Meeting the Demands of Clinical Trials Transparency through ClinicalTrials.gov Compliance

ICTR Third Thursday

June 20, 2019

Presented by: Anthony Keyes, MBA, PMP
Director

Aliya Lalji, MD
Clinical Research Operations Specialist

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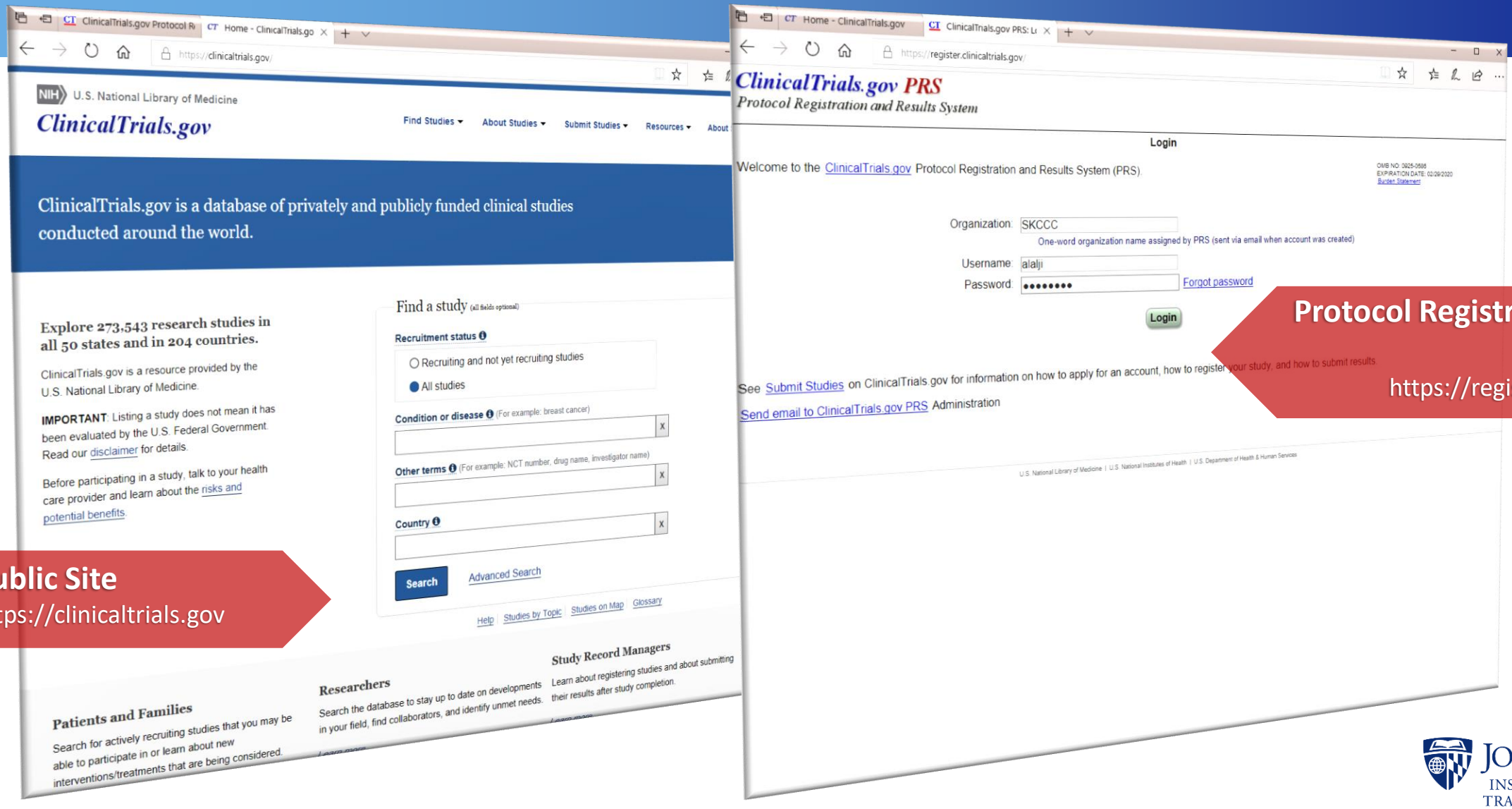
ClinicalTrials.gov



Public Site
https://clinicaltrials.gov

Protocol Registration & Results System (PRS)
https://register.clinicaltrials.gov

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Why is this necessary?

- ✓ Commitment to research participants (including recruitment)
- ✓ Scientific validity/transparency
- ✓ Ethical standards
- ✓ Responsible stewardship of federal funds
- ✓ Help IRB assess value of new studies
- ✓ Required for journal publication (ICMJE)
- ✓ Required by law (FDAAA) and regulations (42 CFR Part 11)
- ✓ Required for all NIH-supported clinical trials (including NCI)
- ✓ Required for CMS
- ✓ Required by WHO
- ✓ Required by grantor foundations, such as Bill & Melinda Gates Foundation

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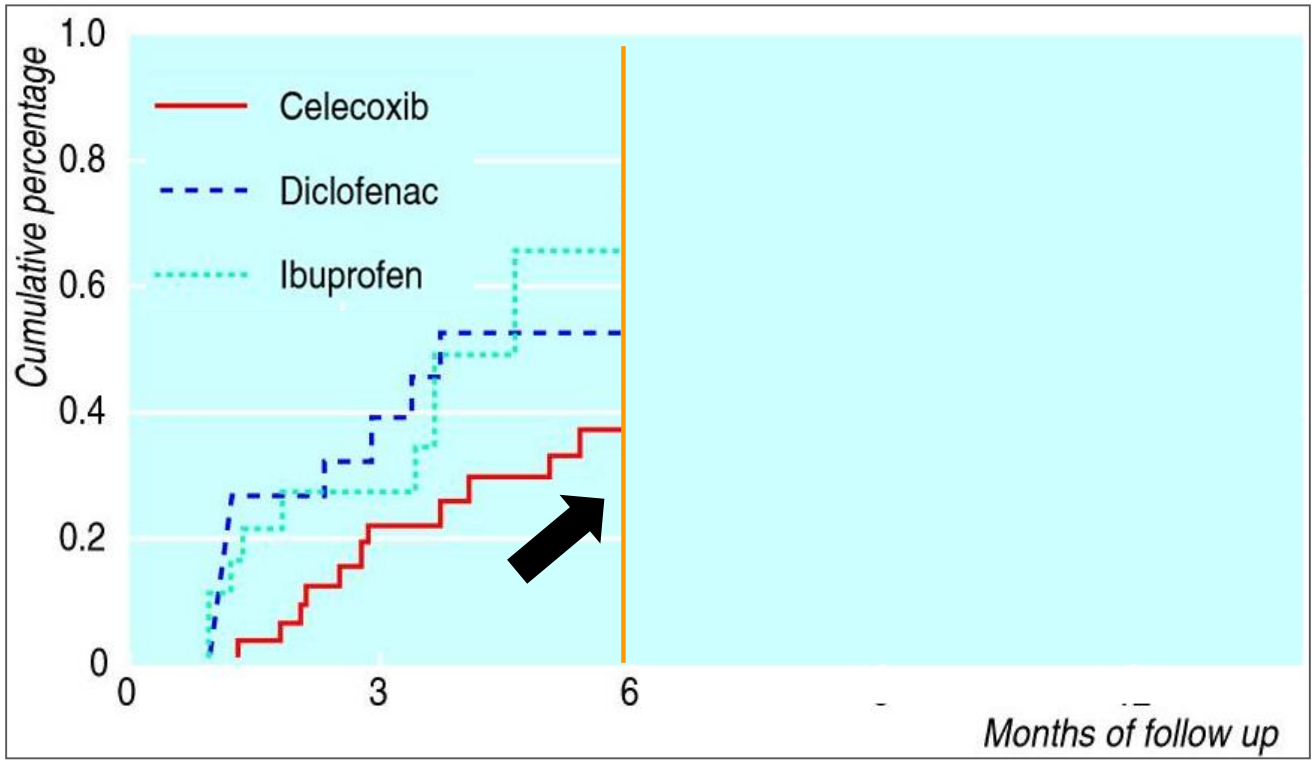
Reporting Bias



- Celecoxib was associated with a lower incidence of gastrointestinal ulcers after 6 months of therapy
- Authors had access to data from the full 12 month study period

Image courtesy of Deborah Zarin, MD, (Former) Director, ClinicalTrials.gov

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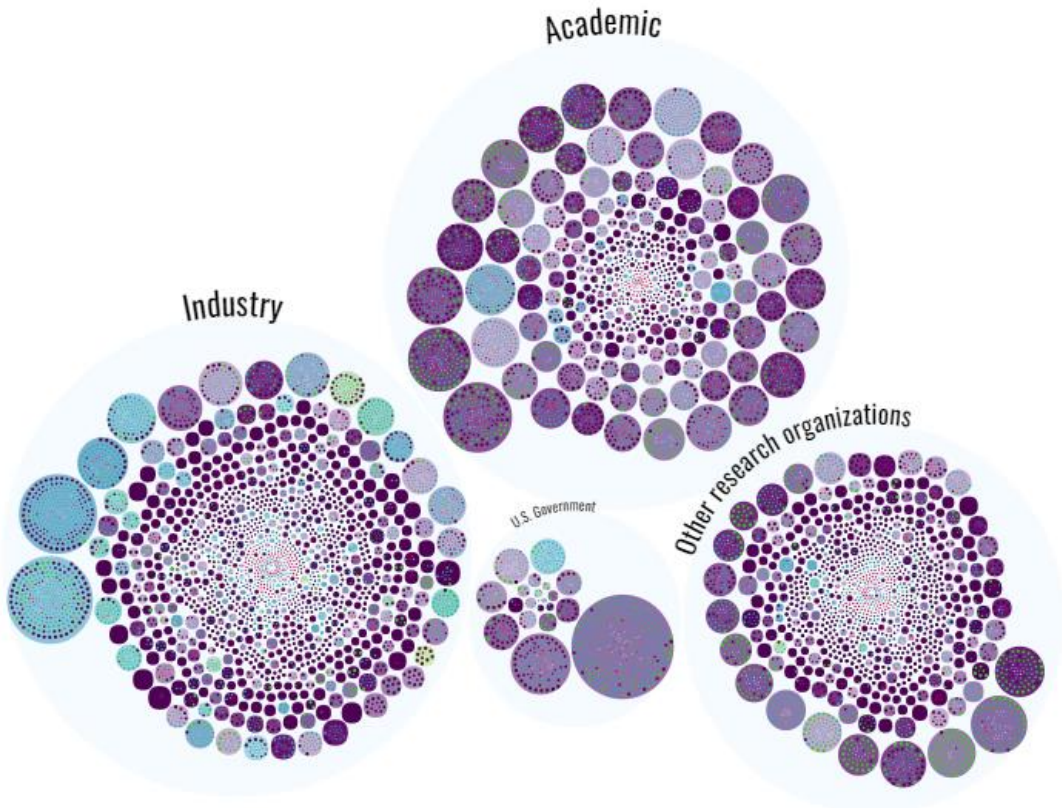
Watchful Eyes – Stat Report 01/09/2018



Percentage of each responsible party's clinical trials that had results reported late or not at all.

0% 20% 40% 60% 80% 100%

Johns Hopkins University

163 of 193 (84%) trials reported late or not at all

49 (30%) results missing in 2015 and 2017

47 (29%) results missing in 2015; posted late as of 2017

8 (6%) results not required in 2015; missing in 2017

14 (9%) results not required in 2015; posted late as of 2017

46 (28%) results posted late before 2015

https://www.statnews.com/2018/01/09/clinical-trials-reporting-nih/

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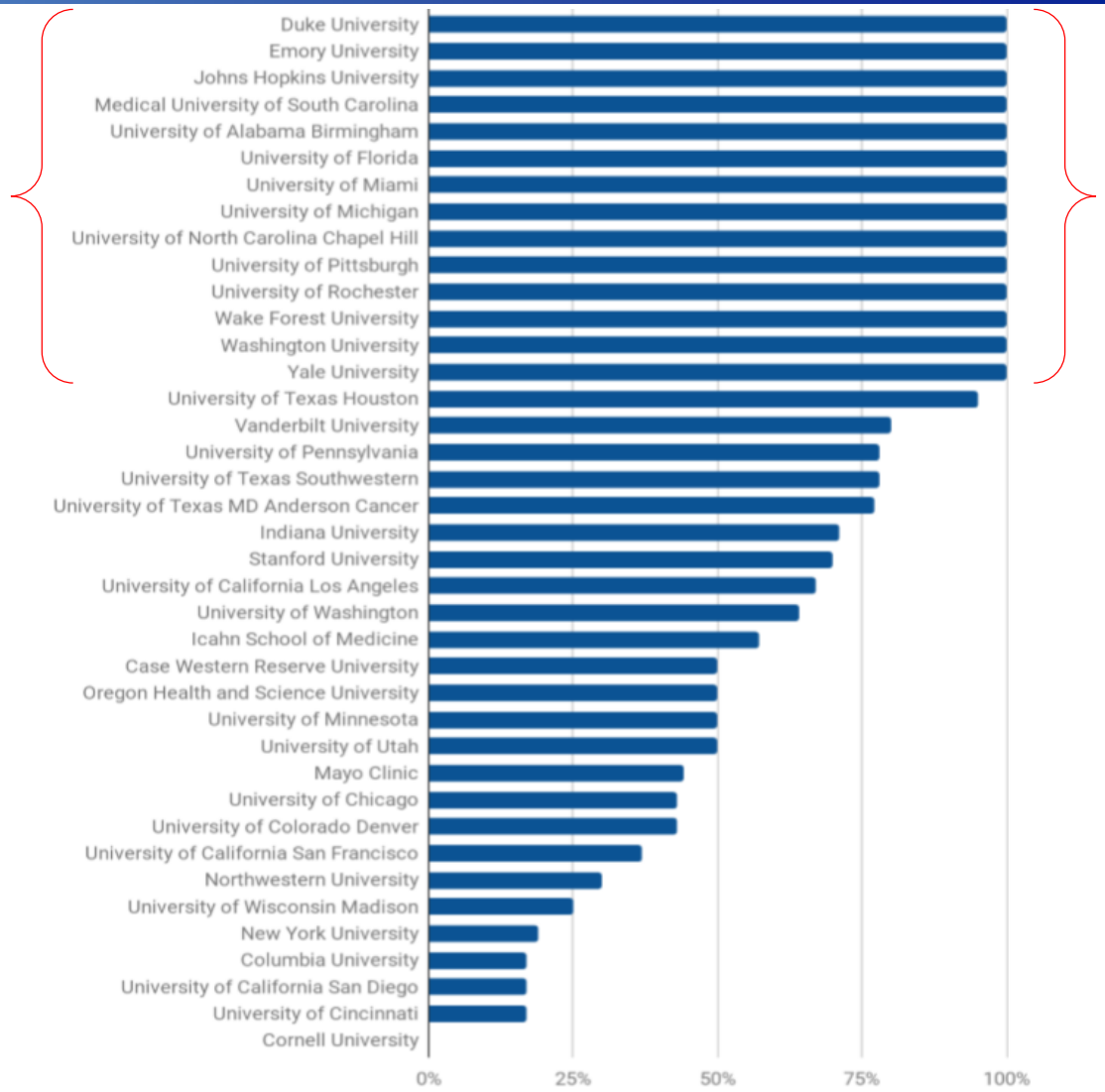
Watchful Eyes – TranspariMED 03/25/2019

TranspariMED

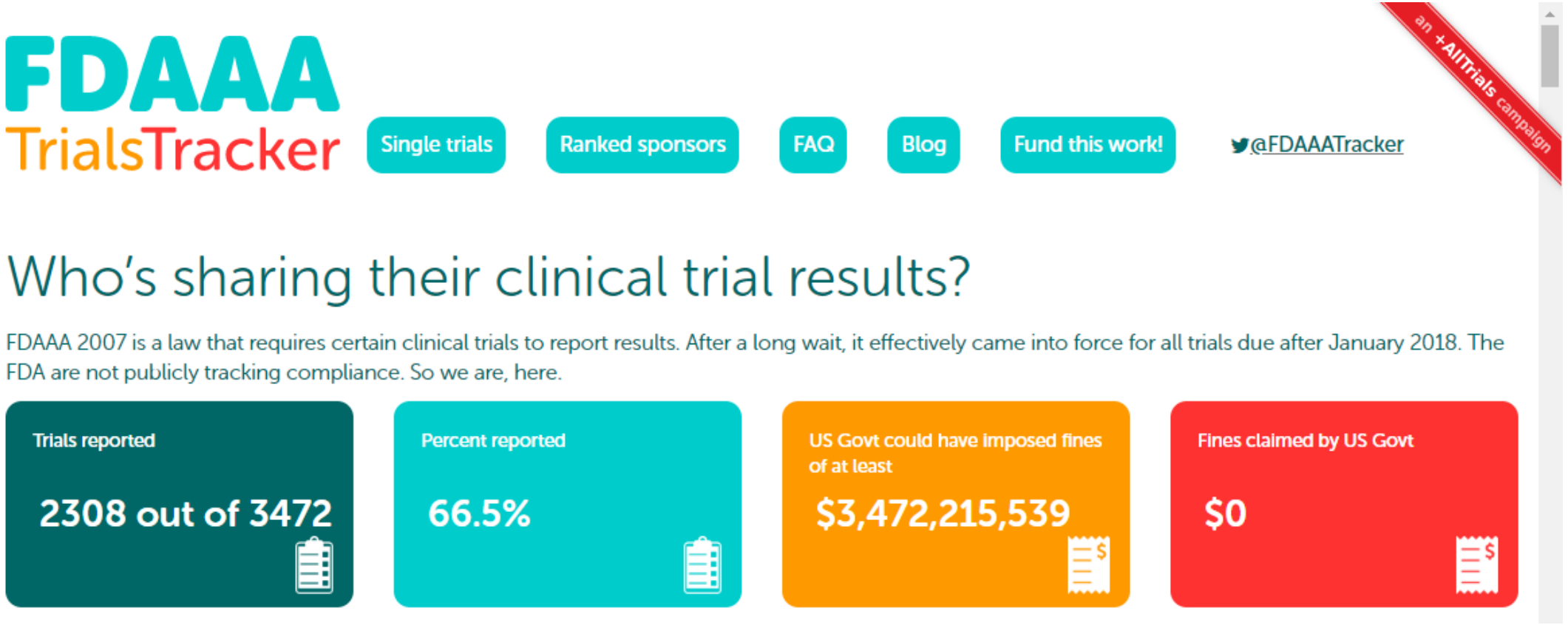
- 40 institutions included in analysis
- 15 institutions, including JHU*, have achieved 100% compliance by reporting results for required clinical trials.
- 25 additional institutions have still not reported required results



*Sidney Kimmel Comprehensive Cancer Center and School of Public Health were not included in this analysis.

New report: 25 major U.S. medical universities violate key transparency law.
https://www.transparimed.org/single-post/2019/03/25/New-report-25-leading-US-universities-violate-key-medical-transparency-law

Watchful Eyes



- Open Letter to FDA Commissioner
- TrialsTracker uses publically-accessible data and is updated daily
- BMJ Opinion publishes *Unreported Trial of the Week*

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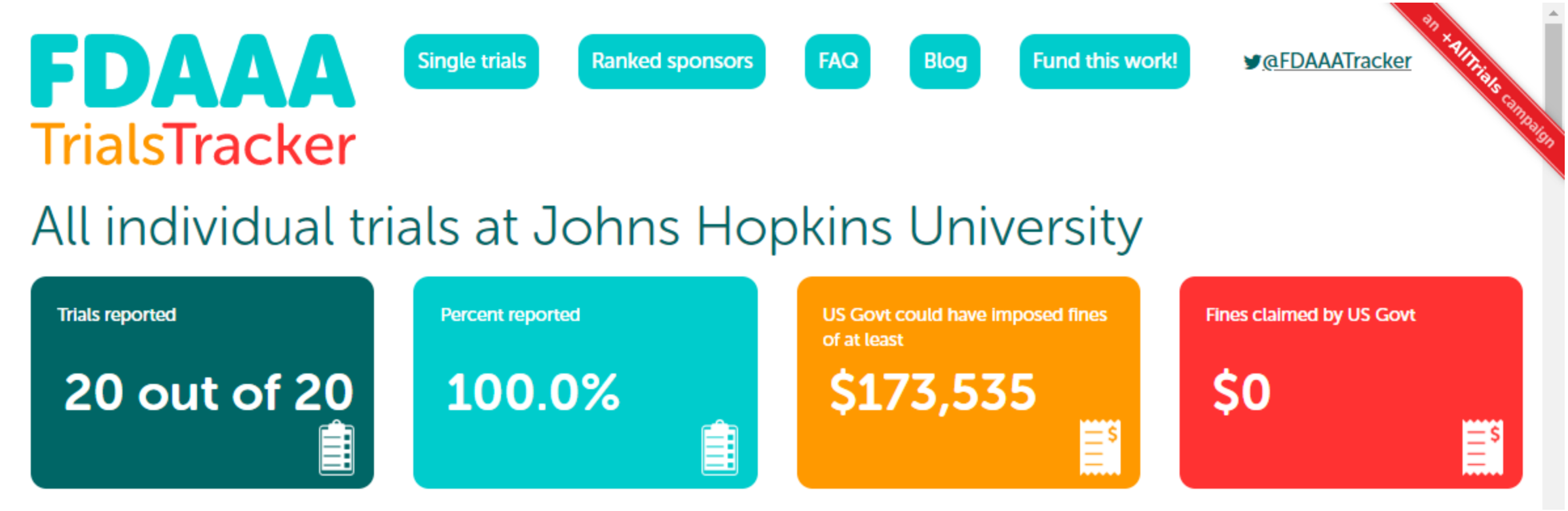
Watchful Eyes



Currently, Johns Hopkins University has reported results for 100% of all required clinical trials!

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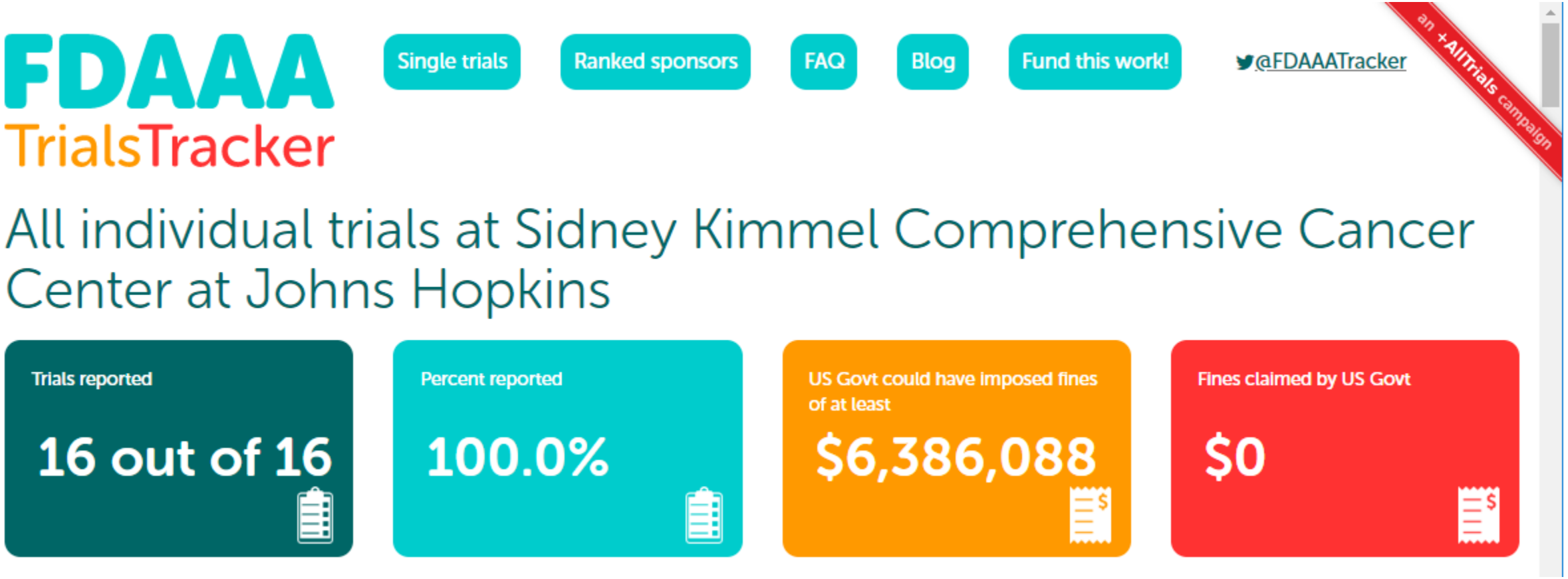
Watchful Eyes



Currently, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins has reported results for 100% of all required clinical trials!

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Updated Regulations and Guidelines

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ClinicalTrials.gov Overview

Year	Entity	Event
1997	Congress	1st U.S. law to require trial registration (FDAMA)
2000	NIH	Releases ClinicalTrials.gov website
2005	ICMJE	Requires registration before enrollment
2006	WHO	All clinical trials should be registered
2007	Congress	Expanded registration, submission of results and adverse events, civil penalties (FDAAA)
2008	NIH	Releases results database
2015	CMS	Mandatory Reporting of Clinical Trial Number on Claims
2015	NCI	Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials
2016	HHS/NIH	Final Rule and Companion Policy (effective January 18, 2017)
2017	HHS	Final Rule compliance date (April 18, 2017)
2019	HHS	Revised Common Rule requiring informed consent form uploading (effective Jan 21, 2019)

FDAMA: Food and Drug Administration Modernization Act

NIH: National Institutes of Health

ICMJE: International Committee of Medical Journal Editors

WHO: World Health Organization

FDAAA: Food and Drug Administration Amendments Act

CMS: Centers for Medicare & Medicaid Services

HHS: Health and Human Services

NCI: National Cancer Institute

Federal Regulations

"Applicable Clinical Trials" per FDAAA

- **Trials of drugs/biologics:** Controlled clinical investigations, other than Phase 1 trials of drugs/biological products subject to FDA regulations.
- **Trials of devices:**
  - —Controlled trials with health outcomes of devices subject to FDA regulation (other than feasibility studies)
  - —Pediatric post-market surveillance required by FDA
- **Trial has one or more sites in the U.S.**
- **Trial is conducted under an FDA IND/IDE application**
- **Trial involves a drug, biologic or device that is manufactured in the U.S. or its territories and exported for research**

ACT Wizard: http://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf
Identifying an ACT under FDAAA http://grants.nih.gov/ClinicalTrials_fdaaa/ACTs_under_FDAAA.htm

Federal Regulations

Trials that meet the NIH Definition of a Clinical Trial

If you answer "yes" to any of the following questions, your study meets the NIH definition of a clinical trial and registration IS required.

1. **Does the study involve human participants?**
2. **Are the participants prospectively assigned to an intervention?**
3. **Is the study designed to evaluate the effect of the intervention on the participants?**
4. **Is the effect being evaluated, a health-related biomedical or behavioral outcome?**

National Institutes of Health

If you answered YES to all 4 the NIH Criteria (on the left), your study is a clinical trial even if it is one of the following scenarios:

- Studying healthy participants
- Do not have a comparison group
- Only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Behavioral intervention

Johns Hopkins Institute for Clinical & Translational Research

Revised Common Rule

According to the revised Common Rule, effective January 21, 2019…

Important considerations regarding the uploading of the informed consent form (ICF):

- Applies to clinical trials conducted or supported by a Federal department or agency
- The Federal department or agency supporting or conducting the clinical trial may permit or require redactions to the information posted
- The consent form must have been used in enrolling participants
- Should be uploaded **no later than 60 days** after the last study visit by any subject, as required by the protocol
- Must be uploaded to either ClinicalTrials.gov or a docket folder on Regulations.gov

§46.116 General requirements for informed consent.

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Penalties

Penalties outlined in the HHS Final Rule

Final Rule (42 CFR Part 11) ***Released: 09/2016, Effective: 01/2017, Compliance date: 04/2017***

- Under FDAAA an organization can be fined up to **$11,805 per study, per day*** for any issue of non-compliance, not only late results.
- NIH may consider compliance as a term and condition of individual awards
- NIH can withhold funding to organizations that are out of compliance

"In addition, NIH will withhold clinical trial funding to grantee institutions if the agency is unable to verify adequate registration and results reporting from all trials funded at that institution."

- Francis Collins, NIH Director

(published viewpoint in JAMA)

*https://www.federalregister.gov/documents/2018/10/11/2018-22005/annual-civil-monetary-penalties-inflation-adjustment

JAMA: Toward a New Era of Trust and Transparency in Clinical Trials

CMS Requirements

Qualifying clinical trials which will render claims for items and services to the Centers for Medicare and Medicaid Services (CMS):

The National Clinical Trial (NCT) number must be included on claims for items and services provided in clinical trials that are qualified for coverage as specified in the "Medicare National Coverage Determination (NCD) Manual," Section 310.1

https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1344.pdf

Funding Stipulations

Studies that are supported by a foundation who is a signatory to the May 18, 2017 WHO, International Clinical Trials Registry Platform (ICTRP)

"It's a 21st century best practice – and an essential part of the social contract that underlies medical research – that clinical trial data should be made publicly available less than one year after a clinical trial's completion. We strongly support WHO's effort to establish a global standard for reporting data within this timeframe, which is a practice we require of our grantees as well."

- **Dr. Trevor Mundel**
  President, Global Health, Bill & Melinda Gates Foundation

http://www.who.int/ictrp/results/jointstatement/en/

Inability to Publish…

"Thank you for submitting your manuscript…to the New England Journal of Medicine.

The International Committee of Medical Journal Editors (ICMJE), and therefore our journal, requires that all clinical trials be registered in a publicly searchable registry before submission for publication. ***As you did not register your study before the first patient was enrolled,*** *or because it was entered into a registry before that registry was publicly searchable,* ***we are returning it to you without further consideration****."*

From the editors at New England Journal of Medicine in response to a manuscript submission

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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Publication Recommendations

Trials that meet the clinical trial definition of The International Committee of Medical Journal Editors (ICMJE) that the investigator may wish to publish…

ICMJE journals will consider [for publication] trials beginning on or after July 1, 2005 **only if** registration occurred **before** the first patient was enrolled ("prospective registration")

Many journals follow the ICMJE criteria for publication.

There have been cases within our institution where a manuscript was rejected for publication simply because the study was not registered on ClinicalTrials.gov before enrolling participants!

http://www.icmje.org/about-icmje/faqsclinical-trials-registration/

Summary of Requirements

Entity	Registration	Results Reporting	Penalties
Health and Human Services (HHS)	Within 21 days of enrollment	Within 365 days of primary completion date for ACTs	• $11,805/study/day • Criminal proceedings
National Institutes of Health (NIH)	Within 21 days of enrollment	Within 365 days of primary completion date for clinical trials receiving NIH funding	Loss of grant funding (to include the institution)
National Cancer Institute (NCI)	Within 21 days of enrollment	Within 365 days of primary completion date of NCI-supported clinical trials (in a peer-reviewed journal and/or ClinicalTrials.gov)	Loss of grant funding
Veterans Health Administration (VHA)	Prior to release of funding. Prior to enrollment	Within 365 days of primary completion date	Loss of grant funding

Summary of Requirements

Entity	Registration	Results Reporting	Penalties
Centers for Medicare & Medicaid Services (CMS)	All qualifying clinical trials	Study-specific	• Coverage denial • Costs and fraud investigations
International Committee of Medical Journal Editors (ICMJE)	Prior to enrollment		Ineligibility to publish
Foundations (ie: Gates, Wellcome Trust)	Study-specific	Study-specific	Loss of grant funding

How to meet the demands for transparency…

When do I register?

Per FDAAA, clinical trials must be registered within 21 days of first enrollment. However, per ICMJE criteria, clinical trials must have been registered BEFORE the first participant is enrolled in order for your manuscript to be considered for publication.

- Estimated time to register: **up to 10 hours**
- It may take up to 7 business days for your record to be reviewed and a National Clinical Trial (NCT) identifier to be assigned after you have submitted your record.

When do I enter results?

Results for the primary outcome measure are due within 12 months of the Primary Completion Date. All remaining results must be reported within 12 months of the Study Completion Date.

- Estimated time to enter results: **up to 40 hours** (depends on proficiency and quality of data sets available)
- It may take multiple review cycles to post your results
- The full protocol (or redacted version) along with the statistical analysis plan is required to be uploaded at the time of results reporting.

Primary Completion Date: the date that the last data point for the primary outcome measure was collected from the last enrolled participant.

Study Completion Date: the date that the last data point for all remaining outcome measures was collected from the last enrolled participant.

What do I need to update?

More frequent updating is required for several data elements to help ensure that users of ClinicalTrials.gov have access to accurate, up-to-date information about important aspects of an applicable clinical trial or other clinical trial.

The following data elements must be updated not later than **30 calendar days after a change occurs:**

- Study start date
- Intervention name(s)
- Availability of Expanded Access
- Expanded Access status
- Overall recruitment status
- Explanation for change in status
- Actual enrollment data
- Individual site status
- IRB status
- Completion Date
- Responsible Party
- Official Title
- Contact Information

Special Considerations

- **If a PI is leaving the institution, then you must update your ClinicalTrials.gov record:**
  - —If there is a Change in PI, update this information in the record
  - —If the study is being transferred to the PI's new institution, you must transfer this record to the new institution and it must be accepted by the new institution
  - —If the study is being closed or terminated, you must update the Study Status.
- **If there is a change of any study team members who are on the access list or listed as a Central Contact on the record, this must be updated in the record.**

JHU ClinicalTrials.gov Program

JHU ClinicalTrials.gov Program

This program is based in the School of Medicine, Institute for Clinical and Translational Research (ICTR). Our staff will be able to assist you and guide you as you work through your ClinicalTrials.gov record.

For School of Medicine, School of Nursing

- Prince Nuamah, MD, MPH – Clinical Research Compliance Specialist
- Oswald Tetteh, MD, MPH – Clinical Research Compliance Specialist

For Sidney Kimmel Comprehensive Cancer Center

- Aliya Lalji, MD – Clinical Research Operations Specialist

For School of Public Health

- Miye Schakne - Research Compliance Officer

For Kennedy Krieger Institute

- Jacqueline Sievers - Compliance and Quality Assurance Manager

To schedule training sessions or presentations to your department contact us at: registerclinicaltrials@jhmi.edu

For more resources, please visit:
http://ictr.johnshopkins.edu/clinicaltrials-gov

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Questions?

Please visit our website for tutorials and more detailed information:

https://ictr.johnshopkins.edu/clinicaltrials-gov

See us on YouTube at "JohnsHopkinsCTgov"

Email us with any questions at

registerclinicaltrials@jhmi.edu

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