Transparency and disclosure of Clinical Trials Information: current status and future challenges

Medical Department

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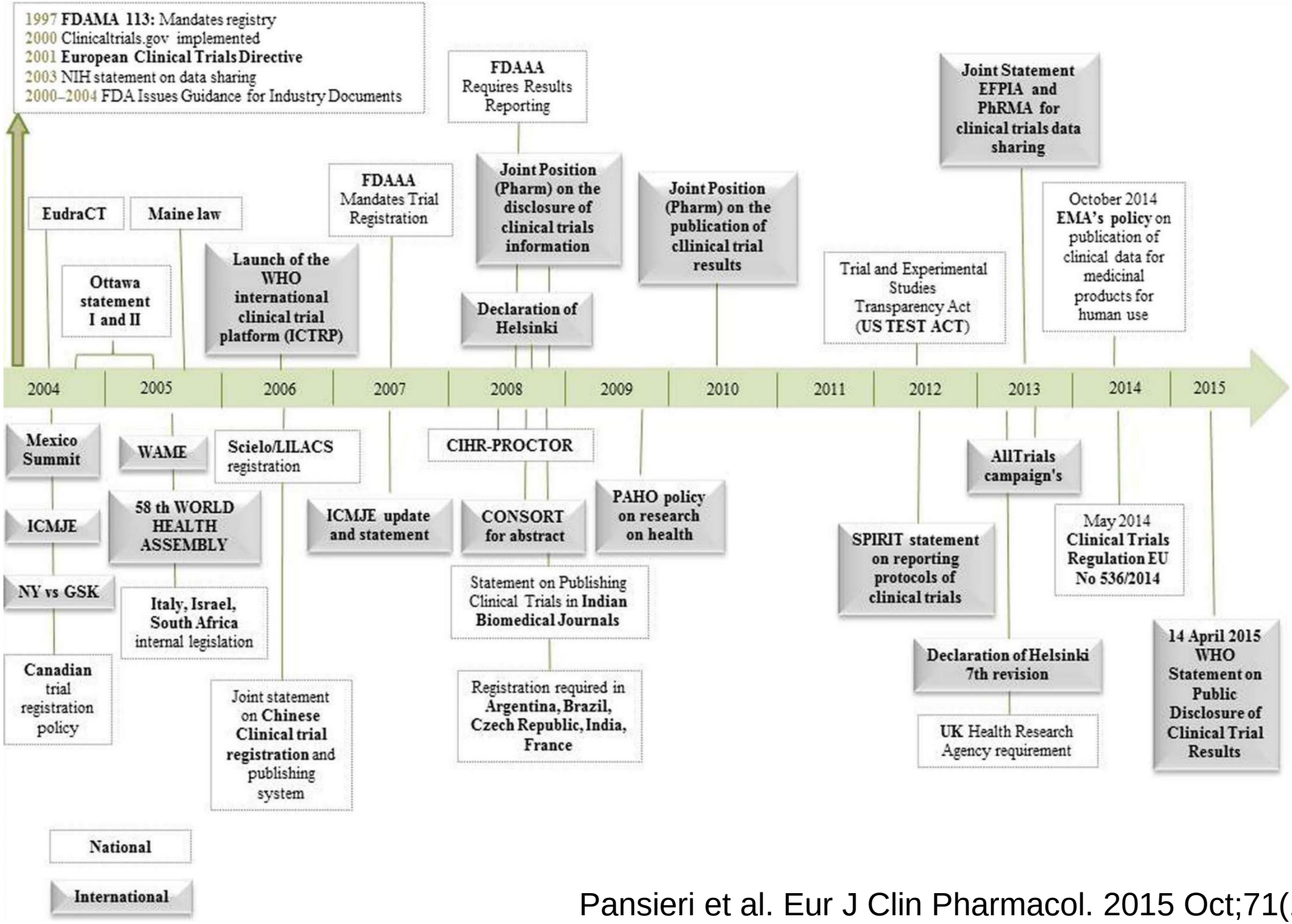
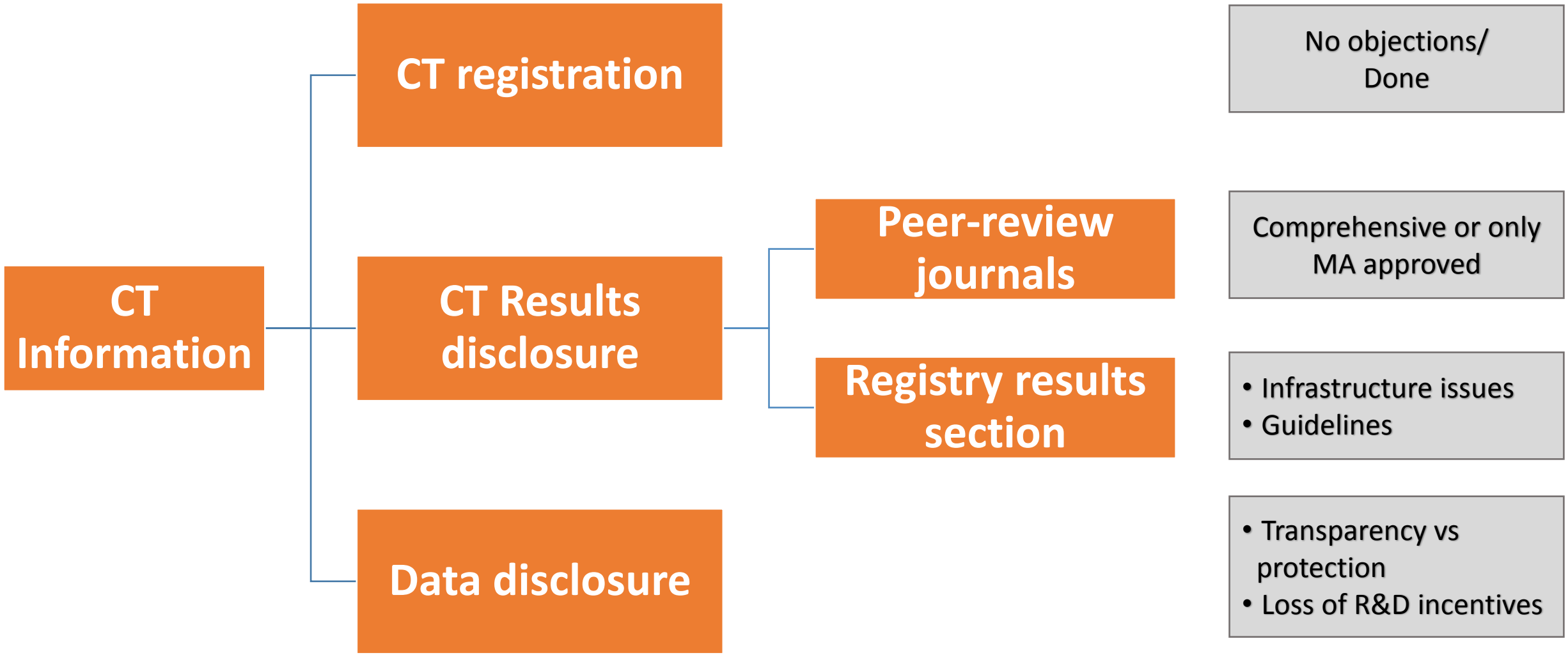


Pansieri et al. Eur J Clin Pharmacol. 2015 Oct;71(10):1159-64

The European Perspective in CT disclosure

EMA Policies on CT data disclosure

CT Information Structure and Stakes



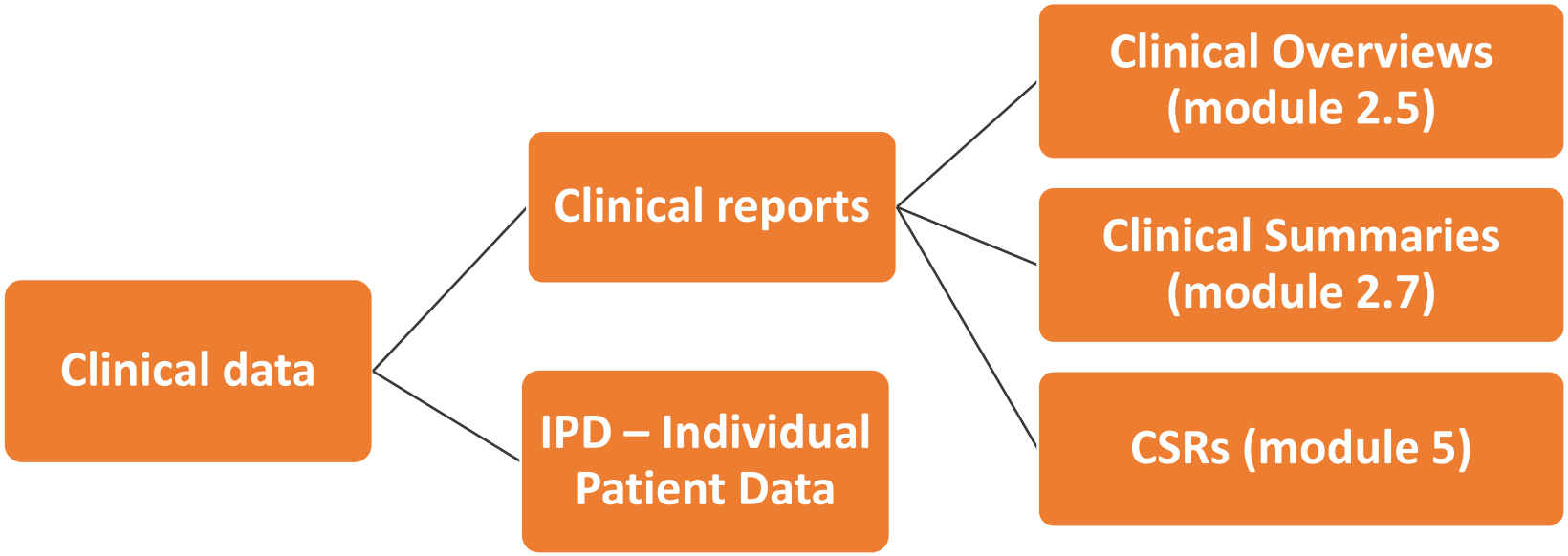
EMA's current policies

- **Policy 0043** **Reactive publication**
  effective date 1 Dec 2010
- **Policy 0070** **Proactive publication**
  effective date 1 Jan 2015

- In general the data included in CSR is considered as data that can be released, the are judged as non-CCI a priori
- In exceptional and substantial cases (innovative study designs/analytical methods) consideration will be given to the need for redaction

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

EMA Policy 0070



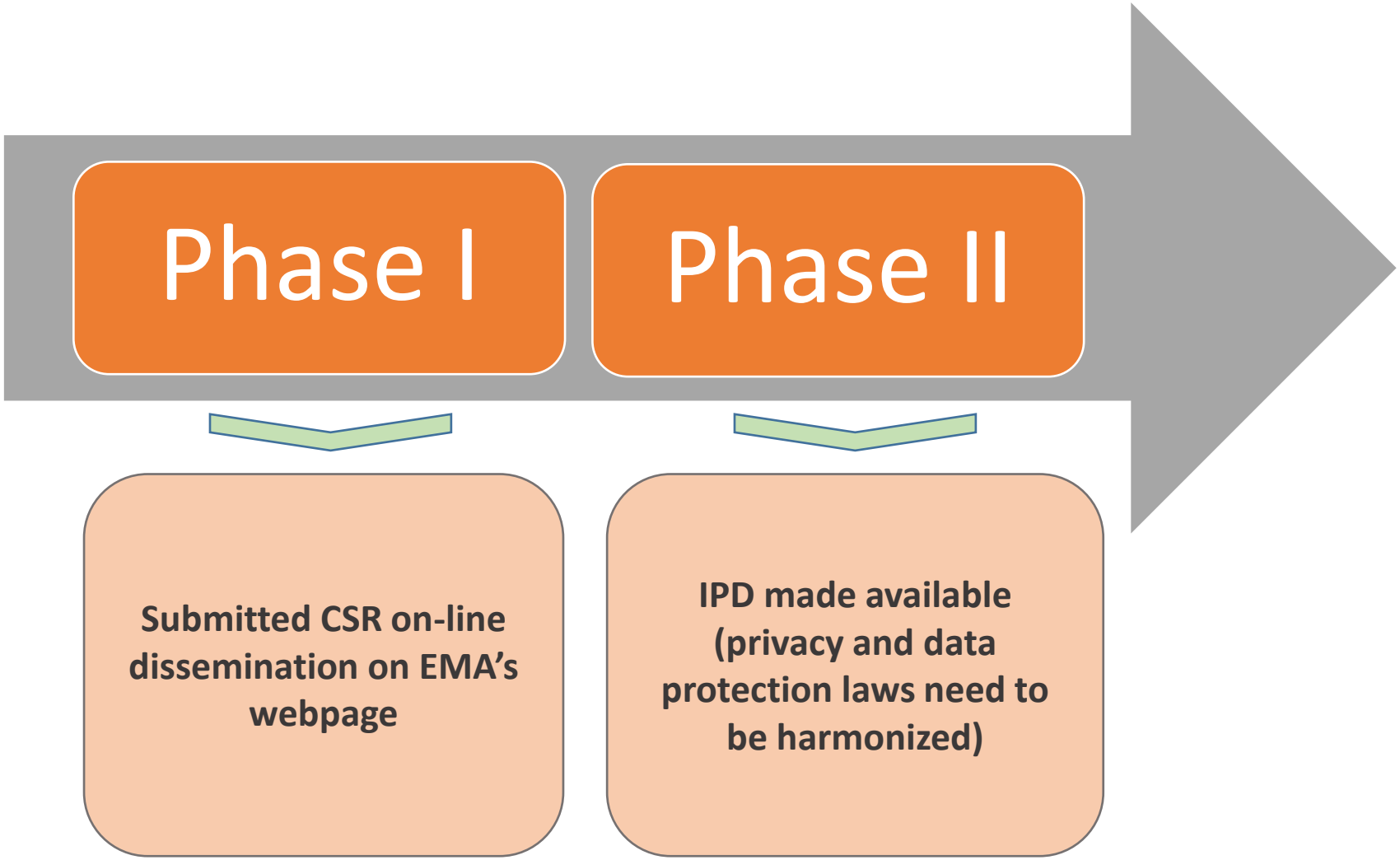
Objectives of the policy:

- Public scrutiny
- Application of new knowledge in future research

EMA Policy 0070 on data disclosure 1/2

- What
  - new marketing authorization under the centralized procedure (1st Jan 2015)
  - Extension application under the centralized procedure (1st Aug 2015)
- When
  - Following EMA's grant
  - Following EMA's refusal
  - Following Sponsors withdrawal
- How
  - Screen-only CR for every user (simple and limited registration)
  - Downloadable CR to identified users (full registration)

EMA Policy 0070 implementation



List of data types that may be considered CCI

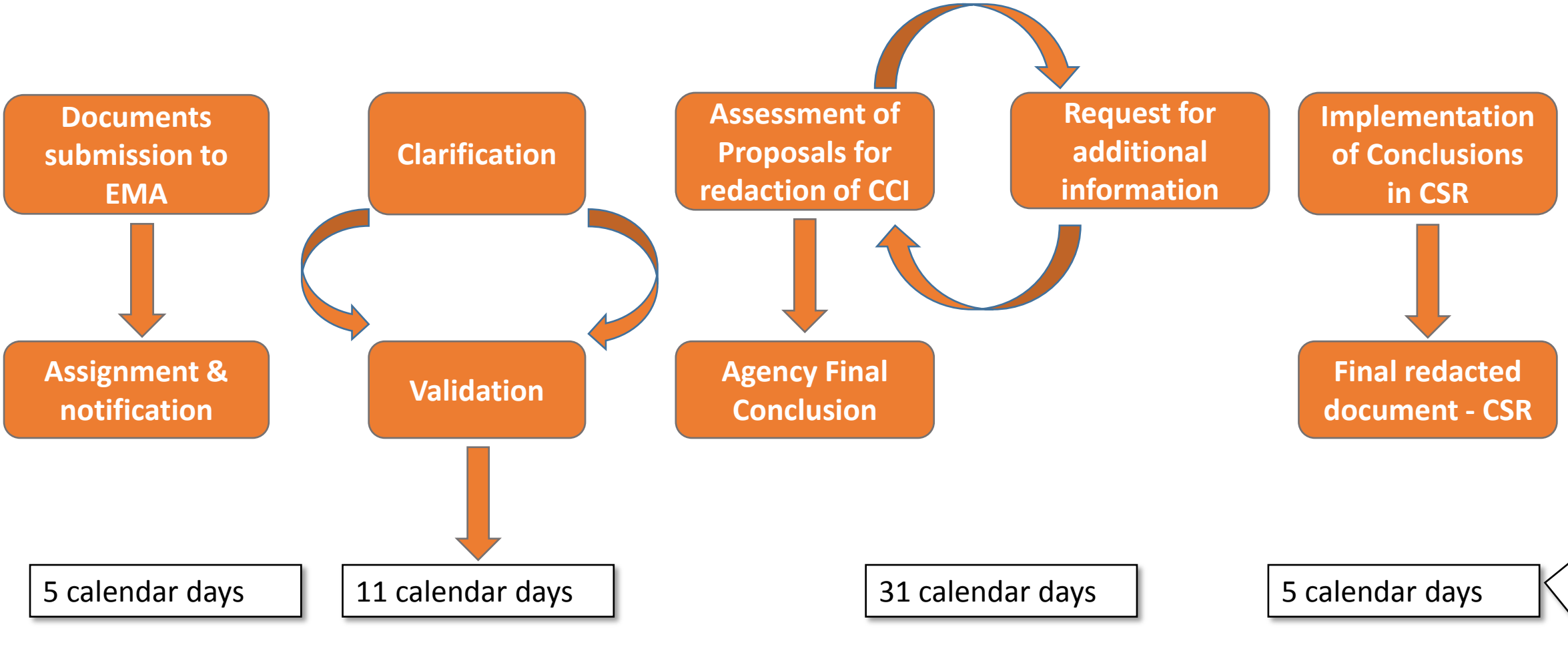
Module 2.5 Clinical Overview	**Product development rationale**
	Overview of biopharmaceutics
	Overview of animal pharmacology
	Benefits and risks conclusions
Module 2.7 Clinical Summaries	**Summary of biopharmaceutics**
	Studies and associated analytical methods
	Summary of clinical pharmacological studies
Module 5 CSR	**Reports of biopharmaceutics studies**
	Introduction
	Study objectives
	Determination of study size
	Methods for DK/PD determination

Redaction Process outlined 1/2

Factors EMA is taking taken into account for assessment (§4.2.2.1)

- Nature of medicine concerned
- Competitive situation of the therapeutic market in question
- Approval status by other authorities
- Novelty of the clinical development
- New development by the same company

Redaction Process outlined 2/2



Adapted from: "Guidance to pharmaceutical industry on redacting CCI., London, 2015

Dispute over Commercially Confidential Information - CCI

- Arguments against proactive publication
  - Damage to commercial interest
  - Undermining regulatory data protection
  - Creates bias against future patent application
- Arguments favoring proactive publication
  - Patient safety, CT efficacy
  - Public interest in identifying deficiencies in health care decision making
  - Accountability of the regulatory system

EFPIA's position on EMA's Policy 0070

- Weaken safeguards intended to ensure the privacy of patients and other individuals identified in marketing authorization application (MA) dossiers;
- Undermine the trust in the regulatory approval system governing biopharmaceutical products and introduce risks of misinterpretation and misuse of clinical data into the process;
- Weaken incentives for companies to invest in biomedical research by disclosing companies" commercially confidential information (CCI), without due consideration of the competing interests that may or may not justify disclosure.

http://www.efpia.eu/uploads/Exec_Summary_EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf
Accessed on the 24th Feb 2015

EFPIA principles on clinical trial data sharing

Principles for Responsible Clinical Trial Data Sharing

1. Enhancing Data Sharing with Researchers
2. Enhancing Public Access to Clinical Study Information
3. Sharing Results with Patients Who Participate in Clinical Trials
4. Certifying Procedures for Sharing Clinical Trial Information
5. Reaffirming Commitments to Publish Clinical Trial Results

What needs to be done

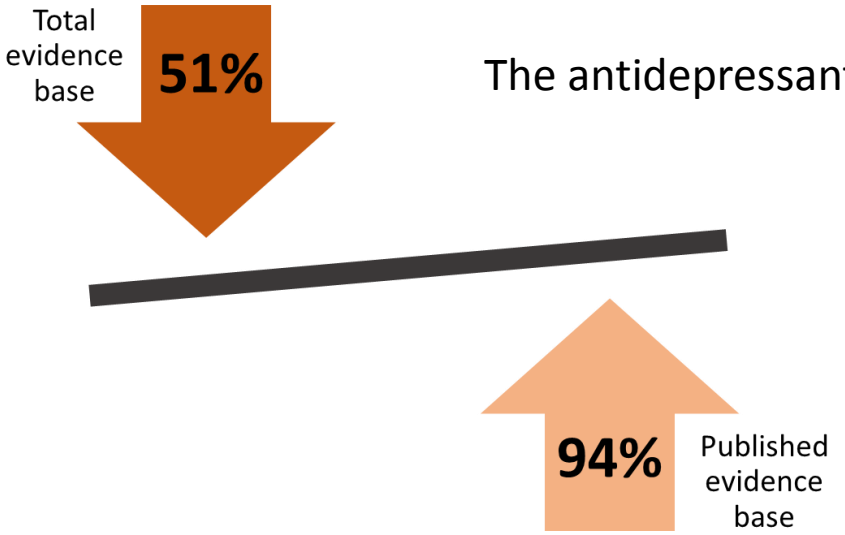
The message to take home

The Policy is out there, what remains to be done is:

- To define a common ground and develop a common frame for universally accepted redaction process regarding the CCI
- Guarantee the anonymity of subjects upon disclosure of IPD (2nd phase of implementation)

Conclusions-bottom line

- Much improvement has been recorded since mandatory registration
  - EMA has published **1.9 billion** pages of clinical data under Policy 0043



The antidepressants trials case

Conclusions

We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both. Selective reporting of clinical trial results may have adverse consequences for researchers, study participants, health care professionals, and patients.

Turner et al N Engl J Med 2008;358:252-60.

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References

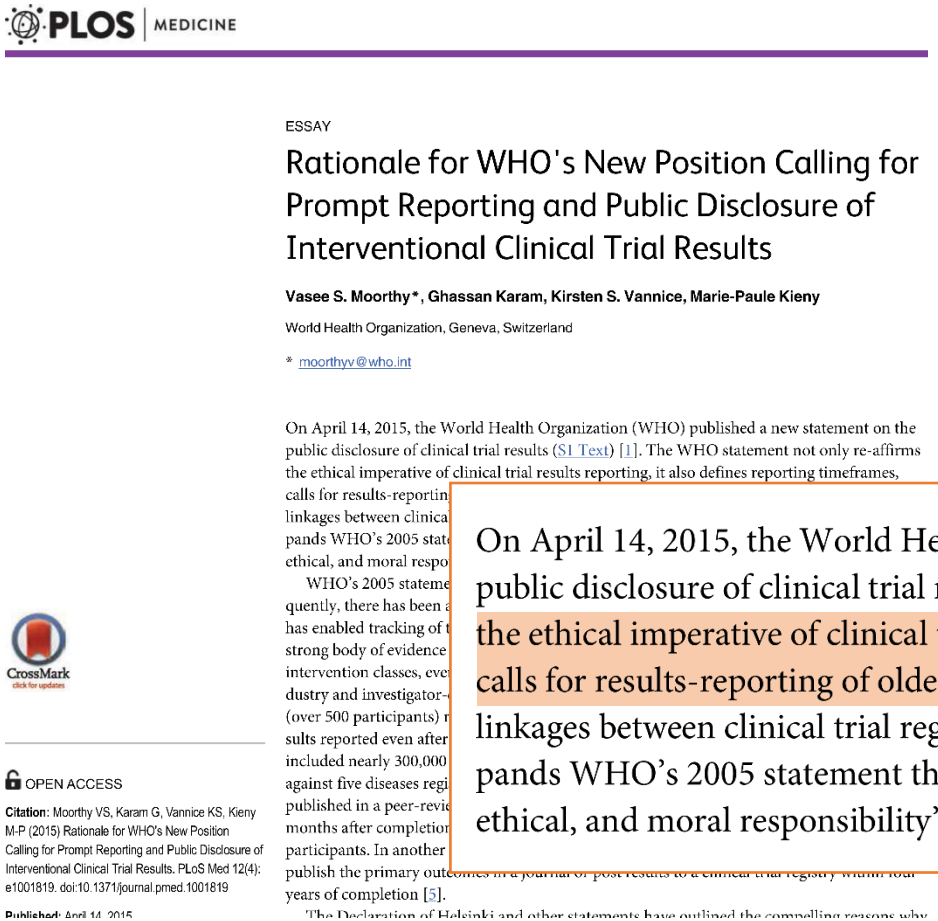
1. WHO, JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.
2. Moorthy et al. PLoS Med 12(4): e1001819.
3. Turner et al, N Engl J Med 2008;358:252-60
4. Sydes et al. Trials (2015) 16:104
5. Pansieri et al. Eur J Clin Pharmacol. 2015 Oct;71(10):1159-64
6. M.C. Rowbotham/ Pain 140 (2008) 401–404
7. IFPMA, Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases
8. EMA Policies 0043-0070 (available on EMA's site)
9. Henry-Eude, Guidance to pharmaceutical industry on redacting CCI – EMA presentation
10. http://www.efpia.eu/uploads/Exec_Summary_EFPIA_comments_on_EMA_draft_policy_access_to_CT_data_FINAL.pdf
11. Lancet Infect Dis. 2014 Jun;14(6):441

International Clinical Trials Registry Platform

- Australia and New Zealand's (ANZCTR)
- Brazilian Clinical Trials Registry (ReBec)
- Chinese Clinical Trial Registry (ChiCTR)
- Clinical Research Information Service (CRiS), Republic of Korea
- Clinical Trials Registry - India (CTRI)
- Cuban Public Registry of Clinical Trials(RPCEC)
- EU Clinical Trials Register (EU-CTR)
- German Clinical Trials Register (DRKS)
- Iranian Registry of Clinical Trials (IRCT)
- Japan's UMIN-CTR
- Thai Clinical Trials Registry
- The Netherlands' Trialregister.nl
- The United States' "Clinicaltrials.gov"
- The International ISRCTN.org
- Pan African Clinical Trial Registry (PACTR)
- Sri Lanka Clinical Trials Registry (SLCTR)

- BACK UP SLIDES

WHO position on CT Results Disclosure



PLOS | MEDICINE

ESSAY

Rationale for WHO's New Position Calling for Prompt Reporting and Public Disclosure of Interventional Clinical Trial Results

Vasee S. Moorthy*, Ghassan Karam, Kirsten S. Vannice, Marie-Paule Kieny

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On April 14, 2015, the World Health Organization (WHO) published a new statement on the public disclosure of clinical trial results (S1 Text) [1]. The WHO statement not only re-affirms the ethical imperative of clinical trial results reporting, it also defines reporting timeframes, calls for results-reportin linkages between clinica pands WHO's 2005 stat ethical, and moral respo

WHO's 2005 stateme quently, there has been has enabled tracking of strong body of evidence intervention classes, eve dustry and investigator- (over 500 participants) sults reported even after included nearly 300,000 against five diseases regi published in a peer-revi months after completio participants. In another publish the primary out years of completion [5].

The Declaration of Helsinki and other statements have outlined the compelling reasons why

CrossMark

OPEN ACCESS

Citation: Moorthy VS, Karam G, Vannice KS, Kieny M-P (2015) Rationale for WHO's New Position Calling for Prompt Reporting and Public Disclosure of Interventional Clinical Trial Results. PLoS Med 12(4): e1001819. doi:10.1371/journal.pmed.1001819

Published: April 14, 2015

- reporting in 2 modalities
  - main findings available within 24 months in peer-reviewed journals
  - Key outcomes available within 12 months in the results section of the primary
- public disclosure of results from older, unreported clinical trials

> On April 14, 2015, the World Health Organization (WHO) published a new statement on the public disclosure of clinical trial results (S1 Text) [1]. The WHO statement not only re-affirms the ethical imperative of clinical trial results reporting, it also defines reporting timeframes, calls for results-reporting of older but still unpublished trials, and outlines steps to improve linkages between clinical trial registry entries and their published results. This updates and expands WHO's 2005 statement that "the registration of all interventional trials is a scientific, ethical, and moral responsibility" [2].

Moorthy *et al*. PLoS Med 12(4): e1001819.

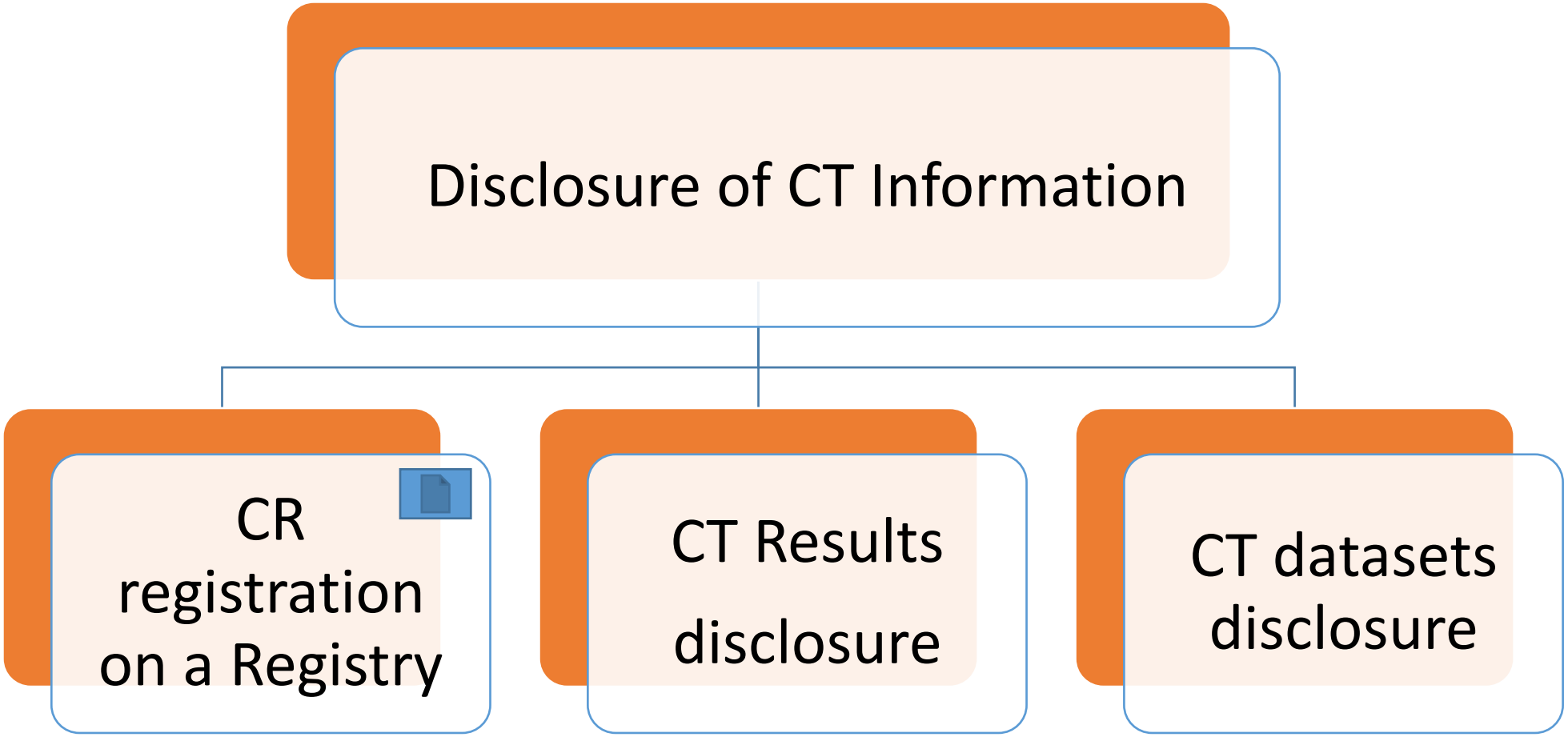
Why should research on humans be disclosed?

- Data protection and access rights
  7th of the Privacy Principles (Organization for Economic Cooperation & Development)
- Social ethical obligation
- Scientific ethical obligation

"Evidence-based medicine is valuable only to the extend that the evidence base is COMPLETE and UNBIASED."

Turner *et al*, N Engl J Med 2008;358:252-60

Dimensions of CT Information disclosure

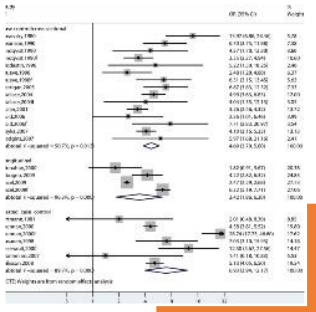


Consequences of undisclosed CTs 1/3

CT Registration

- No traceability
- Duplication
- Waste of resources
- Limited recruitment

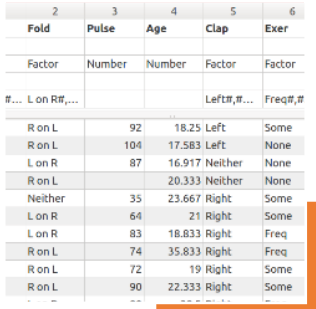
Consequences of undisclosed CTs 2/3



Results reporting

- Publication bias
- Undermining future research
- Suboptimal clinical practice
- Suboptimal public health decision making
- Uninformed investment decision making

Consequences of undisclosed CTs 3/3



2	3	4	5	6
Fold	Pulse	Age	Clap	Exer
Factor	Number	Number	Factor	Factor
#... L on R#,...			Left#,#...	Freq#,#
R on L	92	18.25	Left	Some
R on L	104	17.583	Left	None
L on R	87	16.917	Neither	None
R on L		20.333	Neither	None
Neither	35	23.667	Right	Some
L on R	64	21	Right	Some
L on R	83	18.833	Right	Freq
R on L	74	35.833	Right	Freq
R on L	72	19	Right	Some
R on L	90	22.333	Right	Some

CT data disclosure

- Lack of secondary control
- hindrance for secondary use
- Barrier to innovative study methodologies
- Barrier to innovative analytical methodologies

Sydes et al. Trials (2015) 16:104

Is there a problem at all?

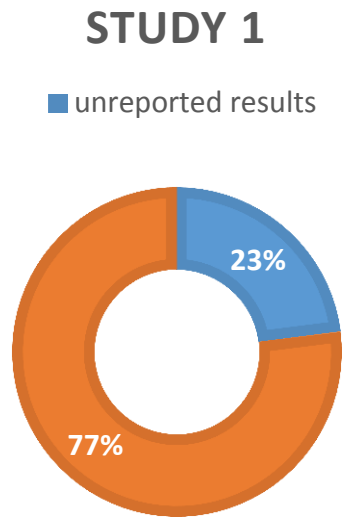
… A beautiful paradox is at work – if the work is not published, how do we know the work is out there?…

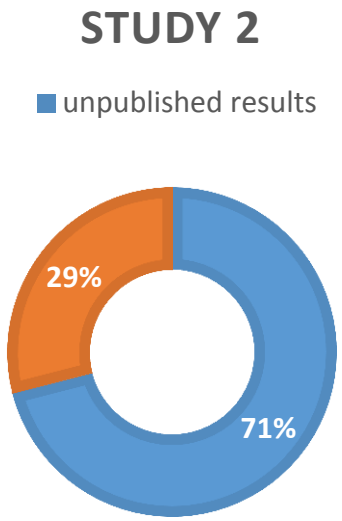
Henry McQuay, Oxford, UK

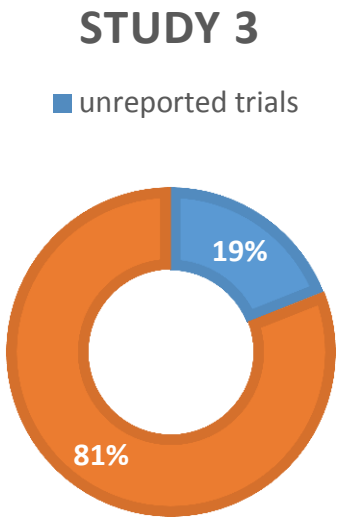
M.C. Rowbotham/ Pain 140 (2008) 401–404

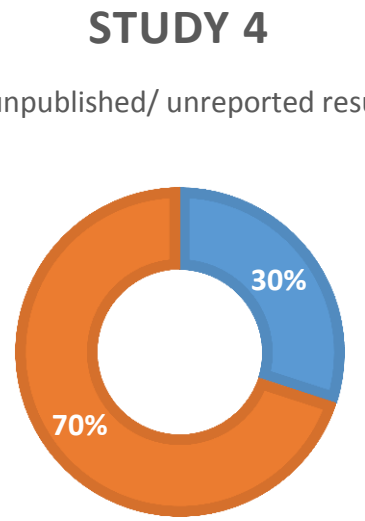
Studies trying to quantify the problem.

"…There is now a strong body of evidence showing failure to comply with results-reporting requirements across intervention classes, even in the case of large, randomized trials…."









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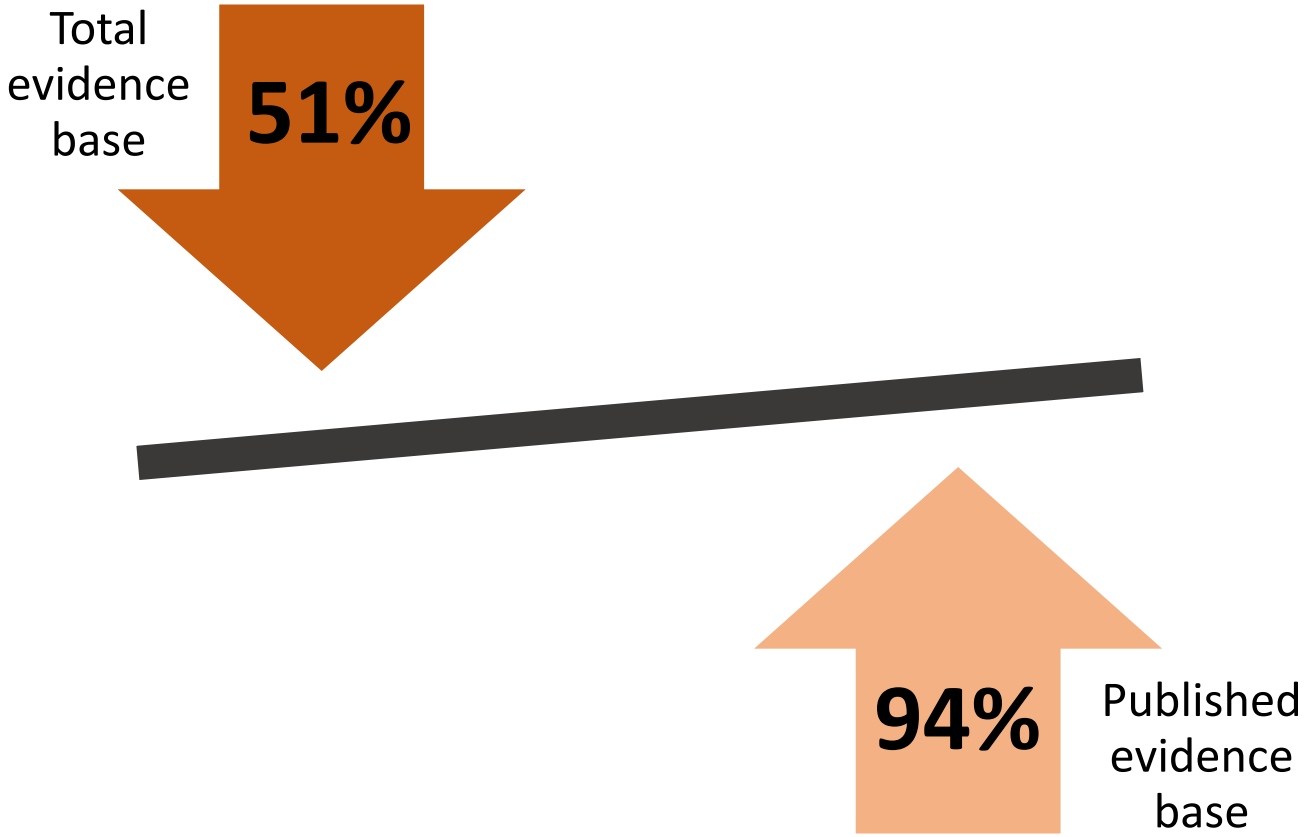
The Antidepressant Trials Paradigm: Publication Bias



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Turner *et al* N Engl J Med 2008;358:252-60.

Why do CTs stay unpublished?

Academia

- Academic Impact
- Lack of publication interest
- Publishing cost

Pharma

- Conflict of interest
- brand protection
- Asset deprivation

Pharma Position concerns

- **Individual Patient Data (IPD) privacy**
- **Commercially Confidential Information (CCI)**
- **Intellectual Property Contract Rights**
- **Patent laws**

IFPMA, Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases

Declaration of Helsinki

(7th Revision, Fortaleza, Brazil, 2013)

article 35.

"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject"

"Negative and inconclusive as well as positive results must be published or otherwise made publicly available"

WHO, JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.

Current and new approaches on data release

Reactive release of CT data

EMA Policy 0043

EMA, and according to its Terms of Use, makes available CSRs to any natural or legal person, upon request

Excluded:
CCIs and Personal Data

Proactive release of CT data

Summaries or "result related information"	CSR
EC Guidance 302/03	EMA Policy 0070
EMA releases result related information based on submitted CSRs to the EU Clinical Trials Registry	Submitted CSR will be made available
	Subject to CCI agreement
	Sponsor suggested reduction