Registration of clinical trials

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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

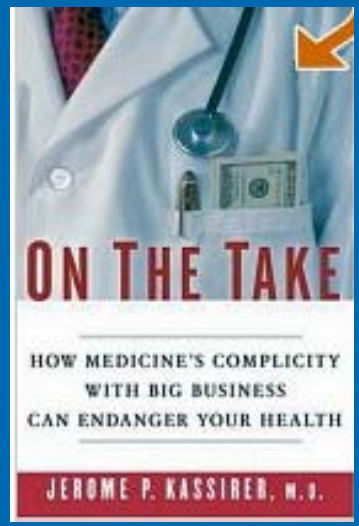
	Published	Registered
No. studies	16	13
Survival ratio	1.16	1.05
95% CI	1.06-1.27	0.98-1.12
P-Value	0.02	0.25

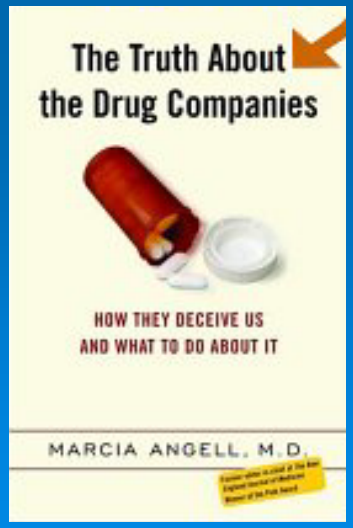
Simes, J. Clin Oncol, 86, p1529

Other research in publication bias

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

Transparency and accountability





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

EDITORIALS

Martin B Van Der Weyden, MJA Vol 180, 16 Feb 2004: 149-151

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 | MEDICINE AND PUBLIC ISSUES

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

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

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)
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Identifying gaps

Moving Dollars Toward the Clinic

Advocacy Groups	2004 Budget (in millions)	No. of ongoing clinical trials
ALS Therapy Development Foundation	$4	1
Cystic Fibrosis Foundation	$157	21
Foundation Fighting Blindness	$16	none yet
Juvenile Diabetes Research Foundation	$147	17
Multiple Myeloma Research Foundation	$11	6
Myelin Repair Foundation (multiple sclerosis)	$1.25	none yet
Nathan's Battle Foundation (Batten disease)	$1	1
Prostate Cancer Foundation	$26	N/A

Science,
May 13, 2005,
308, 940-942

"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,
World Health Assembly, May 16, 2005

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

South African National Clinical Trial Register

Welcome to SANCTR

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides you with information on a trials purpose; who can participate, where the trial is located, and contact details.

The South African National Clinical Trials Register forms part of international calls for making trial information publicly available. The International Committee of Medical Journal Editors, which includes peer reviewed journals from around the world, recently made a statement that from 1 July 2005 no trials will be considered for publication unless they are included on a research register. The World Health Organisation has begun the push for clinical trial registration with the initiation of a Clinical Trials Register platform. Similarly, the global pharmaceutical industry has recently released plans to make trial data more publicly available.

The benefits of a central publicly accessible clinical trial register are numerous. They include:

- Serves to promote collaboration among researchers, the private sector and the community through the sharing of research information;
- Assists people to identify clinical trials they can participate in;
- Decreases publication bias; reduce duplication of research efforts;
- Promotes best use of limited research resources; and
- Contributes to global efforts to reduce / eliminate disease.

The SA National Clinical Trials Register is an important tool for monitoring and managing new clinical trials. The

Other reasons to register

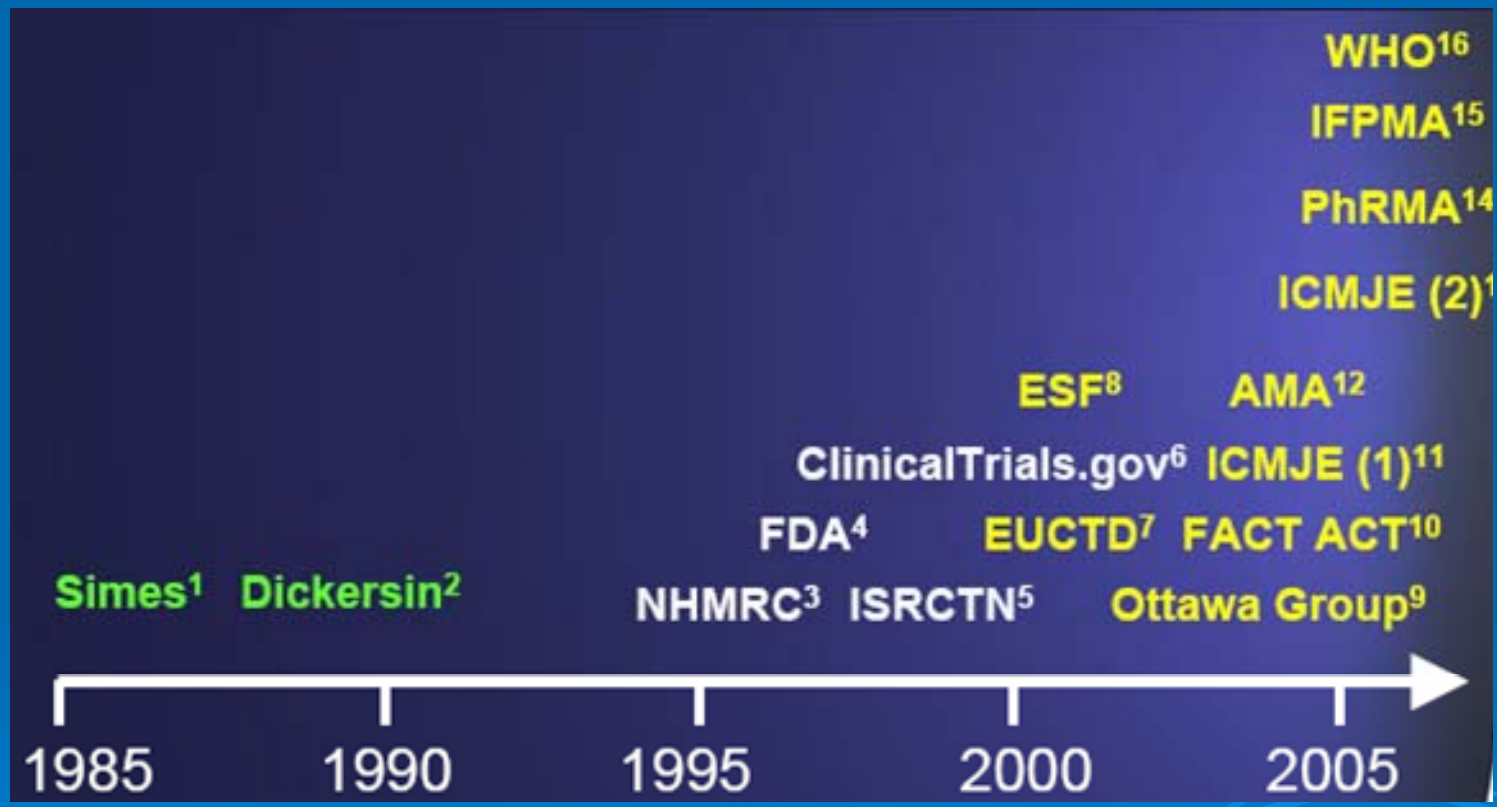
- increase participation in clinical trials
- contribute to systematic reviews
- speed access to results
- increase effectiveness of research funding
- impending increase in number of trials
- improve access to research information

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)

od and Drug Administration Modernization Act (FDAMA) Section 113 and ClinicalTrials.gov - Microsoft Internet Explorer

Edit View Favorites Tools Help

Back Search Favorites

ss http://www.fda.gov/oashi/clinicaltrials/section113/default.htm Go Links

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA

Food and Drug Administration Modernization Act (FDAMA) Section 113 and ClinicalTrials.gov

In November 1997, Congress included a provision in the Food and Drug Modernization Act to mandate that the National Institutes of Health (NIH) establish, maintain, and operate a public resource for information on efficacy studies of drugs.

ClinicalTrials.gov

The NIH, through its National Library of Medicine (NLM), with input from the FDA and others, developed the Clinical Trials Data Bank, a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other

The NIH (through NLM), with input from the FDA and others, developed the Clinical Trials Data Bank, a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions. First made available to the public via the Internet on February 29, 2000. At that time, the data bank, known as ClinicalTrials.gov included primarily NIH-sponsored trials.

FDA's Office of Special Health Issues undertook a multifaceted project to educate sponsors of investigational new drug applications about FDAMA Section 113 and to assess sponsor compliance with the law. The report describes methods used during various components of the

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ISRCTN REGISTER

Our URL has recently changed to: http://isrctn.org - please bookmark this page.

The ISRCTN is a simple numeric system for the unique identification of randomised controlled trials worldwide. The ISRCTN Register also accepts registration of other forms of studies designed to assess the efficacy of health-care interventions.

Search | Apply for ISRCTN | FAQs

The ISRCTN Register is owned by ISRCTN - a not-for-profit organisation. The scheme is administered on

ISRCTN REGISTER

- Trial registration
- Unique identification scheme
- International databases

Find trials
ISRCTN Register
tips on searching

Registration
apply for ISRCTN

Information
introduction
governing board
ISRCTN FAQs
data set
letter of agreement
request information
guidance notes

Publish your protocol

International Standard Randomised Controlled Trial Number Register

Showing records: **1** to **10** of **58**

SEARCH FOR	RESULTS ORDER	DIRECTION	MAX RESULTS	
malaria	Date Assigned	Descending	10 per page	SUBMIT

RESULT PAGE

|< < 1 2 3 4 5 6 > >|

1	A randomised trial to assess the efficacy of arthemeter lumifantrine and dihydroartemisinin-piperquine in the treatment of uncomplicated malaria and its effects on transmission in Kenya	
	ISRCTN:	ISRCTN36463274
	Sponsor:	Royal Tropical Institute (KIT) (The Netherlands)
	Date assigned:	01 February 2007
2	The GAMetocyticidal activity of sulphadoxine-pyremthamine plus artesunate followed by a single dose of PrimaQuine	
	ISRCTN:	ISRCTN61534963
	Sponsor:	The Netherlands Foundation for the Advancement of Tropical Research (NWO-WOTRO) (The Netherlands)
	Date assigned:	04 December 2006
3	Iron fortification and parasite control to reduce anaemia among schoolchildren in Cote d'Ivoire	
	ISRCTN:	ISRCTN21782274

ISRCTN News

- 23 Oct 2006: ISRCTN records can now be accessed directly from relevant PubMed abstracts
- 6 Sep 2006: Country of trial has been added to the data items required for trial registration with the ISRCTN
- 19 May 2006: WHO announces 20 data items required for trial registration
- 01 March 2006: ISRCTN is pleased to announce the current membership of its Governing Board
- 10 Jan 2006: ISRCTN Register is open to other study designs apart from randomised controlled trials

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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

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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."

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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

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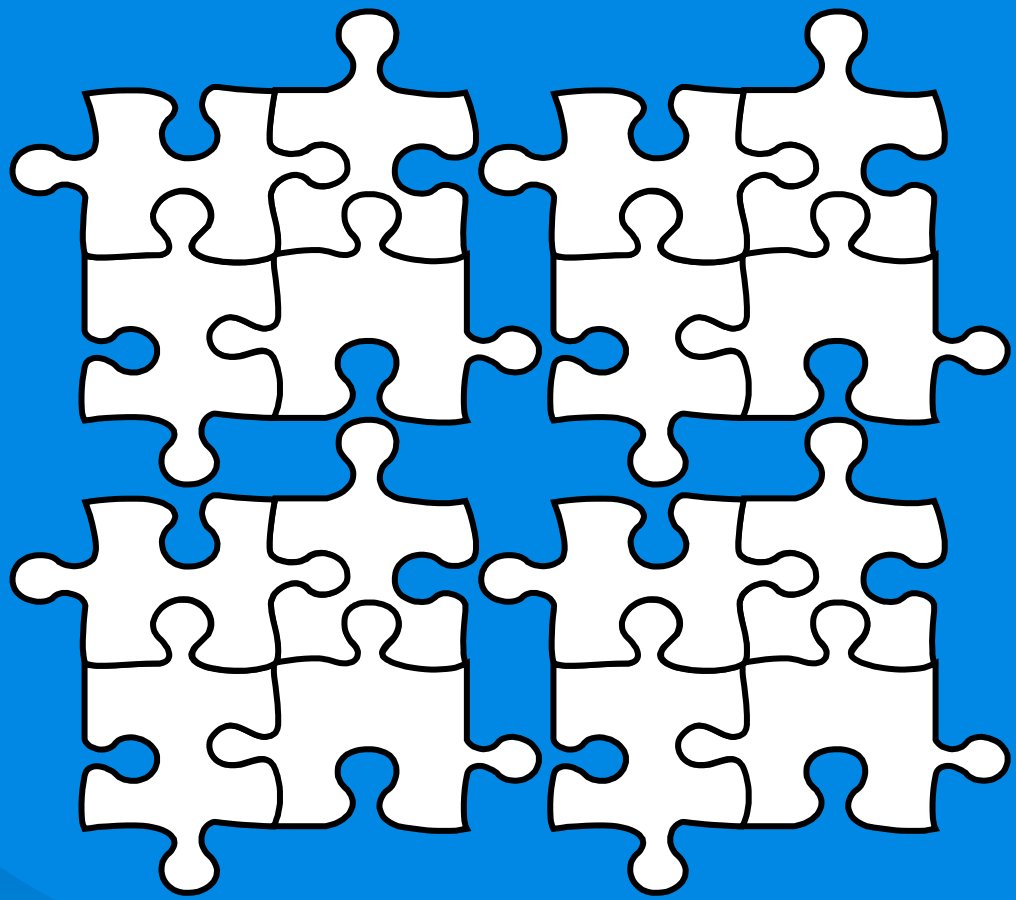
58th WHA Resolution (2005)

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"*

Platform



"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
WHO Director-General

Opening Address to the World Health Assembly
May 16, 2005

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

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

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

Example
Compliance on clinicaltrials.gov

Table 2. Number and Disposition of Records from Industry Providers for Interventional Trials with Nonspecific Entries in the "Intervention Name" Field.

Provider*	May 20, 2005	Interval Period (May 20–Oct. 11, 2005)				Oct. 11, 2005
	Records with Nonspecific Entries	Records Corrected with Addition of Company Serial Number	Records Corrected with Addition of Drug Name	Records Not Corrected	New Records with Nonspecific Entries	Records with Nonspecific Entries
	no./total no. of trials		*no.*		*no./total no. of trials*	
Merck	120/132	25	94	1	0/52	1/184
GlaxoSmithKline	53/104	2	4	47	1/128	48/232
Pfizer	22/75	2	2	18	14/224	32/299
Lilly	3/96	0	0	3	0/136	3/232
Other industry	0/1619	0	0	0	0/1849	0/3468
Total	198/2026	29	100	69	15/2389	84/4415

* Specific providers are listed in descending order of the number of nonspecific records as of May 20, 2005.

Note: Non-specific did not provide "clinically meaningful insight"

Table 3. Use of the "Primary Outcome Measure" Field by 20 Drug Companies from May 20 through October 11, 2005.

Rank According to U.S. Drug Sales*	Company	No. of Records with Primary Outcome Measure	Total No. of Records	Percentage of Records with Primary Outcome Measure
1	Pfizer	221	224	99
2	GlaxoSmithKline	63	66	95
3	Johnson & Johnson	57	63	90
4	Merck	9	46	20
5	AstraZeneca	51	52	98
6	Novartis	8	239	3
7	Amgen	65	70	93
8	Sanofi–Aventis	19	45	42
9	Bristol-Myers Squibb	53	60	88
10	Lilly	121	136	89
11	Wyeth	53	53	100
12	Abbott	19	34	56
13	Hoffmann–La Roche	0	13	0
14	TAP Pharmaceutical	22	22	100
15	Boehringer Ingelheim	48	48	100
16	Teva (Teva Neuroscience)	14	14	100
17	Schering-Plough	1	11	9
18	Forest Laboratories	1	1	100
19	Eisai	31	35	89
20	Watson	15	15	100
Total for the 20 companies		871	1247	70

* Data on rank according to volume of U.S. sales are from IMS Health.[23]

Aim: to determine patterns of completion for the field termed "Primary Outcome Measure"

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

- 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

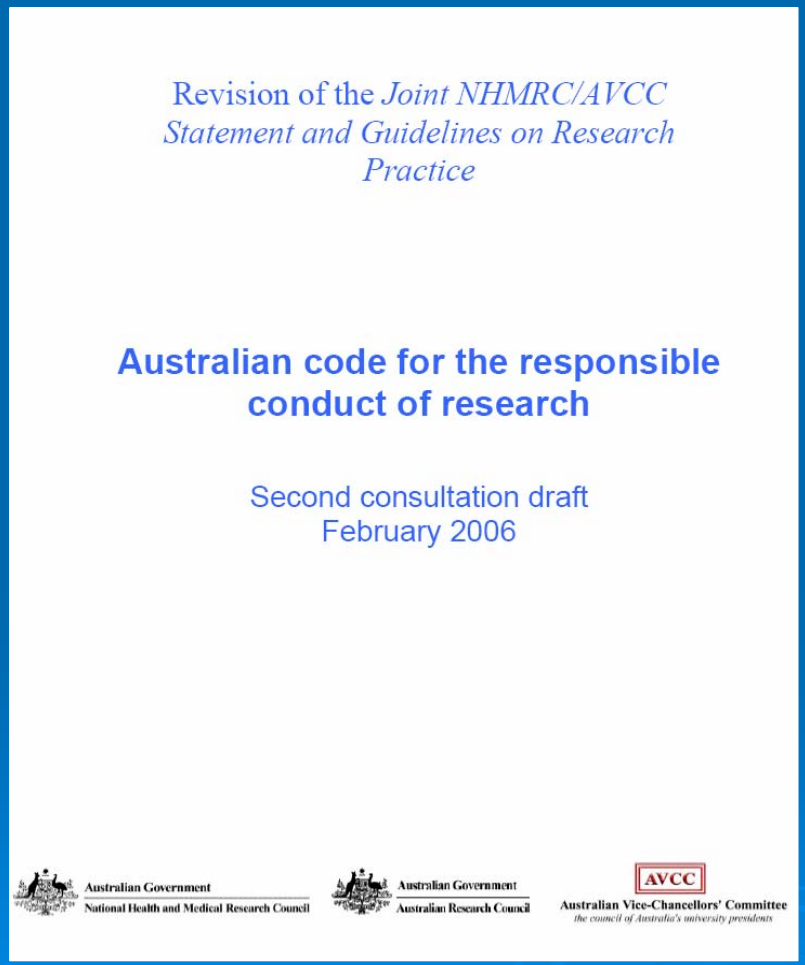
January 2006

Australian Government
National Health and Medical Research Council

Australian Government
Australian Research Council

AVCC
Australian Vice-Chancellors' Committee
the council of Australia's university presidents

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

Fair Access to Clinical Trials (FACT) Act (dated January 31, 2007)

Enhancing Drug Safety and Innovation Act (known as the Enzi-Kennedy Bill)

State-based legislation (eg State of Maine, California, New Jersey, Hawaii)

- If successful, the FACT legislation will require registration as a condition of Institutional Review Board (IRB) approval in the United States

FACT act

It is the purpose of this Act-

- (1) to create a publicly accessible national data bank of clinical trial information comprised of a clinical trial registry and clinical trial results database;
- (2) to foster transparency and accountability in health-related intervention research and development
- (3) to maintain a clinical trial registry accessible to patients and health care practitioners seeking information related to ongoing clinical trials for serious or life-threatening diseases and conditions; and
- (4) to establish a clinical trials results database of all publicly and privately funded clinical trial results regardless of outcome, that is accessible to the scientific community, health care practitioners, and members of the public.

Challenge 3: unambiguous identification

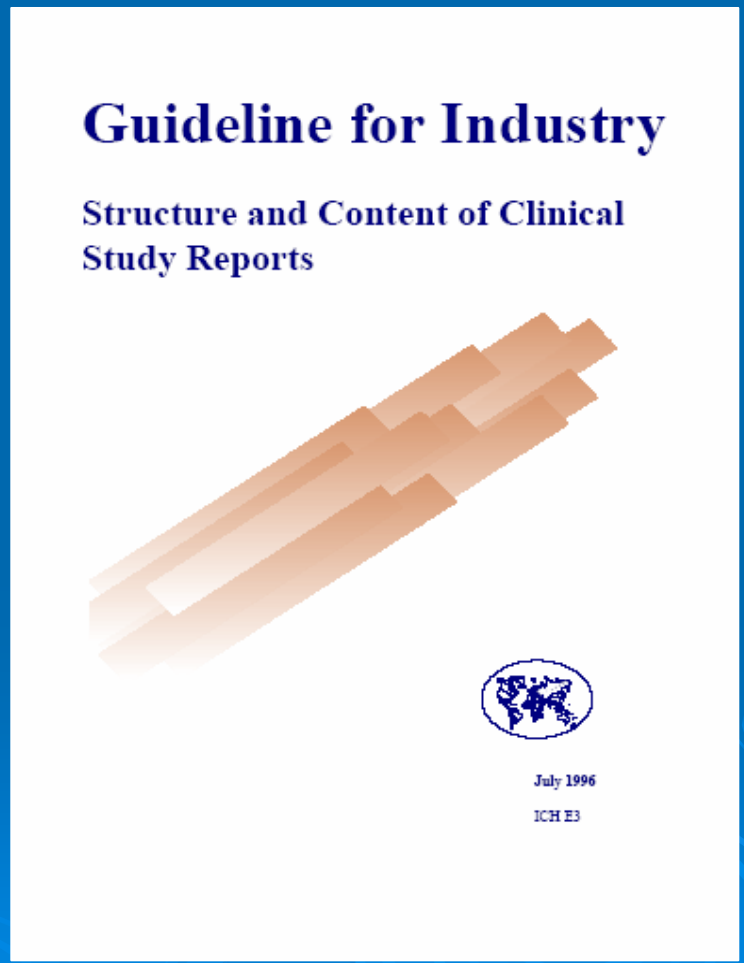
- Multiple registration of single trials
  - Within single registers
  - Across registers
- Collaboration across registers
  - WHO Register Network

Challenge 4: Multiplicity

- Multiple registers require multiple searches to identify trials
- WHO Search Portal

Challenge 5: Results disclosure

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

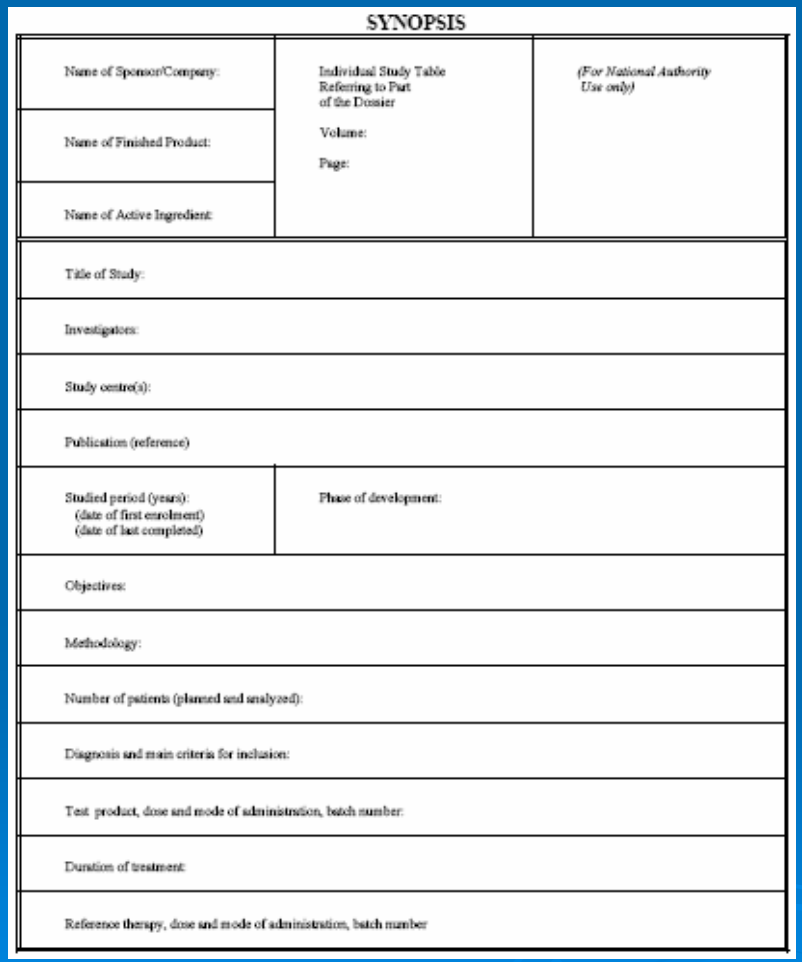


Results reporting:
An ethical responsibility

" 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."

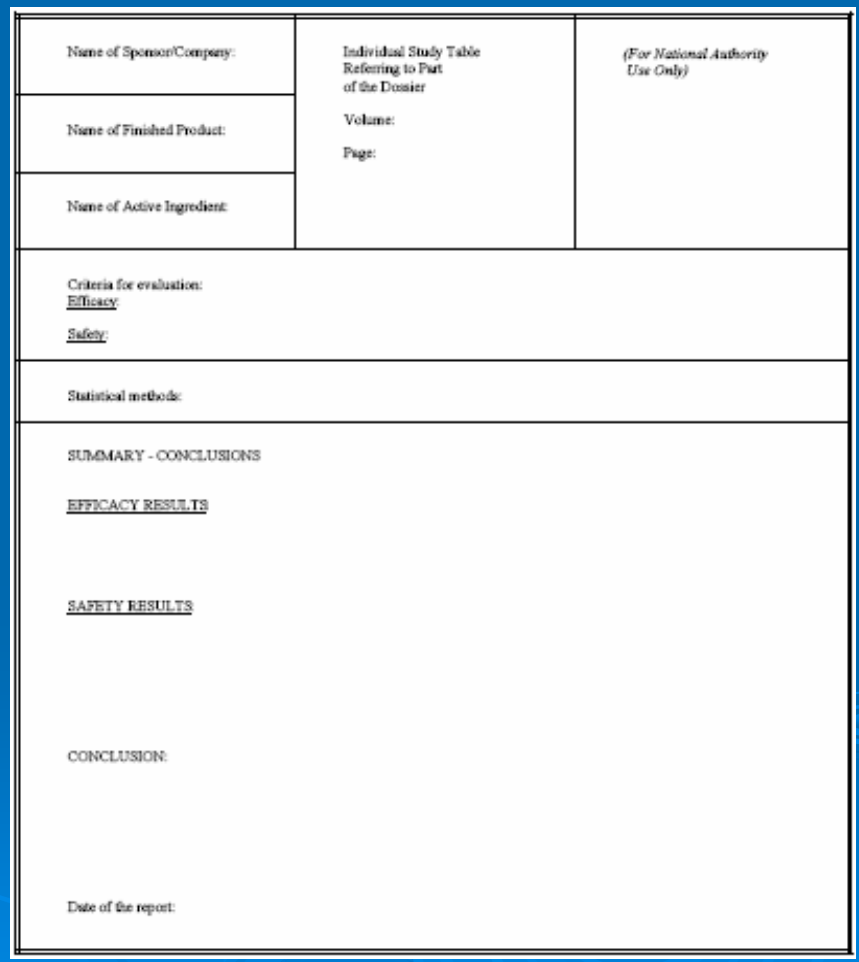
Declaration of Helsinki

ICH E3 synopsis



SYNOPSIS

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

Bristol-Myers Squibb

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Protocol Information for new or existing Bristol-Myers Squibb sponsored trials >>

Clinical Trial Results
Clinical Trial Results from completed Bristol-Myers Squibb sponsored clinical trials >>

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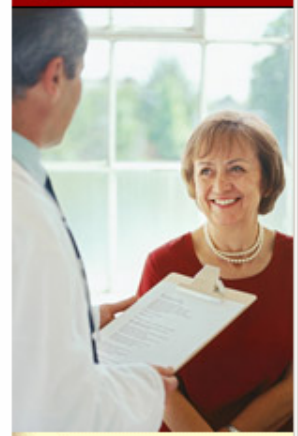

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