

Global opportunities and challenges
for trial registration:
Update from the WHO Registry Platform

October 26, 2006

An-Wen Chan, MD DPhil

Scientist

World Health Organization, Geneva

“All great truths begin as blasphemies.”

George Bernard Shaw

The Guardian
UK news

Glaxo faces drug fraud lawsuit

Firm accused of keeping back negative trial results

Trials Under Fire

UK News

Horror Drug Trial 'Shouldn't Have Happened'

Friday, 13th October 2006, 07:22

Cracking down on medical trials

Doctors need to have unbiased data on effectiveness of new drugs, says
ethicist *Arthur Schafer*



EDITORIALS

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

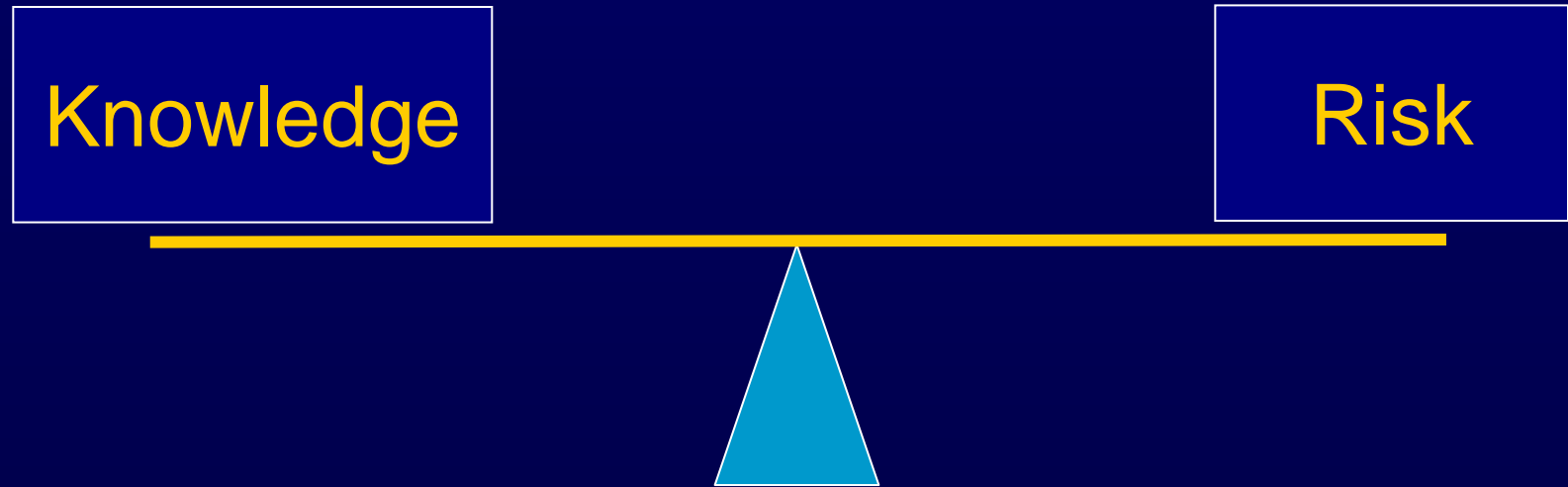
Research Misconduct, Retraction, and Cleansing the Medical Literature: Lessons from the Poehlman Case

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

Outline

- Background and overview
- Global challenges
- Global opportunities

Ethical obligations to participants

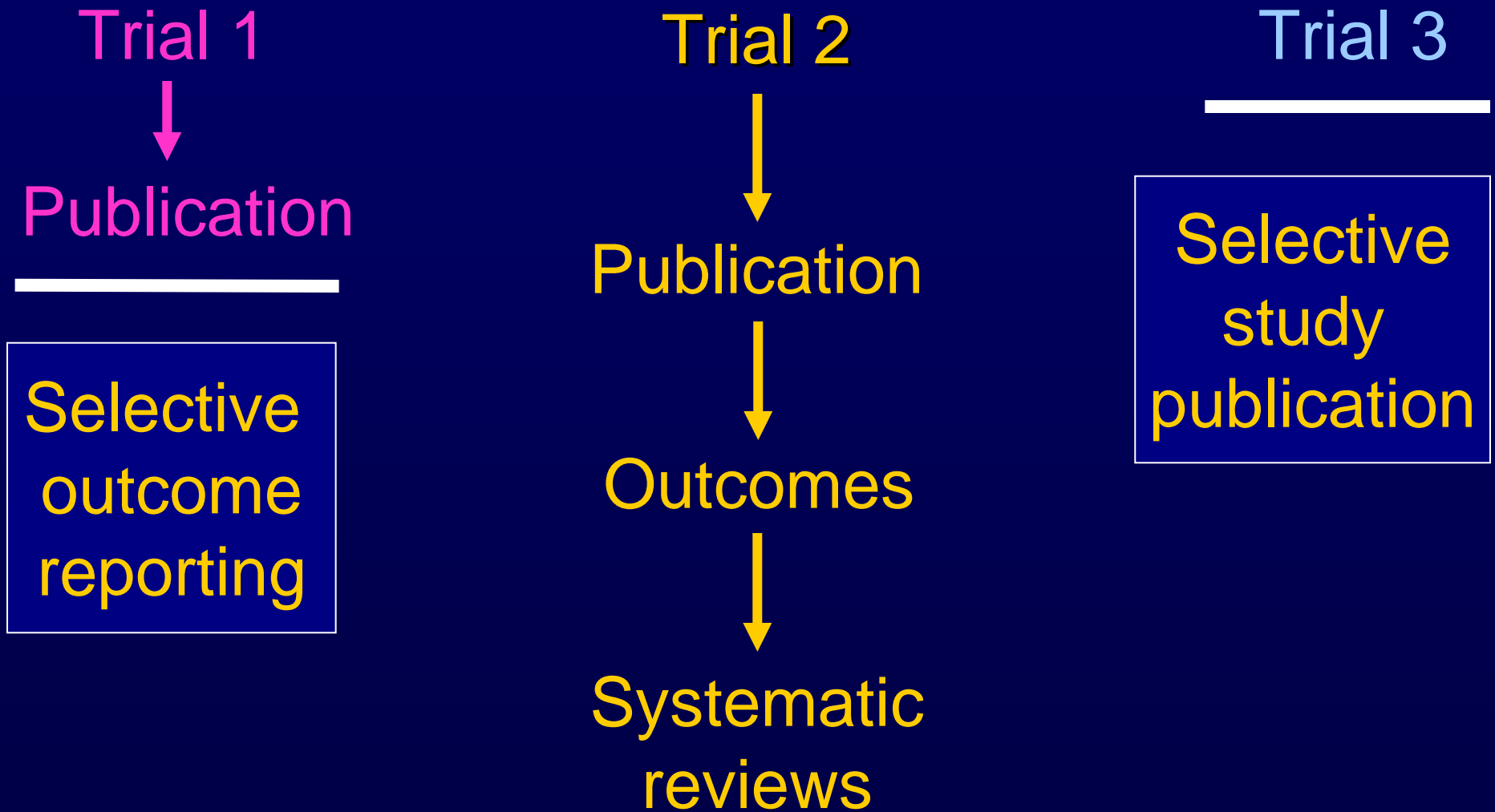


Declaration of Helsinki (2004)

“The design of all studies should be publicly available.”

“Negative as well as positive results should be published or otherwise publicly available.”

Access to trial information



Why is WHO involved?

- Global, neutral, independent body
- Authoritative role
- Capacity building
- Political legitimacy
- Commitment to global equity

Ministerial Summit on Health Research

□ Mexico City, November 2004

- 52 health ministers decided that WHO should:

- establish a network of trial registers
- ensure identification of all trials
- ensure a single website for access

Opening speech to World Health Assembly, May 2005



Dr J.W. Lee
Late Director-General

"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"

WHO International Clinical Trials Registry Platform

- Established in August 2005
- Will NOT create a WHO register
- Define a coordinated global network for trial registration and results reporting

Goal and objectives

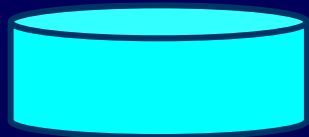
□ Overall Goal

- Strengthen public trust in clinical trials by promoting transparency & accountability

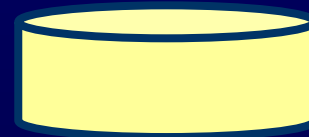
□ Objectives

- Registration of all clinical trials worldwide
- Disclosure of minimum set of results

WHO Registry Platform overview

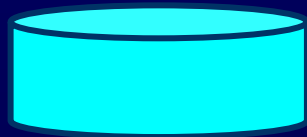


CT.gov, ISRCTN,
ACTR

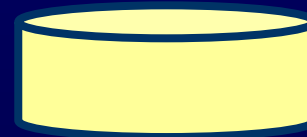


Registers

WHO Registry Platform overview



CT.gov, ISRCTN,
ACTR

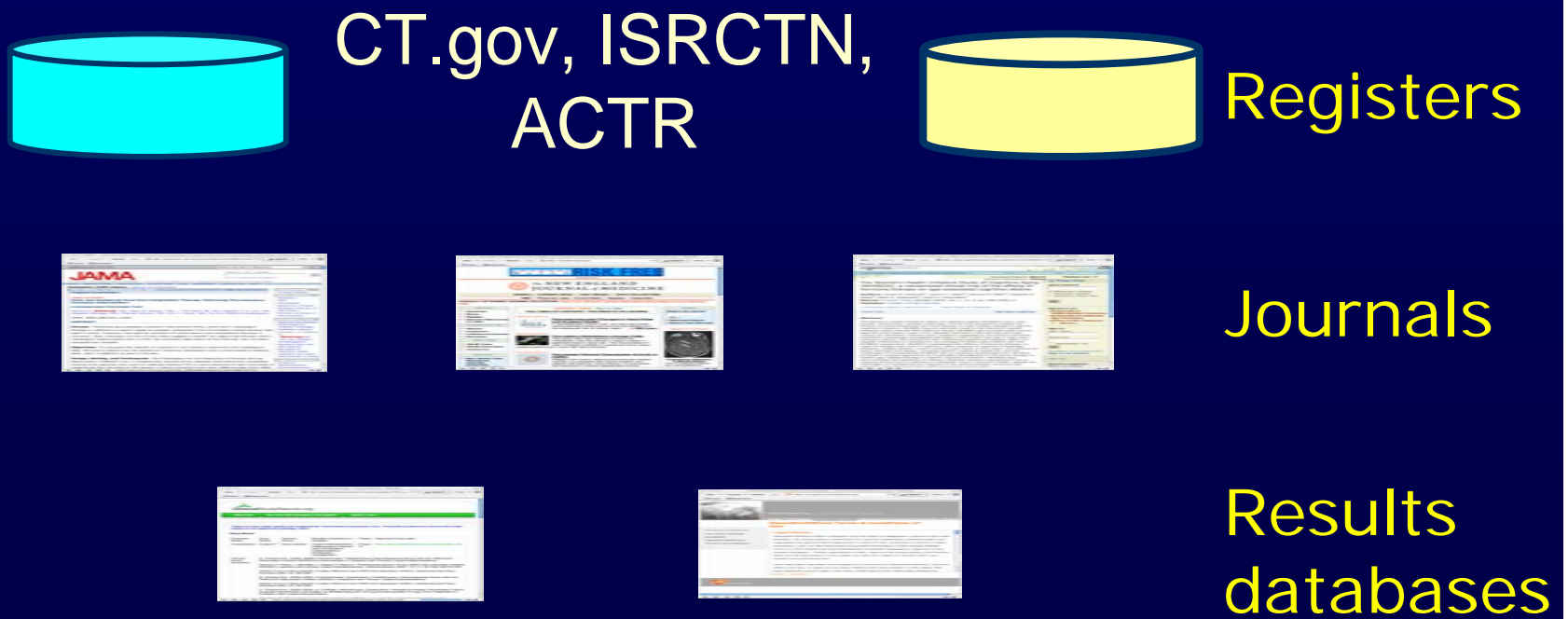


Registers



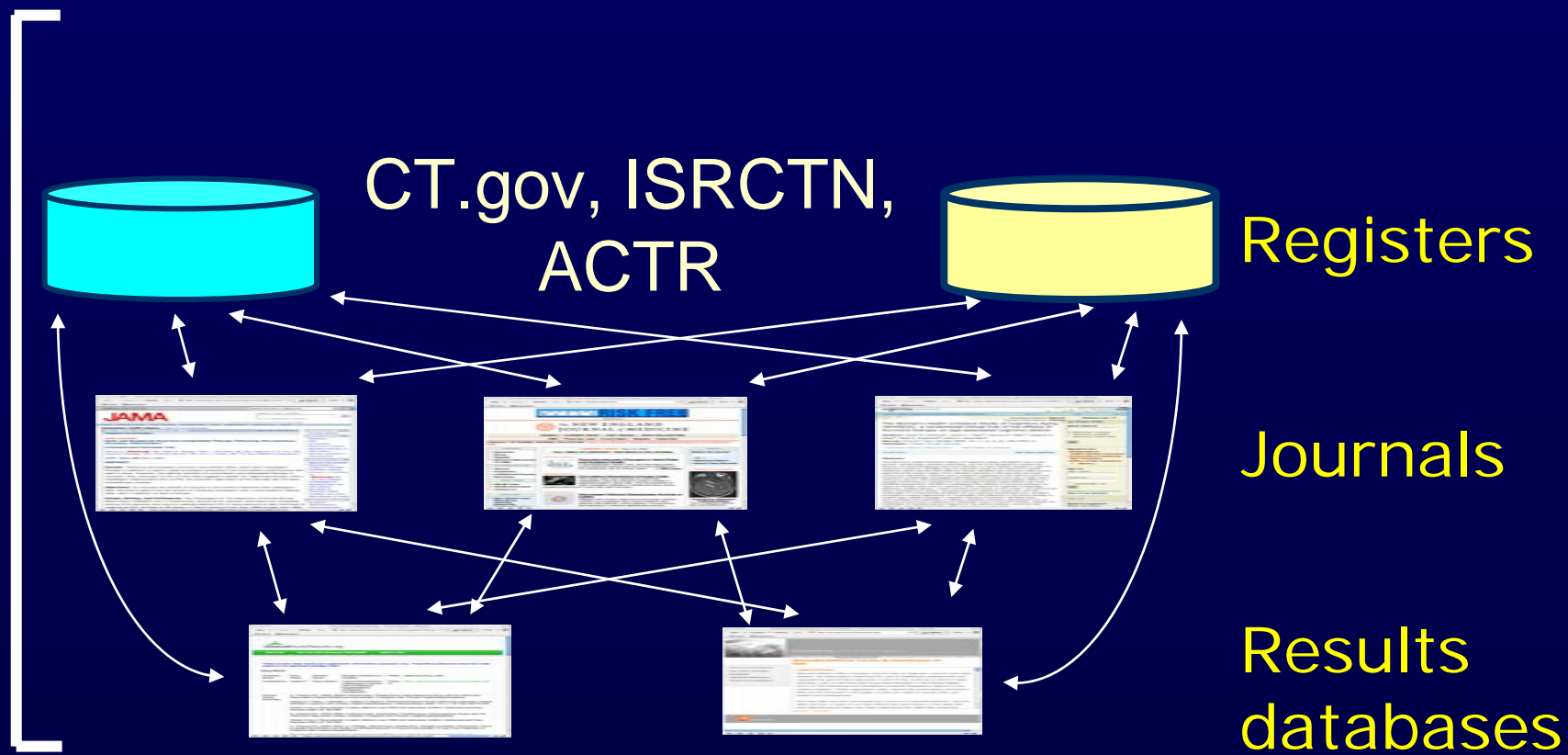
Journals

WHO Registry Platform overview



WHO Registry Platform overview

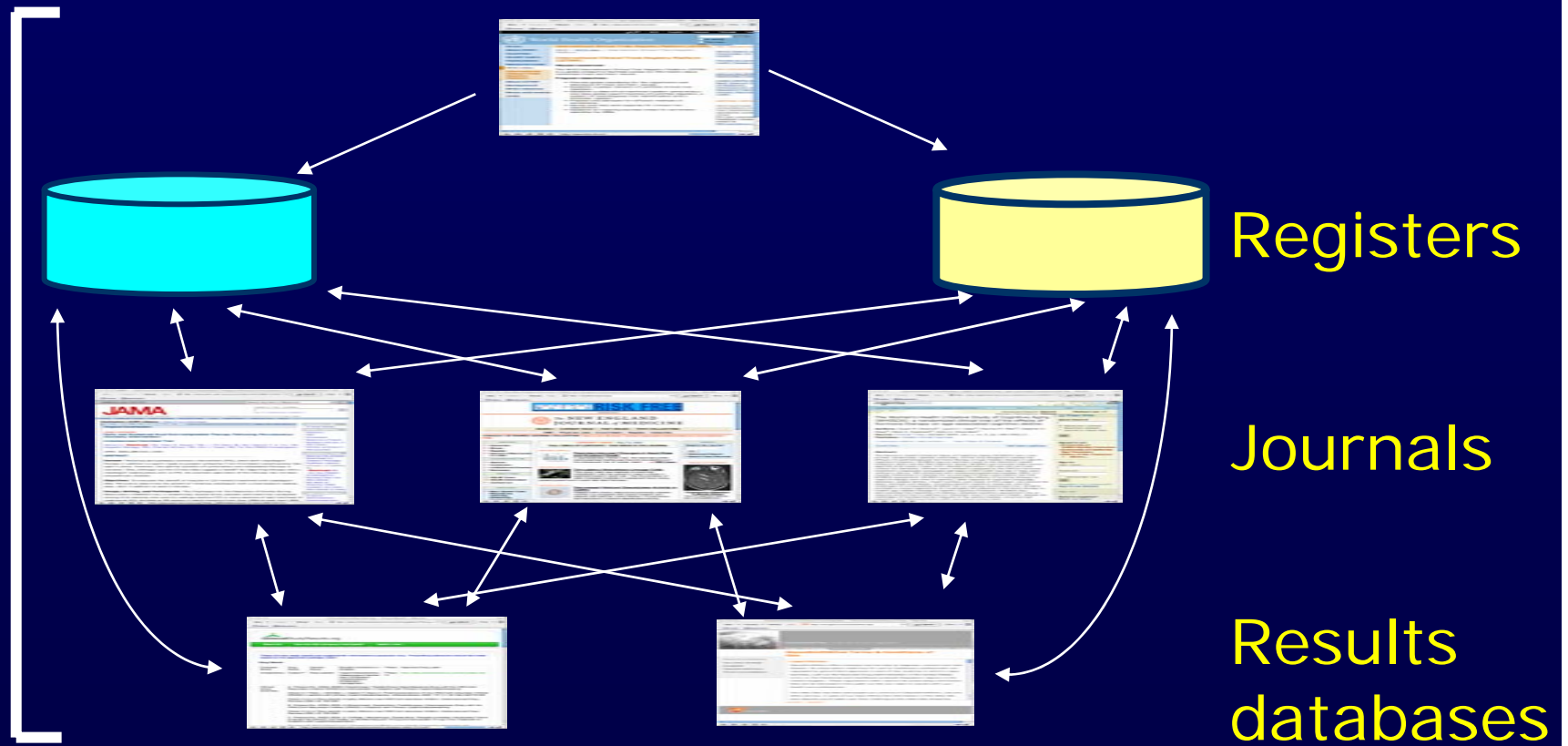
WHO Registry Platform



WHO Registry Platform overview

WHO Search Portal

WHO Registry Platform



Registers

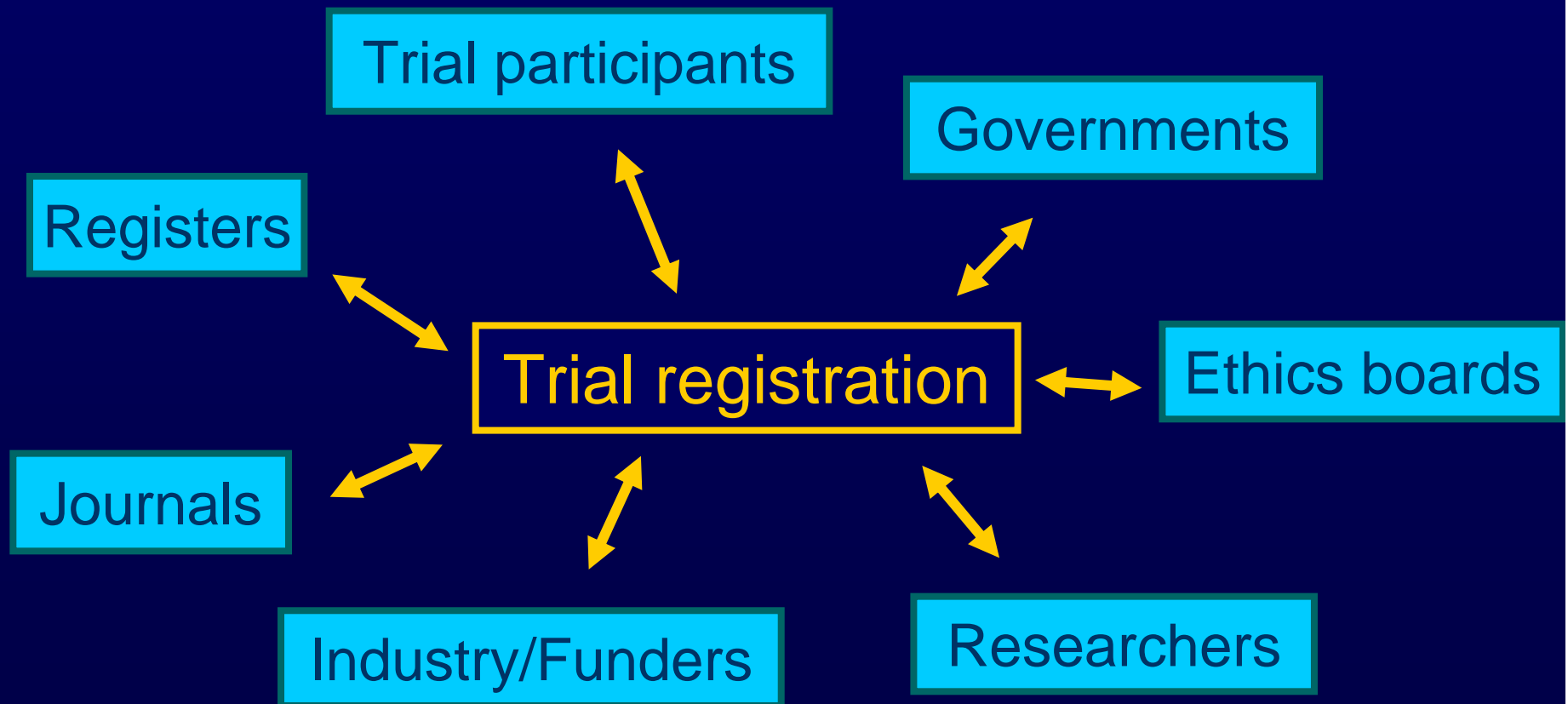
Journals

Results
databases

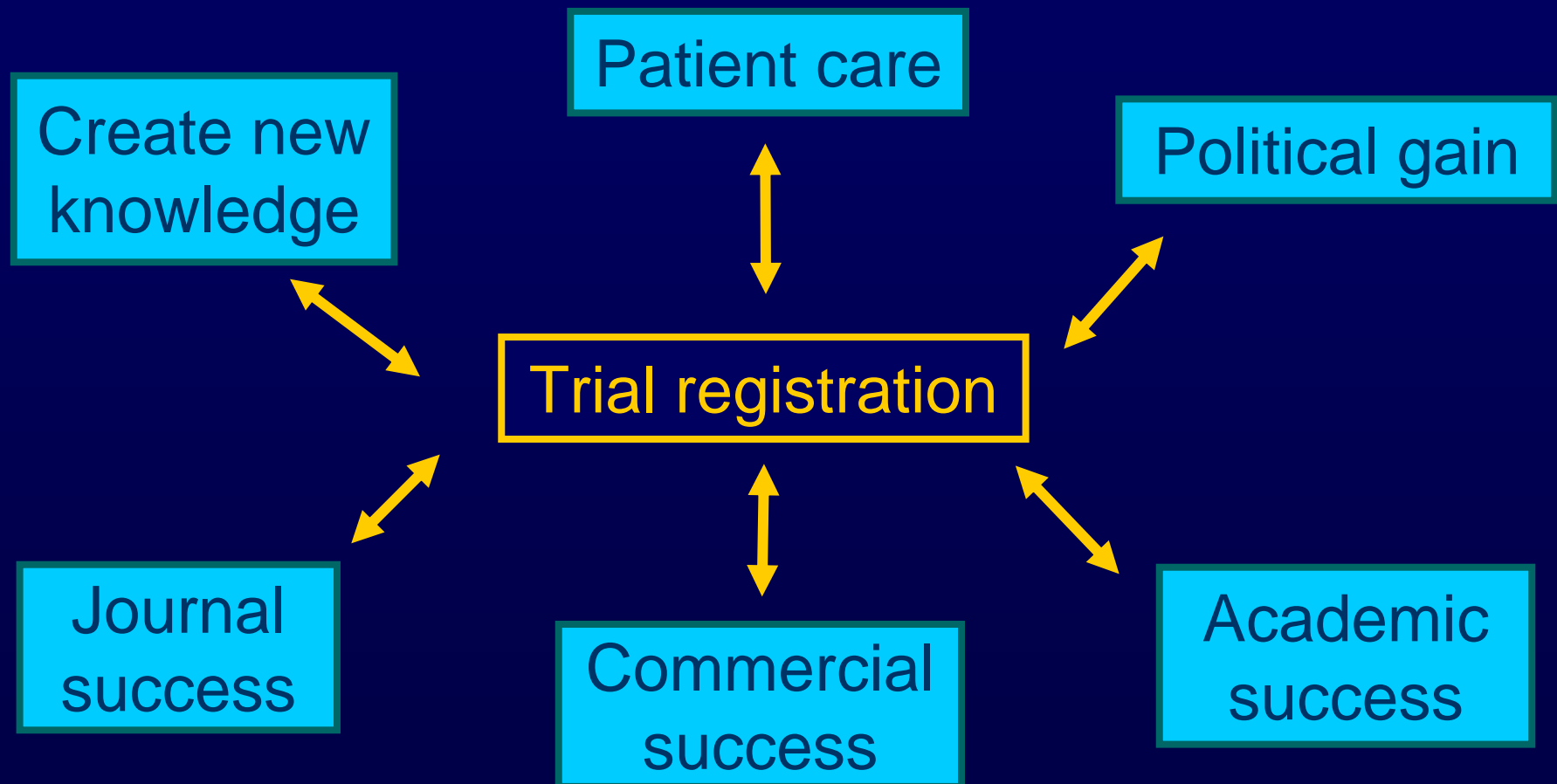
Outline

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Challenge 1: Coordination of multiple stakeholders



Challenge 1: ...with multiple interests



A BILL

To amend the Public Health Service Act to expand the clinical trials drug data bank.

1 *Be it enacted by the Senate and House of Representa-*

he
Editors

n Hoey,
verbeke,



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

**Detailed guidance for the request for authorisation of
a clinical trial on a medicinal product for human use
to the competent authorities, notification of
substantial amendments and declaration of the end of
the trial**

Challenge 2: Establishing global standards

- Trial registration
 - Which trials
 - What data
 - When
- Results disclosure

Which trials to register?

- Any prospective research study that
 - Assigns humans to an intervention
 - Measures effects of the intervention on health outcomes

Why register early 'Phase 1' trials?

- Ethical responsibilities to participants
- Informed enrollment
- Dangers of hidden knowledge
 - Preliminary indication of adverse effects
 - Inform future or ongoing research
- Intellectual property protected by patents

"The rights of trial participants hold primacy over commercial and career interests"

Nuremberg Code (1947)

What data to register?

WHO Registration Data Set (1.0)

Trial administration

1. Primary register and Trial ID#
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

What data to register?

WHO Registration Data Set (1.0)

Trial recruitment	9.	Key Inclusion/Exclusion Criteria
	10.	Countries of Recruitment
	11.	Date of First Enrollment
	12.	Recruitment Status
<hr/>		
Trial topic	13.	Public title
	14.	Scientific title
	15.	Health condition(s)/problem(s)
	16.	Intervention(s)
<hr/>		
Basic methodology	17.	Study type
	18.	Target sample size
	19.	Primary outcome(s)
	20.	Key secondary outcome(s)

When to register and publicly disclose?

- Before recruiting the first trial participant
- Full public disclosure upon registration

'Commercially sensitive' items

- Intervention
- Scientific title
- Primary outcomes
- Key secondary outcomes
- Planned sample size

No delayed disclosure

- Patents protect intellectual property
- No evidence that disclosure threatens competition and hence innovation
 - Large variation in disclosure practices
 - 'Sensitive' information is available
- Who decides what information is 'sensitive'

Sim I et al, Lancet, May 2006

Results reporting

- Timing
- Venue
- Content
- Relation to journal publication (if any)

Challenge 3: Capacity building

- Increasing number of trials in lower income countries:

Non-US trials submitted to FDA

- 271 in 1990 → 4,458 in 1999

(US Dept of Health & Human Services)

% in Latin America

- 2.1% in 1993 → 7.5% in 2000

(IMS Health)

World Health Assembly, May 2005

“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

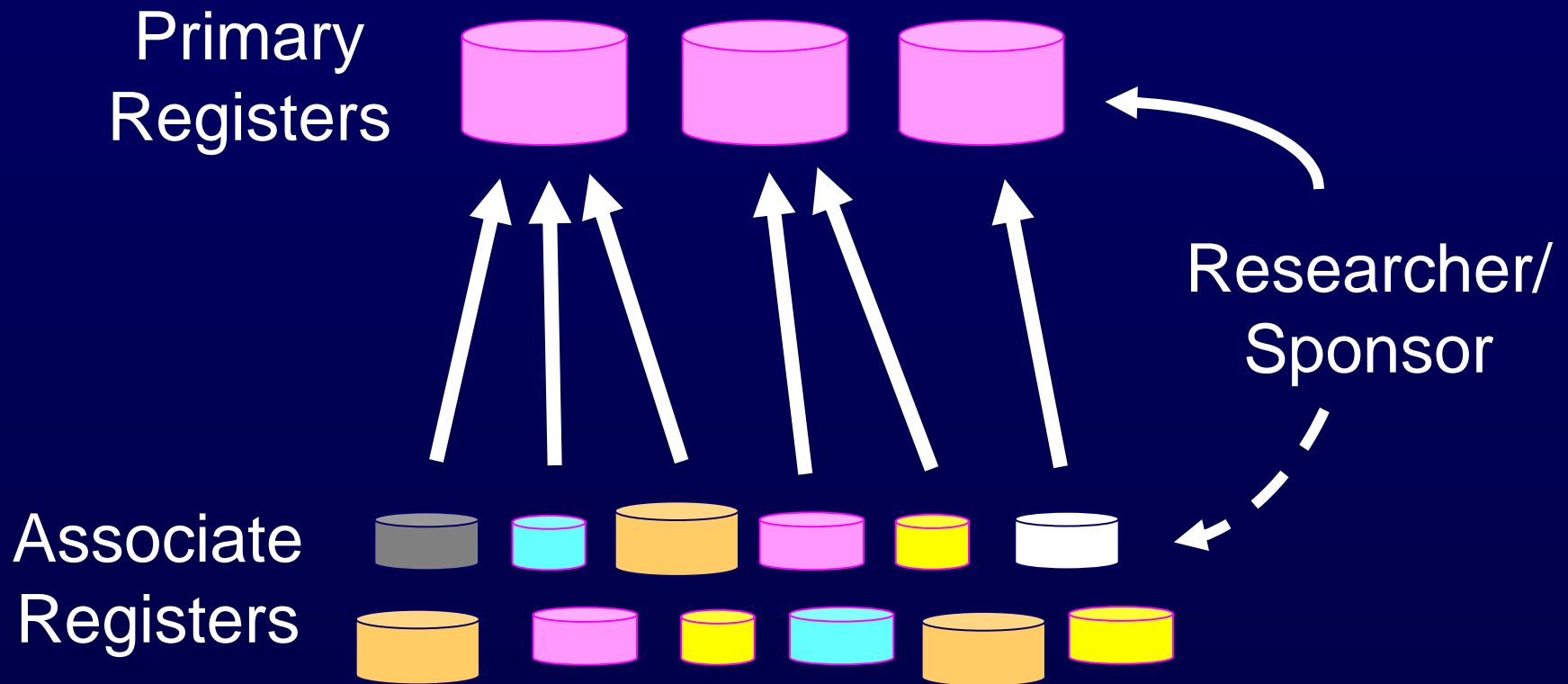


Challenge 4: Global coordination of registers

- >400 listed on TrialsCentral™
- Highly variable:
 - Purpose
 - Scope
 - Content
 - Quality
 - Accessibility



WHO Registers Network



Challenge 5: Compliance with registering trials

- Only 2/3 of US prostate/colon cancer trials of new drugs were publicly registered despite legislation

Manheimer E & Anderson D, *BMJ* 2002

Challenge 5: Compliance with Data Set items

□ ClinicalTrials.gov fields:

Industry trials	Blank	Useless
Primary outcome	24%	36%
Intervention name	0%	2%

□ All non-industry trials had full information

Zarin D et al, *NEJM* 2006

Challenge 5: Compliance with Data Set items

- Review of information recorded in 21 registers in 2005
 - 12 of 20 WHO Data Set items

Moja L et al, *submitted*

Compliance mechanisms

- World Health Assembly resolution
- Legislation
- Journal editors
- Funding agencies
- Research ethics committees
- Register policies

Outline

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Global opportunities

Ethics

- Transparency
- Accountability
- Informed enrollment

Improved public trust

Practice

- Informed policy
- Research efficiency
 - Ethics review
 - Grant review
 - Trial recruitment
 - Collaboration
- Systematic reviews
- Methodological research

How can Cochrane contribute?

- Advocacy and promotion
- Methodological research
- Participation in ongoing discussions

Conclusions

- ❑ Strong rationale for public disclosure
- ❑ WHO is leading a coordinated, global network for trial registration & reporting
- ❑ Policies will be monitored and re-visited

Overriding principle:

To promote ethical & scientific integrity

WHO Registry Platform Team

□ Staff

- Davina Gherzi (coordinator)
- Esther Awit
- An-Wen Chan
- Ghassan Karam
- Ida Sim
- Patrick Unterlerchner

□ Other WHO

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

“The difference between what we do and what we are capable of doing would suffice to solve most of the world's problems.

Mahatma Gandhi