World Health Organization

Why Register Clinical Trials?

Davina Ghersi

Coordinator, WHO International Clinical Trials Registry Platform

Training Course in Sexual and Reproductive Health Research

Geneva 2009

Why register trials

- To improve transparency and accountability
- It is an ethical responsibility
- To improve public trust
- To address publication bias and selective reporting
- To identify gaps
- To build research infrastructure and capacity

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An ethical responsibility

Why register trials?

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

WHO ICTRP Secretariat, Nov 2005

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

- *Includes Phase I to Phase IV trials*

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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

Declaration of Helsinki 2008

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

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Declaration of Helsinki 2008

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Public trust

The science behind the human guinea pig d

Two still critical and questions to answer

By Chris Williams → More by this author
Published Monday 20th March 2006 16:15 GMT
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The race is on to nail down the cause of the catastrophi

Doctors at Northwick Park Hospit
who have shown
support.
last Monday and very quickly showed an ad
went down like dominoes."

Questions are now being asked about why potential problems with the
inflammatory response.

A TeGenero statement says: "The drug was tested extensively in labo
drug-related adverse events and there were no drug-related deaths."

Patients: Oklahomans used as human 'guinea pigs'

2003 7:33 AM

may have used Oklahomans as human

In late 1996 a Tulsa doctor concocted a vaccine designed to fight deadly skin cancer. Sources close to the doctor say he believed in his research. He tested it on about 100 people, mostly Oklahomans, some of whom now believe that research nearly killed them.

Five years ago, Jeff Teel was diagnosed with deadly skin cancer. Doctors gave him a 20 percent chance of survival.

"I mean, I was petrified," he said, "thinking I was going to die."

Surgeons removed a portion of Jeff's arm, but the likelihood of a cancer comeback was high and Jeff thought his best chance was an investigational new drug.

TGN1412 drug trial update: One patient may lose fingers and toes due to drug side effects

Tots Used as Human Guinea Pigs?

May 17, 2006 9:35 AM

Joseph Rhee Reports:

ABC News has learned that a Massachusetts hospital is currently recruiting pre-schoolers to test the safety and effectiveness of a powerful antipsychotic drug called Quetiapine.

The study, conducted by the Department of Pediatri
Psychopharmacology at Massachusetts General Hos
testing subjects from four to six years of age with Bi
Disorder. An earlier Massachusetts General study of
antipsychotic drugs Risperidone and Olanzapine rec
children as young as three years old.

Big Pharma Research Racket Is Killing People

THURSDAY, OCTOBER 18, 2007

Two Million Human Guinea Pigs

Merck announced recently that patients have filled two milli
prescriptions for its new diabetes drug Januvia.

Wall Street Journal "Diabetes Drug Wins New Uses

It also announced that new and potentially worrisome side e
have turned up, all relating to the immune system, including
rashes and swelling and one potentially fatal condition, Steve
Johnson syndrome, where the skin literally peels off the bod

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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)

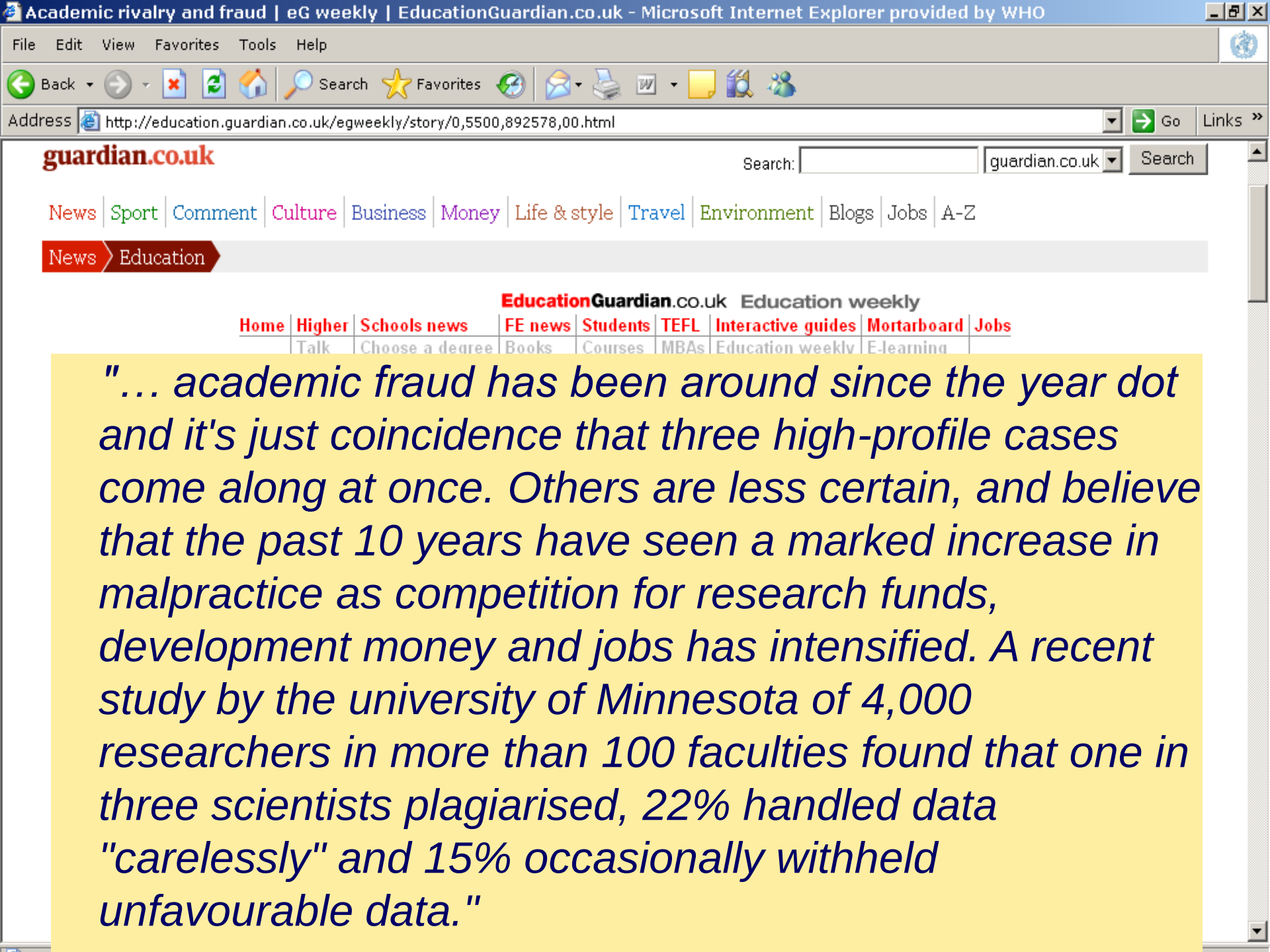
doi:10.1136/bmj.330.7502.0-g

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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Talk Choose a degree Books Courses MBAs Education weekly E-learning
"… academic fraud has been around since the year dot and it's just coincidence that three high-profile cases come along at once. Others are less certain, and believe that the past 10 years have seen a marked increase in malpractice as competition for research funds, development money and jobs has intensified. A recent study by the university of Minnesota of 4,000 researchers in more than 100 faculties found that one in three scientists plagiarised, 22% handled data "carelessly" and 15% occasionally withheld unfavourable data."

Publication bias

Publication bias

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

Selective reporting

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

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"Publication bias has been a perennial concern of reviewers and evidence-based practitioners, but a recent series of events has provided a disturbing example of the potentially serious effects of the failure to publish trial data or to make them available. It has emerged that trials of paroxetine, a selective serotonin reuptake inhibitor, showing negative or neutral results in the treatment of depressive disorders in children and adolescents have been not been published by the trials' sponsor, GlaxoSmithKline."

http://ebmh.bmj.com/cgi/content/full/7/4/98#R6

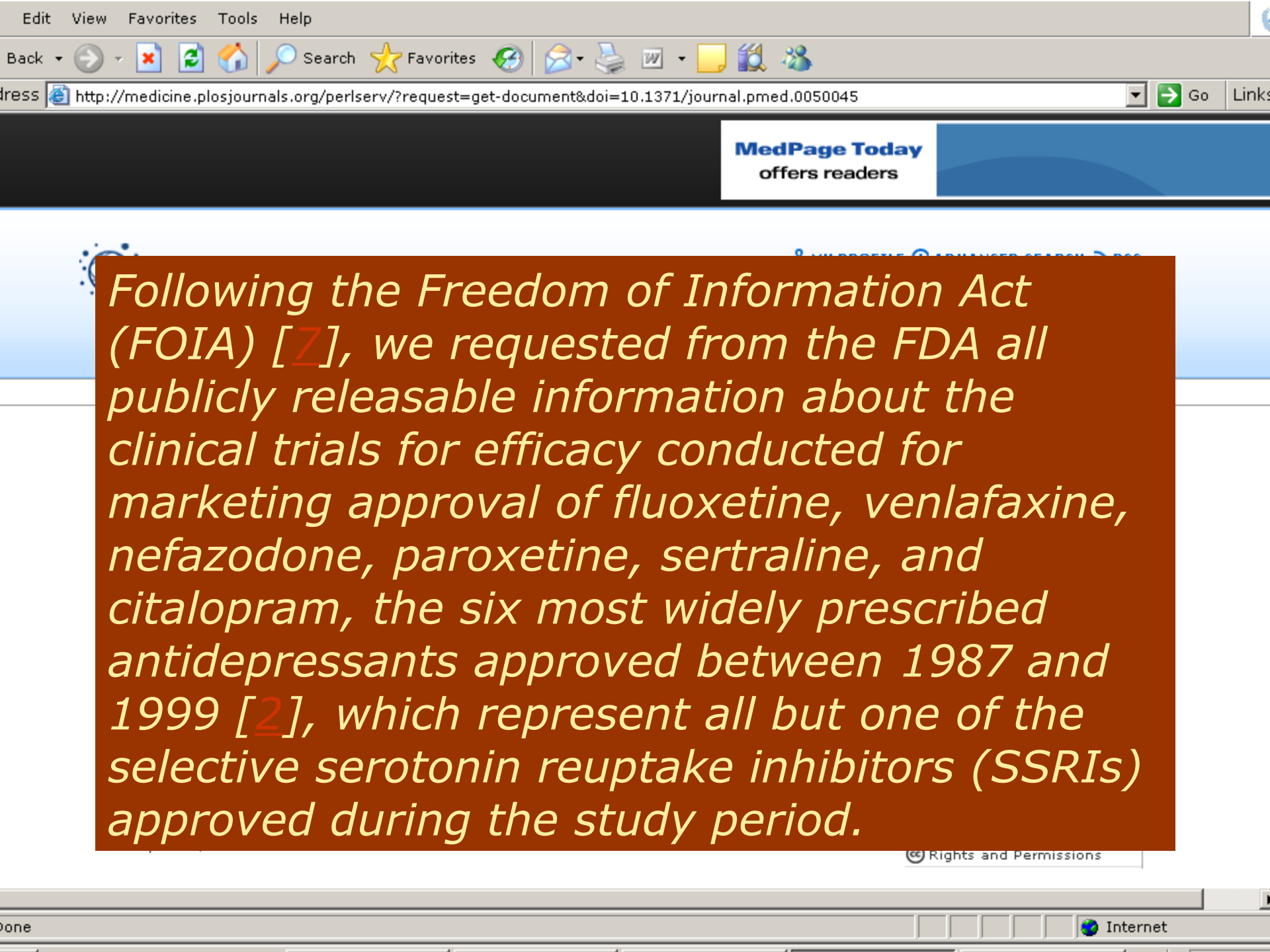
"Legal action against GSK over SSRI data"

CMAJ Canada's leading medical journal

"The New York State Attorney is suing GlaxoSmithKline (GSK) over its alleged failure to disclose important safety and efficacy information concerning the use of its antidepressant paroxetine (Paxil in North America and Seroxat in the UK) by people under 18."

"The concealed information "impaired doctors' ability to make the appropriate prescribing decision for their patients and may have jeopardized public health and safety," stated Attorney General Eliot Spitzer."

CMAJ • July 6, 2004; 171 (1). doi:10.1503/cmaj.1040982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http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050045
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Following the Freedom of Information Act (FOIA) [7], we requested from the FDA all publicly releasable information about the clinical trials for efficacy conducted for marketing approval of fluoxetine, venlafaxine, nefazodone, paroxetine, sertraline, and citalopram, the six most widely prescribed antidepressants approved between 1987 and 1999 [2], which represent all but one of the selective serotonin reuptake inhibitors (SSRIs) approved during the study period.
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Done
Internet

Kirsch et al 2008

"Conventional meta-analyses are often limited to published data. In the case of antidepressant medication, this limitation has been found to result in considerable reporting bias characterized by multiple publication, selective publication, and selective reporting in studies sponsored by pharmaceutical companies [5]."

THE HINDU

"Just 10 days after Kirsch's results were published, GlaxoSmithKline was found to have withheld clinical trial data from the United Kingdom regulator, the Medicines and Healthcare Regulatory Authority (MHRA), that showed that its anti depressant increased the risk of suicide among teenagers, and that it had known this since 1998."

25/3/2008

THE HINDU

"There are many voices in the scientific community calling for public disclosure of full sets of data for review to ensure independent evaluation of data.

Perhaps nowhere is this more relevant than in India, where the government courts investment from overseas companies in clinical trials and its own industries seek to develop new products.

As the subjects of much experimentation, Indians deserve to have the data generated from trials properly analysed."

"We …join the calls on our partners in the pharmaceutical industry to be more transparent and open about their trial data. Failing to do so means, at best, that ineffective treatments are widely used in patients and, at worse, can lead to unnecessary illness and even death if the reported risks of harms are underestimated."

http://ebmh.bmj.com/cgi/content/full/7/4/98#R6

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International Committee of Medical Journal Editors (ICMJE)

"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."

Indian J Med Res 127, February 2008, pp 104-105

Editorial

"It was unanimously decided that the editors have the responsibility to promote the registration of all clinical trials being conducted in India and to urge researchers to register their trials within a stipulated time, to make the clinical trial data transparent and to enable results to be published in good journals."

http://www.icmr.nic.in/ijmr/2008/february/editorial2.pdf

and to disclose details of the 20 mandatory items of the

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Chinese journal editors

- **Joint Statement of Establishing Chinese Clinical Trial Registration and Publication System**

- Chinese Clinical Trial Registration and Publication Collaboration (ChiCTRPC).

"We declare that, from January 1st 2007, the member journals of ChiCTRPC will publish clinical trials with unique register number superior to those who do not have. In future, only clinical trials with register number can be published in those journals. This schedule will be adjusted by members themselves."

Identify gaps

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Example

- AFRO and
  - Children = 100
    - And diarrhoea = 1
    - And pneumonia = 4

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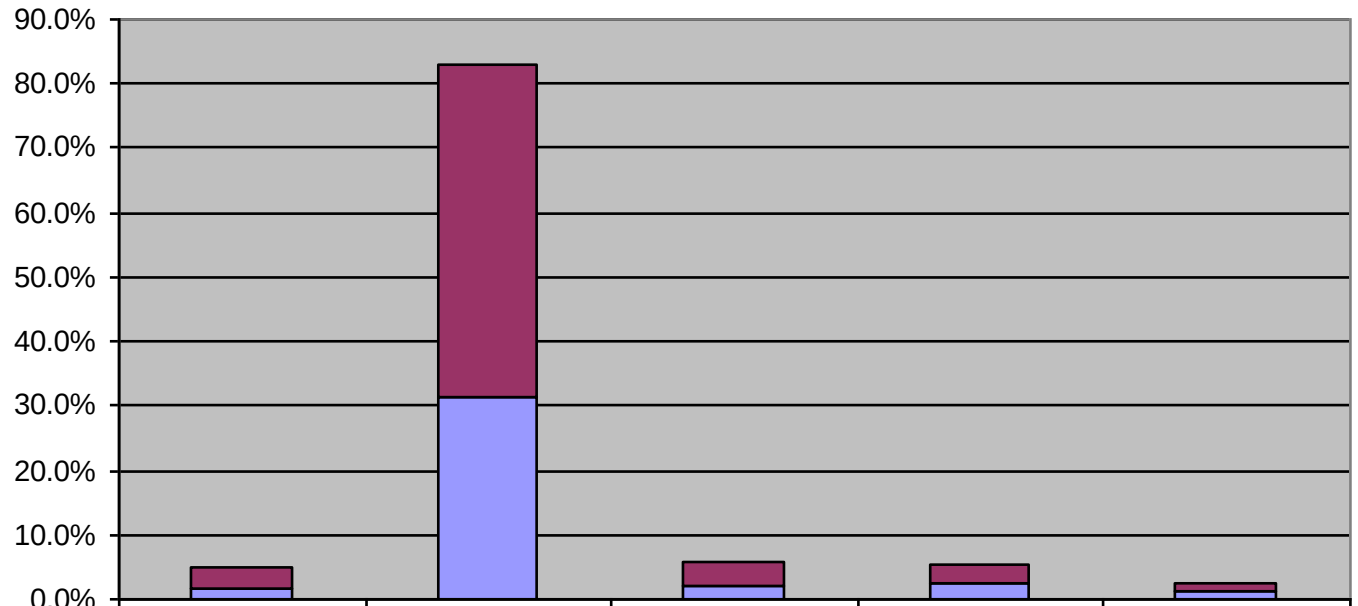
Registration rate by World Bank income level (Oct 13 2008)



	high income non OECD	OECD	upper middle	low er middle	low
%of all trials registered (not recruiting now)	3.1%	51.4%	3.7%	3.1%	1.4%
%of all trials registered (recruiting now)	1.8%	31.4%	1.9%	2.3%	1.1%

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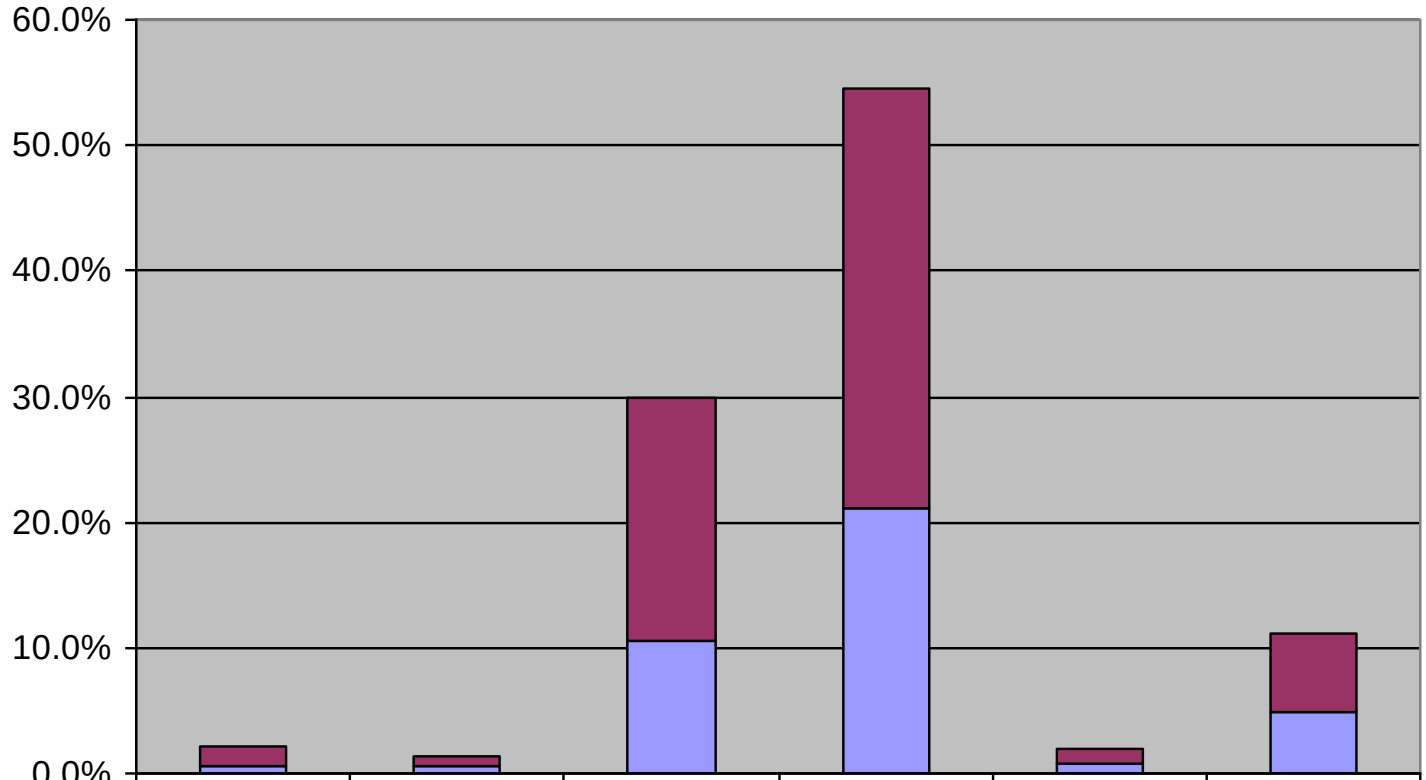
Registration rate by WHO region (Oct 13 2008)



	AFRO	EMRO	EURO	PAHO	SEARO	WPRO
%of all trials registered (not recruiting now)	1.5%	0.9%	19.3%	33.3%	1.1%	6.3%
%of all trials registered (recruiting now)	0.6%	0.5%	10.5%	21.2%	0.7%	4.8%

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At 21st October 2008…

On the WHO ICTRP clinical trials search portal:

- 469: the number of trials recruiting in AFRO countries
- 227: the number of trials registered so far this year that either are recruiting or have recruited participants in the AFRO region

Refer also status report

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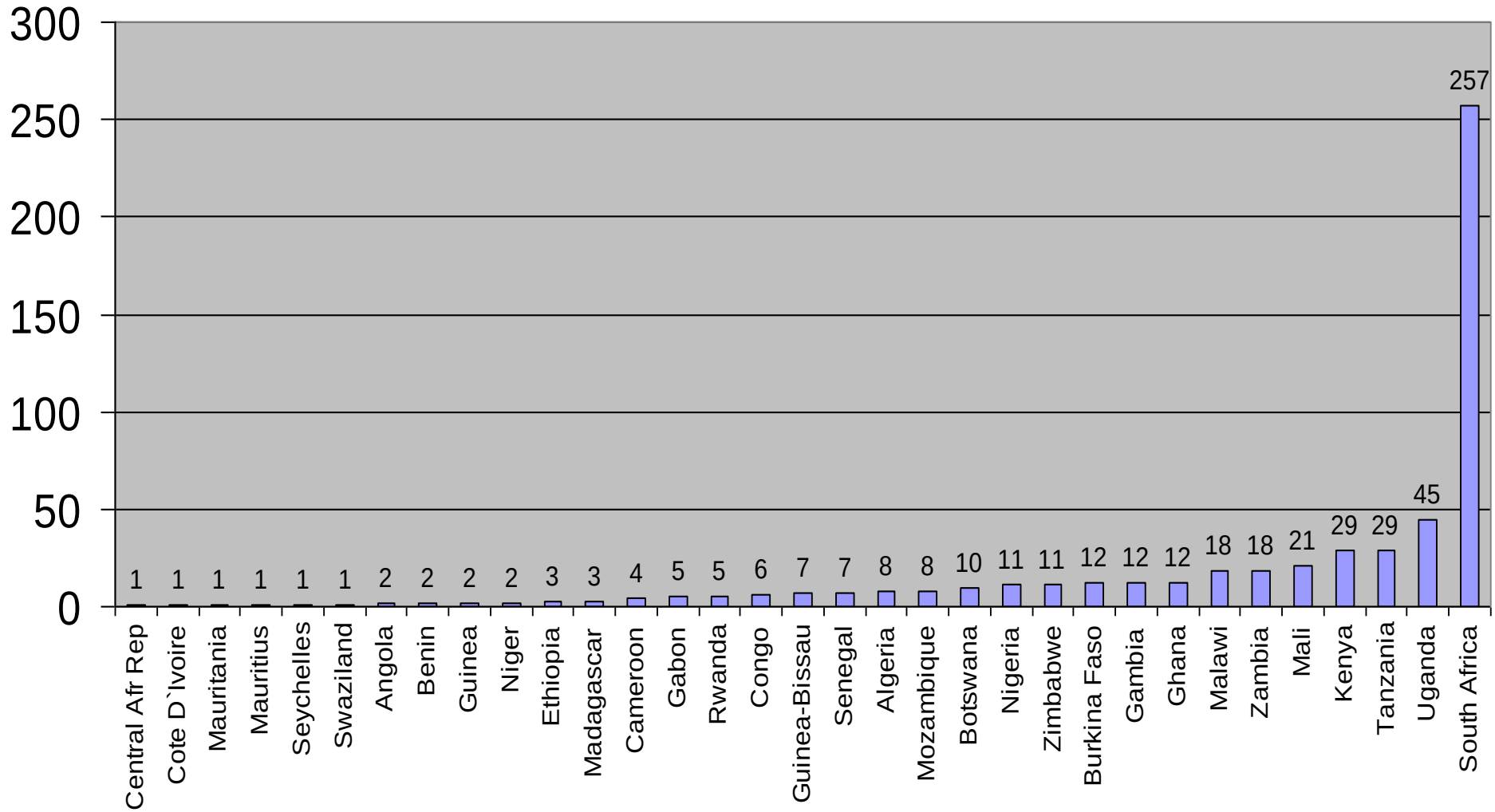
Recruiting at Oct 21 2008



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Research infrastructure

The Promise and Pitfalls of Clinical Trials Overseas -- Normile 322 (5899): 214 -- Science - Microsoft Internet Explo

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NEWS

The Promise and Pitfalls of Clinical Trials Overseas

Dennis Normile

Big pharma has big incentives, including cost savings and more powerful studies, to launch trials in developing countries. But can companies avoid the ethical potholes?

Queuing up. Clinical trials are coming to India--and elsewhere in Asia and Eastern Europe--drawn by low costs and diverse populations.

CREDIT: PALLAVA BAGLA

The results of the clinical trial were puzzling. Some lung cancer patients who received the experimental drug gefitinib several years ago showed almost no benefit; in other patients, tumors shrank so much that one researcher called it a "Lazarus type of response." After intense study, an answer to the riddle emerged: Tumors that respond to gefitinib have a mutation in a key protein affecting cell growth--a mutation common in Asians but rare in other races.

As a result, gefitinib, which is marketed as Iressa by AstraZeneca, is available only under special circumstances in North America, while in Asia it has become an established therapy for non-small cell lung cancer that fails to respond to other treatments. If AstraZeneca had done the initial trials in a global setting, "they might have made the Asian connection sooner and saved a lot of money and time," says Benny Zee, a biostatistician and director of the Comprehensive Cancer Trials Unit at the Chinese University of Hong Kong.

Differing ethnic responses to drugs is one of a host of reasons pharmaceutical companies are globalizing clinical

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Example: China

"The biggest infrastructure gaps in both countries are in trial know-how and ethical oversight."

Wu Taixing, ChiCTR

- Found that 207 of 2235 "randomized" trials reported in Chinese journals were randomized properly.

"Most authors of these reports lack an adequate understanding of rigorous clinical trial design".

Clinical Trials Registry - India (CTRI)

National Institute of Medical Statistics, Indian Council of Medical Research),
Ansari Nagar, New Delhi -110029 - India,Telephone: 91-11-26588803, 91-11-26588725
Fax: 91-11-26589635, Email: ctr.nims@gmail.com

UTRN.WHO	**TEMP UTR**
CTRI No.and Date	**CTRI/200**
Status of TrialWHO	**Open to r**
Last Verified onWHO	03-09-200
Last Updated onWHO	28-08-200
Contact Details:	sonika.sha

IDENTIFIERS

UTRN.WHO*	**TEMP UTRN 025648**
Public Title Study WHO*	This study will evalua prevent blood clots ir hospitalized for acute those of the standar safety of rivaroxaban
Scientific Title of StudyWHO*	MAGELLAN - Multicen for the Prevention Comparing rivaroxab
Secondary IDsWHO	**Secondary ID**: NCT00571649

REGULATORY APPROVALS

Ethics Committee*

Ethics Committee Name	Approval Status
Apollo Hospital	Approved
Narayana Hrudayalaya Institute Of Cardiac Sciences	Approved
K.E.M Hospital, Pune	Approved
PRS Hospital	Approved
Rabindranath Tagore Interantional Institute Of Cardiac Sciences	Approved
Care Hospital	Approved
Lokmanya Tilak Muncipal Government Hospital, Sion	Approved
S.A.L Hospital & Medical Institute	Approved
Bhagawan Mahaveer Jain Heart Centre	Approved
Baby Memorial Hospital	Approved

Regulatory Approval obtained from DCGI*	Obtained

METHODS

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Edwin Cameron, Supreme Court of Appeal

"It is especially important to recognize the thousands of women who globally have volunteered for clinical trials. They deserve our respect and thanks, and we owe them our partnered commitment to ensure that communities understand the benefits of clinical trials. For too long, fear and mistrust have characterized the way many look at clinical trials in Africa. By setting the highest ethical standards and guaranteeing the highest standard of healthcare to trial participants, we can build widespread support for clinical trials across the continent."

http://data.unaids.org/pub/Speech/2006/20060530_SP_ECameron%20Microbicides%20Apri%20l2006_en.pdf

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The official journal of the AMERICAN ASSOCIATION OF DIABETES EDUCATORS

The American Journal of Sports Medicine

Institution: World Health Organisation | Sign In via User Name/Password

Changing Clinical Practice Through Research: The Case of Delirium

Lisa Lacko

Yvonne Bryan

Lehigh Valley Hospital

Cheryl Dellasega

The Pennsylvania State University

Francis Salerno

The Pennsylvania State University

Promoting application of study findings to the clinical setting is a constant challenge for nurse researchers. This project used change theory to include staff RNs in a research study on delirium and to use relevant findings. The research hypothesis was: Staff nurses who use a standardized protocol will have improved ability to identify delirium in elderly hospital patients. Staff nurses on the intervention unit used this protocol to screen for delirium on all consenting inpatients 75 years of age and over, and control unit nurses continued using their standard assessment practices. Intervention unit nurses demonstrated an improved ability to identify the presence and absence of delirium, and voluntarily requested to continue using the protocol after the study was terminated. Use of a theoretical model to include nurses in the study promoted the successful conduct of the research and subsequent use of findings.

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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

Why is WHO involved?

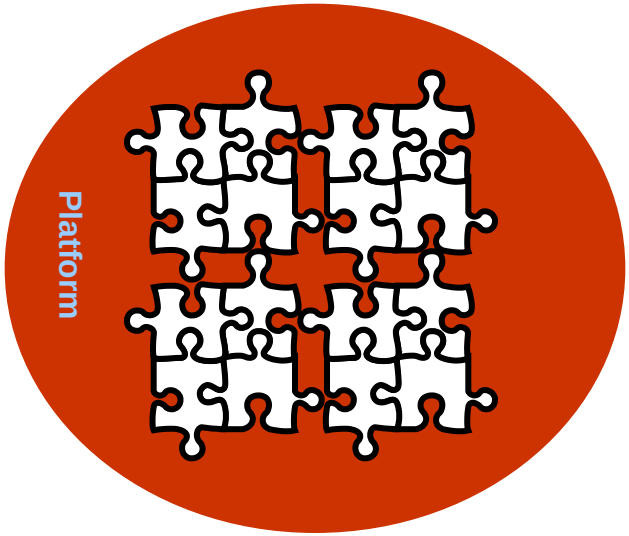
58th WHA Resolution (2005)

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"

The Registry Network

- AIM: to provide a forum for registries to exchange information and work together to establish best practice for clinical trial registration



WHO Primary Registries:

- ANZCTR (Australia)
- ChiCTR (China)
- CTR-I (India)
- ISRCTN (United Kingdom)
- NTR (Netherlands)
- SLTR (Sri Lanka)
- DKTR (Germany)
- JRN (Japan)

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What is a Primary Registry?

- Meet criteria for content, quality and validity, accessibility, unique identification, technical capacity and governance and administration
- Are managed by a not-for-profit agency.
- Have the support of government within the country / region for the proposed Primary Register to act as the Primary Register for the country / region
- Have the support of the ICMJE

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Address http://www.who.int/ictrp/network/primary/en/index.html Go
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International Clinical Trials Registry Platform (ICTRP)

About Registries

WHO Primary Registries

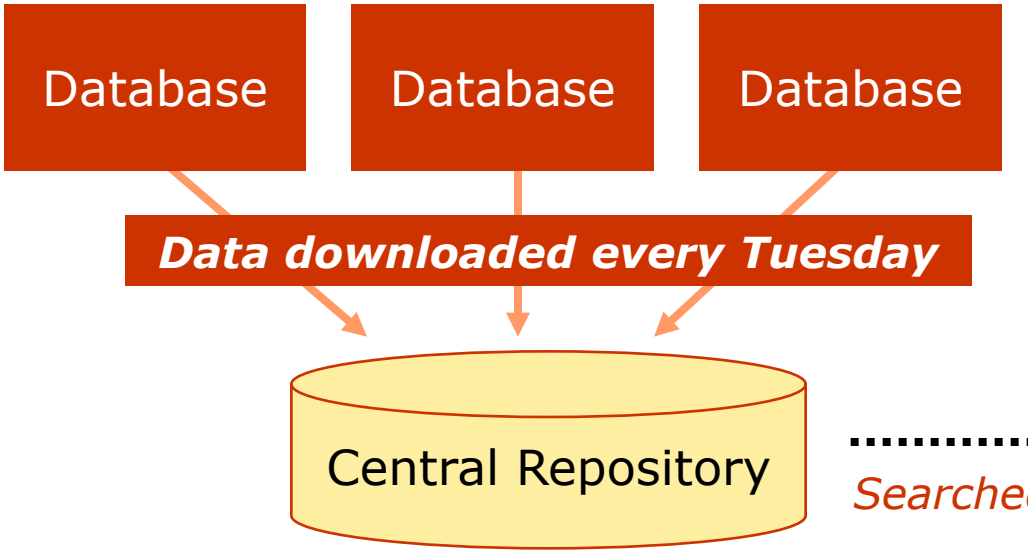
WHO Primary Registries meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. WHO Primary Registries meet the requirements of the ICMJE.

The registries that currently meet these criteria are:

Australian New Zealand Clinical Trials Registry (ANZCTR)	View Profile	Go to Website
Chinese Clinical Trial Register (ChiCTR)	View Profile	Go to Website
Clinical Trials Registry - India (CTRI)	View Profile	Go to Website
German Clinical Trials Register (DRKS)	View Profile	Go to Website
Iranian Registry of Clinical Trials (IRCT)	View Profile	Go to Website
ISRCTN.org	View Profile	Go to Website
Japan Primary Registries Network	View Profile	Go to Website (in Japanese) Network members: Go to UMIN Website Go to JapicCTI Website Go to JMACCT Website
The Netherlands National Trial Register (NTR)	View Profile	Go to Website
Sri Lanka Clinical Trials Registry (SLCTR)	View Profile	Go to Website

Done Local intranet

Search Portal model



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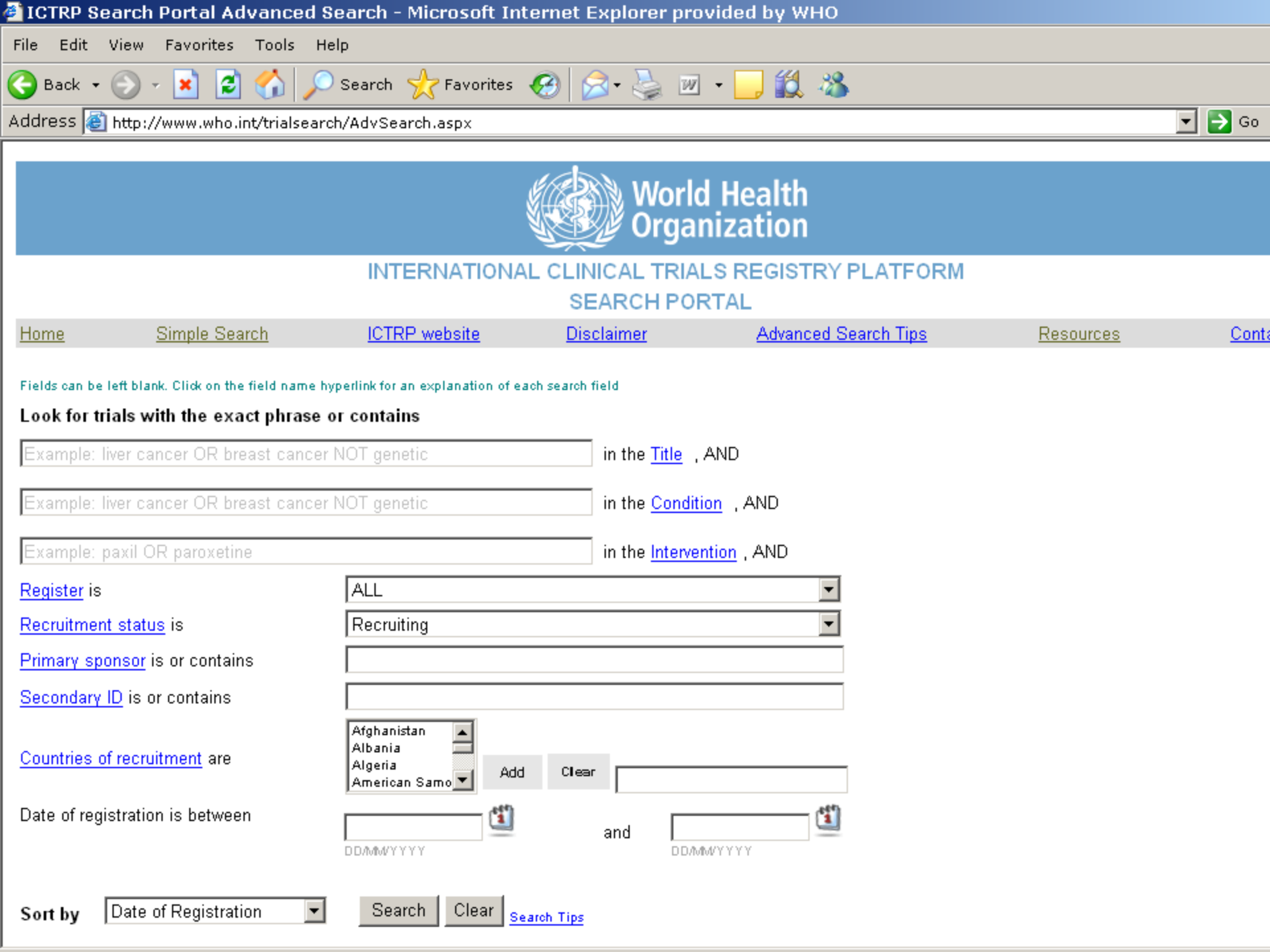
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SEARCH PORTAL
Home Simple Search ICTRP website Disclaimer Advanced Search Tips Resources Conta
Fields can be left blank. Click on the field name hyperlink for an explanation of each search field
Look for trials with the exact phrase or contains
Example: liver cancer OR breast cancer NOT genetic
in the Title , AND
Example: liver cancer OR breast cancer NOT genetic
in the Condition , AND
Example: paxil OR paroxetine
in the Intervention , AND
Register is
ALL
Recruitment status is
Recruiting
Primary sponsor is or contains
Secondary ID is or contains
Countries of recruitment are
Afghanistan
Albania
Algeria
American Samo
Add
Clear
Date of registration is between
DD/MM/YYYY
and
DD/MM/YYYY
Sort by
Date of Registration
Search
Clear
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Why integrate registration with regulation and ethical review?

Why integrate?

- Separate processes but shared information
  - There is an identifiable "core" data set
  - Eg patient population, description of the intervention, sites of recruitment (sites with ethics approval)
- Potential to build purpose-specific add-ons (or modules) to the core
  - Eg a module for ethics committees
  - Eg a module for regulators
- Improve efficiency
  - Developing separate systems to meet separate needs is resource consuming and would result in duplication

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Example: Brazil

- Trial registration is a legal requirement
- Trials must be registered before they are submitted to the regulatory authority (ANVISA)
- WHO trial registration data set to be included in the application form to be used by all ethics committees
  - Agreed to be CONEP: the national authority that coordinates the ethics committees and institutional review boards in Brazil
- The intention is for data to be fed automatically to the Brazilian Registry through ethics committees, then made available to ANVISA

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Example: Italy

- One of the first countries to make trial registration a legal requirement.
- Registration is achieved through electronic submission to Local Ethic Committees (LECs)
- All trials are registered at the National Monitoring Centre for Clinical Trials (OsSC)

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Example: USA

- Registration a legal requirement (FDAAA 2007)
- Data submitted directly to registry by trial sponsors