The Use and Misuse of Clinical Trial Registries

Lessons learned from biomedical metaresearch & reflections for other fields

Dr. Nicholas J. DeVito

University of Oxford

Maia Salholz-Hillel

QUEST Center for Responsible Research

Clinical Trials and Clinical Trial Registration

"Clinical Trials…prospectively assign human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."

World Health Organization

A clinical trial registry houses clinical trial registrations, which contain information about each clinical trial.

How did we get here?

Practical

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

World Health Organization

International Standards for Clinical Trial Registries

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

Ethical

WORLD MEDICAL ASSOCIATION'S
Declaration of Helsinki
7TH REVISION, 2013

+AllTrials

Legal

Public Law 110–85
110th Congress

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.

Sept. 27, 2007
[H.R. 3580]

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

Food and Drug Administration Amendments Act of 2007.
21 USC 301 note.

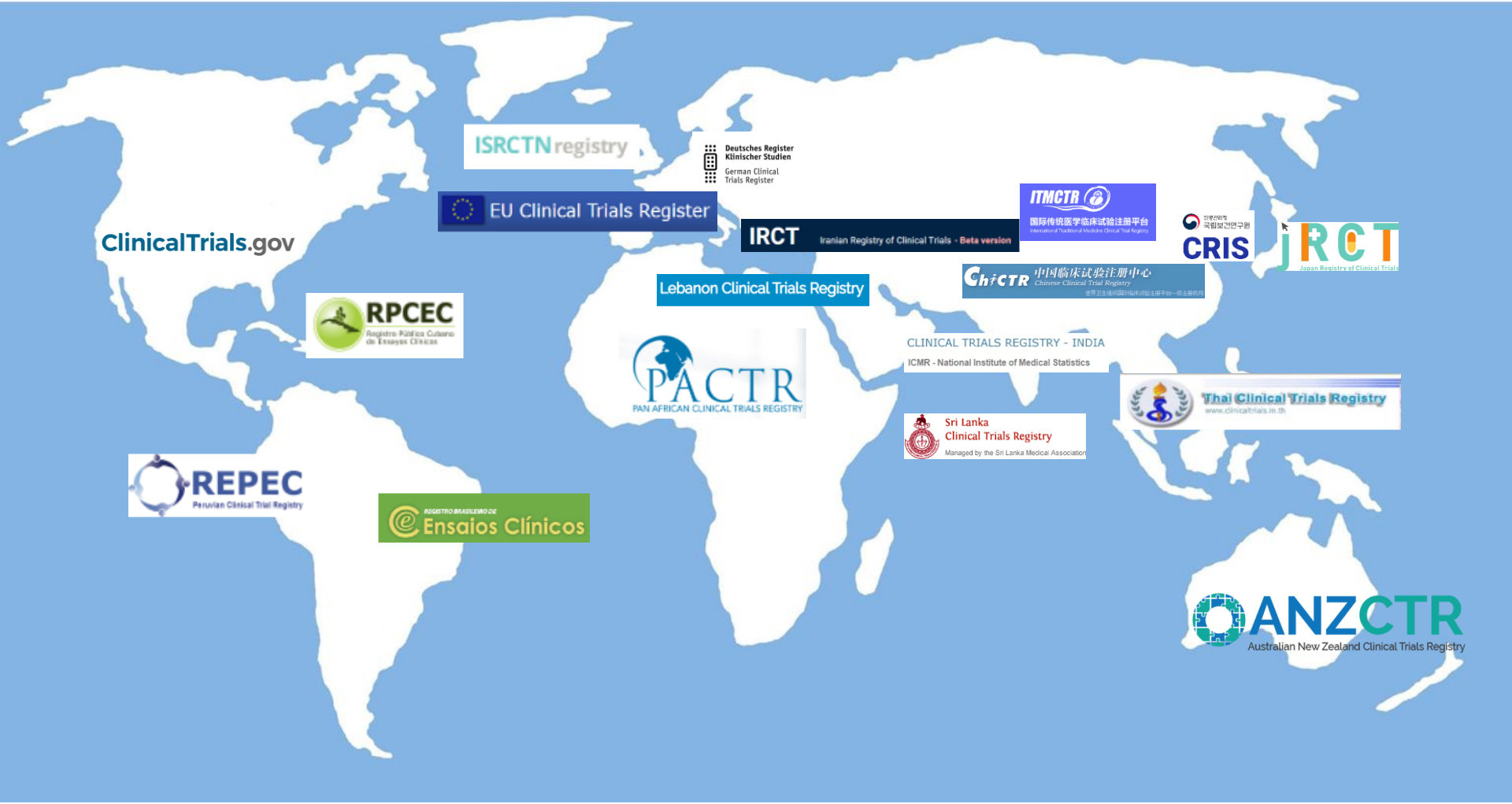
SECTION 1. SHORT TITLE.

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

6.10.2012 EN Official Journal of the European Union C 302/7

Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

(2012/C 302/03)


ISRCTN registry
Deutsches Register Klinischer Studien
German Clinical Trials Register
EU Clinical Trials Register
ClinicalTrials.gov
IRCT
Iranian Registry of Clinical Trials - Beta version
ITMCTR
国际传统医学临床试验注册平台
International Traditional Medicine Clinical Trial Registry
CRIS
jRCT
Japan Registry of Clinical Trials
ChiCTR
中国临床试验注册中心
Chinese Clinical Trial Registry
Lebanon Clinical Trials Registry
RPCEC
Registro Público Cubano de Ensayos Clínicos
PACTR
PAN AFRICAN CLINICAL TRIALS REGISTRY
CLINICAL TRIALS REGISTRY - INDIA
ICMR - National Institute of Medical Statistics
Thai Clinical Trials Registry
www.clinicaltrials.in.th
Sri Lanka
Clinical Trials Registry
Managed by the Sri Lanka Medical Association
REPEC
Peruvian Clinical Trial Registry
REGISTRO BRASILEIRO DE
Ensaios Clínicos
ANZCTR
Australian New Zealand Clinical Trials Registry

ClinicalTrials.gov

RECRUITING

Durvalumab With Carboplatin and Etoposide Chemotherapy in Pulmonary Large-cell Neuroendocrine Carcinoma (LCNEC) (DUPLE)

ClinicalTrials.gov ID NCT06418087

Sponsor Gruppo Oncologico Italiano di Ricerca Clinica

Information provided by Gruppo Oncologico Italiano di Ricerca Clinica (Responsible Party)

Last Update Posted 2024-05-16

More Information

Record History

Study Start (Actual)
2022-05-27

Primary Completion (Estimated)
2026-12-31

Study Completion (Estimated)
2026-12-31

Enrollment (Estimated)
49

Study Type
Interventional

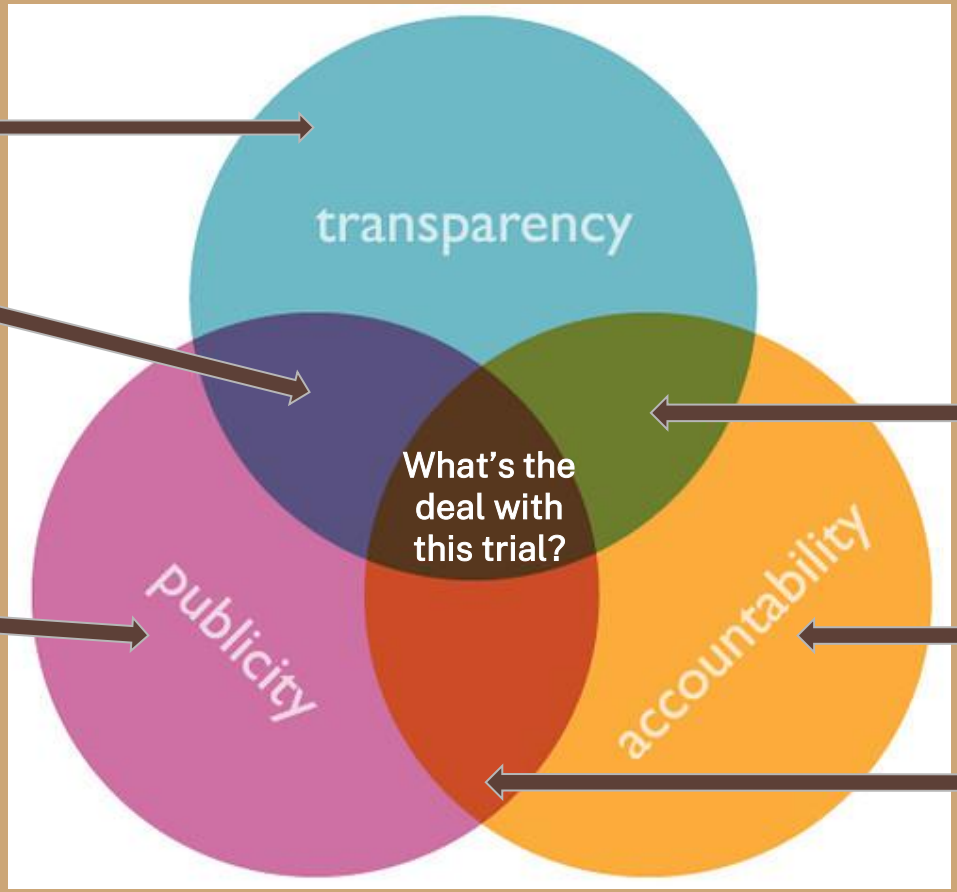
Phase
Phase 2

Why clinical trial registries?

Who is doing what?

Can we easily find things?

Are there trials for my condition?



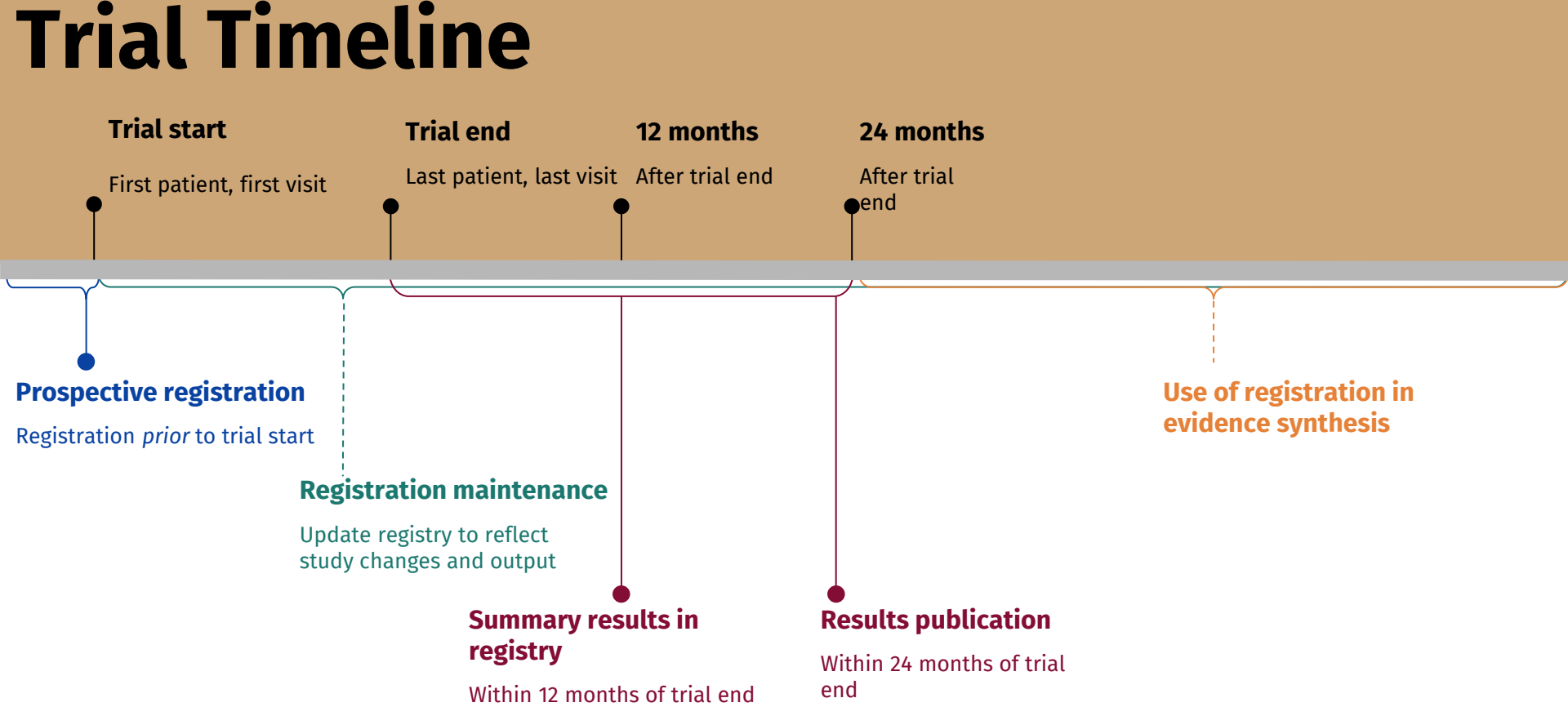
Did you do what you said you would?

Did you do it before you started the trial?

Can everyone check?

Image Source: https://www.flickr.com/photos/notbrucelee/6166628554

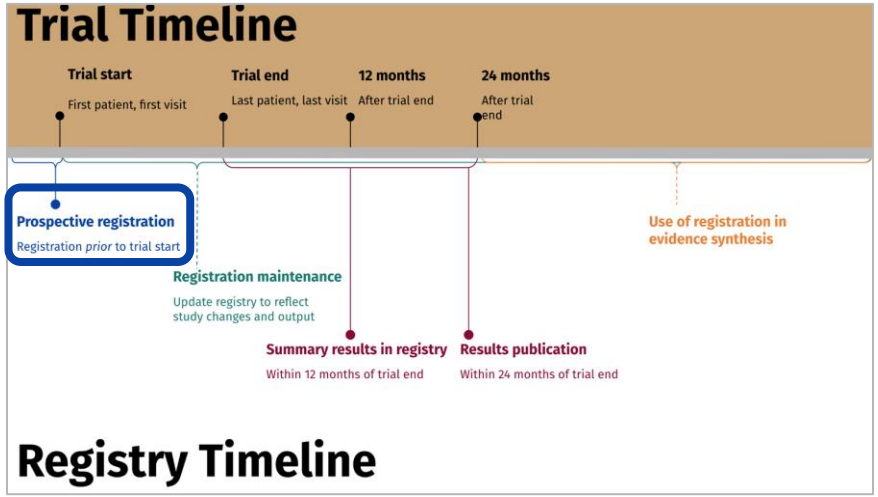
Trial Timeline



Registry Timeline


USE
MISUSE

Registration



Proc Natl Acad Sci U S A. 2018 Mar 13;115(11):2600-2606. doi: 10.1073/pnas.1708274114.

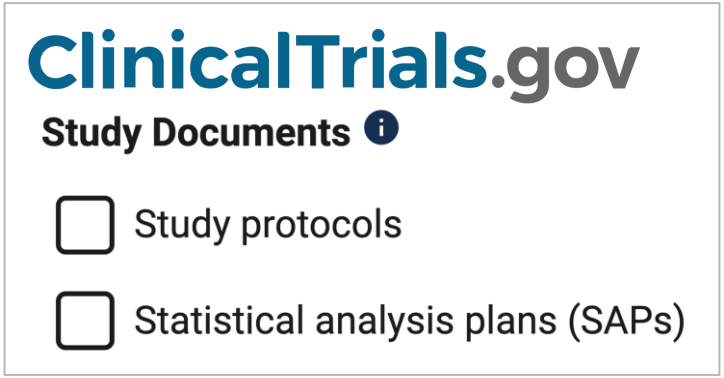
The preregistration revolution

Brian A Nosek [1 2], Charles R Ebersole [2], Alexander C DeHaven [3], David T Mellor [3]

Affiliations + expand

PMID: 29531091 PMCID: PMC5856500 DOI: 10.1073/pnas.1708274114

The standards for preregistration in clinical trials **do not yet require comprehensive specification of analysis plans**...



Footprint of publication selection bias on meta-analyses in medicine, environmental sciences, psychology, and economics

František Bartoš[1,2] | Maximilian Maier[3] | Eric-Jan Wagenmakers[1] |
Franziska Nippold[4] | Hristos Doucouliagos[5] | John P. A. Ioannidis[6,7,8,9,10] |
Willem M. Otte[11] | Martina Sladekova[12] | Teshome K. Deresssa[13] |
Stephan B. Bruns[6,13,14] | Daniele Fanelli[15,16] | T. D. Stanley[5]

"After adjusting for publication selection bias, the median probability of the presence of an effect decreased from **99.9% to 29.7% in economics**, from **98.9% to 55.7%** in **psychology**, from **99.8% to 70.7% in environmental sciences**, and from **38.0% to 29.7% in medicine**."

#MakeItPublic

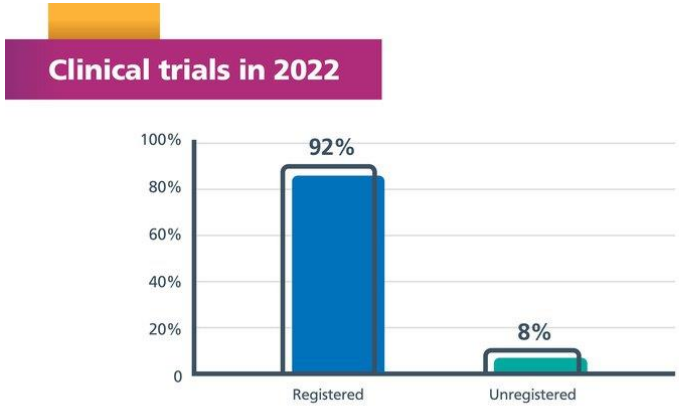


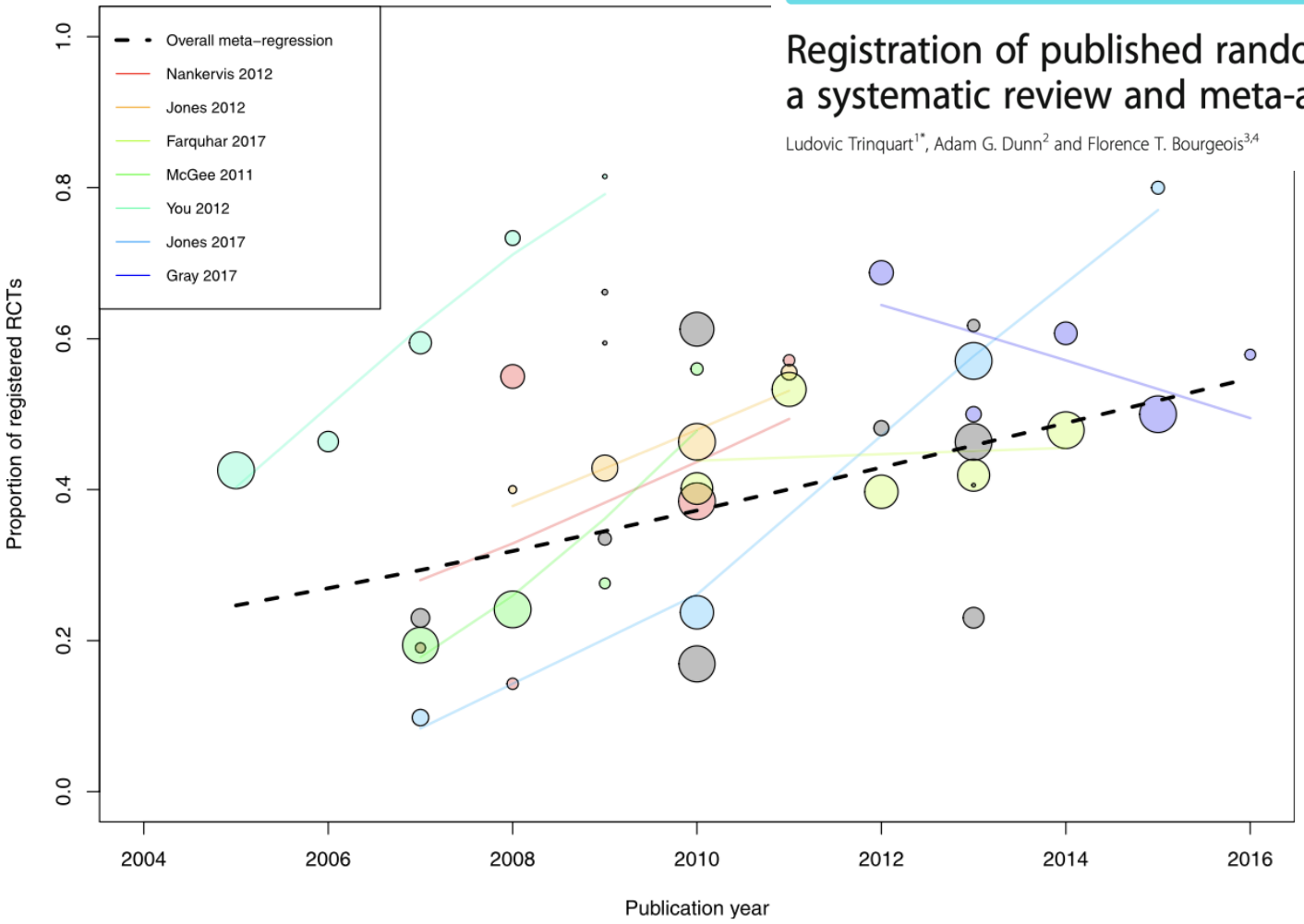
Table 1. FDAAA Compliance and Characteristics in Assessment Areas

	No. (%)									
	Compliant results reporting		Timely registration[a]		Annual data verification		Certificate of delay requests		Document submission[b]	
Detailed compliance data	Total (n = 8863)	Compliant (n = 3499; 39.5%)	Total (n = 27 645)	Compliant (n = 24 429; 88.4%)	Total (n = 16 709)	Compliant (n = 12 632; 75.6%)	Total (n = 1354)	Compliant (n = 893; 66.0%)	Total (n = 5449)	Compliant (n = 5401; 99.1%)

RESEARCH ARTICLE Open Access

Registration of published randomized trials: a systematic review and meta-analysis

Ludovic Trinquart[1*], Adam G. Dunn[2] and Florence T. Bourgeois[3,4]



However...

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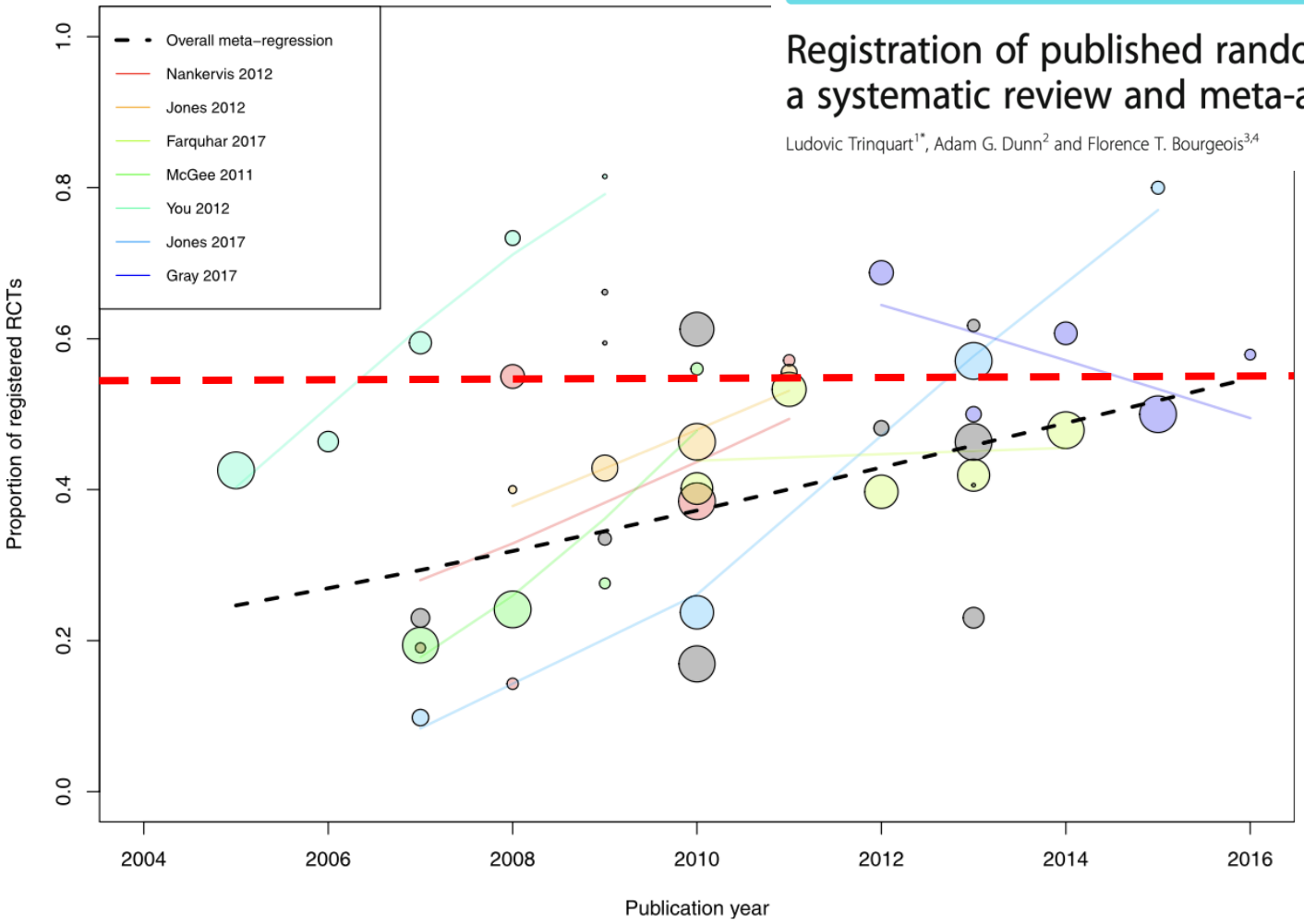
Ludovic Trinquart[1*], Adam G. Dunn[2] and Florence T. Bourgeois[3,4]



Is registration done prospectively?!

Prospective registration and reporting of trial number in randomised clinical trials: global cross sectional study of the adoption of ICMJE and Declaration of Helsinki recommendations

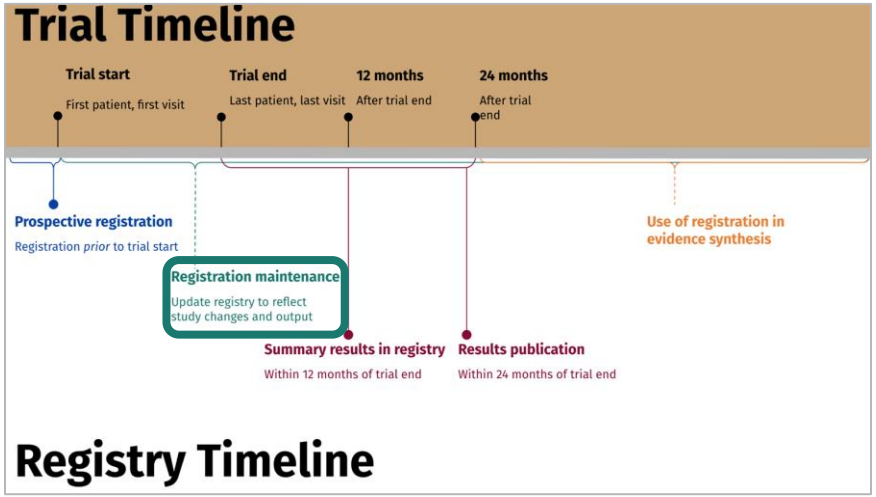
BMJ 2020 ; 369 doi: https://doi.org/10.1136/bmj.m982 (Published 14 April 2020)

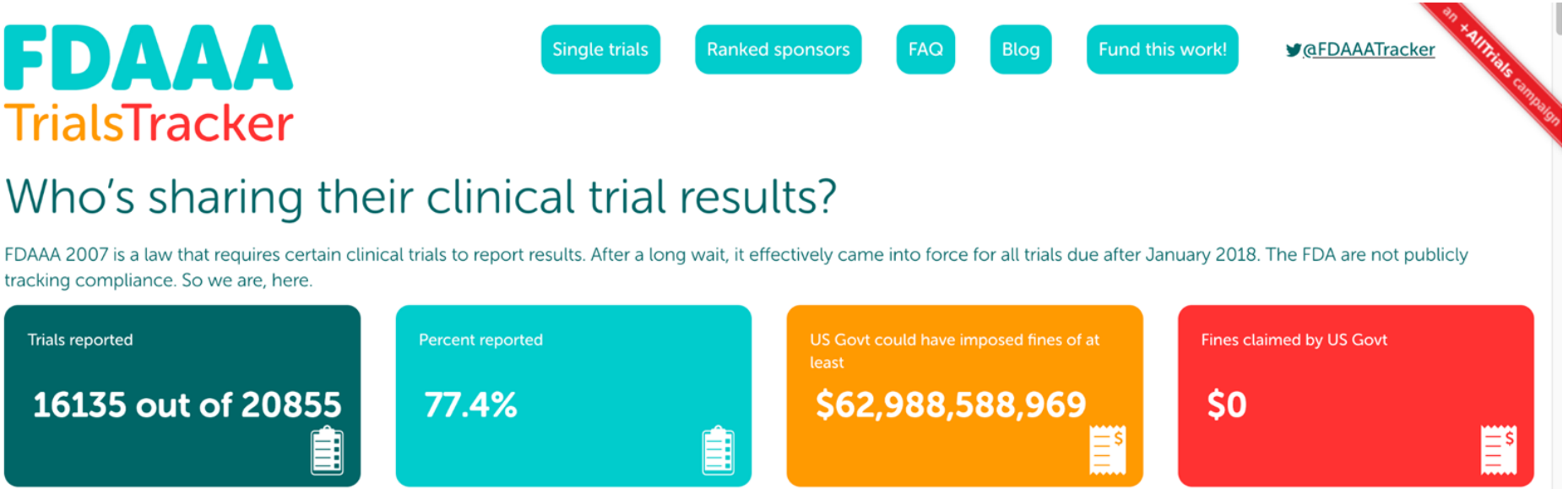
3,013 of 7,218 (42%) published trial reports in 2018 were **retrospectively registered**.

Interventional trials posted to ClinicalTrials.gov (2023)

~1 of every 3 were retrospectively registered.

Registration Maintenance





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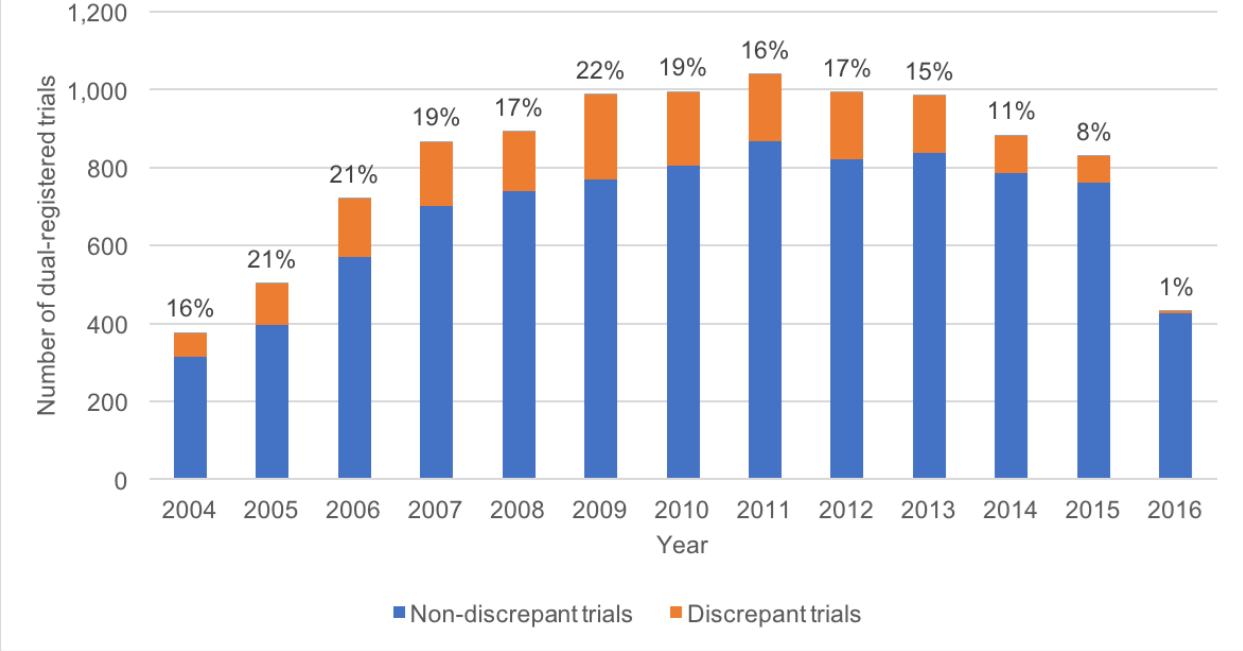
However...

PLoS One. 2018 Mar 7;13(3):e0193088. doi: 10.1371/journal.pone.0193088. eCollection 2018.

Prevalence of clinical trial status discrepancies: A cross-sectional study of 10,492 trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register

Jessica Fleminger [1], Ben Goldacre [1]

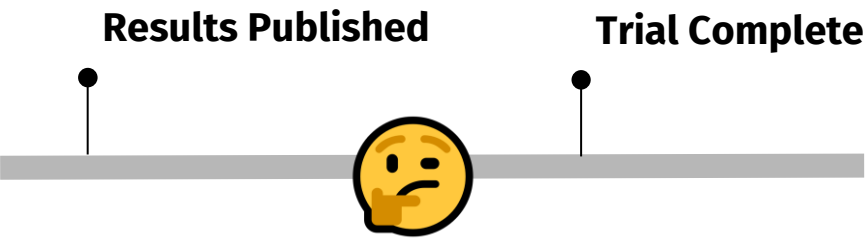


16% of trials had **discrepancies** on completion status

BMC Med. 2023 Nov 29;21(1):475. doi: 10.1186/s12916-023-03161-6.

Dissemination of Registered COVID-19 Clinical Trials (DIRECCT): a cross-sectional study

Maia Salholz-Hillel [1], Molly Pugh-Jones [1], Nicole Hildebrand [1], Tjada A Schult [1], Johannes Schwietering [1], Peter Grabitz [1], Benjamin Gregory Carlisle [1], Ben Goldacre [2], Daniel Strech [1], Nicholas J DeVito [3]



"Our study showed such misspecification of completion dates on the registry:
71 trials, 18% of all results located, had **results published on the same day or prior to the registered completion date.**"

Tracking switched outcomes in clinical trials

Here's what we found.

67	9	354	357
TRIALS CHECKED	TRIALS WERE PERFECT	OUTCOMES NOT REPORTED	NEW OUTCOMES SILENTLY ADDED

On average, each trial reported just 58.2% of its specified outcomes. And on average, each trial silently added 5.3 new outcomes.

58	18	8	32
LETTERS SENT	LETTERS PUBLISHED	LETTERS UNPUBLISHED AFTER 4 WEEKS	LETTERS REJECTED BY EDITOR

Annals of Internal Medicine

“[registries] do not routinely monitor whether the data in the registry match the protocol, and may not be updated when the protocol changes.”

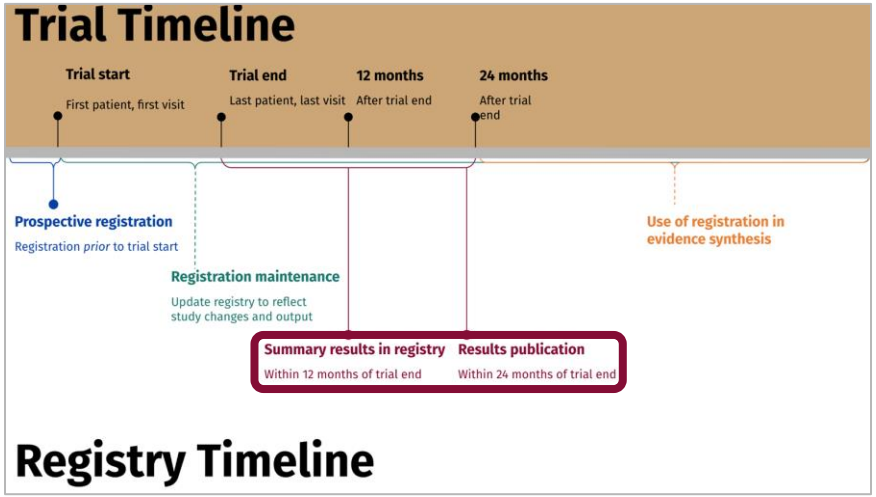
“Registry information can be incomplete or lack sufficient detail.”

“Vague and erroneous entries.”

“Inaccuracies in the trial registration documents are more of an issue for the individual overseeing the trial registries.”

JAMA
The Journal of the American Medical Association

Results Dissemination



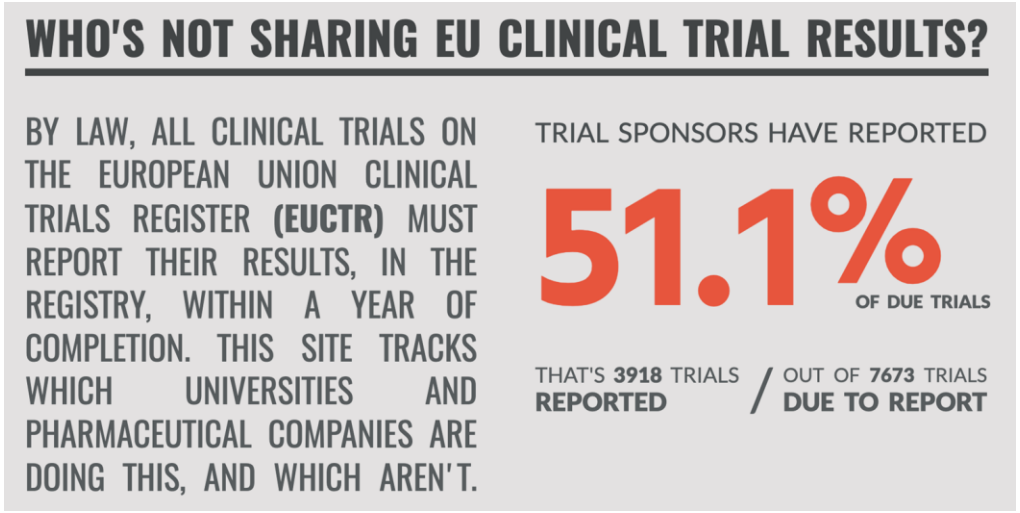
FDAAA TrialsTracker

Single trials | Ranked sponsors | FAQ | Blog | Fund this work! | @FDAAATracker

Who's sharing their clinical trial results?

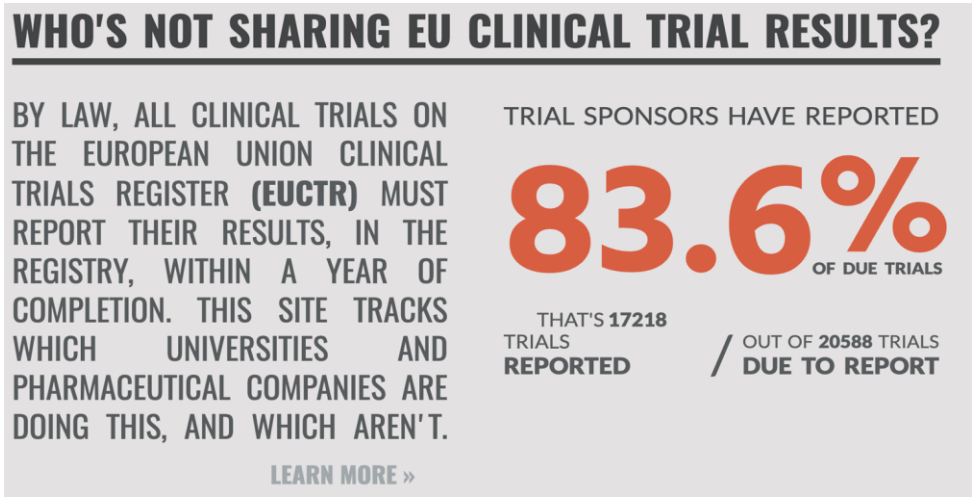
FDAAA 2007 is a law that requires certain clinical trials to report results. After a long wait, it effectively came into force for all trials due after January 2018. The FDA are not publicly tracking compliance. So we are, here.

Trials reported	Percent reported	US Govt could have imposed fines of at least	Fines claimed by US Govt
16135 out of 20855	77.4%	$62,988,588,969	$0



September 2018

May 2024



RESEARCH ARTICLE Open Access

Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles

Eve Tang[1], Philippe Ravaud[1,2,3,4,5], Carolina Riveros[2,4], Elodie Perrodeau[2,4] and Agnes Dechartres[2,3,4,5*]

RESEARCH Open Access

Consistency of trial reporting between ClinicalTrials.gov and corresponding publications: one decade after FDAAA

Ramtin Talebi[1], Rita F. Redberg[1] and Joseph S. Ross[2,3,4*]

OPEN ACCESS Freely available online PLOS | MEDICINE

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

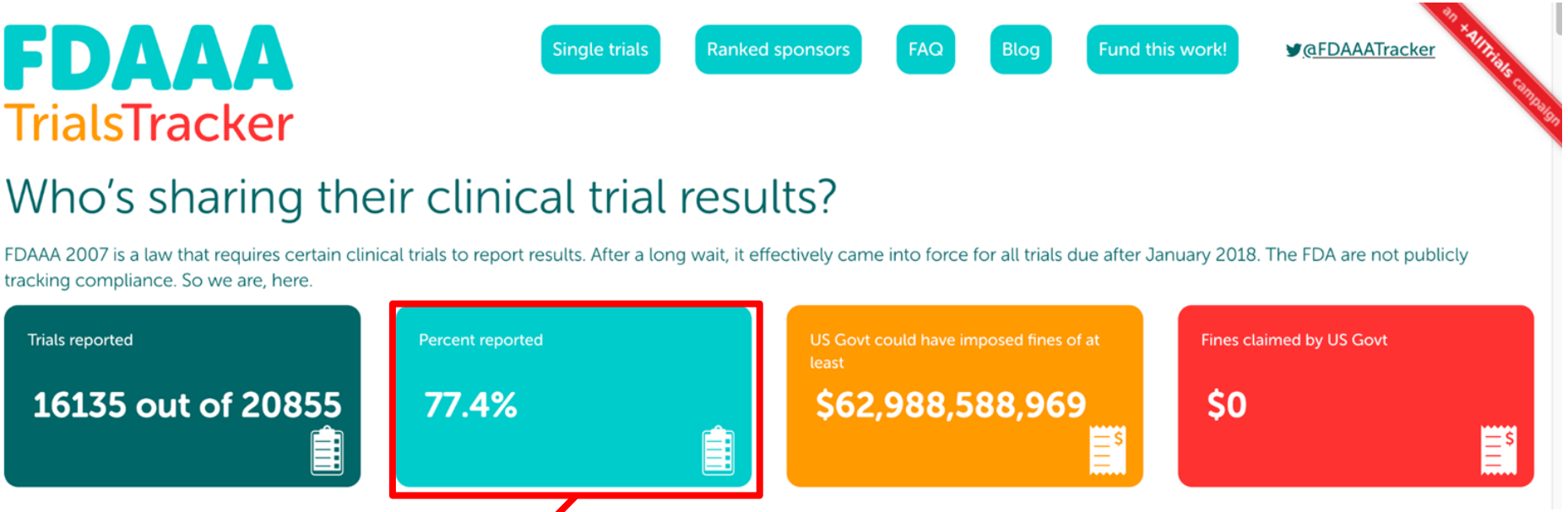
Carolina Riveros[1,2,3], Agnes Dechartres[1,2,3]*, Elodie Perrodeau[1,3], Romana Haneef[1,3], Isabelle Boutron[1,2,3,4], Philippe Ravaud[1,2,3,4,5]

1 INSERM U738, Paris, France, **2** Université Paris Descartes—Sorbonne Paris Cité, Paris, France, **3** Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France, **4** French Cochrane Centre, Paris, France, **5** Mailman School of Public Health, Columbia University, New York, New York, United States of America

Reporting Discrepancies between the ClinicalTrials.gov Results Database and Peer Reviewed Publications

Daniel Hartung, PharmD, MPH[1,*], Deborah A. Zarin, MD[2], Jeanne-Marie Guise, MD, MPH[3], Marian McDonagh, PharmD[3], Robin Paynter, MLS[3], and Mark Helfand, MD, MS, MPH[3,4]

However...



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> PLoS Med. 2023 Mar 21;20(3):e1004175.
doi: 10.1371/journal.pmed.1004175.

Institutional dashboards on clinical trial transparency for University Medical Centers: A case study

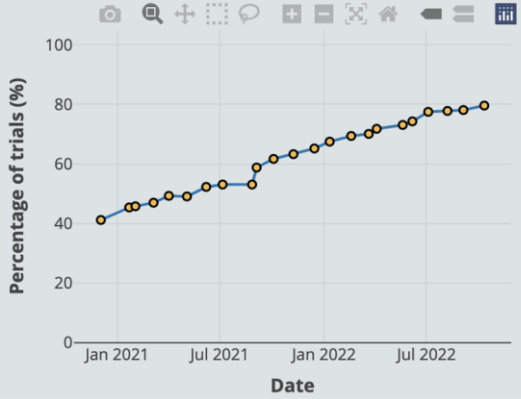
Delwen L Franzen [1], Benjamin Gregory Carlisle [1], Maia Salholz-Hillel [1], Nico Riedel [1], Daniel Strech [1]

https://quest-cttd.bihealth.org/

Summary Results Reporting

79%

of due clinical trials registered in EUCTR (n=804) reported summary results (as of: 2022-11-04)



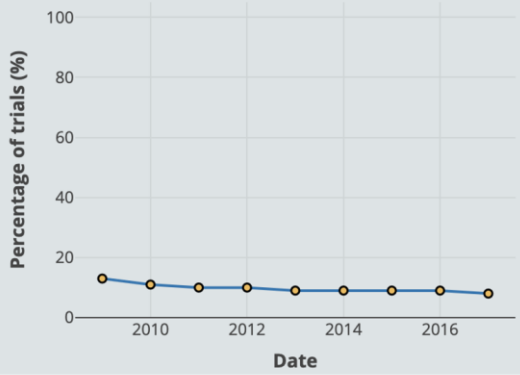
Trial registry

EUCTR

Summary Results Reporting

8%

of due clinical trials registered in ClinicalTrials.gov (n=2253) reported summary results



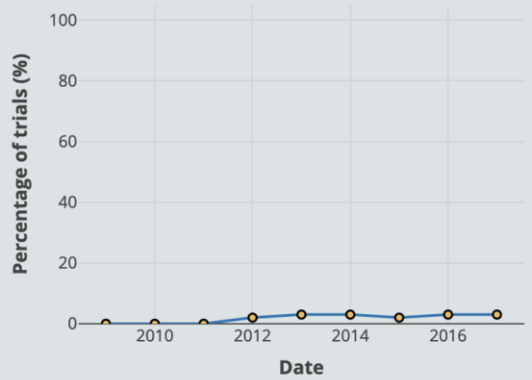
Trial registry

ClinicalTrials.gov

Summary Results Reporting

3%

of due clinical trials registered in DRKS (n=642) reported summary results



Trial registry

DRKS

BMC Med. 2023 Nov 29;21(1):475. doi: 10.1186/s12916-023-03161-6.

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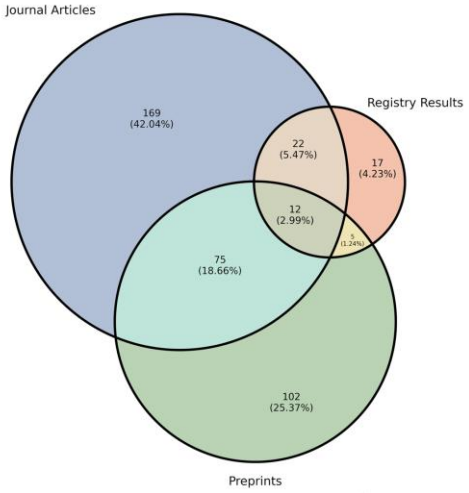
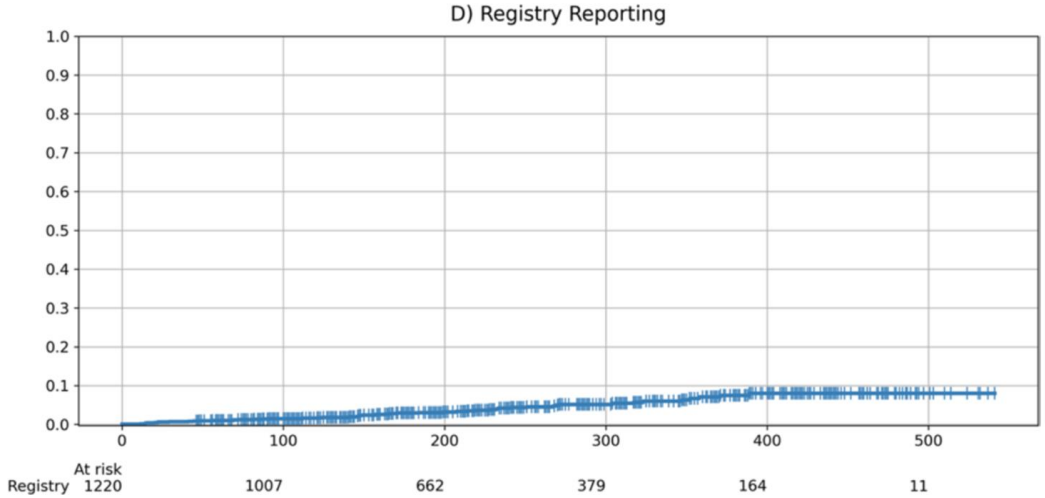
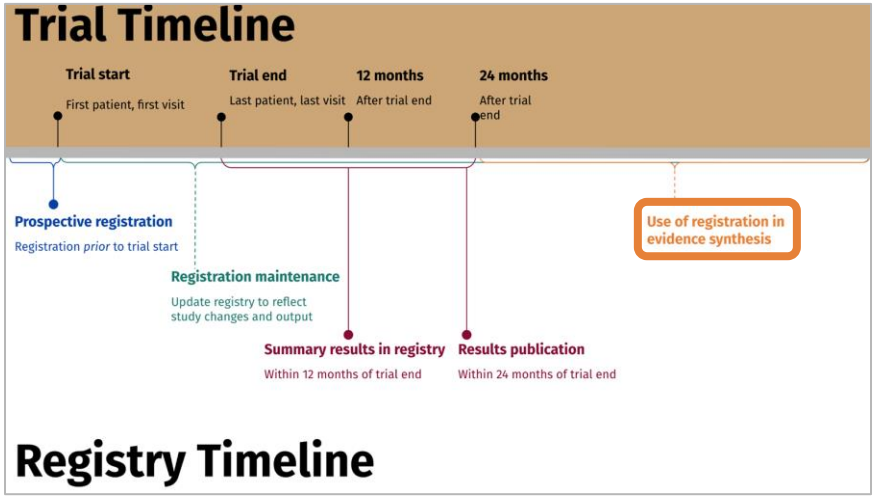


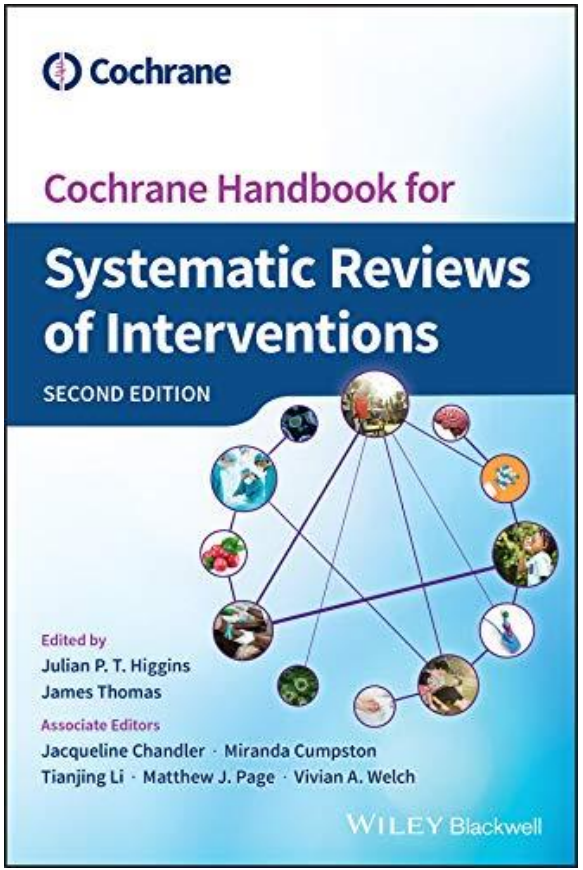


Only 7.2% reported on the registry, even when restricting the population to only the registries most likely to contain results.

Time-to-reporting is slow

Evidence Synthesis





C27: Searching trials registers (**Mandatory**)

Search trials registers and repositories of results, where relevant to the topic, through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate.

Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible. Although ClinicalTrials.gov is included as one of the registers within the WHO ICTRP portal, it is recommended that both ClinicalTrials.gov and the ICTRP portal are searched separately due to additional features in ClinicalTrials.gov.

Review > BMJ. 2017 Feb 17:356:j448. doi: 10.1136/bmj.j448.

Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of meta-analyses

Marie Baudard [1 2], Amélie Yavchitz [3 2 4], Philippe Ravaud [1 2 4 5 6], Elodie Perrodeau [1 2 4 5], Isabelle Boutron [1 2 4 5]

Searching the registry added relevant studies to 43% of 223 reviews which increased the precision of pooled effect sizes.

However...

Review > BMJ. 2017 Feb 17:356:j448. doi: 10.1136/bmj.j448.

Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of meta-analyses

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Among 223 selected systematic reviews,
116 (52%) **did not report a search of trial registries**.

Systematic Reviews Published in Emergency Medicine Journals Do Not Routinely Search Clinical Trials Registries: A Cross-Sectional Analysis

Lukas G. Keil, BS; Timothy F. Platts-Mills, MD, MSc; Christopher W. Jones, MD*

*Corresponding Author. E-mail: cjones.unc@gmail.com.

8/41 (20%) reviews from 2013

Clinical trial registry use in anaesthesiology systematic reviews

A cross-sectional study of systematic reviews published in anaesthesiology journals and the Cochrane Library

Blake A. Umberham, Byron N. Detweiler, Matthew T. Sims and Matt Vassar

49/415 (12%) reviews from 2007-2015

Trial Registry Use in Surgery Systematic Reviews: A Cross-sectional Study

Harrison M. Gray, BS,[a,] Alainna Simpson, DO,[b] Aaron Bowers, BS,[a] Austin L. Johnson, BS,[a] and Matt Vassar, PhD[a]*

252/996 (25%) reviews from 2013-2017

Infrequent use of clinical trials registries in published systematic reviews in urology

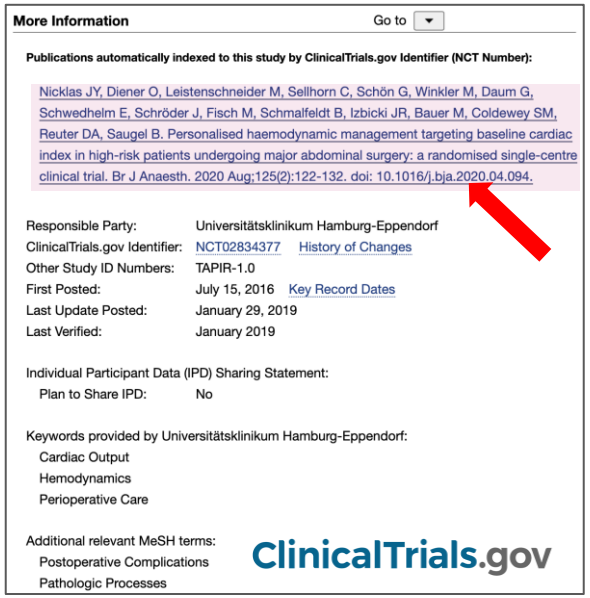
Tareq Aro[1,2] · Kevin Koo[1] · Brian R. Matlaga[1]

16/92 (17%) reviews from 2017

› Clin Trials. 2022 Jun;19(3):337-346. doi: 10.1177/17407745221087456.
Epub 2022 Apr 1.

Results publications are inadequately linked to trial registrations: An automated pipeline and evaluation of German university medical centers

Maia Salholz-Hillel [1], Daniel Strech [1], Benjamin Gregory Carlisle [1]



More Information Go to

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Nicklas JY, Diener O, Leistenschneider M, Sellhorn C, Schön G, Winkler M, Daum G, Schwedhelm E, Schröder J, Fisch M, Schmalfeldt B, Izbicki JR, Bauer M, Coldewey SM, Reuter DA, Saugel B. Personalised haemodynamic management targeting baseline cardiac index in high-risk patients undergoing major abdominal surgery: a randomised single-centre clinical trial. Br J Anaesth. 2020 Aug;125(2):122-132. doi: 10.1016/j.bja.2020.04.094.

Responsible Party:	Universitätsklinikum Hamburg-Eppendorf
ClinicalTrials.gov Identifier:	NCT02834377 History of Changes
Other Study ID Numbers:	TAPIR-1.0
First Posted:	July 15, 2016 Key Record Dates
Last Update Posted:	January 29, 2019
Last Verified:	January 2019

Individual Participant Data (IPD) Sharing Statement:
Plan to Share IPD: No

Keywords provided by Universitätsklinikum Hamburg-Eppendorf:
Cardiac Output
Hemodynamics
Perioperative Care

Additional relevant MeSH terms:
Postoperative Complications
Pathologic Processes

ClinicalTrials.gov

BJA

British Journal of Anaesthesia, 125 (2): 122–132 (2020)

CARDIOVASCULAR

Personalised haemody
cardiac index in high-r
surgery: a randomised

Abstract

Methods

Trial design

Personalised haemodynamic management | 123

Keywords: cardiac output; haemodynamic monitoring; morbidity; outcomes; randomised trial

17% (327 of 1,895) trials had **no link between registration and publication**

Calls to Action

Re-evaluate & re-commit

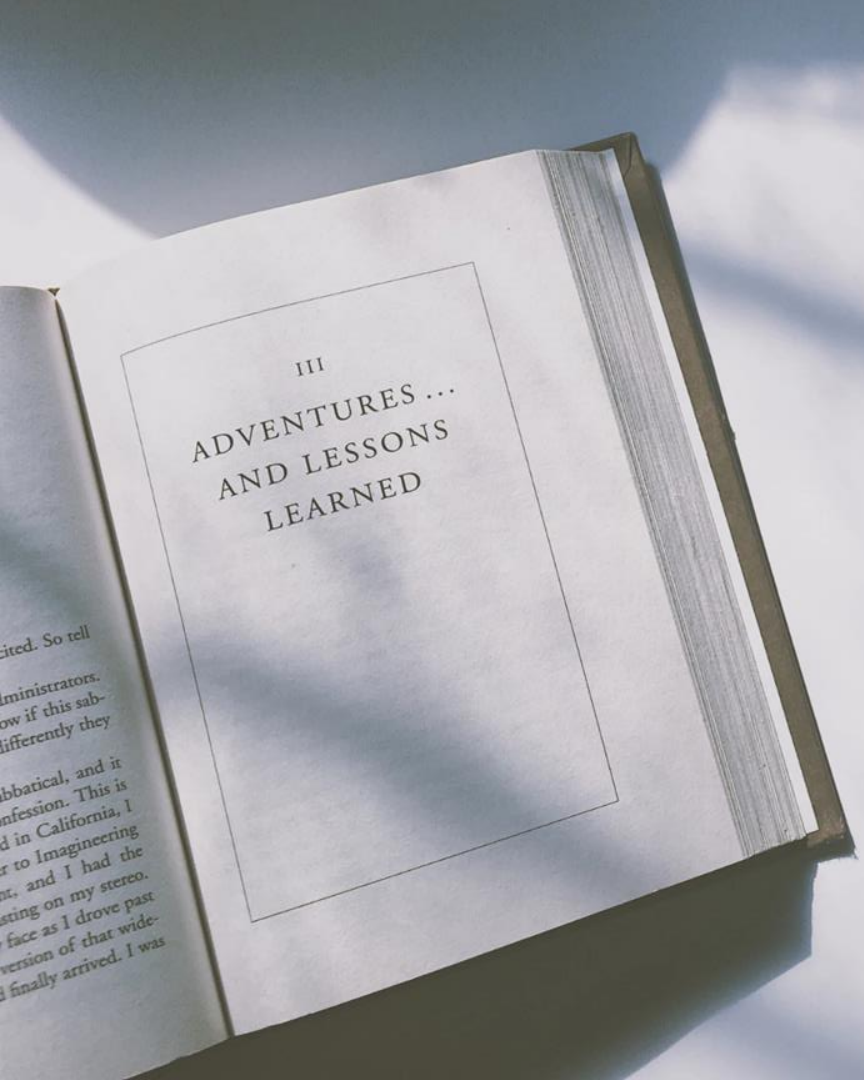
Institutions need to re-evaluate their reasons for initially supporting clinical trial registration and ensure it is serving that function within their current processes.

Modernize infrastructure

Clinical trial infrastructure needs to adapt and modernise to increase utility and avoid becoming little more than a bureaucratic requirement.

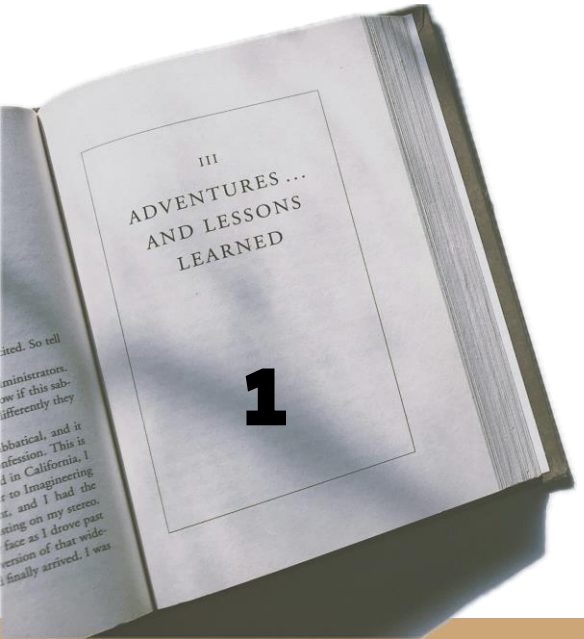
Actionable requirements

Legislative and regulatory transparency requirements need must be meaningful and facilitate, without being overly burdensome.



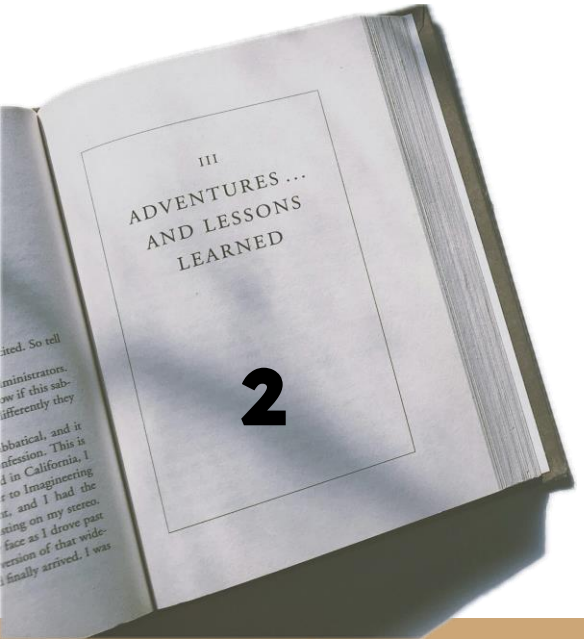
Lessons for other disciplines

Registration as a living record

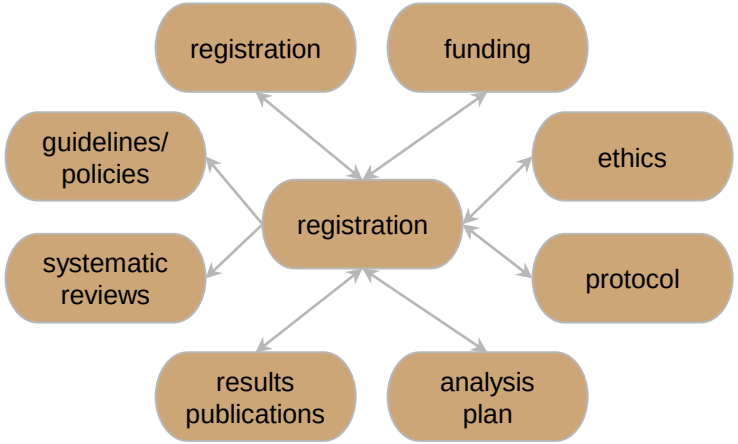


1. (Pre)registration alone is a checkbox exercise and insufficient if no one is engaging further with it.
2. You need accurate and version-controlled information about a study for registration/registries to effectively promote accountability and transparency.

Registration as part of the thread of evidence



Thread of evidence compounds the value of registration and requires infrastructure and implementation across stakeholders.



Altman et al. Linked publications from a single trial: a thread of evidence. Trials. 2014. 10.1186/1745-6215-15-369.

Thank you

Images: Unsplash