

The Use and Misuse of Clinical Trial Registries

Lessons learned from biomedical metaresearch & reflections for other fields

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University of Oxford

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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.”

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



**World Health
Organization**

How did we get here?



Practical



International Standards for Clinical Trial Registries

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

Ethical



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,

SECTION 1. SHORT TITLE.

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

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

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)

ClinicalTrials.gov

ISRCTN registry

Deutsches Register
Klinischer Studien
German Clinical
Trials Register

EU Clinical Trials Register

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

국립중앙연구원
국립중앙연구원
CRIS

JRCT
Japan Registry of Clinical Trials

RPCEC
Registro Público Cubano
de Ensayos Clínicos

Lebanon Clinical Trials Registry

ChCTR
中国临床试验注册中心
Chinese Clinical Trial Registry
世界卫生大会国际临床试验注册中心—临床试验注册中心

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
Ensaio Clínicos

ANZCTR
Australian New Zealand Clinical Trials Registry

ClinicalTrials.gov

RECRUITING ⓘ

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

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

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

More Information

Record History



Why clinical trial registries?



Who is doing what?



Can we easily find things?



Are there trials for my condition?



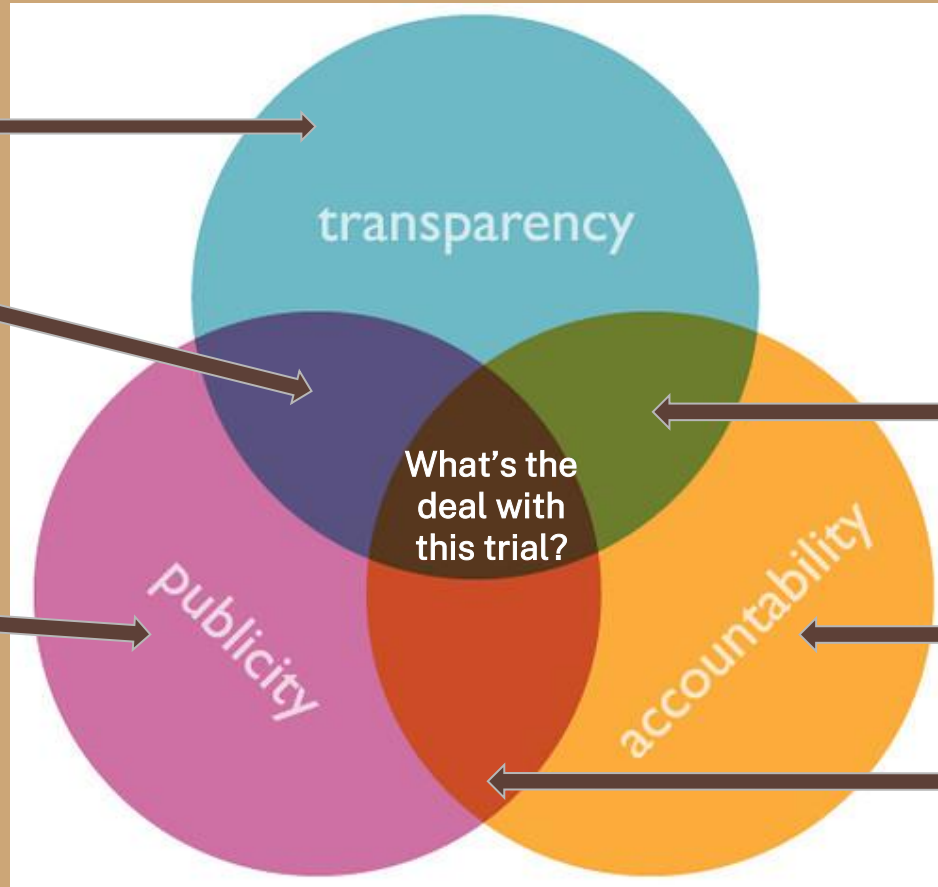
Did you do what you said you would?



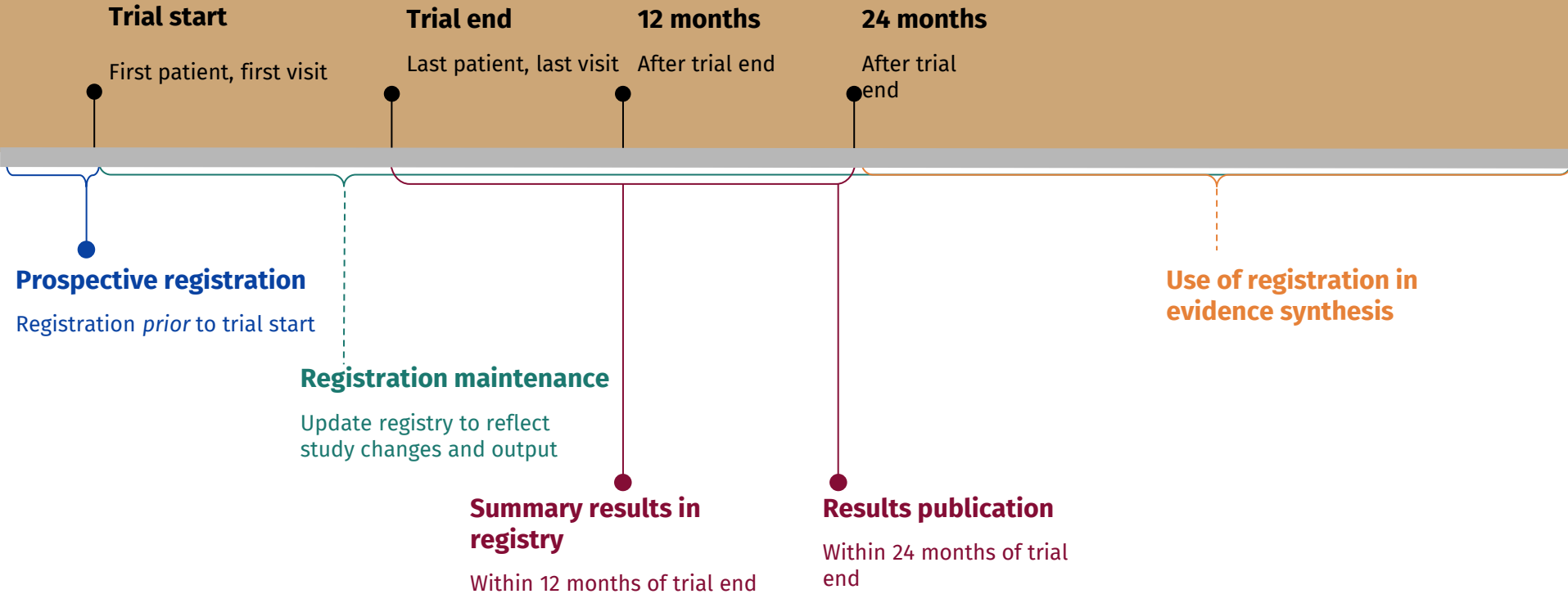
Did you do it before you started the trial?



Can everyone check?



Trial Timeline



Registry Timeline

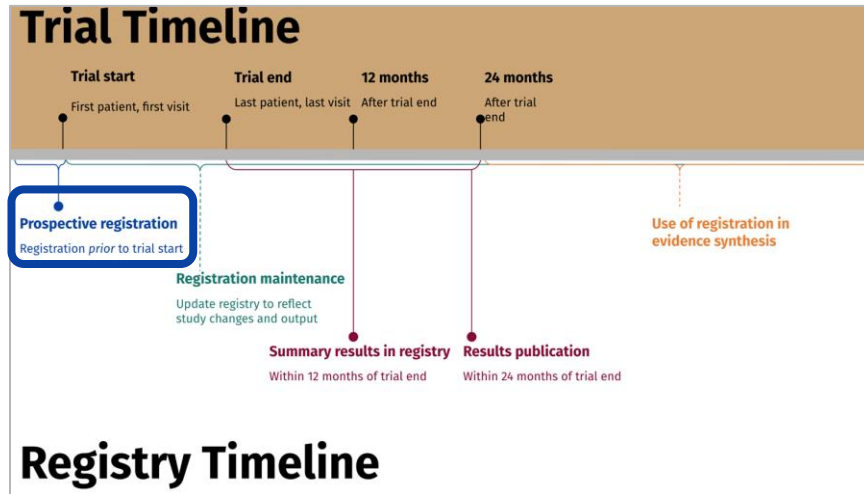
USE



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...**

ClinicalTrials.gov

Study Documents ⓘ

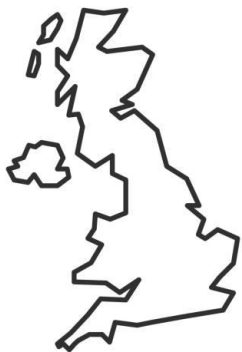
Study protocols

Statistical analysis plans (SAPs)

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

František Bartoš^{1,2}  | Maximilian Maier³  | Eric-Jan Wagenmakers¹  |
Franziska Nippold⁴ | Hristos Doucouliagos⁵  | John P. A. Ioannidis^{6,7,8,9,10}  |
Willem M. Otte¹¹  | Martina Sladekova¹²  | Teshome K. Deressa¹³  |
Stephan B. Bruns^{6,13,14}  | Daniele Fanelli^{15,16}  | T. D. Stanley⁵ 

“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.**”



Clinical trials in 2022

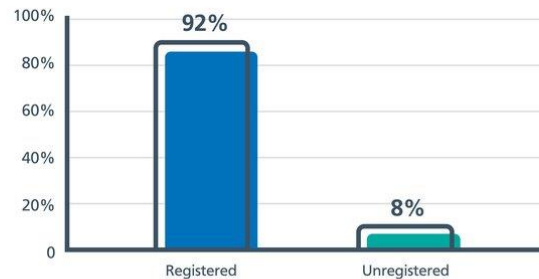


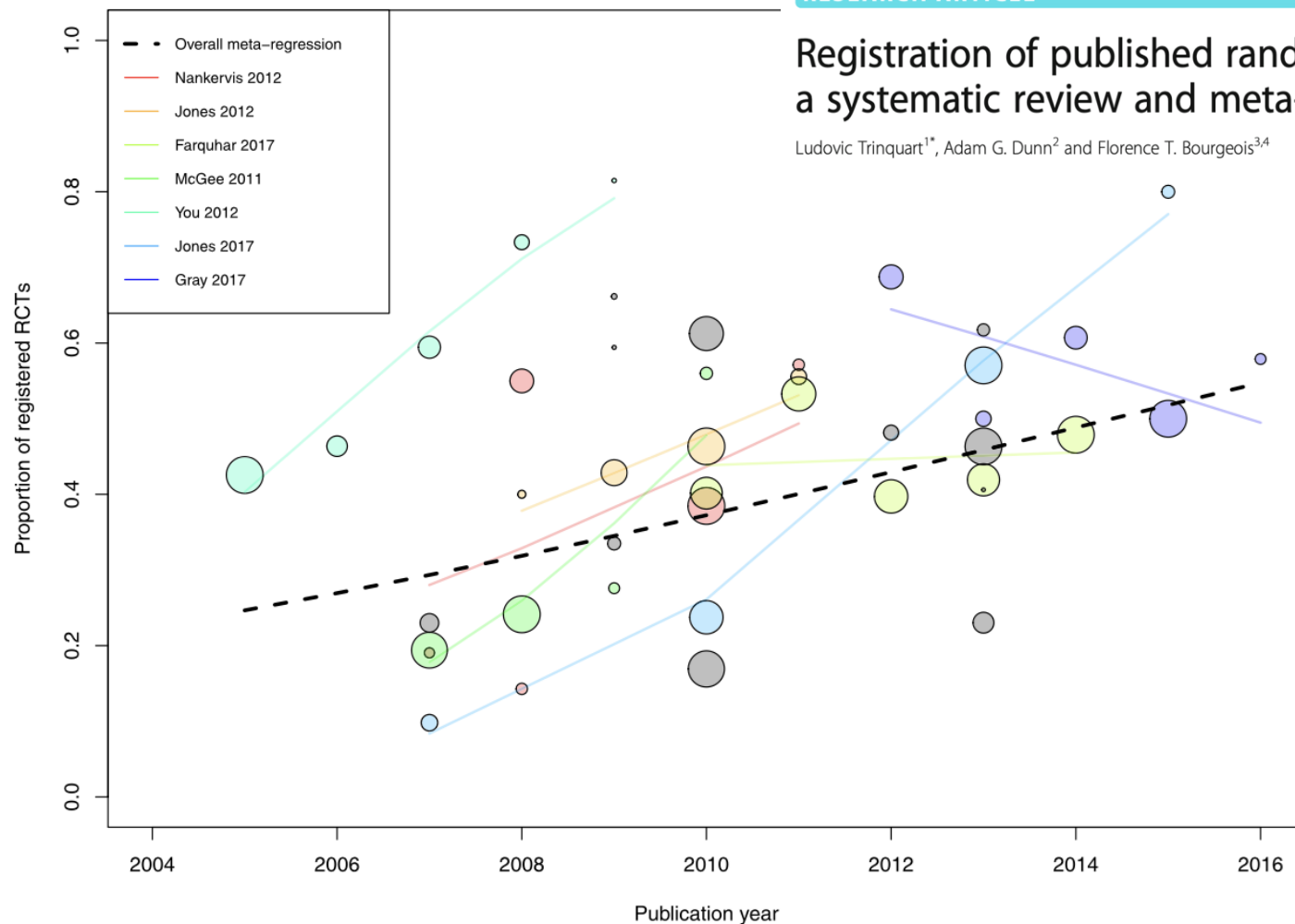
Table 1. FDAAA Compliance and Characteristics in Assessment Areas

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



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

Ludovic Trinquart^{1*}, Adam G. Dunn² and Florence T. Bourgeois^{3,4}



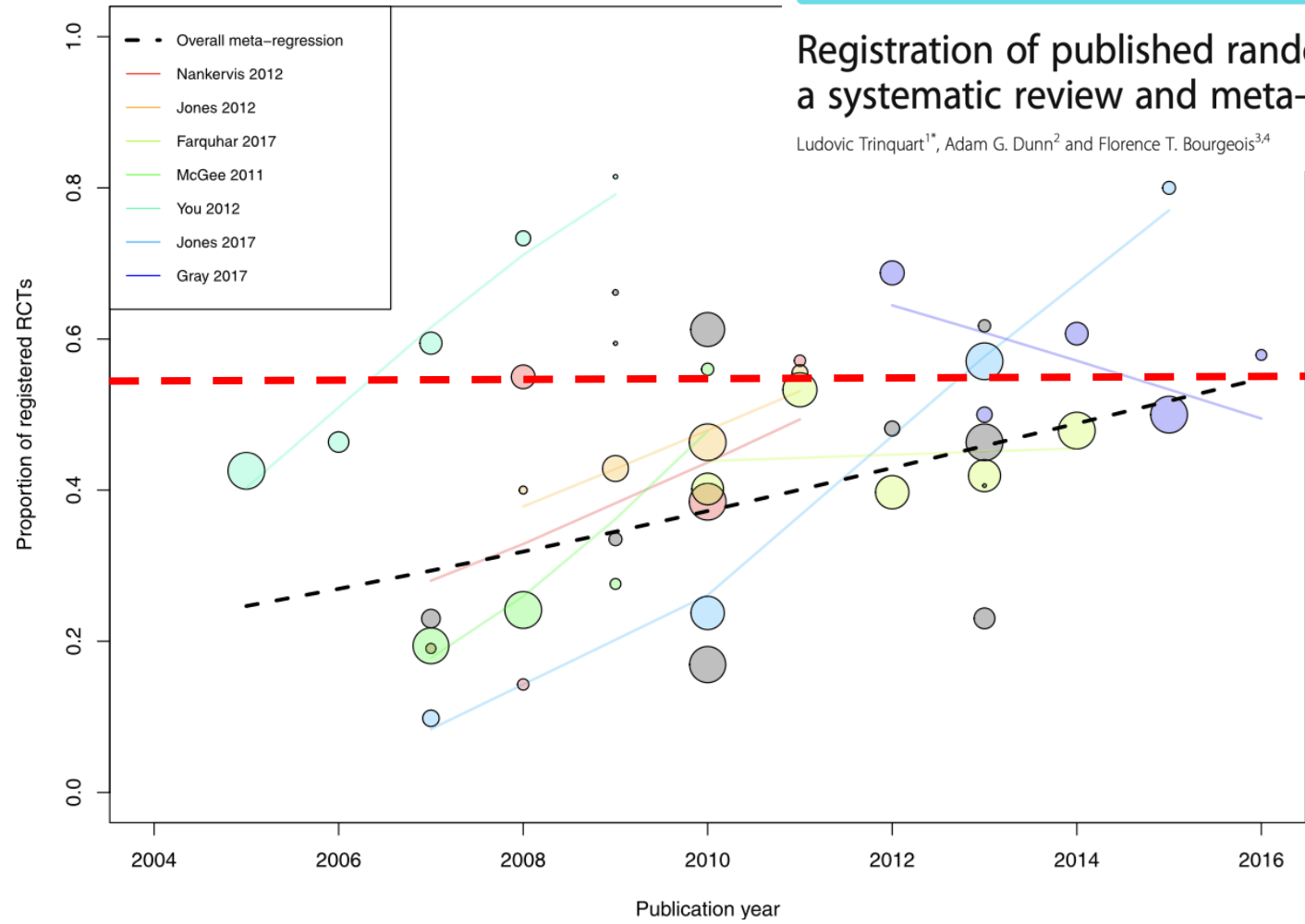
However...





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

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**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)

Search Results

Viewing 1-10 out of 28,811 studies

 Card View

 Table View

None Selected

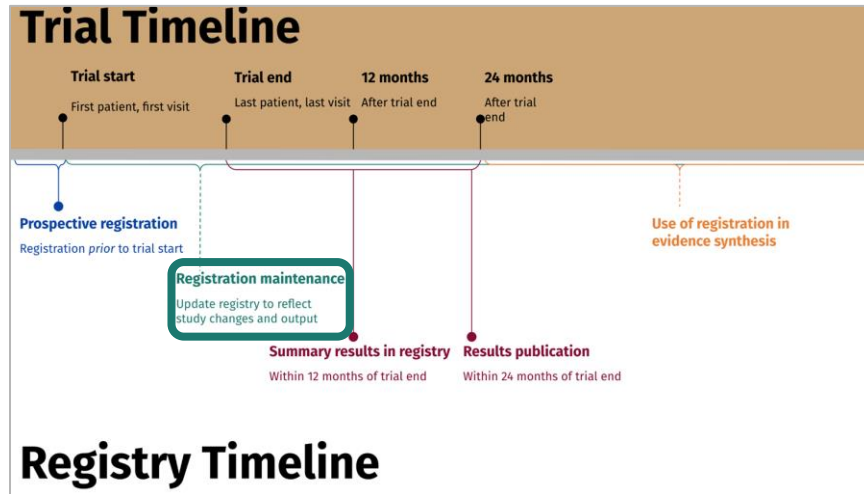


 RSS

 Manage

~1 of every 3 were retrospectively registered.

Registration Maintenance



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

16135 out of 20855



Percent reported

77.4%



US Govt could have imposed fines of at least

\$62,988,588,969



Fines claimed by US Govt

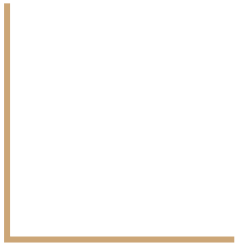
\$0



Table 1. FDAAA Compliance and Characteristics in Assessment Areas

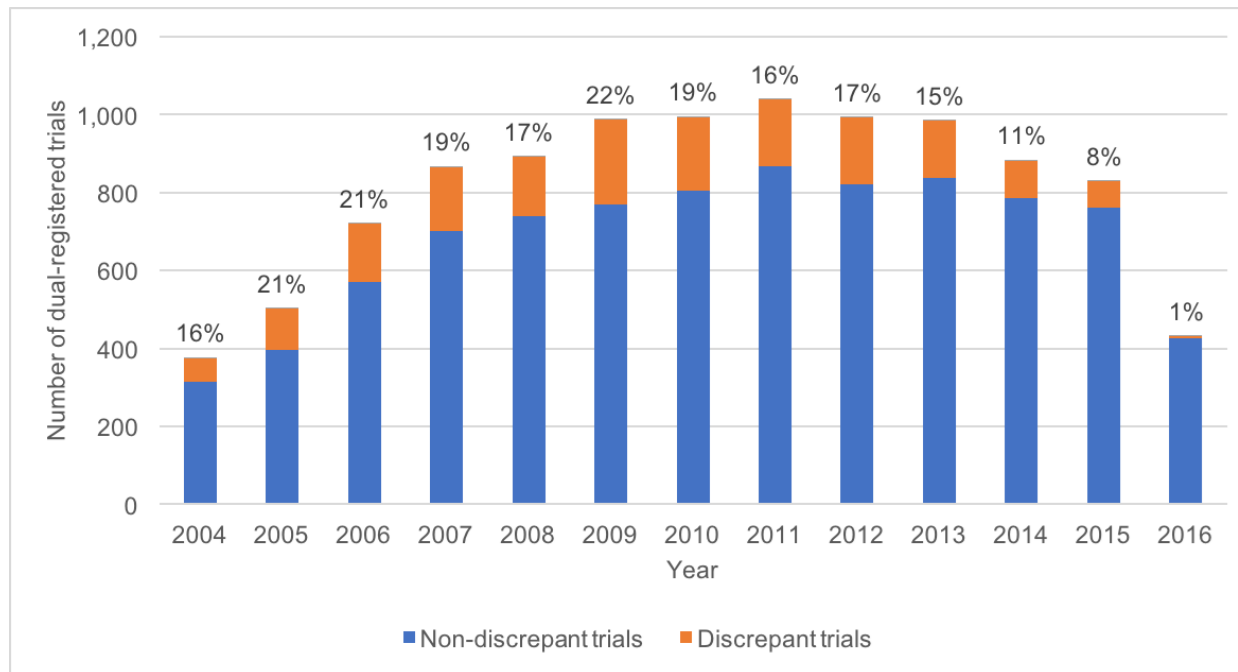
	Compliant results reporting		Timely registration ^a		Annual data verification		Certificate of delay requests		Document submission ^b	
	Total (n =)	Compliant (n = %)	Total (n =)	Compliant (n = %)	Total (n =)	Compliant (n = %)	Total (n =)	Compliant (n = %)	Total (n =)	Compliant (n = %)
Detailed compliance data	8863	39.5%	27 645	88.4%	16 709	75.6%	1354	66.0%	5449	99.1%

However...



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

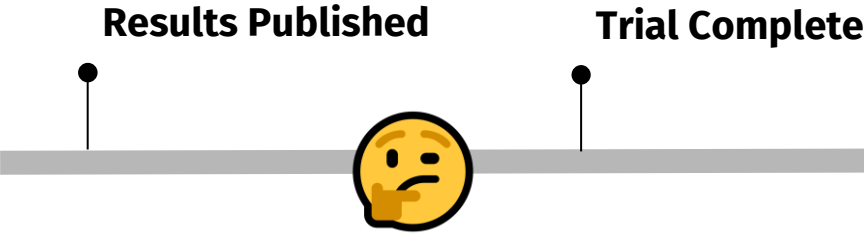
Jessica Fleming¹, Ben Goldacre¹



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

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

Maia Salholz-Hillel¹, Molly Pugh-Jones¹, Nicole Hildebrand¹, Tjada A Schult¹, Johannes Schwietering¹, Peter Grabitz¹, Benjamin Gregory Carlisle¹, Ben Goldacre², Daniel Strech¹, Nicholas J DeVito³



“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

TRIALS CHECKED

9

TRIALS WERE
PERFECT

354

OUTCOMES NOT
REPORTED

357

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

LETTERS SENT

18

LETTERS PUBLISHED

8

LETTERS
UNPUBLISHED AFTER
4 WEEKS

32

LETTERS REJECTED BY
EDITOR

Annals of Internal Medicine®

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

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

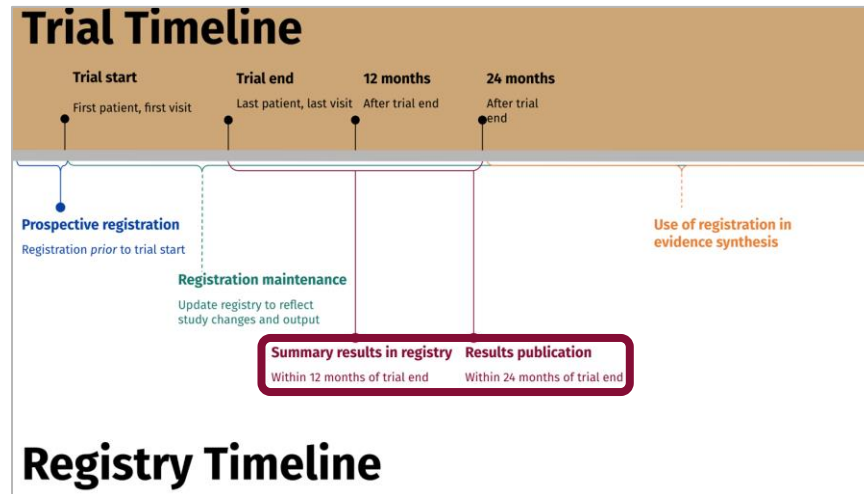
“Registry information can be incomplete or lack sufficient detail.”

“Vague and erroneous entries.”

JAMA

The Journal of the American Medical Association

Results Dissemination



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\$0



WHO'S NOT SHARING EU CLINICAL TRIAL RESULTS?

BY LAW, ALL CLINICAL TRIALS ON THE EUROPEAN UNION CLINICAL TRIALS REGISTER (EUCTR) MUST REPORT THEIR RESULTS, IN THE REGISTRY, WITHIN A YEAR OF COMPLETION. THIS SITE TRACKS WHICH UNIVERSITIES AND PHARMACEUTICAL COMPANIES ARE DOING THIS, AND WHICH AREN'T.

TRIAL SPONSORS HAVE REPORTED

51.1%
OF DUE TRIALS

THAT'S **3918** TRIALS / OUT OF **7673** TRIALS
REPORTED / DUE TO REPORT

September 2018

May 2024

WHO'S NOT SHARING EU CLINICAL TRIAL RESULTS?

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TRIAL SPONSORS HAVE REPORTED

83.6%
OF DUE TRIALS

THAT'S **17218** TRIALS / OUT OF **20588** TRIALS
REPORTED / DUE TO REPORT

[LEARN MORE »](#)

RESEARCH ARTICLE

Open Access

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



Eve Tang¹, Philippe Ravaud^{1,2,3,4,5}, Carolina Riveros^{2,4}, Elodie Perrodeau^{2,4} and Agnes Dechartres^{2,3,4,5*}

OPEN ACCESS Freely available online



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

RESEARCH

Open Access

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



Ramtin Talebi¹, Rita F. Redberg¹ and Joseph S. Ross^{2,3,4*}

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

Daniel Hartung, PharmD, MPH^{1,*}, Deborah A. Zarin, MD², Jeanne-Marie Guise, MD, MPH³,
Marian McDonagh, PharmD³, Robin Paynter, MLS³, and Mark Helfand, MD, MS, MPH^{3,4}

However...

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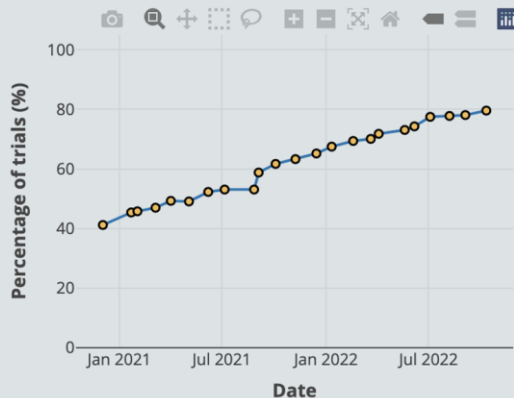
Institutional dashboards on clinical trial transparency for University Medical Centers: A case study

Delwen L Franzen¹, Benjamin Gregory Carlisle¹,
Maia Salholz-Hillel¹, Nico Riedel¹, Daniel Strech¹

Summary Results Reporting

79%

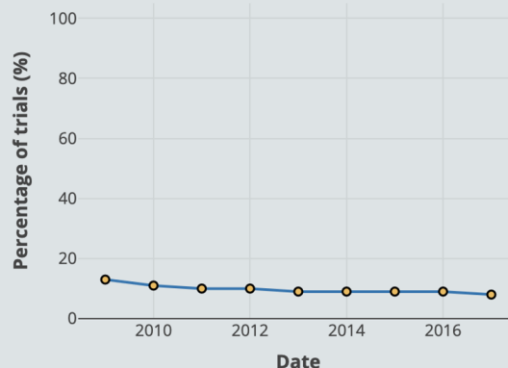
of due clinical trials registered in **EUCTR** (n=804) reported summary results (as of: 2022-11-04)



Summary Results Reporting

8%

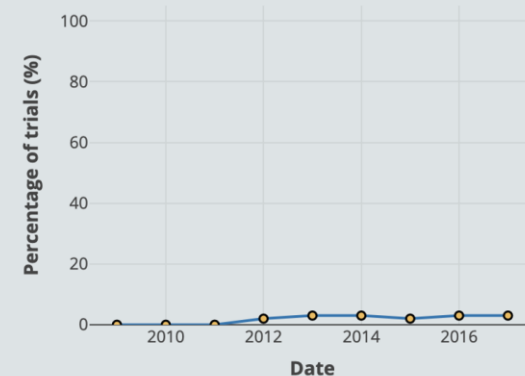
of due clinical trials registered in **ClinicalTrials.gov** (n=2253) reported summary results



Summary Results Reporting

3%

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



Trial registry

EUCTR

Trial registry

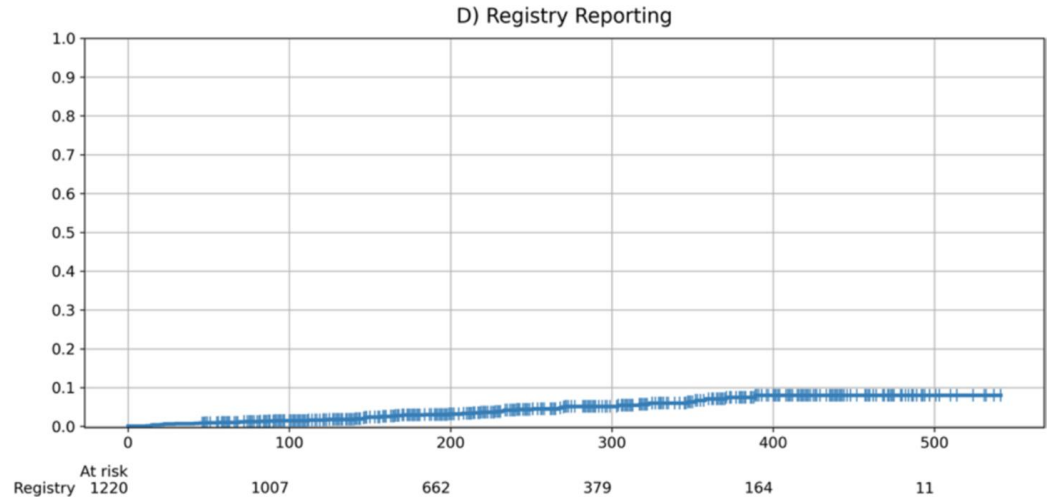
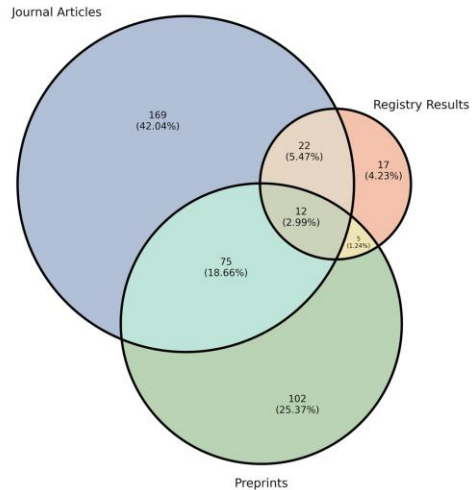
ClinicalTrials.gov

Trial registry

DRKS

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

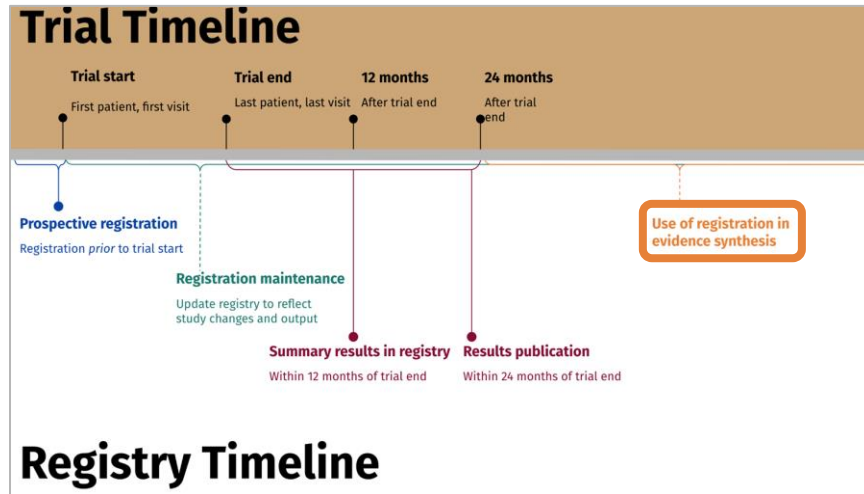
Maia Salholz-Hillel¹, Molly Pugh-Jones¹, Nicole Hildebrand¹, Tjada A Schult¹, Johannes Schwietering¹, Peter Grabitz¹, Benjamin Gregory Carlisle¹, Ben Goldacre², Daniel Strech¹, Nicholas J DeVito³



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





Cochrane Handbook for

Systematic Reviews of Interventions

SECOND EDITION



Edited by
Julian P. T. Higgins
James Thomas

Associate Editors
Jacqueline Chandler · Miranda Cumpston
Tianjing Li · Matthew J. Page · Vivian A. Welch

WILEY Blackwell

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.

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...

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}

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

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

Harrison M. Gray, BS,^{a,*} Alaina Simpson, DO,^b Aaron Bowers, BS,^a
Austin L. Johnson, BS,^a and Matt Vassar, PhD^a

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

**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. Umerham, Byron N. Detweiler, Matthew T. Sims and Matt Vassar

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

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

Tareq Aro^{1,2} · Kevin Koo¹ · Brian R. Matlaga¹

16/92 (17%) reviews
from 2017

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)
doi: 10.1016/j.bja.2020.04.094

CARDIOVASCULAR

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

Julia Y. Nicklas^{1*}, Oliver Diener¹, Gerhard F. Fisch¹, Martin Winkler¹, Barbara Schmalz¹, Daniel A. Reuter¹ and Bernd Saugel¹

Editor's key points

- The optimal target for haemodynamic management of high-risk non-cardiac surgical patients remains unclear.
- Individualised haemodynamic management may be a rational approach to reduce postoperative morbidity.
- In this single-centre study, high-risk patients were randomised to either routine care or a therapeutic algorithm aimed at maintaining preoperative cardiac index.
- The personalised approach reduced major post-operative complications substantially within 30 days after surgery.

Major complications and mortality are common after major surgery,^{1,2} particularly in patients with co-morbidities undergoing major surgical procedures.^{3,4} Postoperative goal-directed haemodynamic therapy may decrease postoperative complications in high-risk patients.⁵⁻⁷ However, because haemodynamic targets have varied between trials, the optimal haemodynamic treatment strategy for high-risk surgical patients remains unclear.⁸

The choice of the haemodynamic target value is likely to be critical,⁹ as indicated by goal-directed therapy algorithms using cardiac output monitors that are associated with reductions in postoperative morbidity.¹⁰ Previous prospective goal-directed therapy trials directly aimed at a minimisation of circulatory volume,¹¹ used dynamic cardiac perfusion variables to maximise cardiac output¹²⁻¹⁴ or used fixed population-based values as a haemodynamic target.¹⁵ However, haemodynamic variables used as targets—including cardiac output—were not consistently among individuals.¹⁶ In contrast to a ‘one-size-fits-all’ approach,¹⁷ a precision or personalised strategy may be most beneficial.¹⁸

We hypothesised that the individual patient’s preoperative cardiac index at rest may be the optimal haemodynamic target to reduce intraoperative management.¹⁹ We conducted a randomised clinical trial to test whether personalised haemodynamic management, by maintaining preoperative personal cardiac index at rest with fluids and the inotropic dobutamine, reduces complications or death within 30 days after surgery, compared with routine management in high-risk patients undergoing major abdominal surgery. We also put forward the secondary hypothesis that personalised haemodynamic management may reduce the systemic inflammatory response and promote neurocognitive recovery after surgery, as suggested by personalised haemodynamic management trials.^{20,21}

Methods

Trial design

We conducted a single-centre prospective randomised controlled clinical trial, ‘Targeting preoperatively Assessed Personal cardiac Index in major abdominal surgery patients (TAPAS)’, at the University Medical Center Hamburg Eppendorf

Randomisation and procedures to minimise bias

Randomisation took place after the baseline cardiac index measurements to minimise study bias and to be able to compare baseline cardiac index between patients in the personalised and routine management groups. The cuff responsible for baseline cardiac index measurements was not blinded to group allocation, because they were also in charge of data collection throughout the study (DO and MG). After baseline cardiac index assessment, the patients were randomised 1:1 without stratification based on computer-generated codes to routine management or to a personalised haemodynamic management algorithm. Allocation was concealed in sequential, permuted opaque envelopes. The patients were blinded to group allocation, but clinicians responsible for intraoperative care in the personalised management group could not be. However, all outcomes were assessed by investigators blinded to patient allocation.

Study interventions

All subjects

We assessed the baseline cardiac index at rest using non-invasive pulse wave analysis finger-cuff technology.²²⁻²⁴ We used the CHAP system (CONIPRESS Medication GmbH, Graz, Austria) that has been validated against pulmonary artery thermodilution.²⁵ A research staff member (not the subject) and measured the baseline cardiac index at rest the evening before surgery on the day with the subject being awake and lying in supine position. The CHAP finger-cuff technology derives a continuous arterial pressure waveform from the finger-cuff pressure that is needed to keep the blood volume in the finger constant during the cardiac cycle.²⁶ The arterial pressure signal derived by the finger-cuff is calibrated to in-trial blood pressure values obtained with an aortic-metric upper-arm cuff. Based on pulse wave analysis, cardiac index is estimated from the noninvasively obtained pressure waveform using a proprietary algorithm.^{27,28} We

Hamburg, Germany) provided written informed consent before study enrollment. The trial was registered at ClinicalTrials.gov (NCT02834377) in May 2016.

Inclusion criteria

Adults >18 yr scheduled for major abdominal surgery expected to last >90 min or cause blood loss exceeding 500 ml were eligible for study enrollment. At least one preoperative patient-related high-risk criterion was also required (details regarding the high-risk criteria are provided in the Supplementary Appendix).

Exclusion criteria

We excluded patients who were pregnant, had palliative or emergency surgery, or who participated in another interventional 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

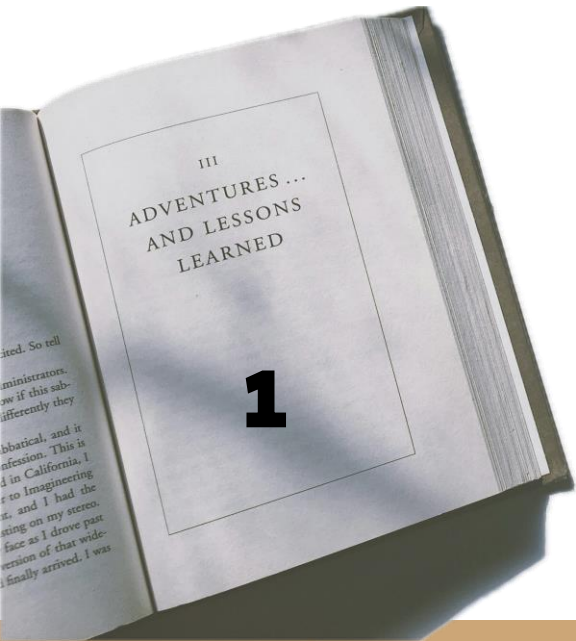
Legislative and regulatory transparency requirements need must be meaningful and facilitate, without being overly burdensome.

III
ADVENTURES ...
AND LESSONS
LEARNED

**Lessons for other
disciplines**

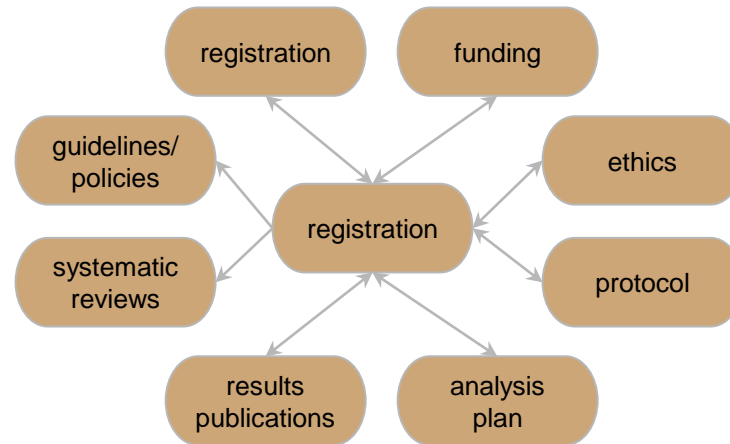
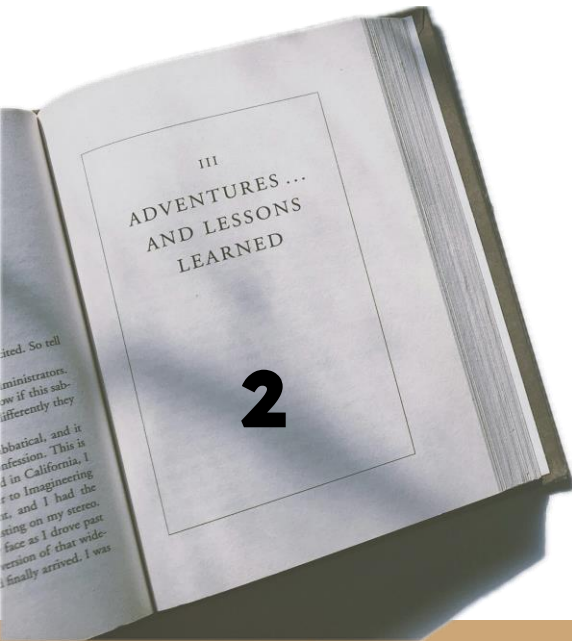
Registration as a living record

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.





Thank you

