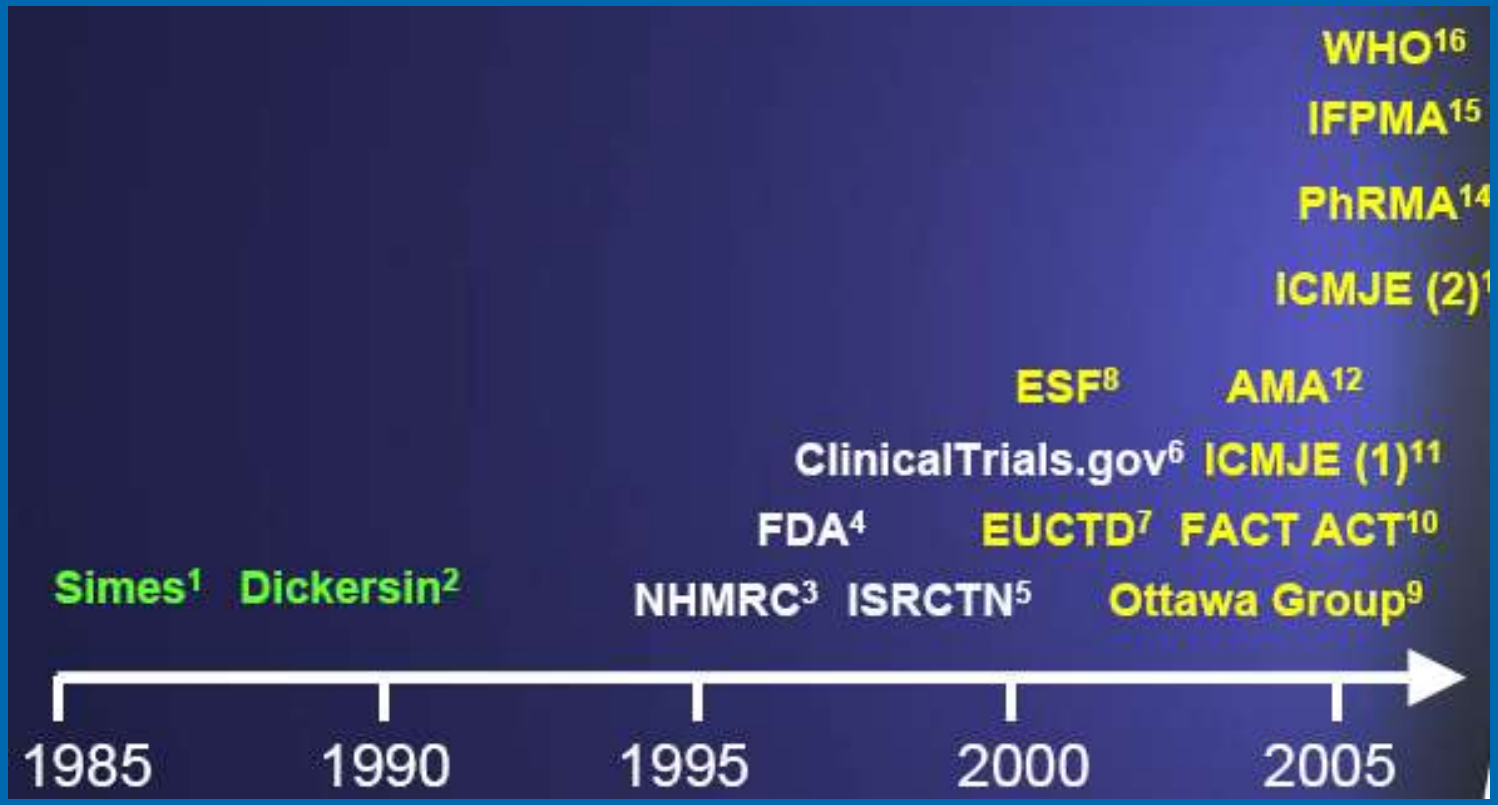
- increase participation in clinical trials
- contribute to systematic reviews
- speed access to results
- increase effectiveness of research funding
- impending increase in number of trials
- improve access to research information

Other reasons to register

- increase efficiency of the research process
  - e.g. ethical review
- enhance transparency and accountability
- improve equity and ownership
- facilitate policy development

Registration: a brief history

Calls for trials registration



1. Simes RJ. *J Clin Oncol*. 1986;4:1529-41

2. Dickersin K. *Control Clin Trials*. 1988:9:76-81

Diary of major events

November 1997	US FDA Modernization Act (mandate public register of NIH trials – clinicaltrials.gov)
March 2000	Current Controlled Trials introduce the ISRCTN
April 2001	Publication of the CONSORT Statement
October 2003	WHO Director General highlights trial registration in global health research
September 2004	Publication of the ICMJE policy on prospective trial registration
28-29 Oct 2004	WHO International Clinical Trials Registry Platform meeting, New York (The New York statement)

Diary of major events

November 1997	US FDA Modernization Act (mandate public register of NIH trials – clinicaltrials.gov)
March 2000	Current Controlled Trials introduce the ISRCTN
April 2001	Publication of the CONSORT Statement (Consolidated Standards for the Reporting of clinical Trials)
October 2003	WHO Director General highlights trial registration in global health research
September 2004	Publication of the ICMJE policy on prospective trial registration
28-29 Oct 2004	WHO International Clinical Trials Registry Platform meeting, New York (The New York statement)

Diary of major events

November 1997	US FDA Modernization Act (mandate public register of NIH trials – clinicaltrials.gov)
March 2000	Current Controlled Trials introduce the ISRCTN
April 2001	Publication of the CONSORT Statement (Consolidated Standards for the Reporting of clinical Trials)
October 2003	WHO Director General highlights trial registration in global health research
September 2004	Publication of the ICMJE policy on prospective trial registration
28-29 Oct 2004	WHO International Clinical Trials Registry Platform meeting, New York (The New York statement)

The CONSORT statement

- Describes various aspects of the protocol when reporting results:
  - planned study population, together with inclusion and exclusion criteria
  - planned interventions and their timing
  - primary and secondary outcome measures, the min. important difference and how sample size was projected
  - Rationale and methods for statistical analyses
  - Prospectively defined stopping rules

Diary of major events

November 1997	US FDA Modernization Act (mandate public register of NIH trials – clinicaltrials.gov)
March 2000	Current Controlled Trials introduce the ISRCTN
April 2001	Publication of the CONSORT Statement
October 2003	WHO Director General highlights trial registration in global health research
September 2004	Publication of the ICMJE policy on prospective trial registration
28-29 Oct 2004	WHO International Clinical Trials Registry Platform meeting, New York (The New York statement)

Calls for trial registration

ICMJE (incl. NEJM, Lancet, JAMA, Ann Int Med, MJA) (2004)

"The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication."

Diary of major events

November 1997	US FDA Modernization Act (mandate public register of NIH trials – clinicaltrials.gov)
March 2000	Current Controlled Trials introduce the ISRCTN
April 2001	Publication of the CONSORT Statement
October 2003	WHO Director General highlights trial registration in global health research
September 2004	Publication of the ICMJE policy on prospective trial registration
28-29 Oct 2004	WHO International Clinical Trials Registry Platform meeting, New York (The New York statement)

WHO "New York statement" (2004)

- **Need for global approach to clinical trials registration**
  - unambiguous identification of trials
  - consensus needed on which trials; data; timing and disclosure of results
  - one-stop search portal; publicly available
  - system is simple, effective, efficient
  - capacity built where appropriate
- **WHO should establish formal process towards a global approach**
  - appropriate governance
  - collaborative process, involving all interested parties
  - existing structures leveraged; identify any need for new structures
  - WHO mindful of ICMJE deadline

Diary of major events

16-20 Nov 2004	Ministerial Summit on Health Research, Mexico City (the Mexico statement)
April 2005	Publication of the Ottawa Statement
25-27 April 2005	Technical Consultation on Trial Registration Standards, Geneva
16-25 May 2005	58th World Health Assembly
30 May 2005	Brainstorming meeting to explore the possibility of establishing an European registry of ongoing clinical trials, Milan

“Mexico statement” (2004)

- 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

Diary of major events

16-20 Nov 2004	Ministerial Summit on Health Research, Mexico City (the Mexico statement)
April 2005	Publication of the Ottawa Statement
25-27 April 2005	Technical Consultation on Trial Registration Standards, Geneva
16-25 May 2005	58th World Health Assembly
30 May 2005	Brainstorming meeting to explore the possibility of establishing an European registry of ongoing clinical trials, Milan

58th WHA Resolution (2005)

Called upon the global scientific community, civil society, international partners, the private sector and other relevant stakeholders *"to establish a platform linking a network of international clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials"*

Diary of Events

22-23 Sep 2005	Critical Issues In Clinical Trial Registries And Registers: A Focus on Operational Considerations & Transparency. Philadelphia
17-18 Nov 2005	Scientific Advisory Group meeting, Geneva
6 Feb 2006	International Advisory Board meeting, London
24-27 Apr 2006	CDISC 2006 European Interchange, Berlin, Germany
26 Apr 2006 27-28 Apr 2006	Formal Consultation on Disclosure Timing Policy, Geneva, Switzerland , and SAG meeting

Diary of Events

May 2007	Launch of WHO Clinical Trials Search Portal
June 2007	Launch of registers in India and China
June 2007	ICMJE statement update
September 2007	FDA Amendment Act signed off

International Clinical Trials Registry Platform (ICTRP)

Welcome to the WHO International Clinical Trials Registry Platform

The mission of the WHO Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

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

What is a clinical trial?

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc

Functions

The Register Network | The International Search Portal

Search for trials

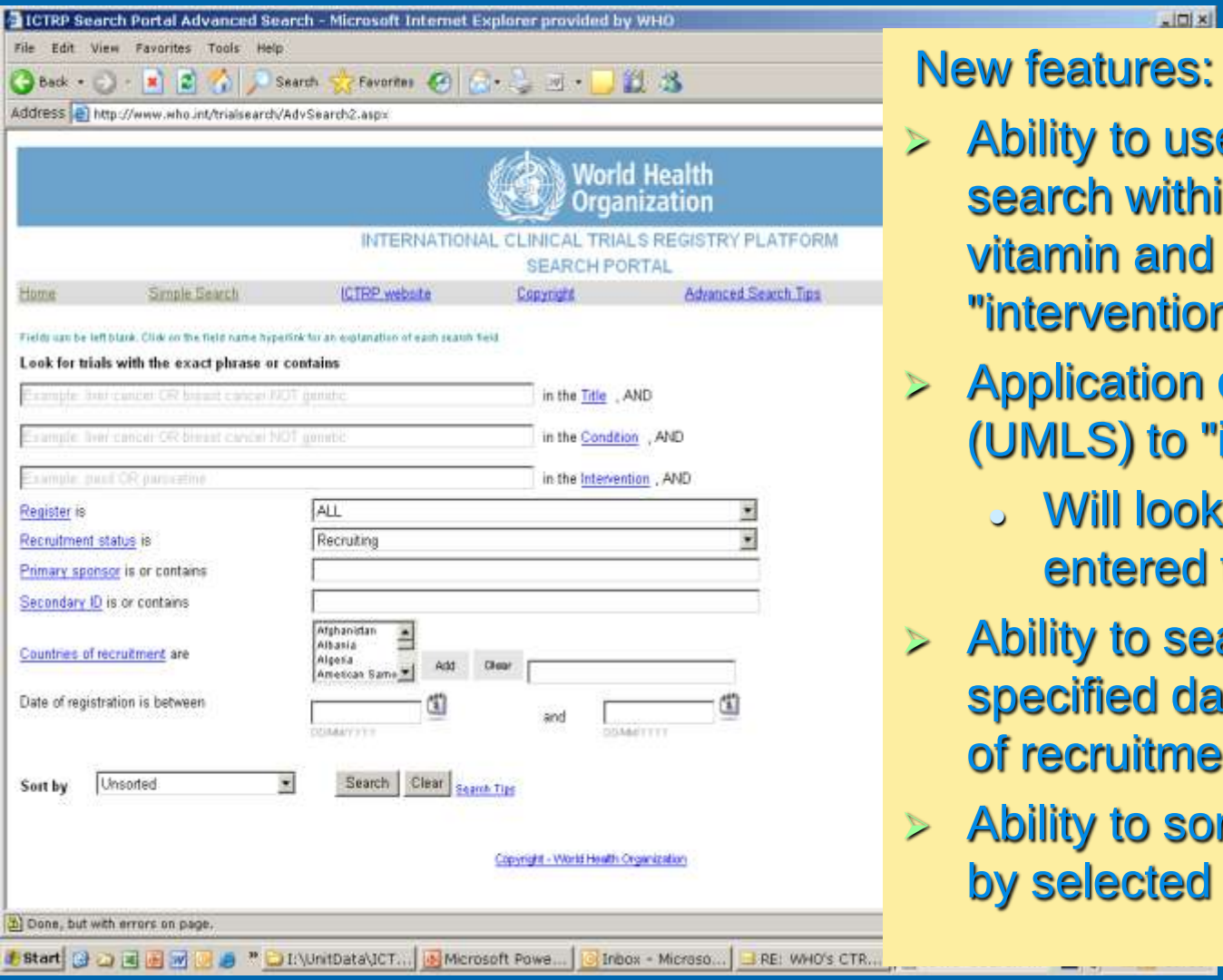
The Register Network

List of Registers

Frequently Asked Questions


ICTRP Search Portal - Microsoft Internet Explorer provided by WHO
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.who.int/trialsearch/
Go Links
World Health Organization
INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM
SEARCH PORTAL
Home Advanced Search ICTRP website Disclaimer Search tips Resources Contact us
Exact phrase match
Search
Search tips
Welcome
The Search Portal is a web site that enables users to search a central database that contains the trial registration data sets provided by Primary Registers.
When a user finds a trial on the Search Portal that they are interested in, they can learn more about the trial by clicking on a link that will take them to the relevant record in the source register.
New users are advised to read the Search Tips before commencing their search.
The Search Portal is not a clinical trials register.
No attempt is made to identify and tag trials that may have been registered on more than one register.
Data Sources
Australian New Zealand Clinical Trials Registry, last data file imported on 5 February 2008
ClinicalTrials.gov, last data file imported on 5 February 2008
ISRCTN, last data file imported on 5 February 2008
Copyright - World Health Organization
Done
Local intranet
Start
Declaration...
Untitled - ...
for RH cour...
WHO | Wel...
ICTRP Sear...
13:37

New advanced search



New features:

- Ability to use boolean terms to search within a field (eg vitamin and placebo in "intervention")
- Application of thesaurus (UMLS) to "intervention" field
  - Will look up synonyms for entered term
- Ability to search within specified dates and countries of recruitment
- Ability to sort results of search by selected fields

Diary of Events

May 2007	Launch of WHO Clinical Trials Search Portal
June 2007	Launch of registers in India and China
June 2007	ICMJE statement update
September 2007	FDA Amendment Act signed off

CLINICAL TRIALS REGISTRY-INDIA

NATIONAL INSTITUTE OF MEDICAL STATISTICS,(ICMR)

SIGN IN TO CTRI

Username

Password

Forgot Password | New User

Trial Registration Set Download: [Word][Pdf]

SEARCH FOR TRIALS

[Advanced Search]

News & Events

CTRI Bulletin Issue 1 Jul 2007
Click here to view CTRI Bulletin Issue 1 Jul 2007

The Clinical Trials Registry- India (CTRI) has been set up by the ICMR's National Institute of Medical Statistics (NIMS) and is funded by the Department of Science and Technology (DST) through the Indian Council of Medical Research (ICMR). It also receives financial and technical support through the WHO, WHO-SEARO, and the WHO India Country office. [Read more...]

Mission

The mission of the Clinical Trials Registry-India (CTRI) is to encourage all clinical trials conducted in India to be prospectively registered before the enrollment of the first participant and to disclose details of the 20 mandatory items of the WHO International Clinical Trials Registry Platform (ICTRP) dataset. [Read more...]

Vision

The vision of the CTRI is to ensure that every clinical trial conducted in the region is prospectively registered with full disclosure of the 20-item WHO ICTRP dataset, as well all items of the CTRI dataset, in order to 1) improve transparency and accountability, 2) improve the internal validity (details of the methods of the trial that produce reliable

WHO ICMR DST

Clinical Trials Registry-India (CTRI)

The CTRI is an online register of clinical trials being conducted in India. Any researcher who plans to conduct a trial involving human participants, of any intervention (drug, surgical procedure, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies and complementary therapies) are expected to register the trial in CTRI before enrollment of the first participant. Registration is voluntary but some fields marked* are mandatory for registration to proceed. Some fields marked WHO also need to be filled if the trial is to receive a registration number and fulfill WHO/ICMJE requirements. Incomplete entries will be given a provisional registration number that will not suffice for purposes of publication in journals that endorse the ICMJE recommendations for trial registration. Registration of trials in the CTRI is free. All registered trials will be made publicly available. The CTRI will be

Diary of Events

May 2007	Launch of WHO Clinical Trials Search Portal
June 2007	Launch of registers in India and China
June 2007	ICMJE statement update
September 2007	FDA Amendment Act signed off

ICMJE June 2007

- In addition to accepting registration in any of the 5 existing registries, the ICMJE will accept registration of clinical trials in any of the primary registers that participate in the WHO ICTRP. Registration in a partner register only is insufficient.
- The ICMJE will begin to implement the WHO definition of clinical trials for all trials that begin enrollment on or after 1 July 2008. This definition states that a clinical trial is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.”

Diary of Events

May 2007	Launch of WHO Clinical Trials Search Portal
June 2007	Launch of registers in India and China
June 2007	ICMJE statement update
September 2007	FDA Amendment Act signed off

FDA Amendment Act 2007

- Applicable clinical trials
- Basic results:
  - Demographic and baseline characteristics
  - Primary and secondary outcomes
  - A technical and a non-technical (non-promotional) summary
- The full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial
- Results to be submitted not later than 1 year after the earlier of the estimated completion date of the trial or the actual date of completion

Challenges in trial registration

Challenge 1: what to disclose and when

- Competitive advantage
  - Industry: commercial sensitivity
  - Academia: novel ideas, methods
- Delayed disclosure

What to disclose:
WHO minimum dataset

1. Unique, primary ID
2. Date registration
3. Secondary ID(s)
4. Funding source(s)
5. Primary sponsor
6. Secondary sponsor
7. Contact for public queries
8. Contact for scientific queries
9. Public title
10. Scientific title
11. Countries of recruitment
12. Health condition studied
13. Intervention(s)
14. Key inclusion/exclusion criteria
15. Study type
16. Date first enrolment
17. Target sample size
18. Recruitment status
19. Primary outcome(s)
20. Secondary outcome(s)

Ottawa Statement

http://ottawagroup.ohri.ca

- WHO items are the ***minimum*** data set
  - Intention is to revisit after 2 years
- Ottawa Statement argues:
  - registration and public release of all 20 WHO items are necessary but insufficient for transparency
  - Suggests additional items including:
    - Registration of full protocol and consent forms
    - Details of ethics committee approval
    - Additional design information

When to disclose

- Some stakeholders have suggested delaying disclosure of one or more of the WHO 20 items
- “arguments for delayed disclosure were neither convincing nor compelling”
  - Large variation in disclosure practice
  - Information claimed to be sensitive is often available for a fee
  - No evidence that disclosure threatens competition and hence innovation

WHO ICTRP Platform (Lancet May 2006)

When to disclose

The WHO Registry Platform “calls for full public disclosure of all registration data items at the time of registration and before recruitment of the first participant”

Challenge 2: Compliance

- Compliance
  - Registration of all items on the minimum data set
    - Quality control and quality assurance
  - Registration of all trials
    - National incentives

Mandatory vs Voluntary registration

- National ethical, regulatory, legal or funding requirements.
- Example: Australia
  - Ethical requirement
  - Code for the responsible conduct of research
- Example: US
  - Legal requirement

Registration as an ethical requirement

16. Every **bio**medical research project involving human ~~subjects~~ **beings** should be preceded by careful assessment of predictable risks and burdens **to the individuals and communities involved in the research** in comparison with foreseeable benefits to ~~the subject~~ **them** or to others **individuals or communities affected by the condition under investigation**. ~~This does not preclude the participation of healthy volunteers in medical research.~~ The design of all studies should be publicly available. **In particular, before recruitment of the first participant, each clinical trial should be included in a database register that is freely accessible by members of the public.**

6th revision of Declaration of Helsinki

Registration as an ethical requirement

- Proposal to AHEC review of National Statement
  - That evidence of registration be provided at the time of submission to an REC as a pre-condition
  - Some Australian RECs have voluntarily adopted such a policy

DRAFT OF THE

NATIONAL STATEMENT ON ETHICAL CONDUCT IN HUMAN RESEARCH

Second consultation

Developed jointly by

National Health and Medical Research Council
Australian Research Council
Australian Vice-Chancellors' Committee

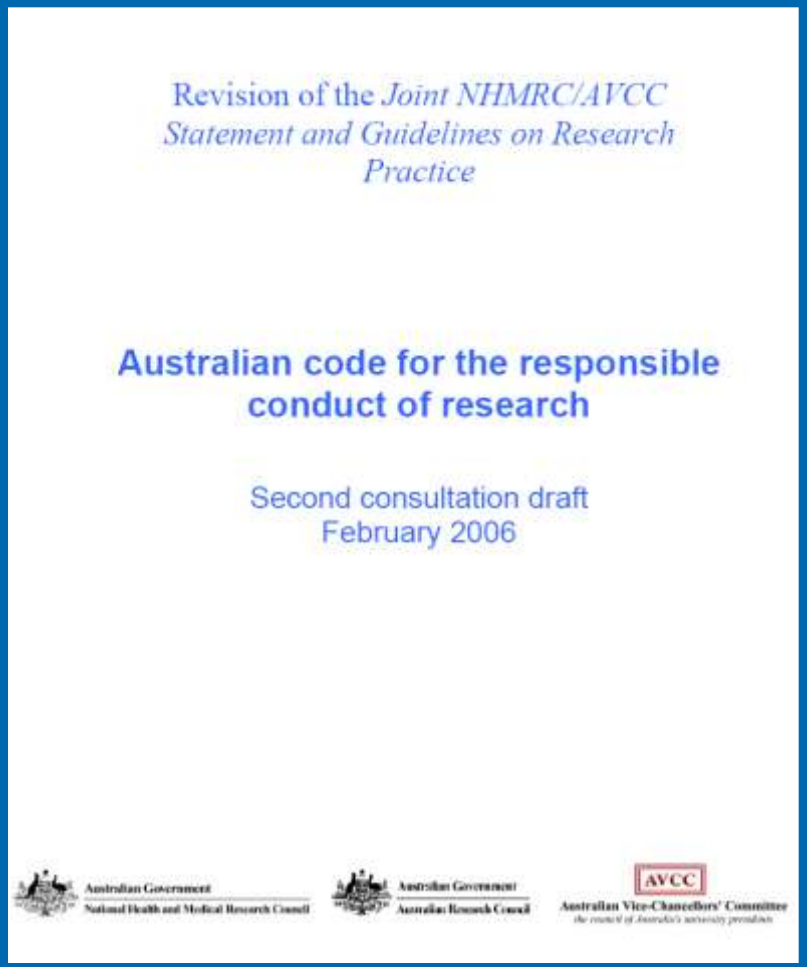
January 2006

Australian Government
National Health and Medical Research Council

Australian Government
Australian Research Council

AVCC
Australian Vice-Chancellors' Committee

Responsibilities of researchers

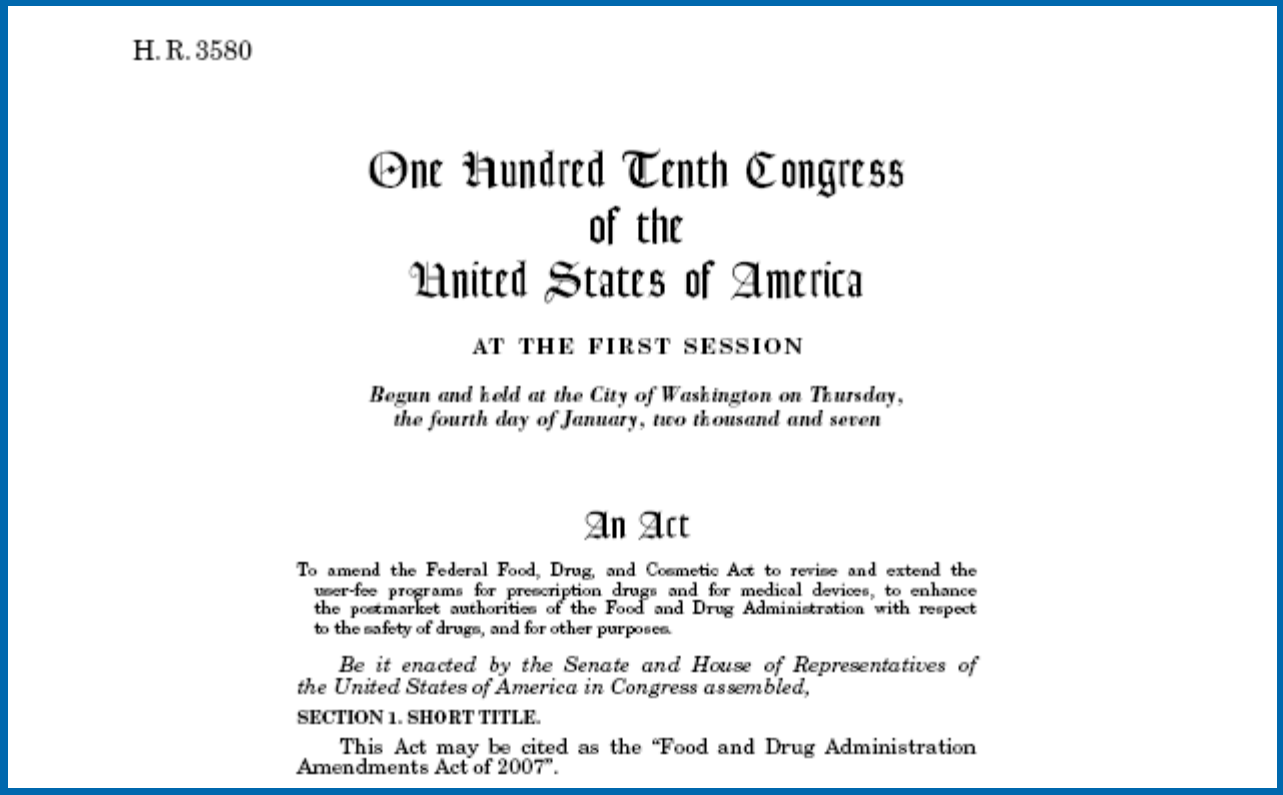


"*5.5 Register clinical trials: Researchers must register clinical trials with a recognised register to promote access to the results of all clinical trials*"

Compliance with the code of conduct is an ethical requirement

Registration as a legal requirement

- FDA Amendment Act 2007
  - Sec 801: expansion of clinical trials databank



H. R. 3580

One Hundred Tenth Congress
of the
United States of America

AT THE FIRST SESSION

Begun and held at the City of Washington on Thursday, the fourth day of January, two thousand and seven

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Amendments Act of 2007".

Challenge 3: unambiguous identification

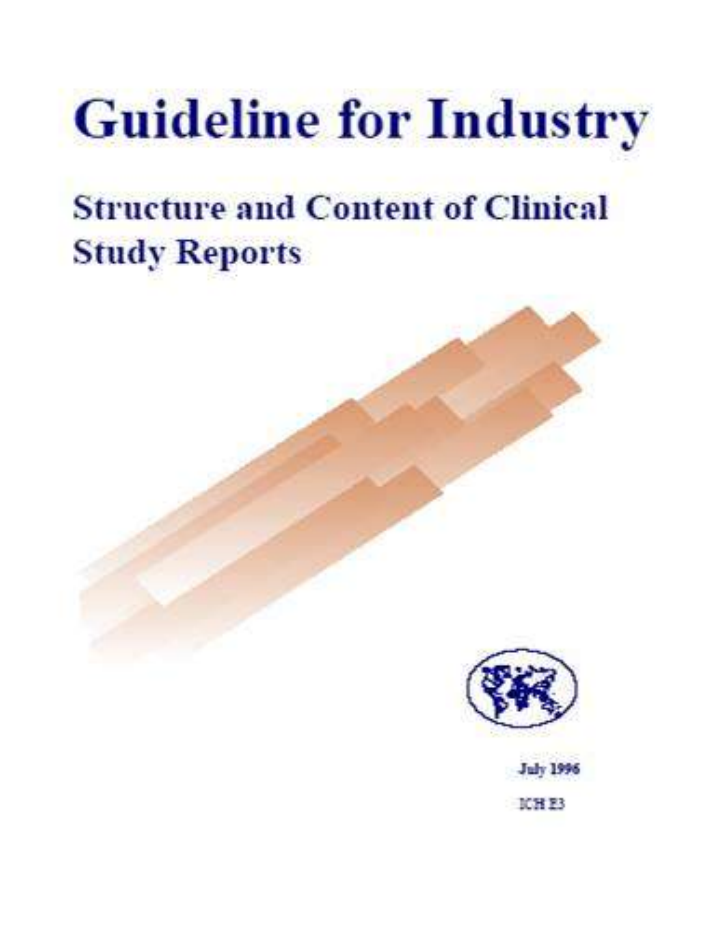
- Multiple registration of single trials
  - Within single registers
  - Across registers
- Collaboration across registers
  - WHO Register Network

Challenge 4: Multiplicity

- Multiple registers require multiple searches to identify trials
- WHO Search Portal
- Bridging
  - Using secondary identifiers
  - Universal Trial Reference Number (UTRN)

Challenge 5: Results disclosure

- Results disclosure
  - Discussion ongoing internationally regarding:
    - When to disclose
    - What to disclose
    - How it should be disclosed



Results reporting:
An ethical responsibility

" Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."

Declaration of Helsinki

ICH E3 synopsis

SYNOPSIS

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient:		
Title of Study:		
Investigators:		
Study centre(s):		
Publication (reference)		
Studied period (years): (date of first enrolment) (date of last completed)	Phase of development:	
Objectives:		
Methodology:		
Number of patients (planned and analyzed):		
Diagnosis and main criteria for inclusion:		
Test product, dose and mode of administration, batch number:		
Duration of treatment:		
Reference therapy, dose and mode of administration, batch number		

Name of Sponsor/Company:	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		
Criteria for evaluation: Efficacy Safety		
Statistical methods:		
SUMMARY - CONCLUSIONS EFFICACY RESULTS SAFETY RESULTS CONCLUSION: Date of the report:		