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INSTITUTE *for* CLINICAL & TRANSLATIONAL RESEARCH

UMB Session IV: June 6, 2023

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Program Administrator, Clinical Research Operations

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JHU ClinicalTrials.gov Program

- 1.8 FTE
  - —Monitor >2,000 records across 4 PRS accounts
    - SOM, SON
    - SKCCC
    - JHSPH
    - All Children's
- Regularly assist other AMCs to develop programs
- Maintain 99% compliance and one of the top success rates of all academic sites

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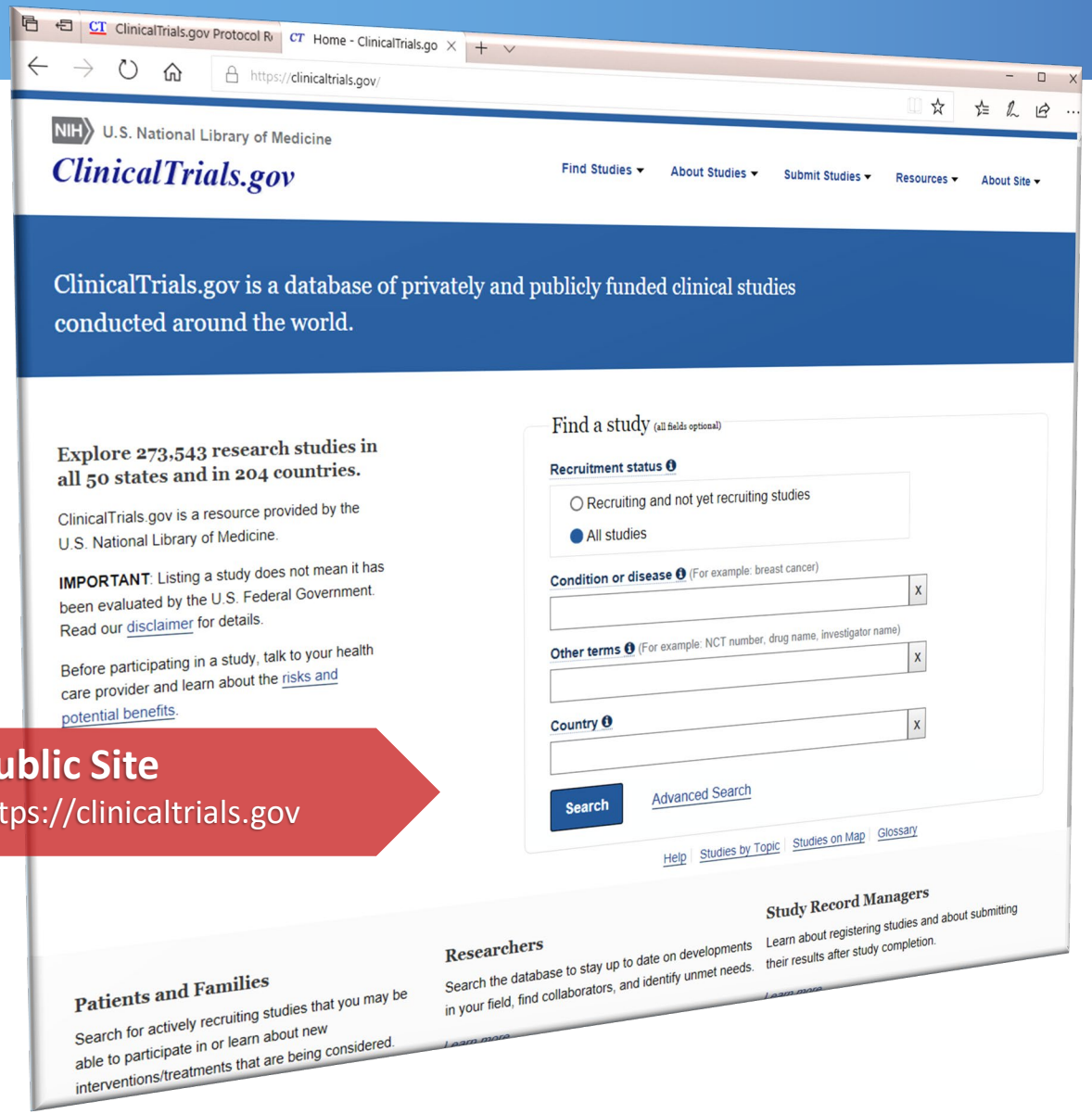
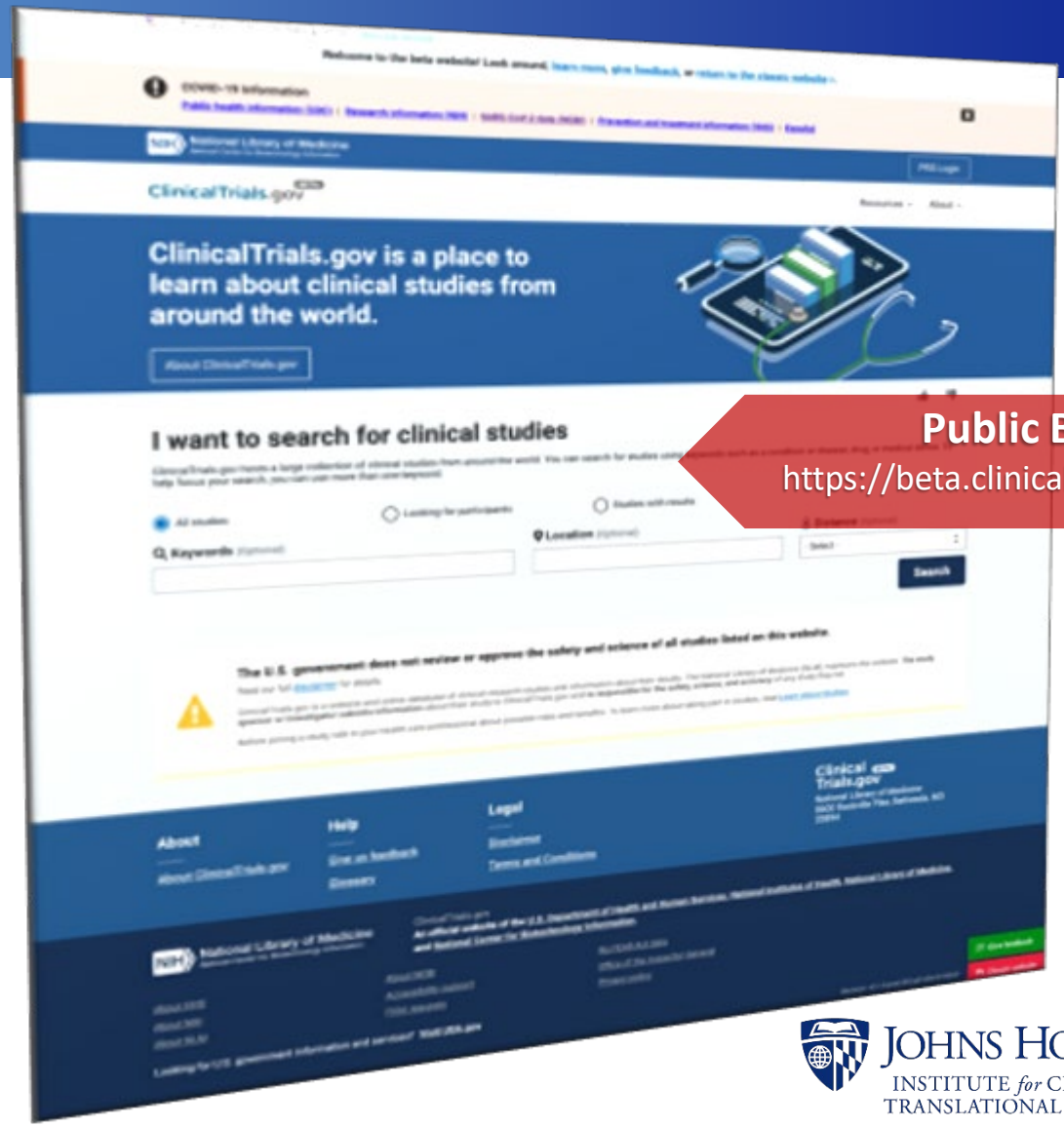
ClinicalTrials.gov – Public Site



Public Site
https://clinicaltrials.gov



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

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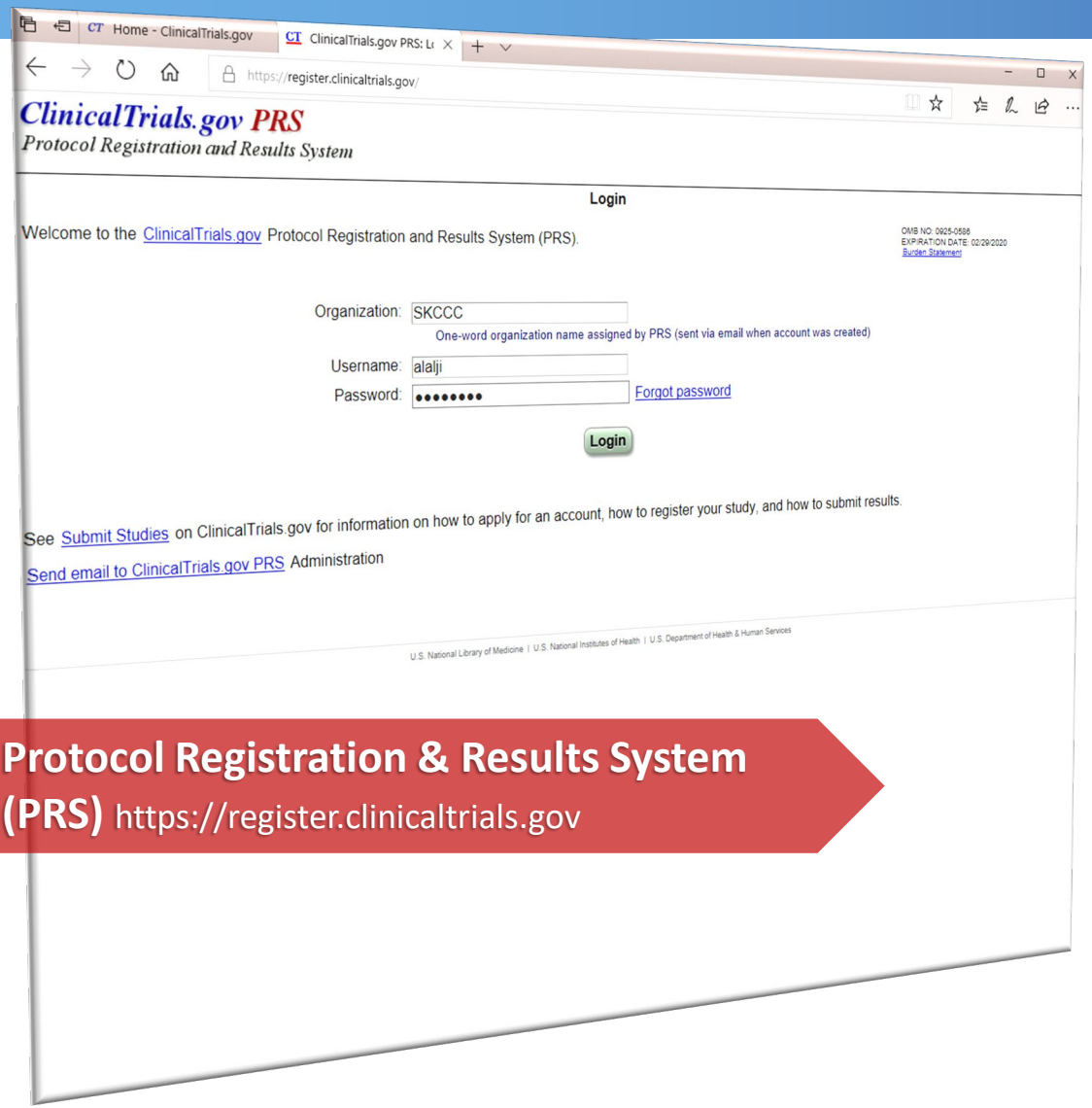
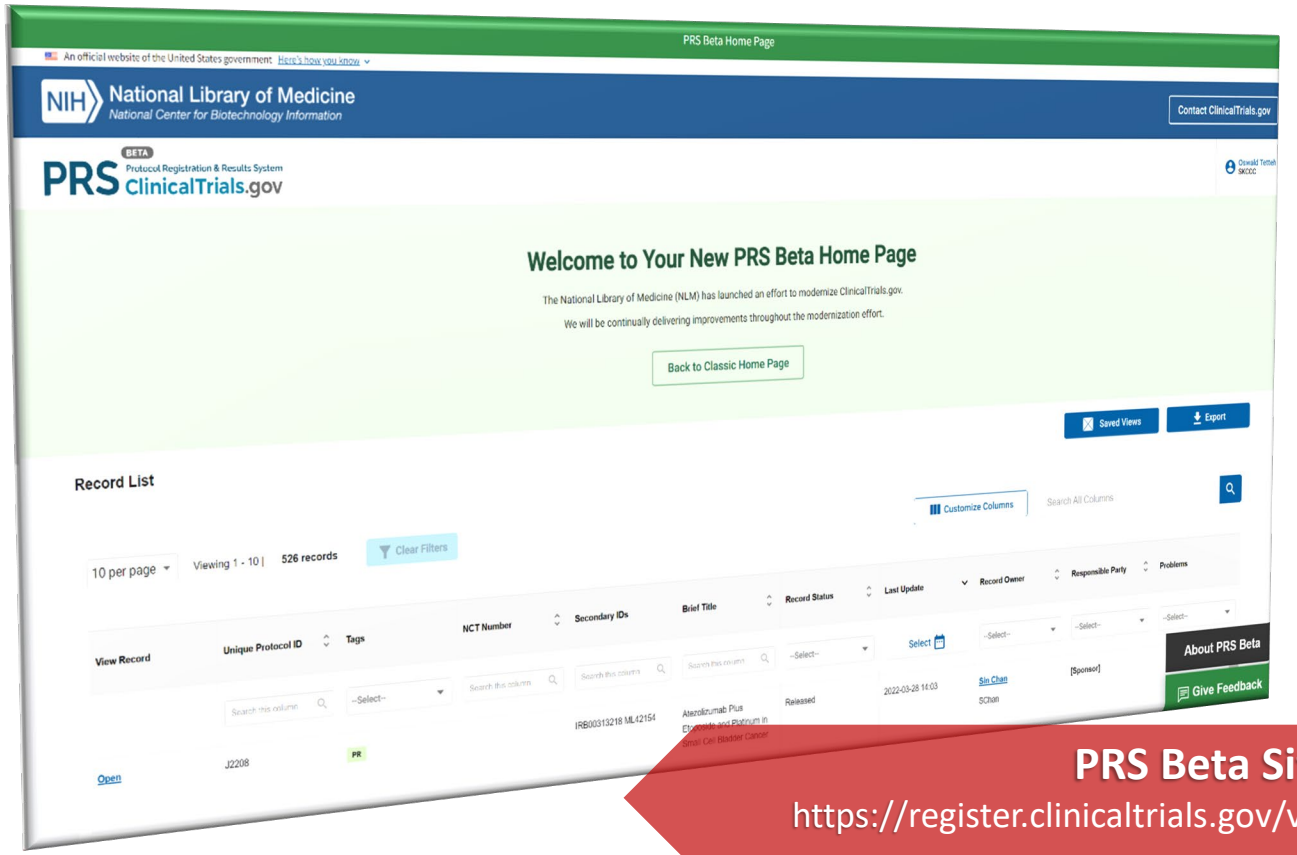
ClinicalTrials.gov - PRS



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



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

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Why a ClinicalTrials.gov Program?

1.) Commitment to participants, scientific validity/transparency, responsible stewardship

2.) Avoid non-compliance penalties

- —Civil or criminal judicial actions
- —Civil monetary penalties up to $12,462 per study, per day
- —Withholding of current or future funding
- —Reputational risk (also upside!)

3.) Faculty support

- —Steep learning curve (institutional efficiency)*
- —Changing regulations and modernization

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*Keyes A, Mayo-Wilson E, Atri N, et al. Time From Submission of Johns Hopkins University Trial Results to Posting on ClinicalTrials.gov. *JAMA Intern Med.* Published online October 28, 2019. DOI: https://doi.org/10.1001/jamainternmed.2019.4710

Registration

- Due **prior to enrollment**
- 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
- Any research from a foundation that requires registration as a term or condition of the grant/award

Results Reporting

- Due **12 months after *primary completion date**** – Need to start 3-4 months early
- Results reporting reminders are sent to PI/Study team
- Assistance with results reporting
- Assistance with PRS reviewer comments (25 calendar days)
- Changes to PI/Study team (including when a PI leaves)
- Direct services at $50 per hour (optional)

* Final data collection date for primary outcome measure.

Record Maintenance

- If your record has an NCT number but isn't approved in the IRB.
- If the study has an Overall Status of **Withdrawn**, the number enrolled/consented is 0, and an explanation must be entered.
- If the Overall Study status is **Terminated**, the number enrolled is entered and an explanation is required.
- If the Overall Study status is **Completed**, the Primary and Study completion dates (final data collection) are changed to actual dates and the actual enrollment number is provided.

Record Transfer

- Obtain email of PI to maintain communication, and follow up regarding the transfer
- PI provides transferring organization the contact information of the receiving organization PRS administrator
- Transferring organization confirms via email from the receiving organization or responsible party that the record will be accepted
- The email to Register@ClinicalTrials.gov should include:
  - Confirmation the record will be accepted at the receiving organization
  - Organization name
  - New username of the PI
  - NCT record number

Departing Faculty

- UMB is considering instituting a Checklist for departing faculty
- Each clinical trial needs action
  1. Will the study/grant be closed?
  2. Will the study/grant be transferred to a new PI at UMB?
  3. Will the study/grant be transferred to the new institution?

- Data from clinical trials are property of UMB and not the PI
  - —Cannot be taken
  - —If taken must be returned immediately
  - —Refusal to return may involve legal action

Violations and Enforcement

Anthony Keyes, MBA, PMP

Program Administrator, Clinical Research Operations

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FDAAA 801 Violations

- Applies to Applicable Clinical Trials (ACT)
- Notices are 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

https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

FDA Enforcement

- FDA has sent 53 **Pre-Notice Letters**
- **FDA has sent 4 Notice of Noncompliance** Letters

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	

- FDA has, **so far**, not issued any civil monetary penalties

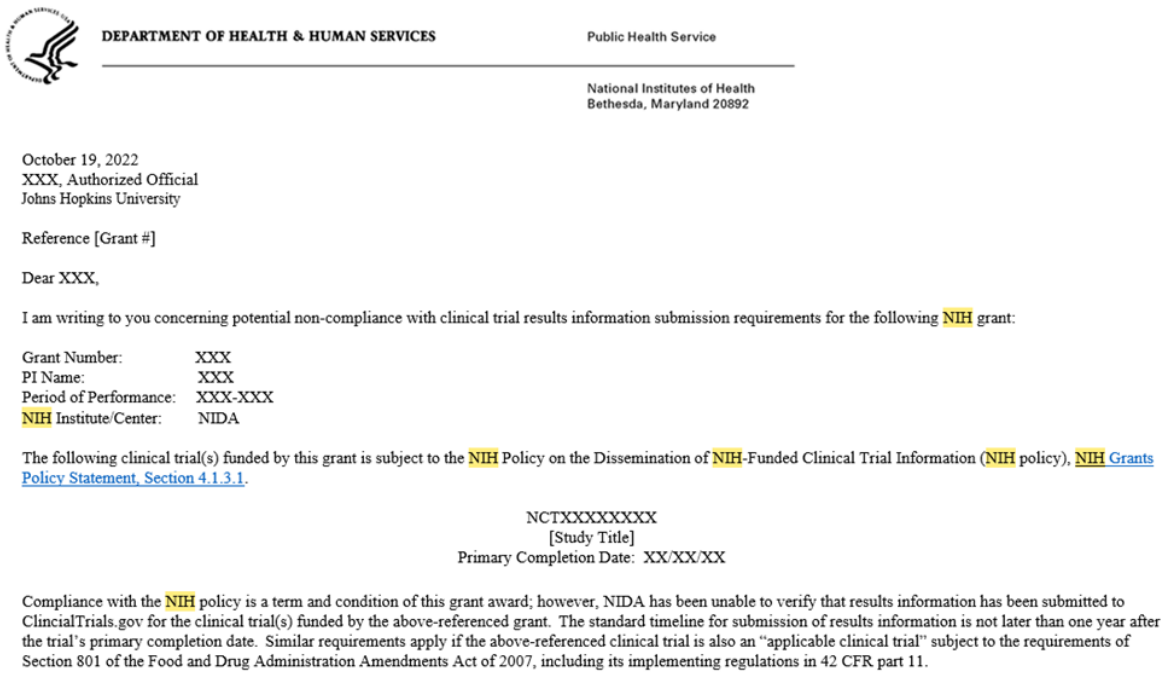
https://www.fda.gov/science-research/fdas-role-clinicaltrialsgov-information/clinicaltrialsgov-notices-noncompliance-and-civil-money-penalty-actions#:~:text=FDA%20has%20the%20authority%20to,or%20misleading%20clinical%20trial%20information

FDA/NIH Enforcement

- August 2022 Office of Inspector General (OIG) Report

  "NIH did not ensure that all NIH-funded Intramural and Extramural clinical trials complied with Federal reporting requirements"

- FDA and NIH are working together to identify and target noncompliance
- NIH has sent >300 Noncompliance Letters



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

October 19, 2022
XXX, Authorized Official
Johns Hopkins University

Reference [Grant #]

Dear XXX,

I am writing to you concerning potential non-compliance with clinical trial results information submission requirements for the following NIH grant:

Grant Number: XXX
PI Name: XXX
Period of Performance: XXX-XXX
NIH Institute/Center: NIDA

The following clinical trial(s) funded by this grant is subject to the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information (NIH policy), NIH Grants Policy Statement, Section 4.1.3.1.

NCTXXXXXXXX
[Study Title]
Primary Completion Date: XX/XX/XX

Compliance with the NIH policy is a term and condition of this grant award; however, NIDA has been unable to verify that results information has been submitted to ClincialTrials.gov for the clinical trial(s) funded by the above-referenced grant. The standard timeline for submission of results information is not later than one year after the trial's primary completion date. Similar requirements apply if the above-referenced clinical trial is also an "applicable clinical trial" subject to the requirements of Section 801 of the Food and Drug Administration Amendments Act of 2007, including its implementing regulations in 42 CFR part 11.

https://oig.hhs.gov/oas/reports/region6/62107000.asp

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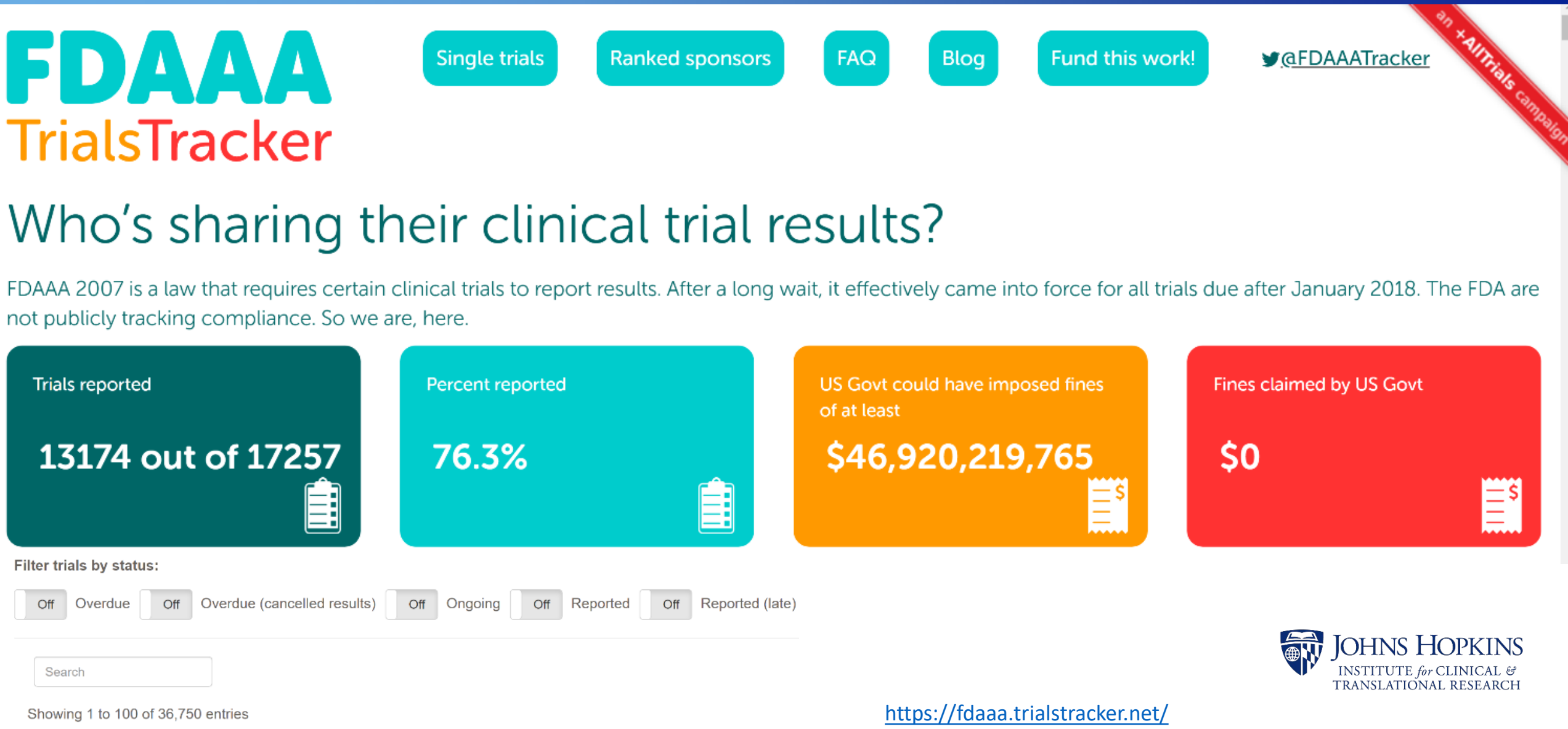
FDAAA TrialsTracker



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https://fdaaa.trialstracker.net/

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

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

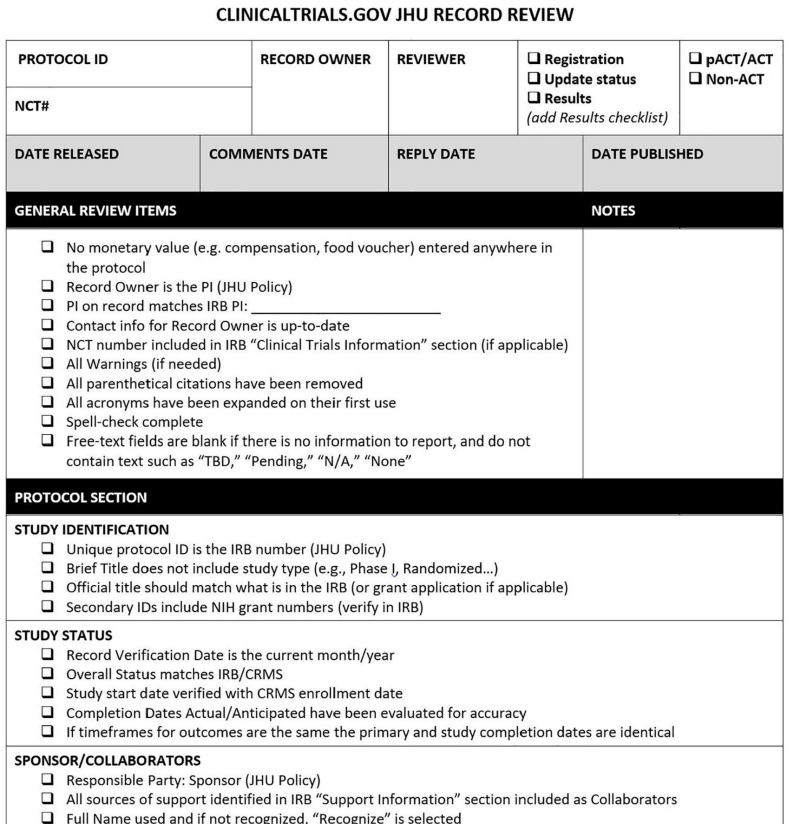
Summary of Requirements

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

Using the Checklist

- Developed a Quality Review Checklist

	Pre-checklist	Post-checklist	p value
Registration, N	**107**	**104**	
Success rate (%)	44.86	79.81	<0.001
Submission cycles, mean (SD)	1.74 (0.78)	1.22 (0.46)	<0.0001
Total days in review, mean (SD)	18.90 (26.72)	2.12 (3.85)	<0.0001
Results—Overall, N	**44**	**22**	
Success rate (%)	11.36	40.91	0.010
Submission cycles, mean (SD)	2.23 (0.68)	1.64 (0.58)	0.0011
Total days in review, mean (SD)	115.80 (129.33)	39.27 (19.84)	<0.0001



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
❑ No monetary value (e.g. compensation, food voucher) entered anywhere in the protocol ❑ Record Owner is the PI (JHU Policy) ❑ PI on record matches IRB PI: _____ ❑ Contact info for Record Owner is up-to-date ❑ NCT number included in IRB "Clinical Trials Information" section (if applicable) ❑ All Warnings (if needed) ❑ 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 number (JHU Policy) ❑ Brief Title does not include study type (e.g., Phase I, Randomized…) ❑ Official title should match what is in the IRB (or grant application if applicable) ❑ Secondary IDs include NIH grant numbers (verify in IRB)	
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	

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

ClinicalTrials.gov at UMB

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Communication Process at UMB

Communication	PI	Auditing and Monitoring (OAC)	Chair/Dean /IO
Email/CICERO	✓		
Email/CICERO #2	✓	✓	
Email/CICERO #3	✓	✓	✓

Escalation

Escalation

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UMB OAC

- OAC monitors compliance
- OAC will send periodic e-mails to PIs with non-compliant or soon to be non-compliant issues

UMB HRPO

- Problem records will impact future HRPO review
- Continuing Review will be delayed/denied with annual verification
- Appropriate handoff for new PIs (data, reporting obligations)
- Use the checklist to increase quality and decrease time in review

Continued Success

- Registering Records
  - —Keep them updated!
    - Within 30 days of changes
    - Annually
- Departing faculty
  - —Nationwide the biggest barrier
  - —Communicate!
- Transferring Records
  - —Register@ClinicalTrials.gov

ClinicalTrials.gov Taskforce

- 650 members, 220 Academic Centers
- Monthly Meetings (NLM, FDA, OHRP, NCI, NCATS)
- Many best practices developed
- Active listserv
- Revamping website to be ADA accessible
- Ongoing initiatives (i.e., dashboard for CTSA PIs, train the trainer, follow-up survey*)

*Mayo-Wilson, E., Heyward, J., Keyes, A. *et al.* Clinical trial registration and reporting: a survey of academic organizations in the United States. *BMC Med* 16, 60 (2018) doi:10.1186/s12916-018-1042-6

https://ctrrtaskforce.org/

Co-Leads: Sarah White, MRCT; Tony Keyes, JHU

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Questions

- https://ictr.johnshopkins.edu/service/study-conduct/rcss/
- akeyes1@jhmi.edu

- https://ictr.johnshopkins.edu/service/regulatory/ct-gov/
- registerclinicaltrials@jhmi.edu