Registering Clinical Trials: The what, when, where and why

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Oswald Tetteh, Clinical Research Compliance Specialist

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What needs to be registered?

- Any research study meeting the definition of a clinical trial
  - International Committee for Medical Journal Editors (ICMJE)
  - Food and Drug Administration Amendments Act (FDAAA)
  - National Institutes of Health (NIH)
- Any research study with funding from an agency that requires registration

- Sub categorization of studies
  - applicable and non applicable clinical trials
  - phase of clinical trial

ICMJE

- “The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome.”
- Health-related interventions - drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes
- Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html#:~:text=The%20ICMJE%20defines%20a%20clinical,intervention%20and%20a%20health%20outcome.

“Applicable Clinical Trials” per FDAAA

Question	Yes	No
1. Is the study interventional (a clinical trial)? *Study Type* data element is “Interventional”	☐	☐
2. Do ANY of the following apply (is the answer “Yes” to at least one of the following sub-questions: 2a, 2b, OR 2c)?	☐	☐
a. Is at least one study facility located in the United States or a U.S. territory? *Facility Location – Country* data element is “United States,” “American Samoa,” “Guam,” “Northern Mariana Islands,” “Puerto Rico,” “U.S. Virgin Islands,” or other U.S. territory.		
b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)? *U.S. Food and Drug Administration IND or IDE Number* data element is “Yes.”		
c. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country? *Product Manufactured in and Exported from the U.S.* data element is “Yes.”		
3. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)? *Studies a U.S. FDA-regulated Device Product* data element is “Yes” and/or *Studies a U.S. FDA-regulated Drug Product* data element is “Yes.”	☐	☐
4. Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study? For drug product trials, *Study Phase* data element is NOT “Phase 1” and for device product trials, *Primary Purpose* is NOT “Device Feasibility.”	☐	☐

Identifying an ACT under FDAAA
https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

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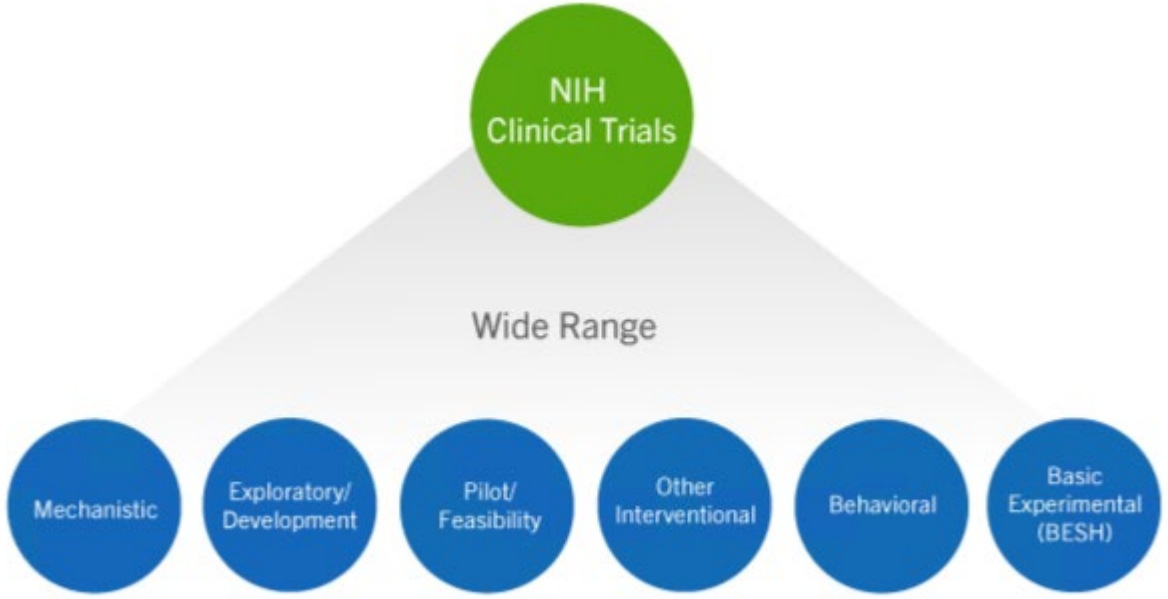
NIH Definition of a Clinical Trial

- A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.



https://grants.nih.gov/policy/clinical-trials/definition.htm

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Trials that meet the NIH Definition of a Clinical Trial

If you answer "yes" to the following questions, your study meets the NIH definition of a clinical trial and registration and results reporting ARE 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?**

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

https://grants.nih.gov/policy/clinical-trials/definition.htm

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When do you register?

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	• $13,237/study/day • Criminal proceedings • Loss of grant funding
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

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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
Patient-Centered Outcomes Research Institute (PCORI)	All Clinical studies (including observational)	Expected of all PCORI Clinical studies – 500 word abstract published on PCORI website	• Loss of grant funding
International Committee of Medical Journal Editors (ICMJE)	Prior to enrollment		Ineligibility to publish
Department of Defense (DoD)	Prior to enrollment. Prior to release of funding.	Study-specific	• Withholding or recovery of award funds

When do you do updates?

Registering and Updating the Record

❑Register the record within **21 days of enrollment** (HHS) –OR- **prior to enrollment** (ICMJE)

❑Update the following data elements no 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

Annual Verification

- ❑ Verify the record **annually** – Record Verification date

JHU enforcement - IRB Continuing Review will be held for studies that are not verified annually

Responding to Comments

- Respond to PRS Review Comments
  within **15 calendar days** (registration) –OR-
  25 calendar days (results)

Entering results

❑**Report** results within 12 months of the completion dates.

- Estimated time to enter results: **up to 40 hours***
- It may take multiple review cycles to post your results
- Comments must be responded to within **25 calendar days**

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.

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*HHS estimated burden statement

Uploading the Consent Form

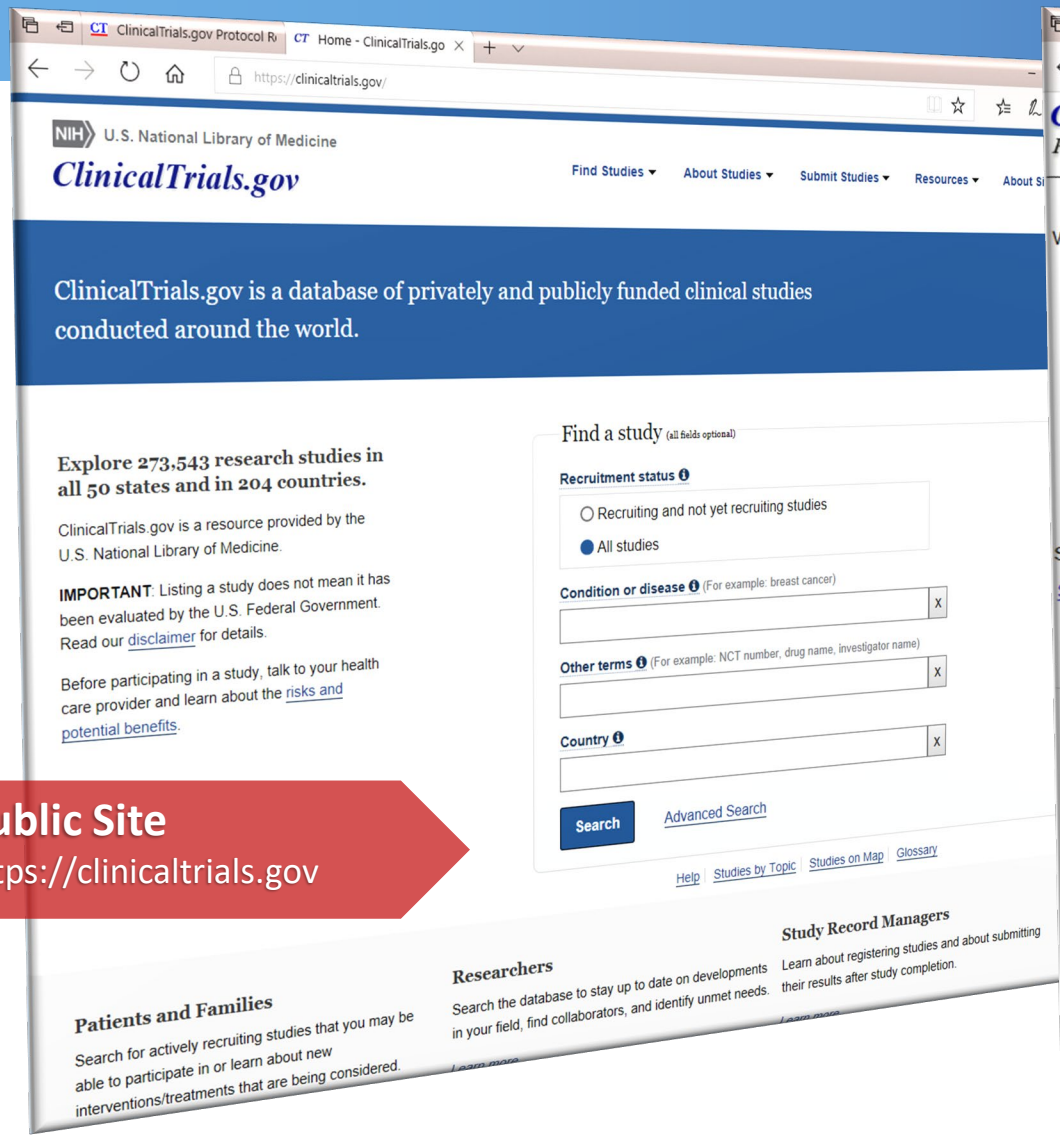
According to the revised Common Rule, effective January 21, 2019…

- ***Important considerations regarding the uploading of the informed consent form (ICF):***
- Applies only to clinical trials conducted or supported by a Federal department or agency* using the Common Rule
- The consent form must have been used in enrolling participants
- Should be uploaded when recruitment ends and **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

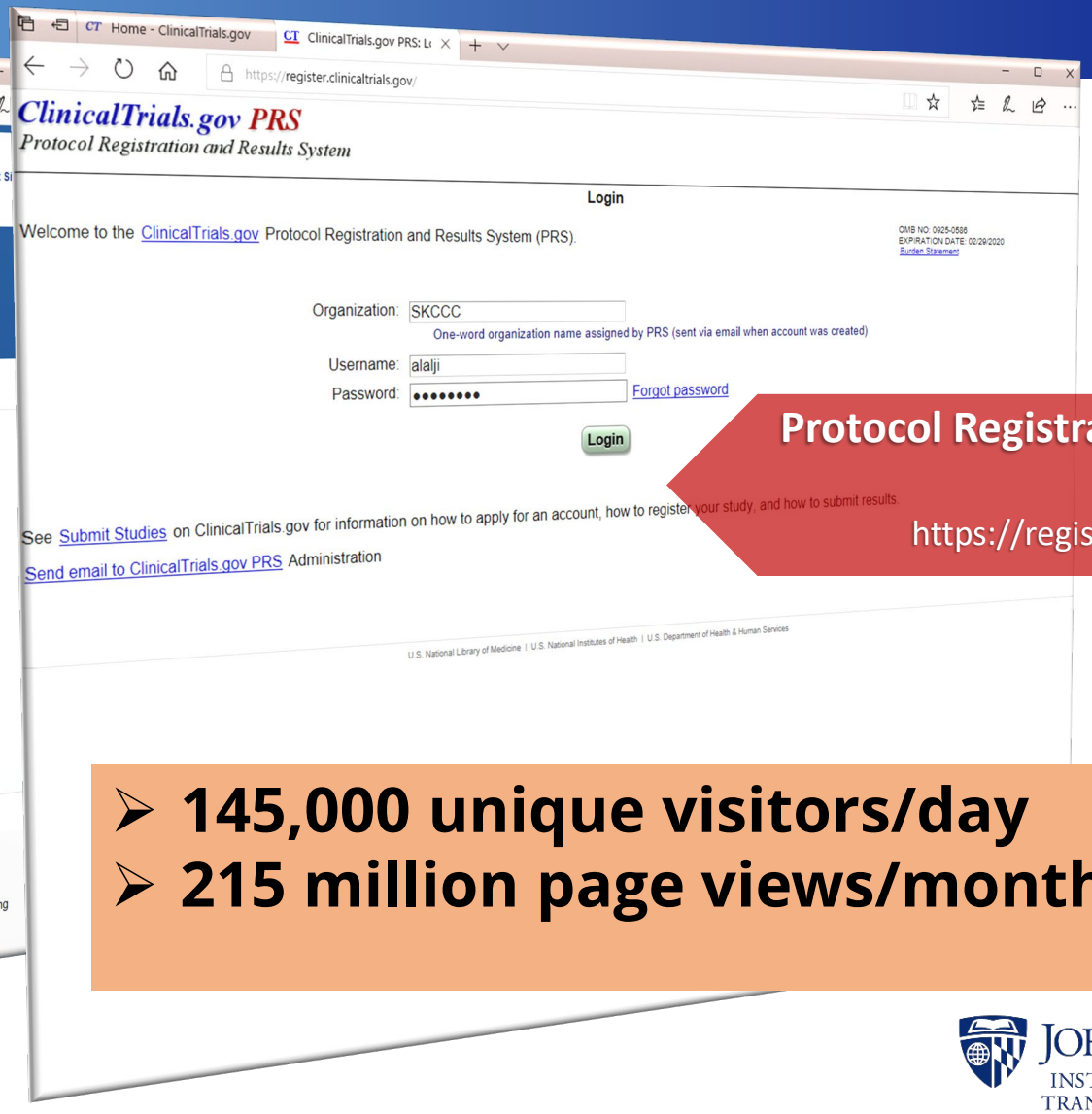
§46.116 General requirements for informed consent.
Agencies* https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Where do you register and do updates?

ClinicalTrials.gov



Public Site
https://clinicaltrials.gov



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

- **145,000 unique visitors/day**
- **215 million page views/month**

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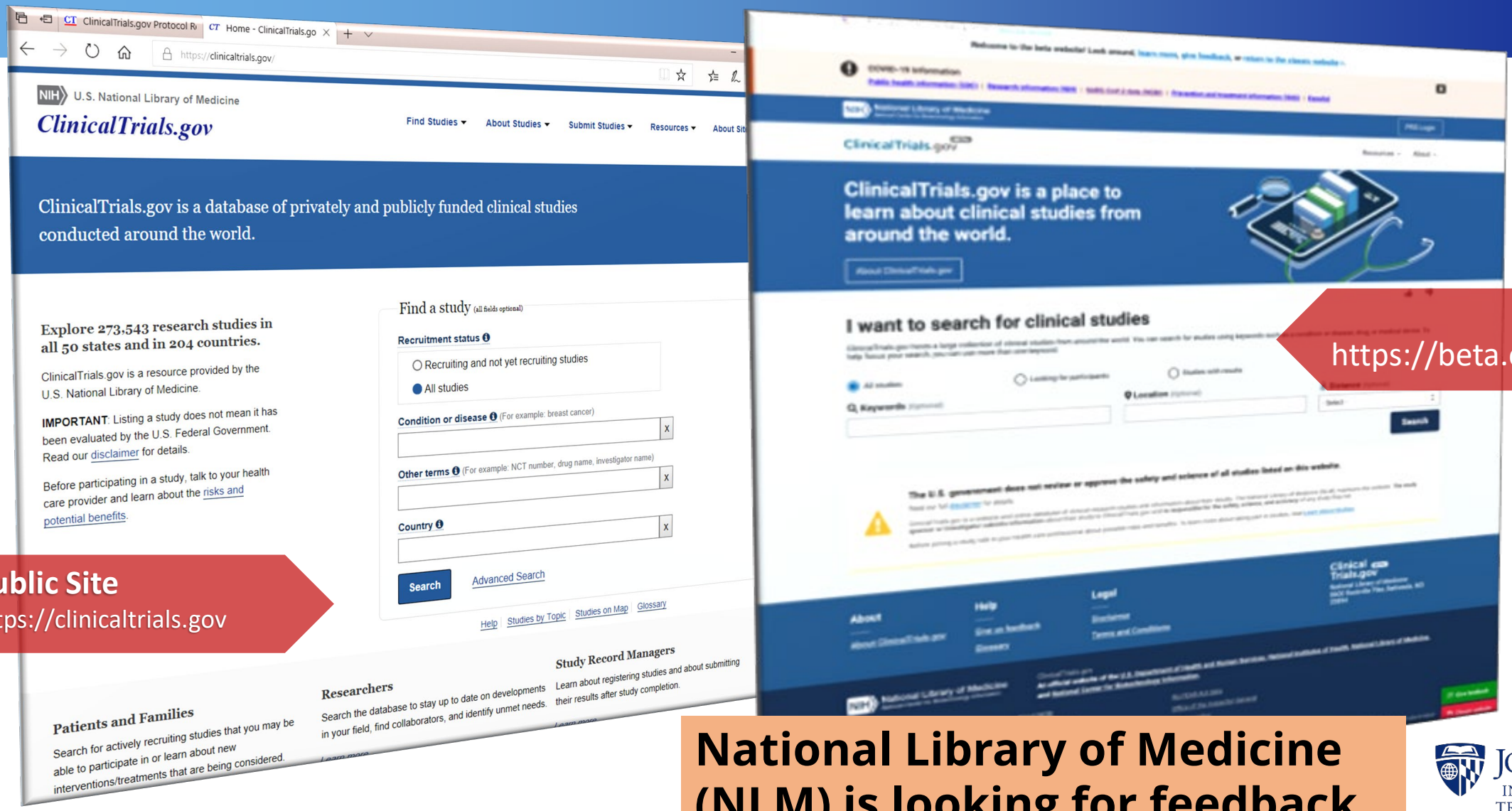
ClinicalTrials.gov



Public Site
https://clinicaltrials.gov

Beta Site
https://beta.clinicaltrials.gov/

National Library of Medicine (NLM) is looking for feedback

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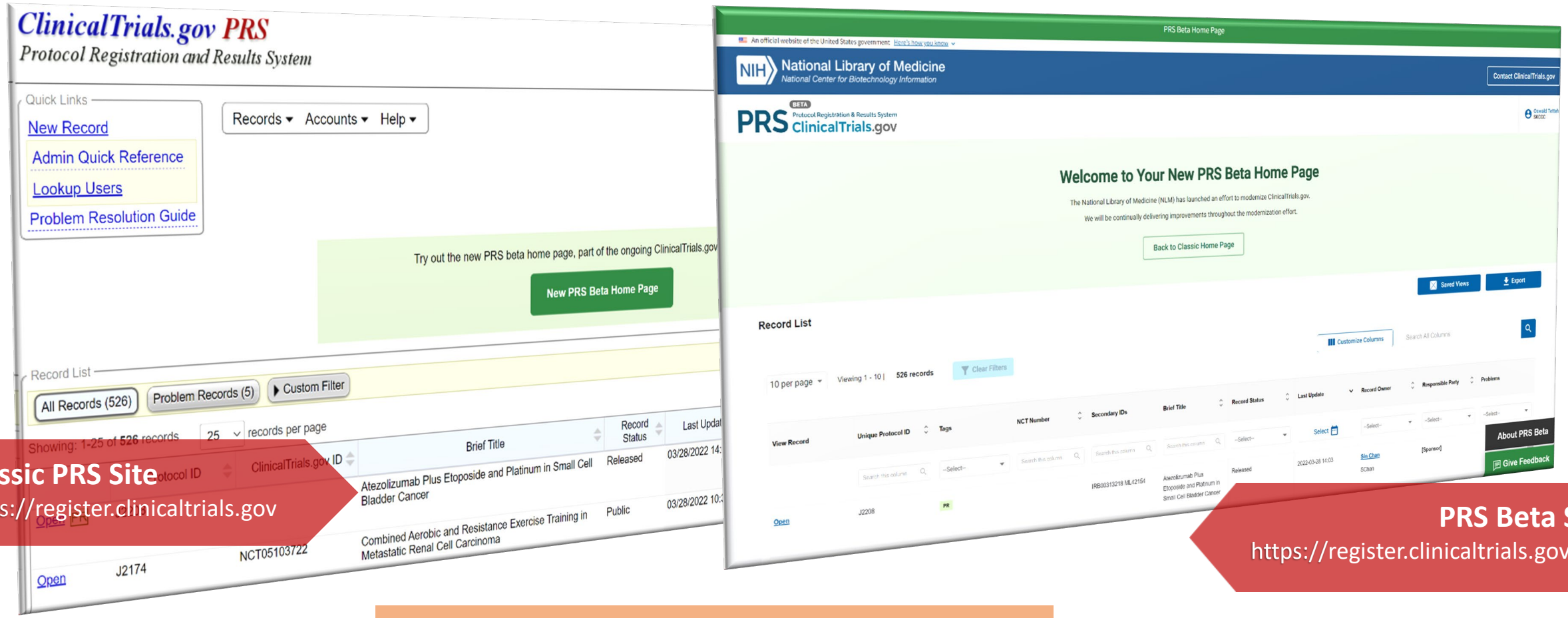
ClinicalTrials.gov - PRS



Classic PRS Site
https://register.clinicaltrials.gov

PRS Beta Site
https://register.clinicaltrials.gov/v2/

National Library of Medicine (NLM) is looking for feedback

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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 Foundations, such as Wellcome Trust

Penalties

Penalties outlined in the FDA Final Rule

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

1. Civil or criminal judicial actions
2. Civil monetary penalties up to ~~$10,000~~ ~~$12,316~~ ~~$12,462~~ $13,237 per study, per day
3. Withholding of current or future funding to organizations that are out of compliance

These penalties are for any data element FDA determines was, "not submitted as required, or was false or misleading" not just late results

21 U.S.C. 333(f)(3)(A) https://www.federalregister.gov/documents/2021/11/15/2021-24672/adjustment-of-civil-monetary-penalties-for-inflation-and-the-annual-civil-monetary-penalties

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/

FDA Enforcement

FDAAA 801 Violations

- Notice is sent to the Responsible Party
- **Pre-Notice Letters** are **not** identified as an FDAAA 801 Violation and **not** identified in ClinicalTrials.gov
- **Notice of Noncompliance** Letters are identified as an FDAAA 801 Violation in ClinicalTrials.gov

Responsible Party/Submitter	NCT Number	Notice of Noncompliance	Response Letter (if any)	Civil Money Penalty Amount (if any)
Ocugen	NCT03785340	4/15/2022	08/01/2022	
Petrikovets, Andrey M.D.	NCT03052816	8/31/2021	12/20/2021	
Accuitis Inc.	NCT03064438	7/26/2021	05/26/2022	
Acceleron Pharma, Inc.	NCT01727336	4/27/2021	12/13/2021	

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https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions#:~:text=FDA%20has%20the%20authority%20to,or%20misleading%20clinical%20trial%20information

FDAAA 801 Violations

Study Details | Tabular View | Study Results | **FDAAA 801 Violations** | Disclaimer | How to Read a Study Record

Information on FDAAA 801 Violations

More Information: Notices of Noncompliance [FDA]

Available on ClinicalTrials.gov	Issued by FDA	Study Record Submitted	Notice Type	FDAAA 801 Notice
January 6, 2022	December 20, 2021	October 3, 2021	Correction Confirmed by FDA	The responsible party has corrected the violation.
September 3, 2021	August 31, 2021	December 15, 2018	Violation Identified by FDA	Failure to Submit. The entry for this clinical trial was not complete at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry.

https://clinicaltrials.gov/ct2/show/violations/NCT03052816?term=NCT03052816&draw=2&rank=1
https://www.fda.gov/media/151965/download

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FDAAA 801 Violations

Researchers from Yale, Columbia, and Universities Allied for Essential Medicines (UAEM) submitted a Freedom of Information Request

- 58 Preliminary Notice of Noncompliance Letters sent
- 57 for Results, 1 for Registration
- 32 to drug makers
- 0 to Federal Agencies

- 90% reported to ClinicalTrials.gov (median = 3 weeks)
- UAEM released the full text of all 58 letters

Strengthening the FDA's Enforcement of ClinicalTrials.gov Reporting Requirements
https://jamanetwork.com/journals/jama/fullarticle/2786399
https://www.uaem.org/freedom_of_information_act

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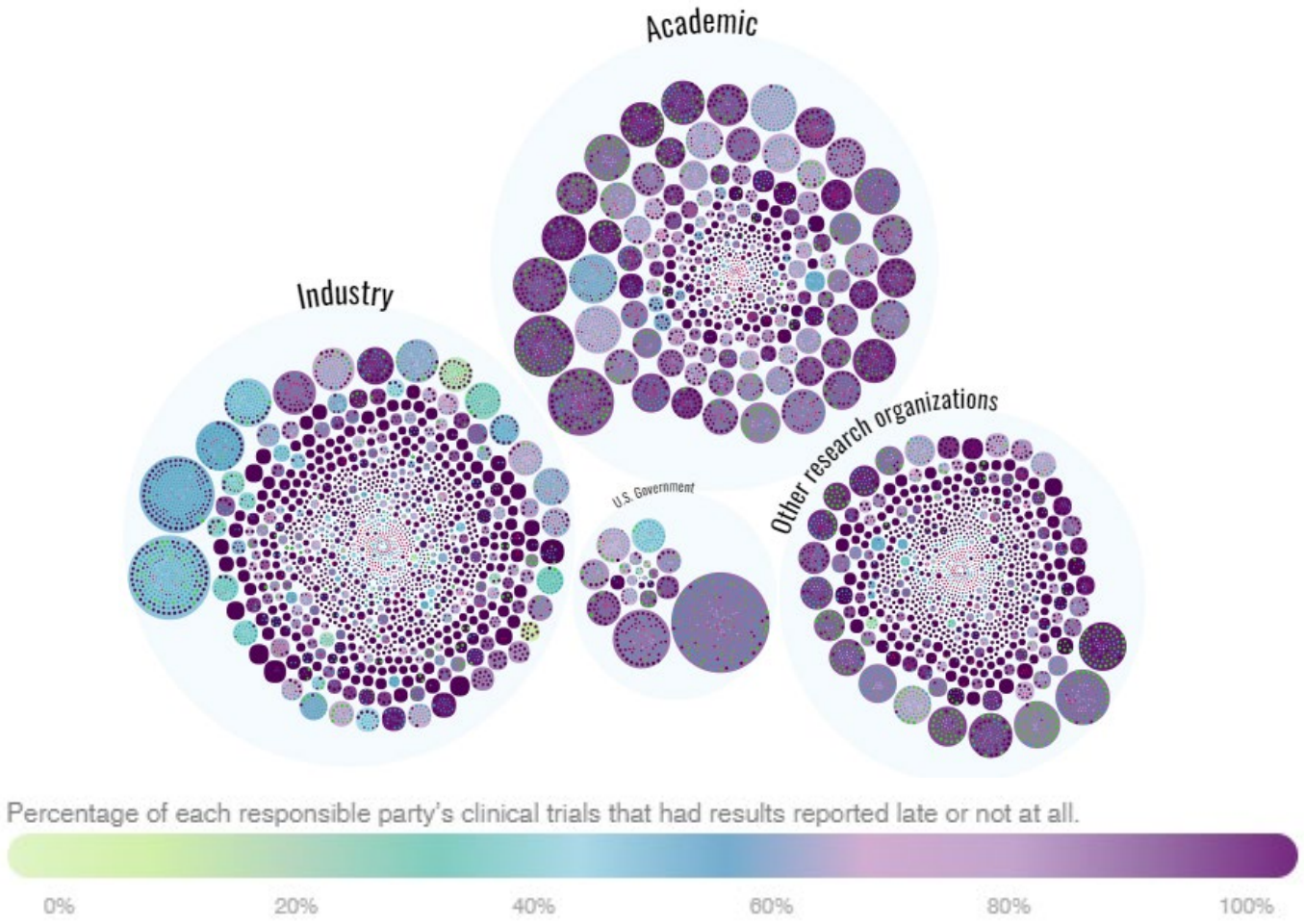
Who’s watching?

Watchful Eyes – Stat Report 01/09/2018



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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 (5%) 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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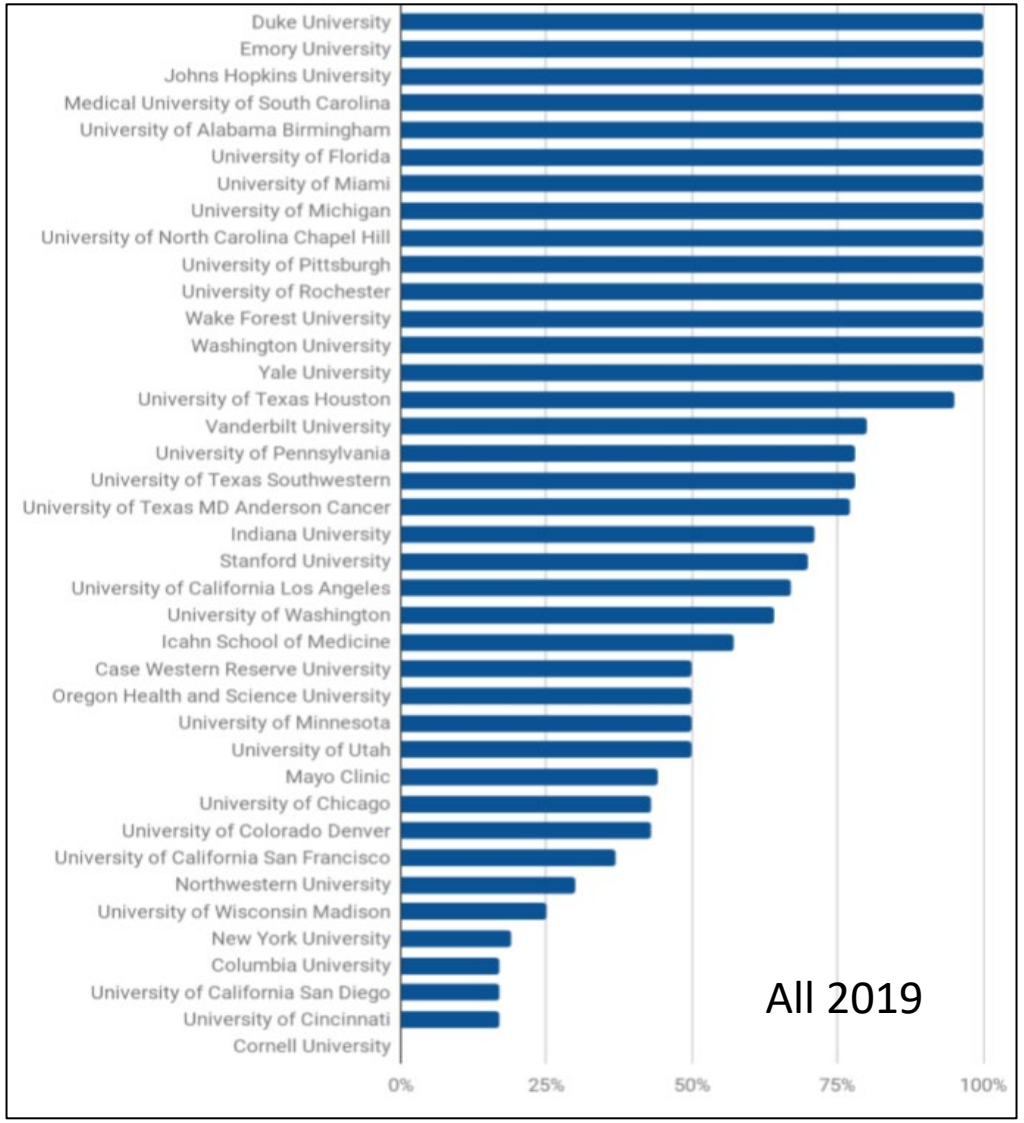
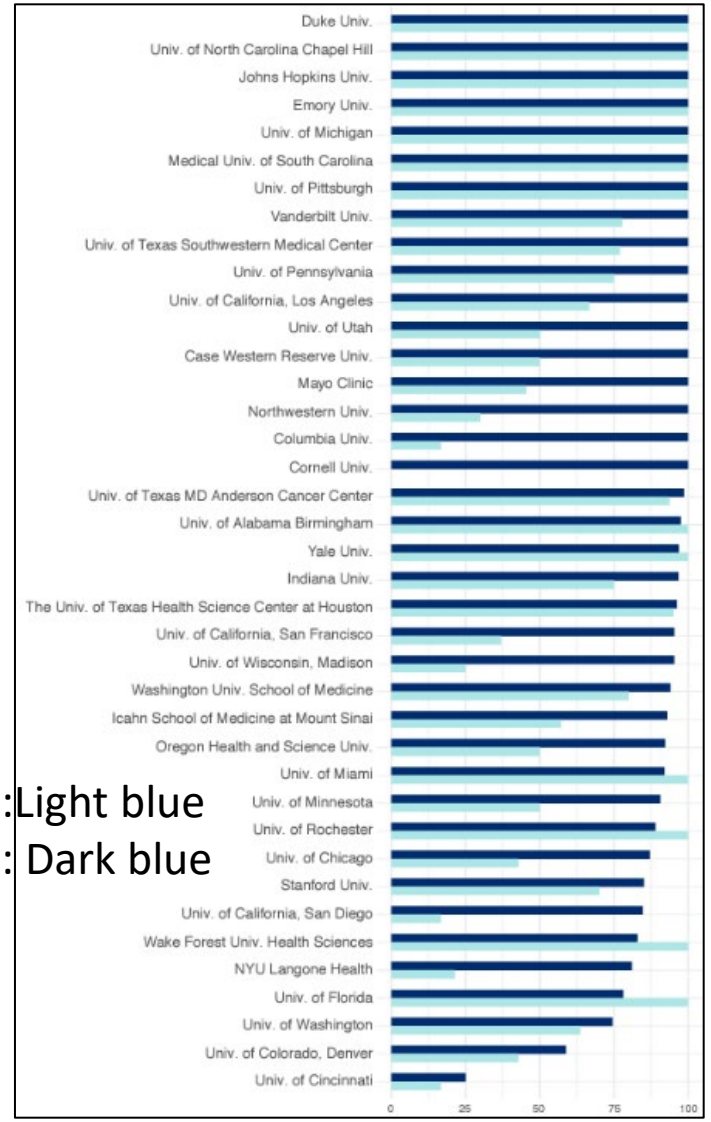
TranspariMED/UAEM Compliance reporting results

- 40 institutions included in analysis
- 2019: 16 = >80%
- 2021: 36 = >80%
  - —2019 = Light blue
  - —2021 = Dark Blue

UAEM: Universities Allied for Essential Medicines
chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://altreroute.com/clinicaltrials/assets/download/Clinical_Trials_Transparency_Report_UAEM_v5.pdf





2019:Light blue
2021: Dark blue

2023 Articles

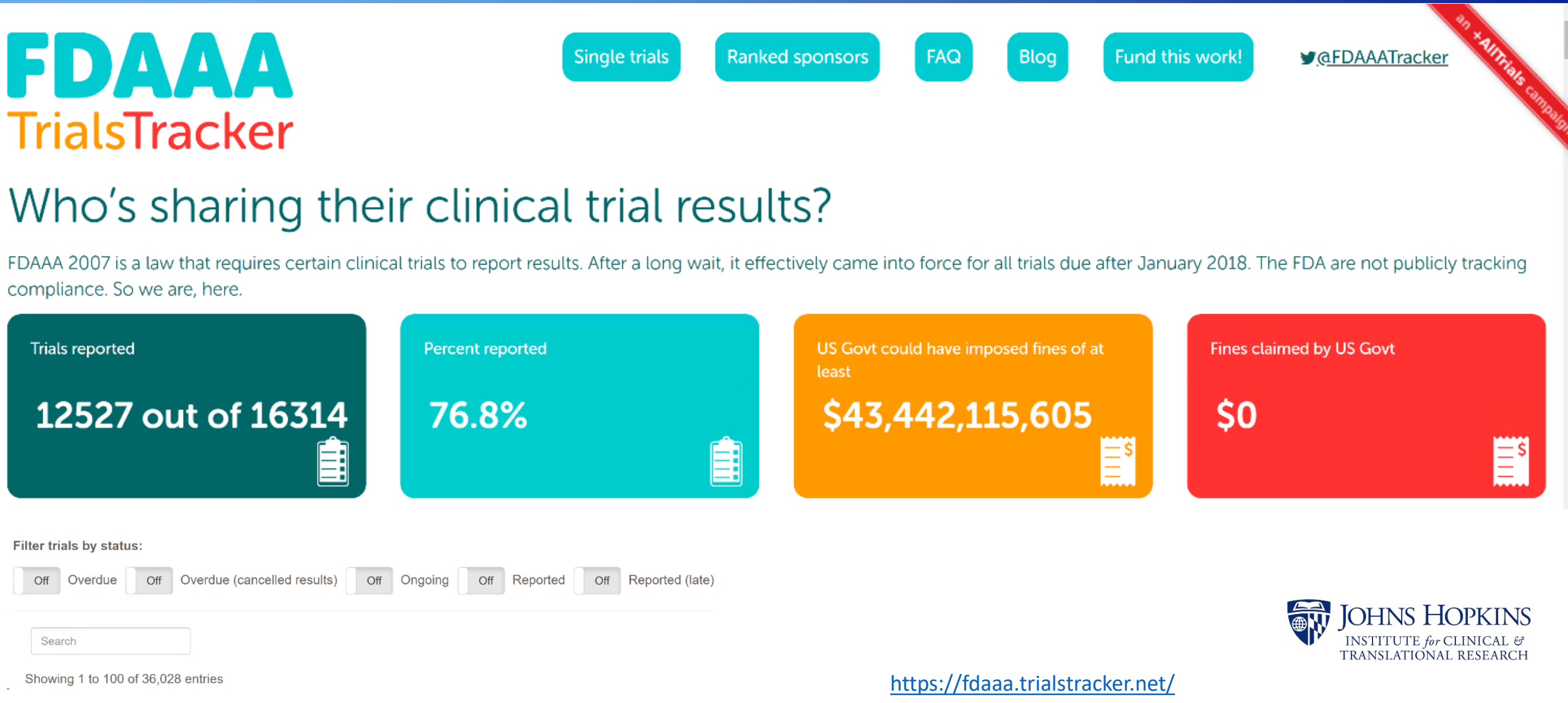
Congress demands that FDA and NIH sanction sponsors that fail to report clinical trial results

FDA is petitioned to boost enforcement of trial sponsors that fail to register studies or report results

NIH waste far over $100 million in medical research funding every year – new study

https://www.transparimed.org/single-post/fdaaa-pallone
https://www.statnews.com/pharmalot/2023/02/27/fda-petition-clinical-trials-transparency-nih/
https://www.transparimed.org/single-post/nih-research-waste

Watchful Eyes – FDAAA TrialsTracker



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https://fdaaa.trialstracker.net/

Tips and Tricks for Entering Data

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Using the Checklist - Registration

CLINICALTRIALS.GOV JHU RECORD REVIEW

PROTOCOL ID	RECORD OWNER	REVIEWER	❑ Registration ❑ Update status ❑ Results *(add Results checklist)*	❑ pACT/ACT ❑ Non-ACT
NCT#				

DATE RELEASED	COMMENTS DATE	REPLY DATE	DATE PUBLISHED

GENERAL REVIEW ITEMS	NOTES
❑ Record Owner is the PI or Coordinator (SKCCC) ❑ Contact info for Record Owner is up-to-date ❑ PI on record matches IRB PI: _____ ❑ NCT# included in IRB "Clinical Trials Information" section ❑ All Warnings/Errors addressed ❑ All parenthetical citations have been removed ❑ All acronyms have been expanded on their first use ❑ Spell-check complete ❑ Free-text fields are blank if there is no information to report, and do not contain text such as "TBD," "Pending," "N/A," "None"	

PROTOCOL SECTION

STUDY IDENTIFICATION
- ❑ Unique protocol ID is the IRB# or J# (SKCCC) (JHU Policy)
- ❑ Brief Title does not include study type (e.g., Phase I, Randomized…)
- ❑ Secondary IDs include NIH grant #s (verify in IRB), and IRB# (SKCCC)

STUDY STATUS
- ❑ Record Verification Date is the current month/year
- ❑ Overall Status matches IRB/CRMS
- ❑ Study start date verified with CRMS enrollment date
- ❑ Completion Dates Actual/Anticipated have been evaluated for accuracy
- ❑ If timeframes for outcomes are the same the primary and study completion dates are identical

SPONSOR/COLLABORATORS
- ❑ Responsible Party: Sponsor (JHU Policy)
- ❑ All sources of support identified in IRB "Support Information" section included as Collaborators
- ❑ Full Name used and if not recognized, "Recognize" is selected

OVERSIGHT
- ❑ IND/IDE information completed (if applicable)

Verify Human Subjects Review
- ❑ Board Status verified
- ❑ Approval Number is a valid IRB number
- ❑ Board Name: Office of Human Subjects Institutional Review Boards
- ❑ Board Affiliation: Johns Hopkins School of Medicine
- ❑ Phone: (410) 955-3008, Email: jhmeirb@jhmi.edu
- ❑ Address: 1620 McElderry Street, Reed Hall Suite B130, Baltimore, MD, 21205

STUDY DESCRIPTION
- ❑ Brief Summary does not unnecessarily duplicate information provided for other data elements
- ❑ Brief Summary clearly states the study's hypothesis or the purpose (for interventional and observational)
- ❑ Brief Summary and Detailed Description are written in complete sentences with no formatting errors
- ❑ Record does not use personal pronouns:
  "I, we, our, us, they, them, their" – becomes "the investigator(s)"; "you, your" – becomes "the participant(s)"

CONDITIONS
- ❑ Conditions/Focus of study are discrete and does not use verbs or complete sentences
- ❑ Keywords are not numbered or bulleted, each condition and keyword is listed individually, one per line

STUDY DESIGN
- ❑ All required fields are completed
- ❑ Verify Study Design based on protocol in IRB
- ❑ "Allocation" marked as "N/A" for single-arm studies
- ❑ Enrollment number Actual/Anticipated verified

ARMS/INTERVENTIONS
- ❑ Arm Title or Group/Cohort Label is brief and informative (even if there is only 1 arm)
- ❑ Interventions and intervention descriptions are entered correctly
- ❑ Arms/interventions are cross-referenced appropriately

OUTCOME MEASURES
- ❑ Title is specific and states WHAT is being measured, only 1 variable must be assessed per outcome measure
- ❑ Description explains WHAT is being measured, not WHY it is being measured
- ❑ Scoring scale name, score range, significance of upper and lower limits specified (if applicable)
- ❑ Unit of measure specified
- ❑ Time frame specified as a single time point or change between 2 time points

  INCORRECT: "Safety and Toxicity", Description: "Safety of study drug."
  CORRECT: *"Safety as assessed by number of participants experiencing adverse events"* Description: *"Number of participants experiencing adverse events grade 3 or higher, as defined by Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0)"*

ELIGIBILITY
- ❑ Age Limits are consistent with the Eligibility Criteria and with other parts of the record
- ❑ Eligibility criteria is divided into Inclusion/Exclusion criteria in bulleted format

CONTACTS/LOCATIONS
- ❑ Central Contact Person specified and accurate (JHU Policy)
- ❑ Study Officials match IRB
- ❑ All study sites specified matches CRMS
- ❑ Recruiting status for each study site accurate (if at least one study site is recruiting then Study Status reflects "Recruiting")
- ❑ Each facility is listed in a separate field

IPD Sharing Statement
- ❑ The Plan to Share IPD selection is consistent with the IPD Sharing Plan Description.

REFERENCES
- ❑ Each citation is listed in a separate field (if applicable)

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Using the Checklist – Results Entry

RESULTS SECTION

PARTICIPANT FLOW
- ❑ Protocol Enrollment refers to total number of subjects who consented to protocol (including screen failures, withdrawals, etc.)
- ❑ Recruitment details (optional) explains any specifics used at time of recruitment
- ❑ Pre-assignment details explains (in detail) what happened to subjects who signed consent but were not assigned to an arm/intervention (i.e., how many screen failures, withdrawals, etc.)
- ❑ Arms and arm descriptions specified consistent with protocol section
- ❑ Number of Participants Started refers to total number of participants assigned to each arm
- ❑ Number of Participants Completed refers to total number of participants who completed study intervention
- ❑ Reason(s) for Not Completed provided
- ❑ Divided into periods/milestones appropriately
- ❑ Total number of participants started cannot be greater than enrollment number
- ❑ Total number completed is equal to or less than "started"

BASELINE CHARACTERISTICS
- ❑ Overall Number of Baseline Participants should match Number of participants Started (from Participant Flow)
- ❑ Baseline Analysis Population Description explains if there is a discrepancy between Overall & Started numbers
- ❑ Arm titles/descriptions are consistent with participant flow and/or protocol section
- ❑ Data is presented per arm
- ❑ If "number of participants" is reported, make sure Measure Type is "Count of Participants"
- ❑ Measure description is specified for all Study-specific measures

OUTCOME MEASURES
- ❑ Titles/descriptions/time frame meet the criteria (as specified on prior checklist)
- ❑ Results are reported per arm
- ❑ Population Analysis Description includes reason why Number of Participants analyzed is different than total number of participants completed (if applicable)
- ❑ Type and Number of Units analyzed is indicated, if other than "number of participants" (ie: # of Lesions)
- ❑ Unit of measure matches what is stated in Outcome Title/Description
- ❑ Sum of all results entered for each arm equals overall number of participants analyzed
- ❑ Verify true data is entered and there are no placeholders
- ❑ Statistical Analysis portion is optional

ADVERSE EVENTS
- ❑ Time frame specified
- ❑ Collection Approach specified
- ❑ Arm titles/descriptions consistent with other sections in the record
- ❑ Data presented per arm
- ❑ All-cause mortality specified (cross-check with number "not completed due to death" from participant flow and any mortality measures in outcome section, if applicable)
- ❑ Total Number "At Risk" must be equal to total number of participants who started the study

CERTAIN AGREEMENTS
- ❑ Principal Investigators are employed by the organization sponsoring the study

RESULTS POINT OF CONTACT
- ❑ Information is correct and valid email address/phone number entered

DOCUMENT SECTION
- ❑ Protocol (required for primary completion date after January 18, 2017)
- ❑ Statistical Plan (required for primary completion date after January 18, 2017)
- ❑ Informed Consent Form (required for studies approved on or after January 21, 2019)
- ❑ Cover Page
  - ❑ Record (NCT) Number
  - ❑ Study Title
  - ❑ PI Name
  - ❑ Date of Document (must match date within actual document)
- ❑ Additional Documents: _____

REFERENCES
- ❑ Links are verified (if applicable)

This record was reviewed by:	

Tetteh, O., Nuamah, P., Keyes, A. Addressing the quality of submissions to ClinicalTrials.gov for registration and results posting: The use of a checklist. Society of Clinical Trials. Published online August 5, 2020. https://doi.org/10.1177/1740774520942746

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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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