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Office for Research

Building Trust and Protecting Participants: Maintaining Compliance with ClinicalTrials.gov

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Office for Research
Research Regulatory Affairs
Human Research Protection Program (HRPP)

October 29, 2024
2024 SRAI Annual Meeting
Chicago, IL

Join at www.menti.com and use code **9977 9717**

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Office of the Executive Vice President for Academic Affairs

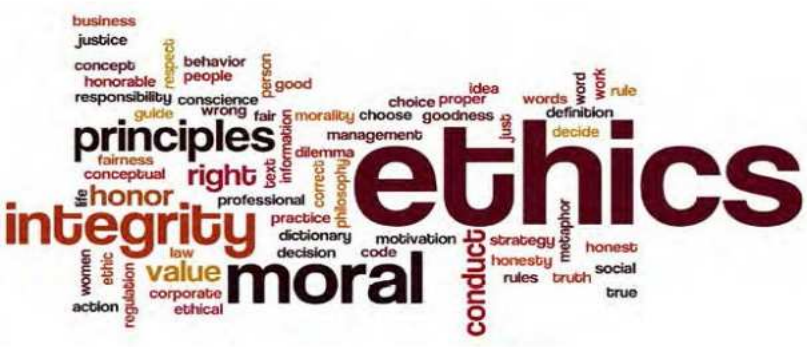
Getting to Know You!

1. Your name & title
2. Your organization
3. What brought you to this session?

Fun Facts about Rutgers

Disclosure

Speaker does not have conflicts of interest to disclose in relation to this educational activity.



Learning Objectives

1. Describe why clinical trials disclosure matters; list resources to assist investigators in maintaining compliance

2. Identify key elements to establish a system in your organization to facilitate and monitor clinical trials registration and results reporting

Roadmap

1. Human Subjects Protection – IRB & ClinicalTrials.gov
2. Why Do We Care?
3. What Are the Registration Requirements?
4. Record Update & Results Reporting Requirements
5. Recent Ramification of Non-compliance
6. Establish a System in an Organization
7. Latest Updates and Modernization
8. Resources

Human Subjects Protection

- Increase Public Trust
- Promote Transparency

IRB

an **independent committee** established to review and approve research involving human subjects, its purpose is to protect the rights and welfare of the human subjects.

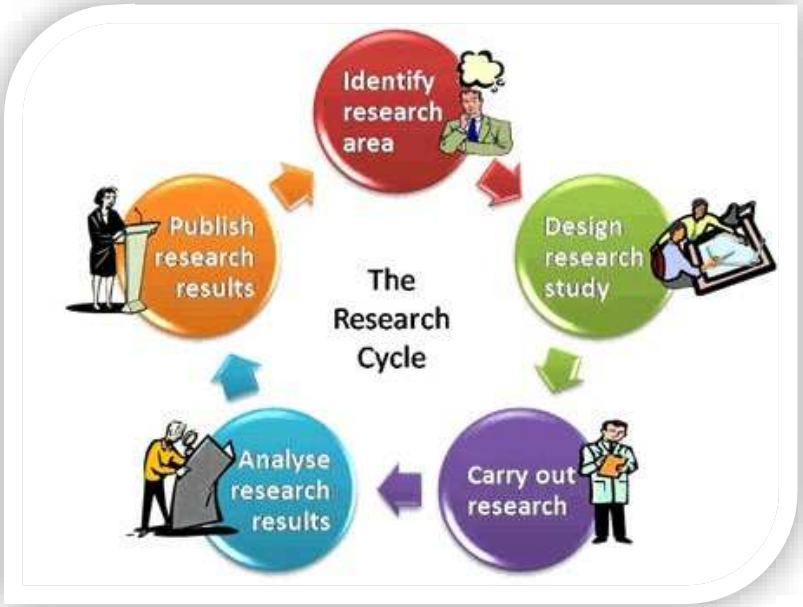
ClinicalTrials.gov

A **registry** and results database of clinical studies involving human participants conducted around the world.
A resource provided and maintained by the US NLM.

- Ensure Research Rigor and Integrity
- Improve Oversight

The Research Cycle

The Investigator's Perspective



The Compliance Perspective

Results reporting should not be considered a burden. Reporting results is an essential part of the scientific process; it is an integral component of the scientific method.

--- Michael S. Lauer, MD, Extramural Research, NIH

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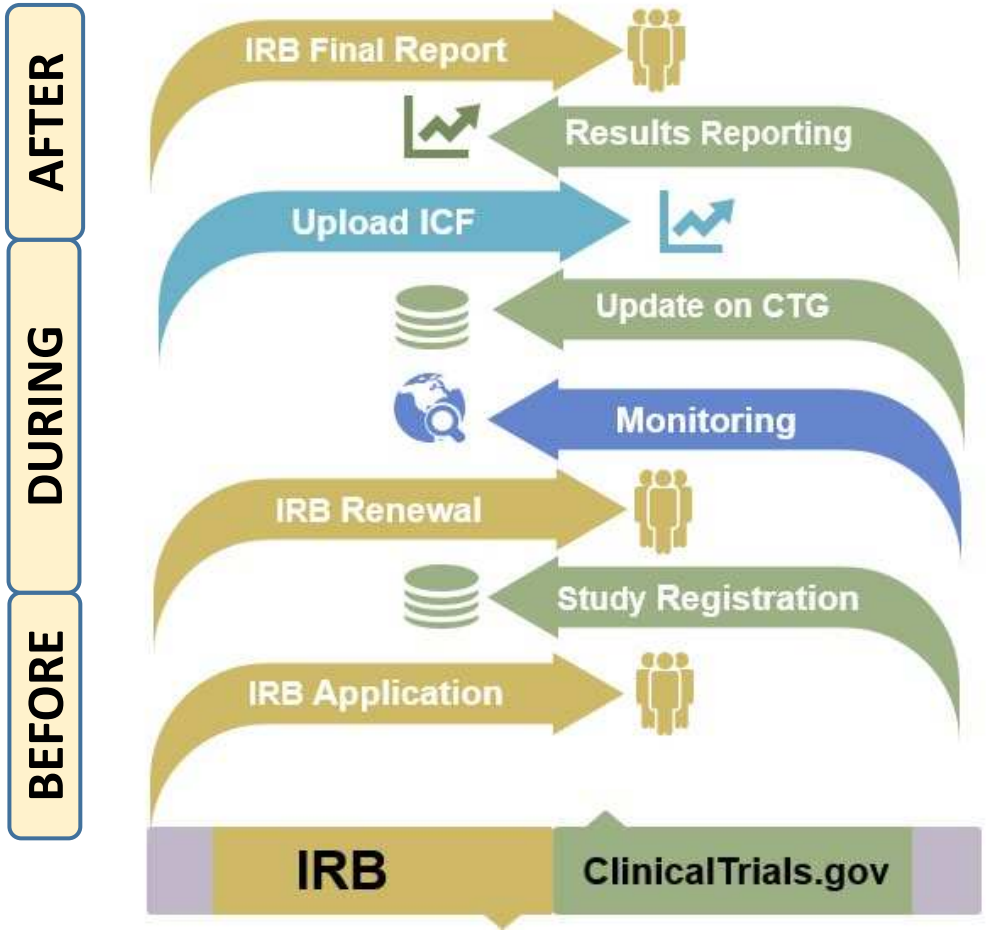
Human Subjects Protection

thru IRB & Clinicaltrials.gov



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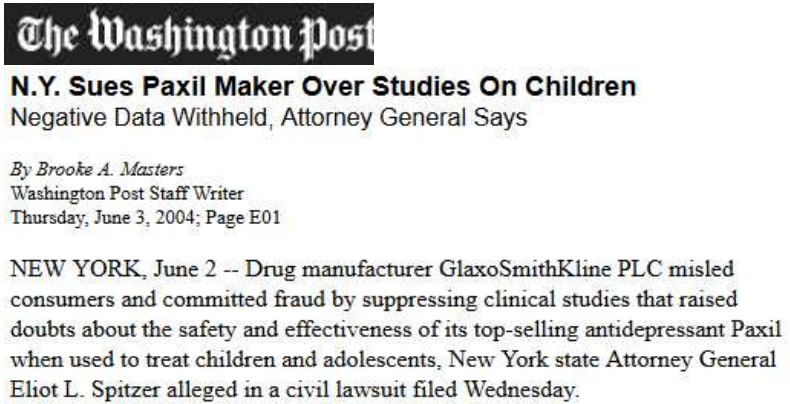
Three Pivotal Cases

- **Paxil**
  - GSK suppressed evidence on harms and lack of efficacy in children



The Washington Post

N.Y. Sues Paxil Maker Over Studies On Children

Negative Data Withheld, Attorney General Says

By Brooke A. Masters
Washington Post Staff Writer
Thursday, June 3, 2004; Page E01

NEW YORK, June 2 -- Drug manufacturer GlaxoSmithKline PLC misled consumers and committed fraud by suppressing clinical studies that raised doubts about the safety and effectiveness of its top-selling antidepressant Paxil when used to treat children and adolescents, New York state Attorney General Eliot L. Spitzer alleged in a civil lawsuit filed Wednesday.

- **Vioxx**
  - Merck failed to report heart attacks

The Washington Times

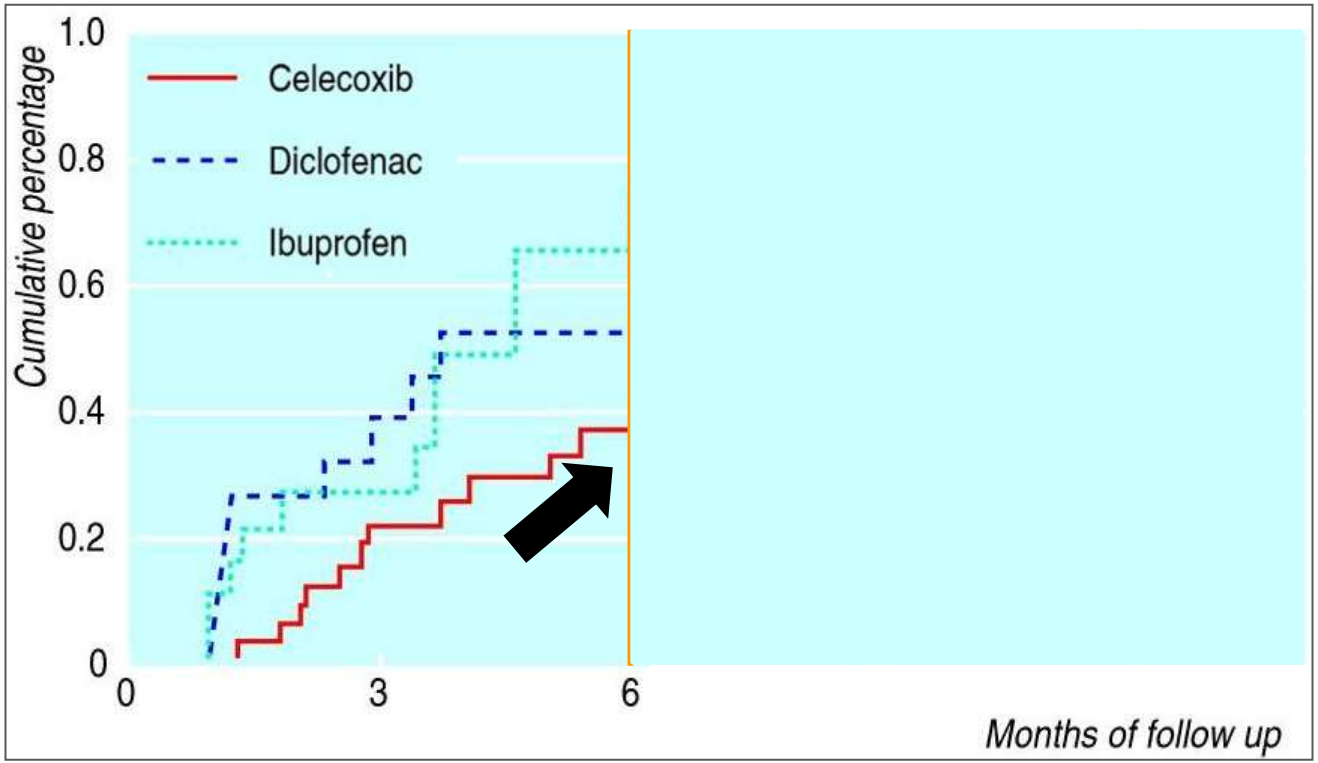
Merck recalls Vioxx

Heart risk found in arthritis drug

PAINFUL

- **Celebrex**
  - Pfizer reported misleading results

Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. (Adapted from Lu 2001.)



Jüni P, Rutjes AW, Dieppe PA. *BMJ*. 2002 Jun 1;324(7349):1287-8.

Takeaway

It is scientifically and ethically imperative for researchers to understand that clinical trial registration and results reporting is a key commitment to our research participants.

We all need the results of clinical trials to advance knowledge and inform our medical decisions.

Benefits to Register & Report Results

- **Human Subject Protections**
  - Allows potential participants to find studies
  - Assists ethical review boards and others to determine appropriateness of studies being reviewed
  - Promotes fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge
- **Research Integrity**
  - Facilitates tracking of protocol changes
  - Mitigates information bias (e.g. non publication)
  - Increases transparency of research enterprise
- **Scientific Values/ Evidence Based Medicine**
  - Facilitates tracking of studies and outcome measures
  - Allows for more complete identification of relevant studies
  - Provides data to support evidence-based medicine"
- **Allocation of Resources**
  - Promotes more efficient allocation of resources

All Contribute to Increased Public Trust in Clinical Research

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What is a "Clinical Trial"?

The definition is agency-specific.

Applicable Clinical Trial (ACT) (Federal): Clinical trial include **interventional** studies (with one or more arms) of FDA-regulated drugs, biological products, or devices.

Clinical Trial (NIH): 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.

Clinical Trial (ICMJE): A research project that prospectively assigns human participants or groups of humans to one or more health-related **interventions** to evaluate the effects on health outcomes.

Which Studies Must Register? 1 of 2

- **Applicable Clinical Trial (ACT) (FDAAA):** Clinical trial include **interventional** studies (with one or more arms) of **FDA-regulated drugs, biological products, or devices**.

- **Clinical Trial (NIH):** 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**.
  - **BESH (NIH): B**asic **E**xperimental **S**tudy involving **H**umans uses an **intervention** to understand fundamental aspects of a phenomena **without** specific application toward processes or products in mind.

(Continued)

Which Studies Must Register? 2 of 2 (Continued)

- **CED Clinical Trial (CMS)** All studies seeking **Medicare coverage** for items and services on a condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data, where the study has **therapeutic intent**, tests whether the intervention potentially improves participant **health outcomes** [**Coverage with Evidence Development** (CED)]

- **Clinical Trial (ICMJE)**: A research project that prospectively assigns human participants or groups of humans to one or more health-related **interventions** to evaluate the **effects on health outcomes**.

- **Funding agencies (PCORI)**: Funded/supported by the agency and applies to Clinical Trial, Observational studies and Patient Registry

1. **Does this study have an *Interventional* research design?**
An intervention is defined as a manipulation of the subject or the subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include
   - Drugs, small molecules or compounds
   - Biologics
   - Devices
   - Procedures (e.g., surgical techniques)
   - Delivery systems (e.g., telemedicine, face-to-face interviews)
   - Behavioral strategies (e.g. diet, cognitive therapy, exercise, development of new habits)
   - Treatment strategies
   - Prevention strategies
   - Diagnostic strategies

   In a clinical trial, *interventional* is defined to mean that human subject participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect(s) of the intervention(s) on a health-related biomedical or behavioral outcomes. See NIH FAQ

2. **Does the study evaluate at least one drug, biological or device product regulated by FDA?**
This includes clinical trials that investigate a drug or biological product that is the subject of an approved new drug application (NDA) or biologic license application (BLA) or that would require an approved NDA or BLA to be legally marketed in the United States. The FDA Orange Book provides a list of licensed drug products with FDA approval. The FDA Purple Book provides a list of licensed biological products with FDA approval.
Also included for the criteria are clinical trials that investigate a device for which approval by the FDA has been attained or is being sought; these are device products subject to the Food, Drug & Cosmetic Act regulations (510(k), 515, or 520(m)). The FDA Medical Devices website provides lists and searchable databases for FDA-approved devices.

3. **Is the study other than a Phase 1 drug/biological study or other than a device feasibility study?**
Phase 1 trials include studies that introduce an investigational new drug into humans, have primary objectives of safety measurements, may include normal volunteer subjects, can be designed to determine the metabolism and pharmacologic actions of the drug, study the side effects associated with increasing doses, and if possible, gain early evidence on effectiveness. A device feasibility study is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. Phase 1 clinical trials and device feasibility studies are exempted from FDA requirements for ClinicalTrials.gov registration and results reporting. For additional details, refer to the Applicable Clinical Trial Checklist.

4. **Is the study fully or partially funded by NIH?**
The NIH defines a clinical trial as "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 these interventions on health-related biomedical or behavioral outcomes. The NIH Policy, effective January 18, 2017, requires all investigators conducting clinical trials funded by the NIH to register and report results of these trials at ClinicalTrials.gov.
The NIH policy is applicable to all clinical trials funded in whole or in part by the NIH, regardless of study phase, intervention type (including behavioral interventions), or whether they are investigating an FDA regulated drug, biologic or device.

5. **Does the PI/Sponsor intend to publish results in an ICMJE journal?**
A complete list of journals that follow the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals can be found here. **ICMJE standards require registration of clinical trials in a public trials registry (such as ClinicalTrials.gov) at or before the time of first patient enrollment as a condition of consideration for publication.**
More information about ICMJE and registration requirements can be found on the ICMJE website.

V3 March 16, 2023

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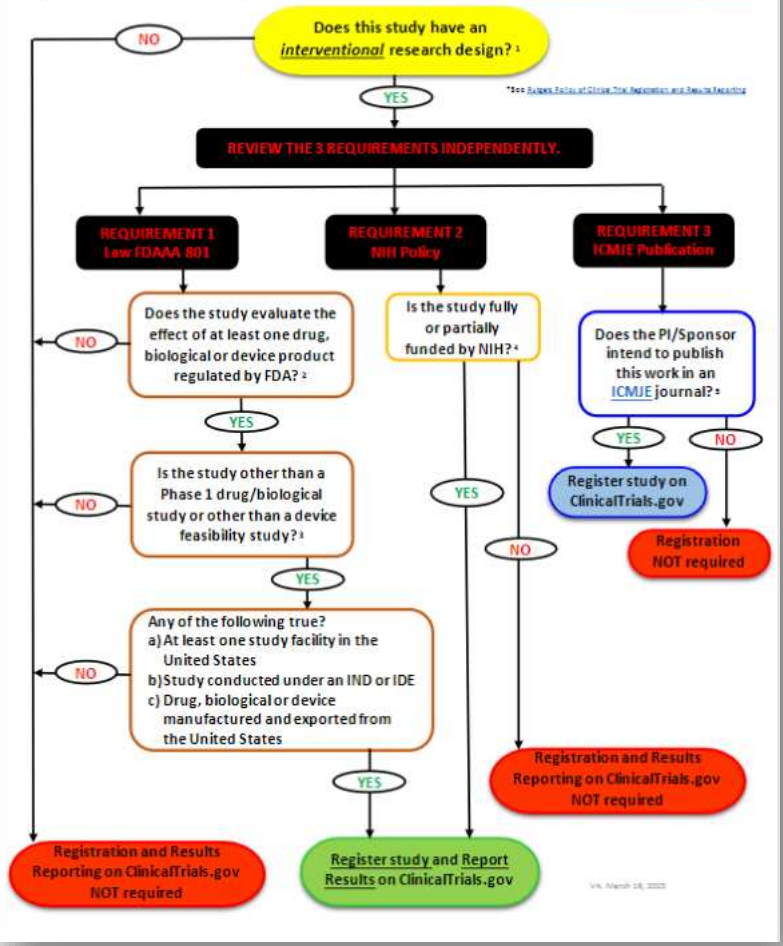
Clinical Trials Registration Decision Tree

Questions? Please email Rutgers ClinicalTrials.gov Support at rutgersctgsupport@research.rutgers.edu



Access **Decision Tree – clinical trial registration**

Agencies Requiring Registration

- Department of Health and Human Services
  - Law: FDA, NIH, WHO
  - Funding Agency: NIH, PCORI
  - Billing: CMS

- Publishers/ Journals: ICMJE

- International: WHO
  - Scientific, ethical and moral responsibility

Who Registers the Studies?

Responsible Party (RP) is responsible for study registration and results reporting.

- **Sponsor**: The entity that initiates the study
- **Principal Investigator(PI):** The individual designated as responsible party by the sponsor
  - Have access to and control over the data
  - Have rights to publish study results, AND
  - Are able to satisfy ClinicalTrials.gov submission requirements
- **Sponsor-Investigator (S-I):** The individual who both initiates and conducts the study

Investigator Initiated Studies @ Rutgers University

RP = PI or S-I

When to Register

- DHHS, NIH, NCI, FDA: Register the record within 21 days of enrollment
- ICMJE, CMS: Prior to enrollment (ICMJE, CMS)
- VHA, DOD, PCORI: Prior to release of funding and prior to enrollment

Recommendation / Tip:
Register before study activation for ALL studies

Which Platform? ClinicalTrials.gov

- There are two different systems:
  - ❑ Public site: https://www.clinicaltrials.gov/
  - ❑ User site: **Protocol Registration and Results System (PRS)** https://register.clinicaltrials.gov/

- There are two basic functions of ClinicalTrials.gov:
  - ❑ Registration (creating and updating the record)
  - ❑ Results Reporting (to be completed within 12 months of "Primary Completion")

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Record Update and Maintenance

Records must be updated

- Every 12 months/ Annual Verification; until all results reported* or study closed
- Within **30 days** of the following:
  - Recruitment Status changes (Open, Pause, Close)
  - Amendments affecting information in ClinicalTrials.gov record
    - location, contact information, IRB Status, Responsible Party
  - Discrepant Dates
    - "Anticipated" completion dates have passed

"30 days" includes
- Update
- RP approval & release
- PRS review and posting

*Not all studies require results; record updated until complete

Documents: Informed Consent Form

§46.116 General requirements for informed consent.

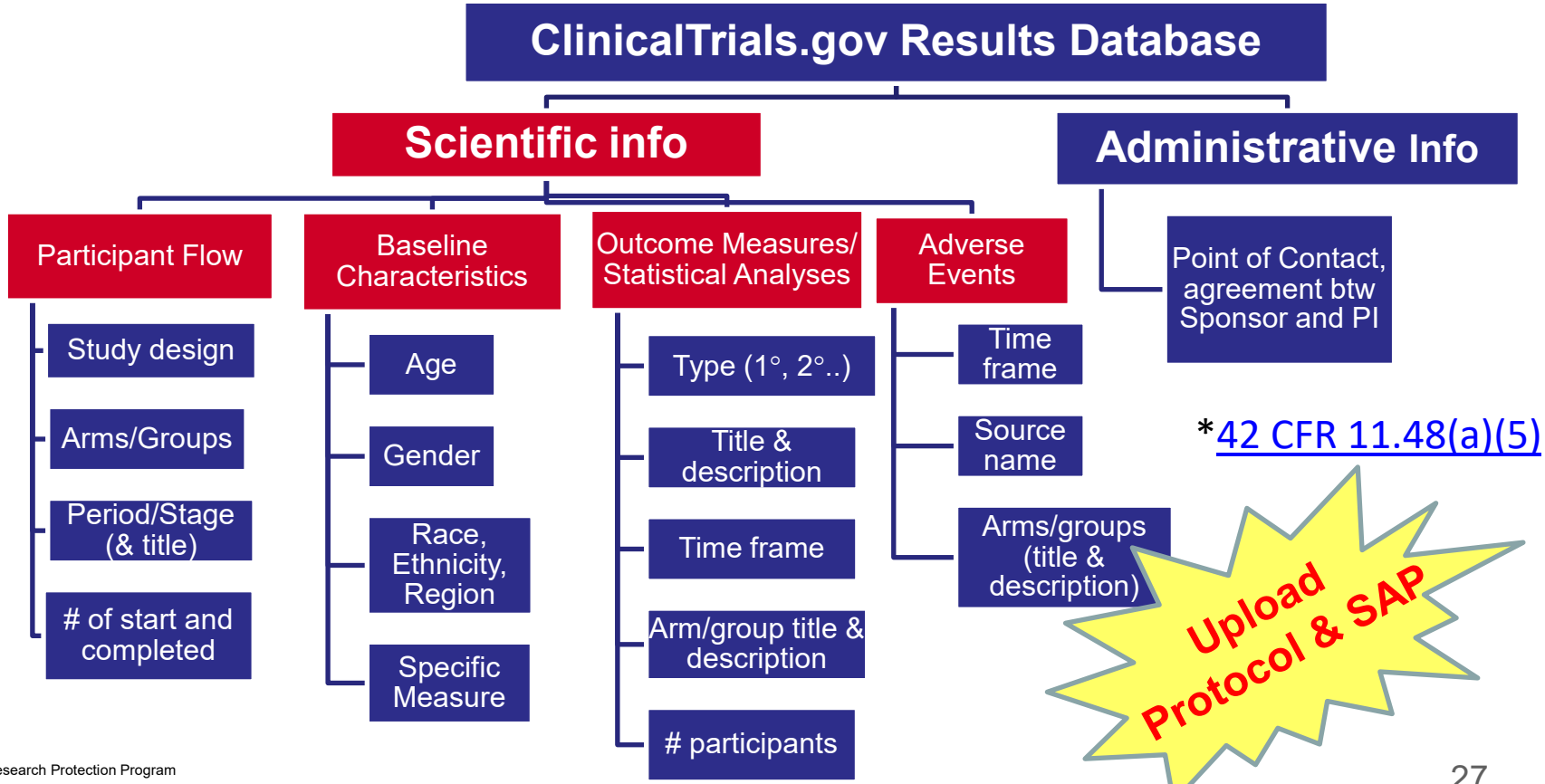
- **Revised Common Rule (45CFR46)**
  - Transparency of consent forms used
  - Improve the quality of consent forms
- **Applicable Trials**
  - Clinical Trials initiated on or after January 21, 2019
  - Conducted or supported by a Common Rule department or agency
- **Posting Requirements**
  - After recruitment closes AND
  - No later than 60 days after last study visit by any subject

Example Agencies (20 Total)
- Homeland Security
- Dept. of Defense
- Dept. of Veterans Affairs
- Dept. of Health And Human Services (Includes NIH, AHRQ, CDC)
- National Science Foundation

Repost as necessary

Tip: Use CTG update to help with tracking

Overview - Results Database



Results Reporting*

- **FDA and NIH**
  - Applicable Clinical Trial (ACT) or Federally Funded Studies require results reporting
  - Report results within 12 months of the **completion dates** (see below)
    - Estimated time to enter results: **up to 40 hours***
    - It may take **multiple review cycles** to post your results – JHU average = 2.26 review cycles and 76.23 total days in review
      - 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.

NOT: Data analysis, publication, manuscript submission

Tip: Budget 90 days for review cycles & aim for submission within 9 months of the Primary Completion Date.

*Not every study requires results; Check Funding Agency Requirements

Which type of ClinicalTrials.gov support is available at your institution? (Multiple Choice)

1. Self-service (e.g. relying on investigator)
2. Individualized support at the department level
3. Centralized ClinicalTrials.gov support (e.g. Clinical Trials Office type of support)
4. I don’t know

Join at www.menti.com and use code
9977 9717

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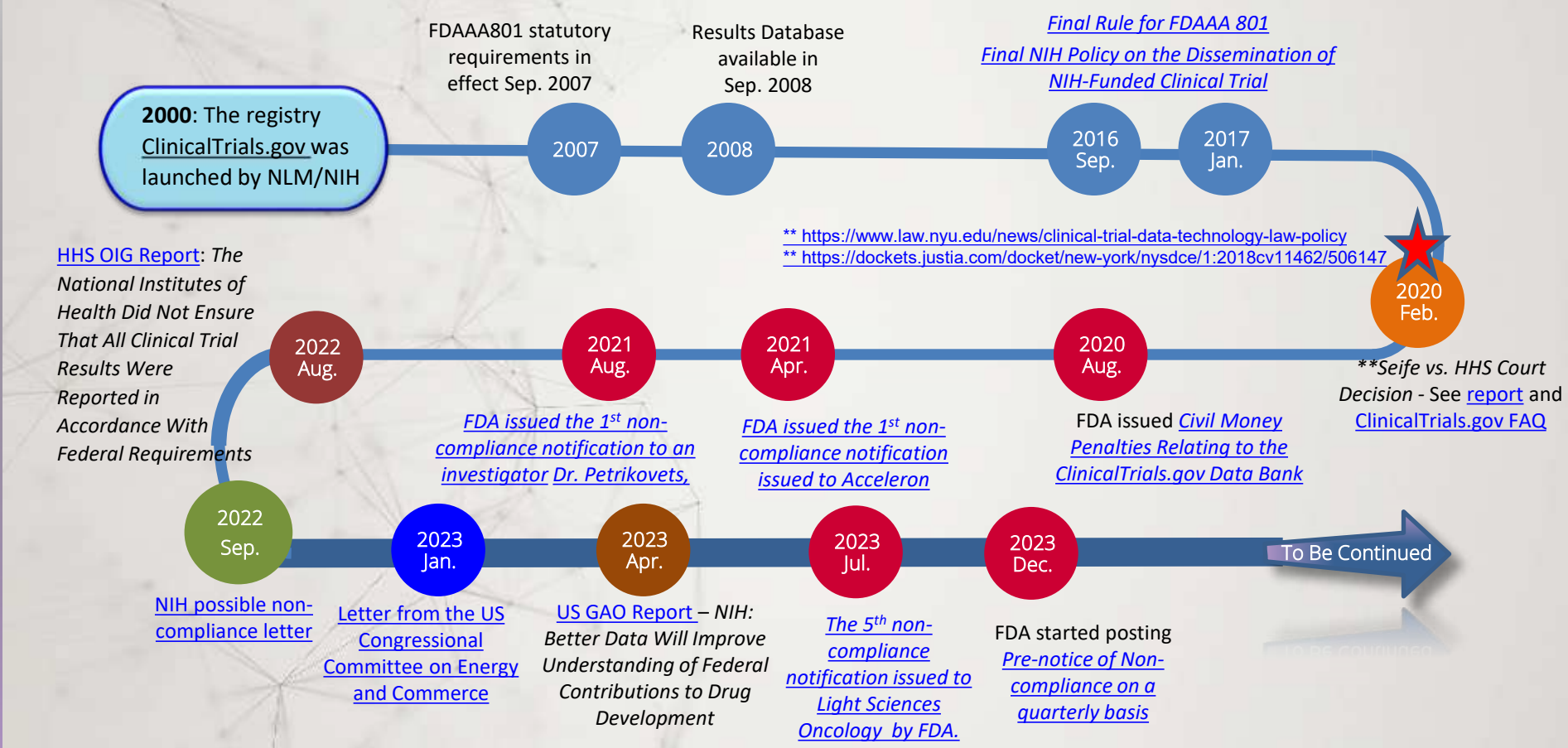
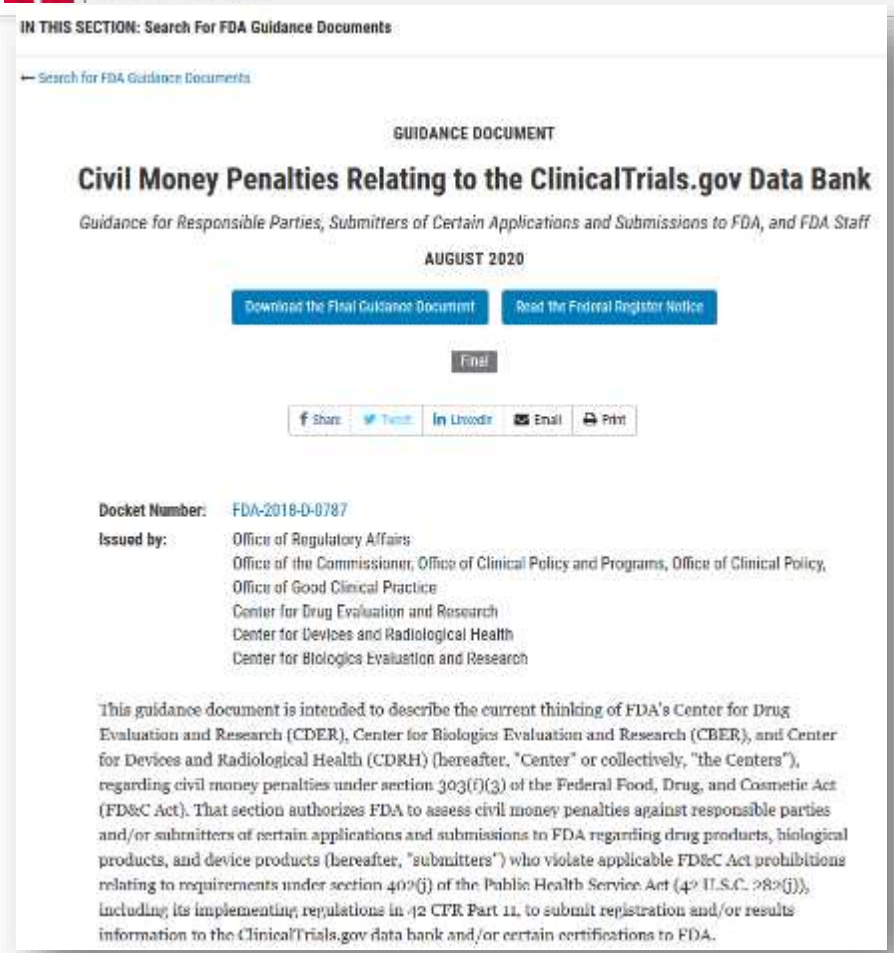
US Clinical Trials Reporting Requirements

	FDAAA	NIH	ICMJE	CMS
Time - Registration	Within 21 days of enrollment	Within 21 days of enrollment	Prior to enrollment	Prior to enrollment
Time – Results Reporting	Within 12 months of completion date	Within 12 months of completion date	Not required	Not required
Effective	January 18, 2017	January 18, 2017	2005/ July 1, 2008	---
Ramification of Non-Compliance	• Criminal proceedings and civil penalties (up to $14,262 per day per study); • Loss of funding	• Withhold funding • Deny renewal • Reject request for new funding	Rejection of manuscripts	Medicare claims without NCT# for qualified services covered under a clinical trial will not be reimbursed
Action of Enforcement	Initiated since 2013/ April 2021	Initiated since September 2022	Prior to 2014 & journal-specific	---
Link for more information	https://clinicaltrials.gov/ct2/manage-recs/fdaaa	https://grants.nih.gov/policy/clinical-trials/reporting/index.htm	https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html	

Key Milestones: ClinicalTrials.gov Regulations





IN THIS SECTION: Search For FDA Guidance Documents

← Search for FDA Guidance Documents

GUIDANCE DOCUMENT

Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff

AUGUST 2020

Download the Final Guidance Document | Read the Federal Register Notice

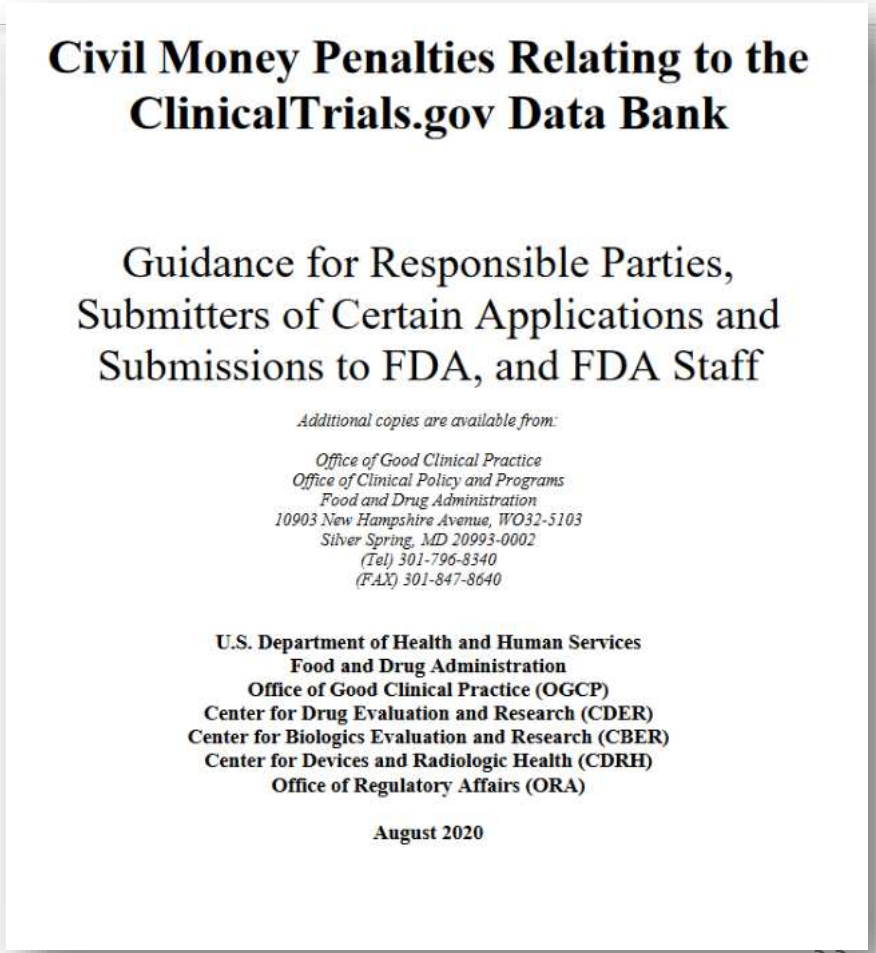
Final

Share | Tweet | LinkedIn | Email | Print

Docket Number: FDA-2018-D-0787

Issued by: Office of Regulatory Affairs
Office of the Commissioner, Office of Clinical Policy and Programs, Office of Clinical Policy, Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

This guidance document is intended to describe the current thinking of FDA's Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) (hereafter, "Center" or collectively, "the Centers"), regarding civil money penalties under section 303(f)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). That section authorizes FDA to assess civil money penalties against responsible parties and/or submitters of certain applications and submissions to FDA regarding drug products, biological products, and device products (hereafter, "submitters") who violate applicable FD&C Act prohibitions relating to requirements under section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)), including its implementing regulations in 42 CFR Part 11, to submit registration and/or results information to the ClinicalTrials.gov data bank and/or certain certifications to FDA.



Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

Guidance for Responsible Parties, Submitters of Certain Applications and Submissions to FDA, and FDA Staff

Additional copies are available from:

Office of Good Clinical Practice
Office of Clinical Policy and Programs
Food and Drug Administration
10903 New Hampshire Avenue, WO32-5103
Silver Spring, MD 20993-0002
(Tel) 301-796-8340
(FAX) 301-847-8640

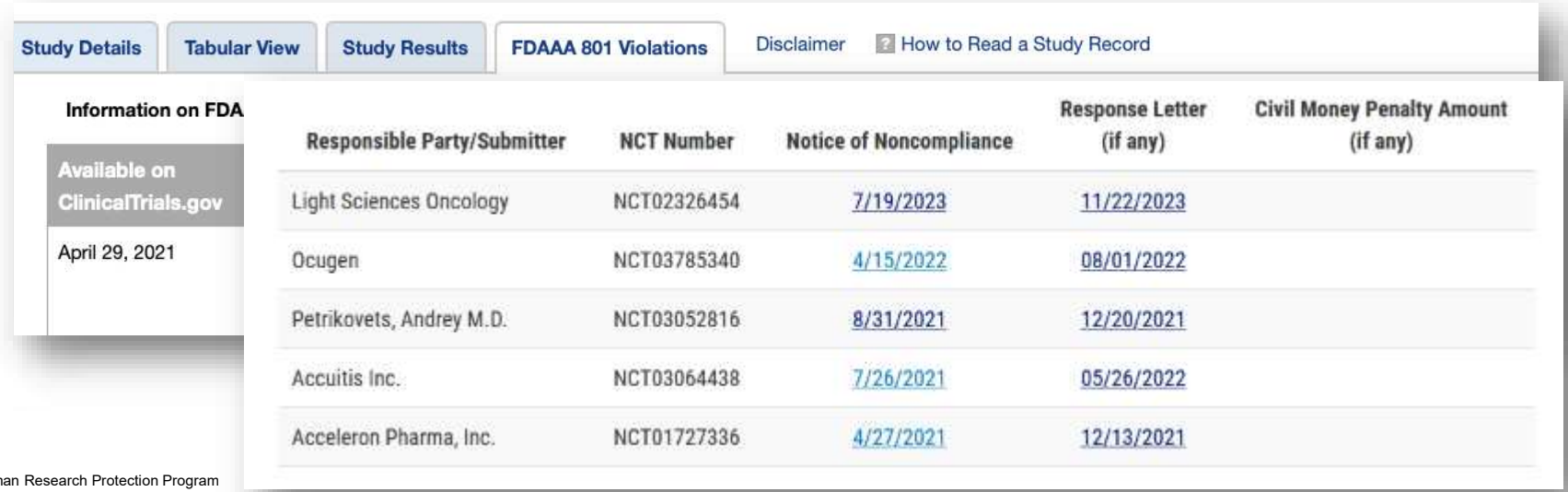
U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiologic Health (CDRH)
Office of Regulatory Affairs (ORA)

August 2020

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/civil-money-penalties-relating-clinicaltrialsgov-data-bank

Ramifications of Non-Compliance

- FDAAA 801 Violations
  - Notice is sent to the Responsible Party identified in the ClinicalTrials.gov record
  - **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)
Light Sciences Oncology	NCT02326454	7/19/2023	11/22/2023	
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 Pre-Notice of Noncompliance

FDA started the posting of these in December 2023, and stated that the agency intends to post pre-notices on a quarterly basis.

- 131 notices, Dec. 2023
- 149 notices, Apr. 2024
- 169 notices, Sep. 2024

Responsible Party	NCT Number(s) (if any)	Pre-Notice (YYYY-MM-DD)
Casi Pharmaceuticals	NCT02234986	2024-09-24
Kristin Hudock	NCT04492514	2024-09-24
Cogent Biosciences	NCT02401815	2024-09-24
Oncotelic Therapeutics	NCT02641639	2024-09-18
Glia LLC	NCT03990051	2024-09-13
OncoNano Medicine	NCT04950166	2024-09-13
Syros Pharmaceuticals, Inc.	NCT03512756	2024-08-28
Senhwa Biosciences, Inc.	NCT04663737	2024-08-28
Abionyx Pharma	NCT02697136	2024-08-28
JCR Pharmaceuticals Co., Ltd.	NCT04227600	2024-08-28

Showing 1 to 10 of 169 entries

Previous 1 2 3 4 5 … 17 Next

HHS OIG Report

Report in Brief
Date: August 2022
Report No. A-06-21-07000

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF INSPECTOR GENERAL

Why OIG Did This Audit

The National Institutes of Health (NIH) provides funding for clinical trials carried out by NIH scientists in NIH laboratories on its campuses (Intramural) and through awards to the community of scientists at universities, medical centers, hospitals, and research institutions throughout the United States and abroad (Extramural). NIH is responsible for ensuring that NIH-funded Intramural and Extramural clinical trials are reported on ClinicalTrials.gov. Our preliminary review of data from ClinicalTrials.gov showed that most NIH-funded clinical trials that were completed in calendar year 2018 did not have their results posted.

Our objective was to determine whether NIH ensured that NIH-funded Intramural and Extramural clinical trials complied with Federal reporting requirements.

How OIG Did This Audit

We reviewed all 72 NIH-funded Intramural and Extramural clinical trials for which Federal law and NIH policy required the results to be reported in calendar year 2019 or 2020. To determine whether responsible parties complied with reporting requirements, we compared the date the results should have been submitted with the date they were submitted. We also determined whether NIH posted the clinical trial results submitted by the responsible parties to ClinicalTrials.gov within 30 days of the submission date.

The National Institutes of Health Did Not Ensure That All Clinical Trial Results Were Reported in Accordance With Federal Requirements

What OIG Found

NIH did not ensure t
complied with Fede
submit the results o
the number of clinic
that were submitte

Table: Summary o

Submitted on Time

Submitted Late
Results Not Submitted
Subtotal of Noncompliar

Total

The noncompliance
NIH did not have ad
submitted the resul
there was noncomp
parties that had not
For the 47 NIH-fund
their results (35 sub
the Federal reportir

What OIG Recon

We recommend tha
responsible parties
submit results to Cli
actions against resp
not submit results, i
their challenges rela
address the challen

In written comment
recommendations a
address them. For
improvements to its
take compliance act

OIG's RECOMMENDATIONS

We recommend that the NIH:

- improve its procedures to ensure that responsible parties of NIH-funded clinical trials comply with requirements to submit results to ClinicalTrials.gov in a timely manner,
- take enforcement actions against responsible parties that are late in submitting trial results or do not submit results, and
- work with the responsible parties to understand their challenges related to ClinicalTrials.gov and implement procedures to address the challenges.

NIH's COMMENTS

In written comments on our draft report, NIH concurred with our recommendations and described actions it has taken or plans to take to address them. NIH stated that it has already begun to implement a series of improvements to enhance its internal procedures to work with responsible parties to ensure that they are complying with requirements to register studies and submit results to ClinicalTrials.gov. Further, NIH indicated that it is implementing activities that will enhance NIH's ability to take compliance actions against responsible parties that are late in submitting trial results or do not submit results. NIH also mentioned that it has invested substantially in making ClinicalTrials.gov an accessible and usable resource for the community. In addition, NIH stated that it has implemented significant improvements related to working with responsible parties to understand the challenges they face in submitting their results to ClinicalTrials.gov and that it has implemented procedures to address the challenges. Lastly, NIH suggested a minor revision to the language in our third recommendation, which we made.

eport: https://oig.hhs.gov/oas/reports/region6/62107000.pdf
Report in Brief: https://oig.hhs.gov/oas/reports/region6/62107000RIB.pdf

The full report can be found at https://oig.hhs.gov/oas/reports/region6/62107000.asp.

NIH Enforcement

- Policy: NIHGPS 4.1.3 Clinical Trials Registration and Reporting in ClincialTrials.gov Requirement
  - Applies to 1) FDA ACTs, and 2) All NIH-funded “clinical trial” per NIH policy
- Workflow:
  1. eRA generates reports identifying records with overdue results
  2. OPERA advises ICs of grants that are out of compliance
  3. ICs send initial non-compliance letters to recipients (ISO)
  4. recipients non-compliant after 30 days receive a letter from OPERA
  5. DDER “final call” outreach
  6. Enforcement actions
- Specific enforcement actions depend on the specific circumstances
  - No new competing awards
  - Refer to FDA for civil money penalties
  - Cost disallowance and recovery

NIH Possible Non-Compliance Letter

Since Sep. 22, 2022, NIH has issued possible non-compliance letters to investigators who are due to report the results for their NIH-funded research studies. A redacted version of this letter from NIH can be viewed here.

Compliance with the NIH policy is a term and condition of this grant award; however, the [redacted] 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.

If you believe that you have complied with applicable requirements, please provide us with your reasoning and any supporting information for our consideration. Please respond to this letter no later than 30 days from receipt of this letter with the following information pertaining to the above-referenced clinical trial(s):

- Evidence that clinical trial results information has been submitted to ClinicalTrials.gov.
- Evidence that submission of clinical trials results information is not required at this time.

Please submit this information to me at the e-mail address below.

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****."*

ICMJE
INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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

Inability to Publish…

"Thank you for your submission to Journal of Clinical Oncology. Please read this message in its entirety, as it contains important instructions for resubmitting your manuscript.

The protocol submitted to JCO seems to differ from that posted on ClinicalTrials.gov…PFS2 did not seem to be a secondary endpoint in the original protocol on ClinicalTrials.gov, so that discussion should be removed."

From the reviewers at Journal of Clinical Oncology in response to a manuscript submission

Denied Publication as of March 25, 2024

Background: A PI was denied publication in a Wiley Journal for having submitted registration materials to ClinicalTrials.gov 21 days after first enrollment into a study that was registered as **Observational**. Wiley returned with the following details:

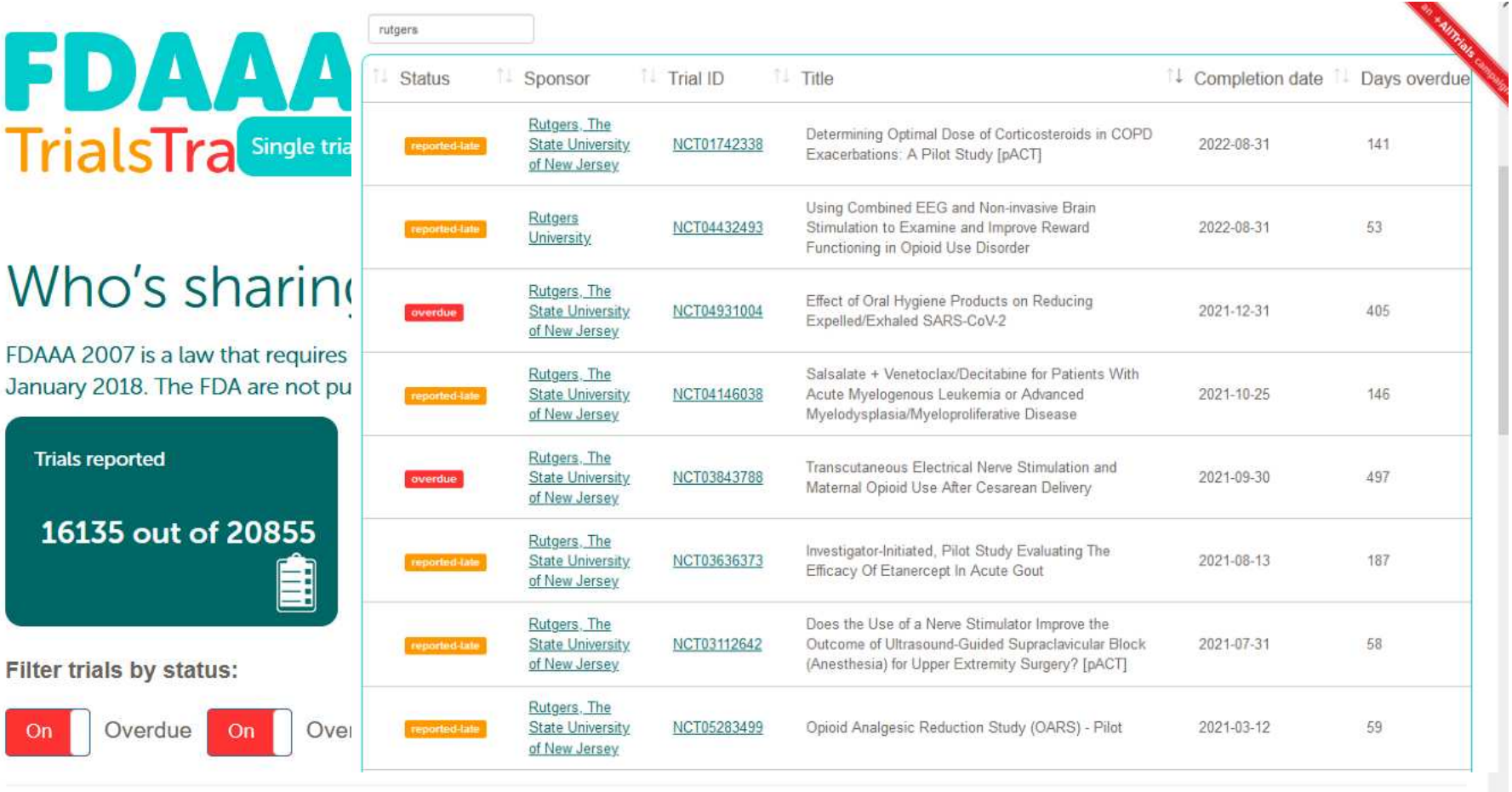
We acknowledge that the dates are close but to be eligible for publication in a WILEY journal the trial needs to be prospectively registered before the first participant was recruited. JAN [Journal of Advanced Nursing] is audited externally for compliance to ALLTrials and journal eligibility criteria. Please see:

https://urldefense.com/v3/__https://onlinelibrary.wiley.com/doi/full/10.1111/jan.15620__;!!Mak6IKo!MY_SM7AM5XBgCu46PBgcgnYTPiwe3KHxfT8MMbDiBNa54saP3vAttpHaNPMWN82fKvZd0WwvS5CnbQ7hw53wgIK5ENcL_A$

… Please do not submit this manuscript to another WILEY journal as it is not eligible for publication. I appreciate that this will be very disappointing news but this is an absolute rule and the trial registration entry is a public document. We undertook no further checks of trial integrity when compared to the trial registration entry.

Ramifications of Non-Compliance

Avoid being publically listed as Non-compliant: https://fdaaa.trialstracker.net/



Summary of Requirements 1 of 2

Entity	Registration	Results Reporting	Penalties
Health and Human Services (HHS)	Within 21 days of enrollment	Within 365 days of primary completion date for ACTs	• $14,262 /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 2 of 2

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	• $14,262/study/day • Withholding or recovery of award funds

From what I know, efforts to advance compliance with clinicaltrials.gov in my institution have been shown in the following aspects: (Multiple Choices)

1. 1. No difference compared to the time before April 2024
2. 2. Work in progress yet Investigators are still struggling
3. 3. Resources have been designated by leadership to support needed areas
4. 4. I don’t know.

Poll Time

Join at www.menti.com and use code **9977 9717**

Roadmap

1. Human Subjects Protection – IRB & ClinicalTrials.gov
2. Why Do We Care?
3. What Are the Registration Requirements?
4. Record Update & Results Reporting Requirements
5. Recent Ramification of Non-compliance
6. Establish a System in an Organization
7. Latest Updates and Modernization
8. Resources

A. Identify a Key Person to Assist Investigators in Your Organization

1. **Who does this position(s)/ ClinicalTrials.gov PRS Administrator fall under at your institution**?
2. Consider the following to house the PRS Administrator :
   - Full Time Employee (FTE)
   - Securely Funded
   - Chain of Command to Leadership that has bought in

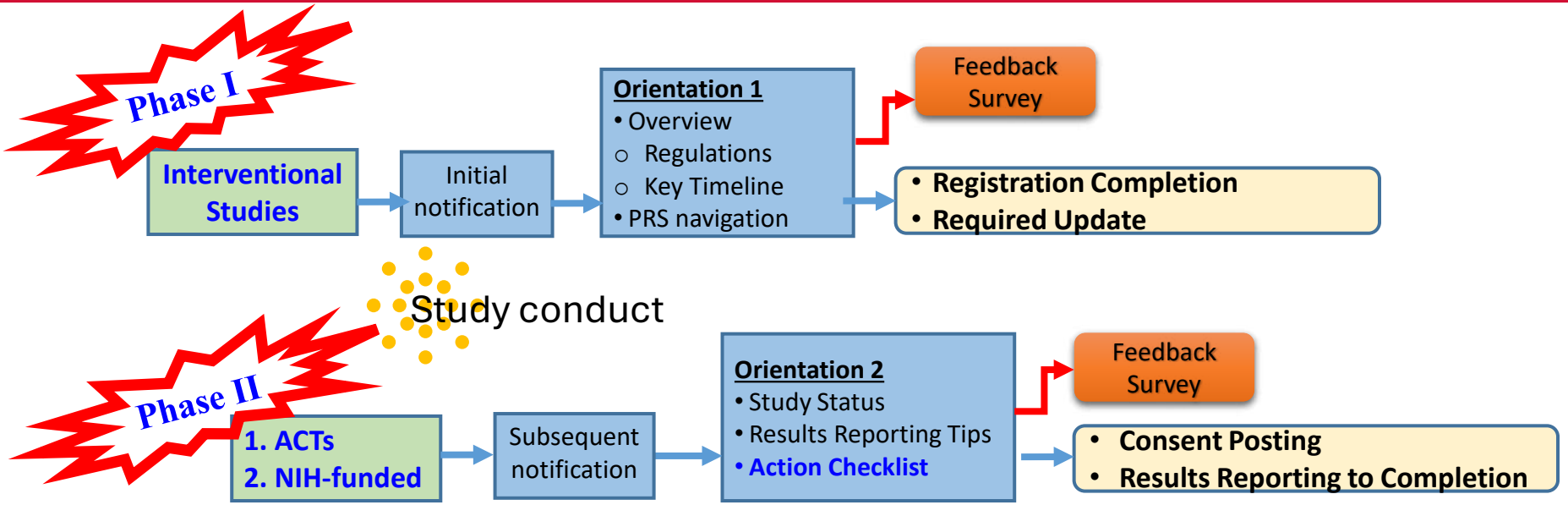
Recommended Key Capacities for the PRS Administrator ….

1. Access to IRB study database, including funder information
2. Ability to conduct QA review of protocols newly registered on ClinicalTrials.gov
3. Ability to monitor non-compliance with federal regulations
4. Access to Clinical Trial Management System (helps with study status updates if available)

B. Establish a Robust Mechanism to Maximize Performance

- Informative and organized website
- Institutional Policy & Procedure
- Customized education & training sessions
- Monthly HSPP/IRB Bulletin has ClinicalTrials.gov section
- Tools and review process for investigators:
  - Protocol templates to discern “interventional studies” and “non-interventional studies”
  - Built-in questions of clinical trials disclosure in IRB applications
- Mechanism for monitoring:
  - In-house dashboard/ database that generate IRB reports
  - ClinicalTrials.gov PRS Planning and other reports

C. Implement a ClinicalTrials.gov QA/QI Monitoring Review



Key Characteristics:

- Proactive approach to establish partnership and lasting relationship
  - Investigators are to "be informed to empower"
- Motivate investigators to take the moral responsibility that will
  - promote welfare for participants and
  - advance the benefits for all

Roadmap

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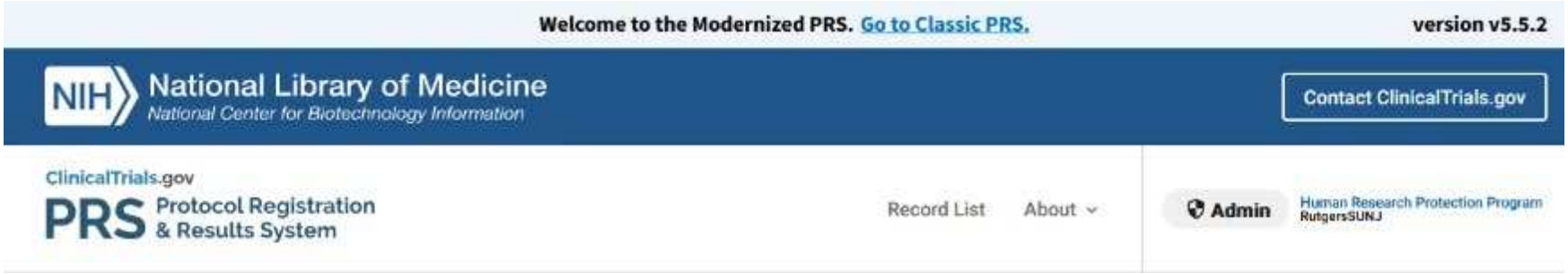
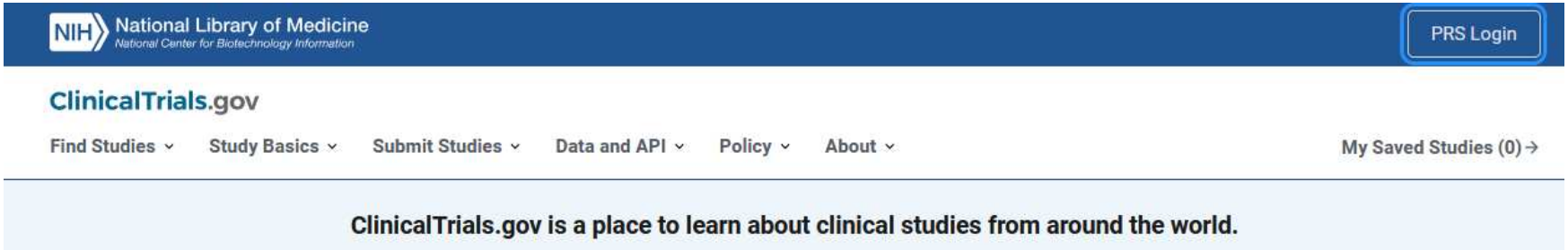
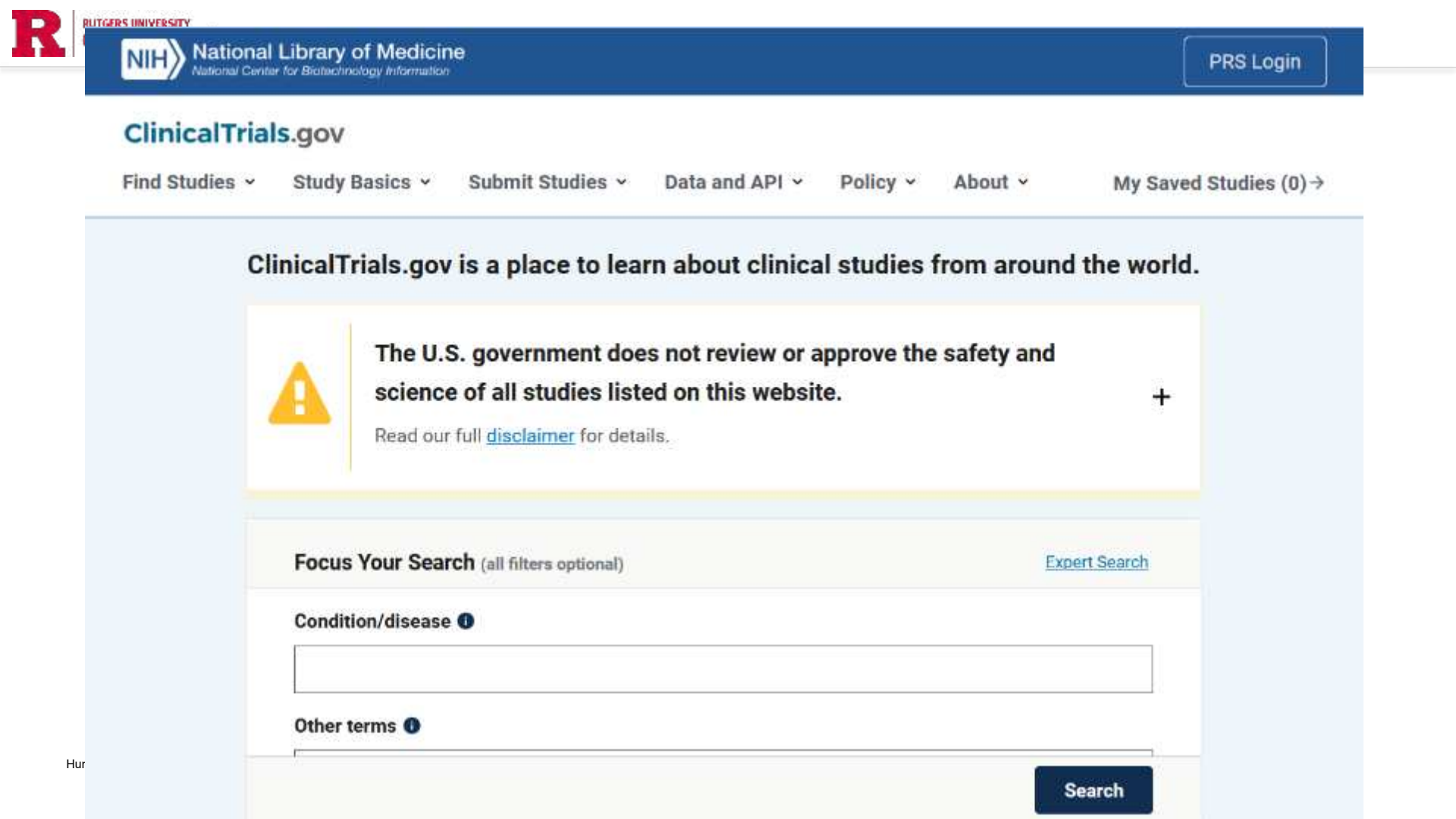
RUTGERS UNIVERSITY
Office for Research

ClinicalTrials.gov Modernization






RUTGERS UNIVERSITY
NIH National Library of Medicine
National Center for Biotechnology Information
PRS Login
ClinicalTrials.gov
Find Studies
Study Basics
Submit Studies
Data and API
Policy
About
My Saved Studies (0)
ClinicalTrials.gov is a place to learn about clinical studies from around the world.
The U.S. government does not review or approve the safety and science of all studies listed on this website.
Read our full disclaimer for details.
Focus Your Search (all filters optional)
Expert Search
Condition/disease
Other terms
Search

Welcome to the Modernized PRS. Go to Classic PRS. version v5.5.2

National Library of Medicine
National Center for Biotechnology Information

Contact ClinicalTrials.gov

ClinicalTrials.gov
PRS Protocol Registration & Results System

Record List About

Admin Human Research Protection Program
RutgersSUNJ

Welcome to the Modernized PRS! Please use it to enter, review, and submit a study protocol. Close

- Work seamlessly with the classic PRS by saving changes on one website and moving to the other.
- Note that you may have to go to the classic PRS to resolve some validation issues.
- Records with Results, Delayed Results, and Study Documents can only be opened in classic PRS.

Record List—Default View

Admin Quick Reference Problem Resolution Guide Record

Roadmap

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8. Resources

FDA ClinicalTrials.gov Webinars

On August 9th 2023, the FDA released webinars titled ClinicalTrials.gov – a Three-Part Series, that provide an overview of ClinicalTrials.gov and examples of compliance and enforcement activities that CDER/FDA has taken to encourage compliance.

These videos may be accessed directly through YouTube:

- ClinicalTrials.gov: Part 1 - Meeting Transparency and Reporting Requirements (12:17)
- ClinicalTrials.gov: Part 2 - Definitions, Laws, and Regulations (15:32)
- ClinicalTrials.gov: Part 3 - CDER's Compliance and Enforcement Activities (16:32)

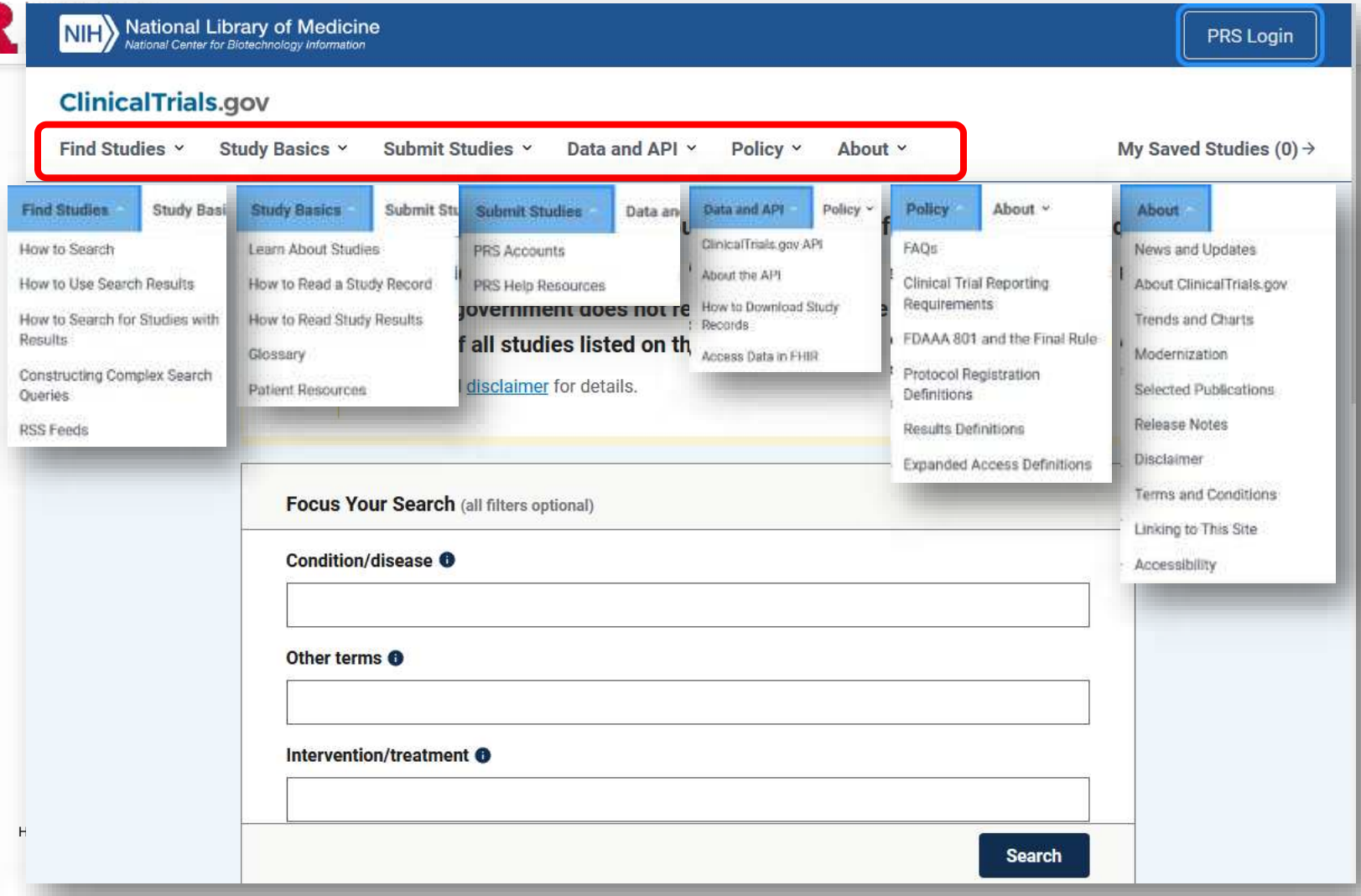
CONSORT 2010 Flow Diagram

https://www.equatc
http://www.consort-

Sections/Topics	Checklist Items
Title and abstract	Trial title; Structured summary of design, methods, results & conclusion
Introduction	Background and objectives
Methods	Design, participants, interventions, outcomes, sample size, randomization, blinding, statistical methods
Results	Participant flow, baseline data, number analyzed, outcomes and estimation, harms, ancillary analyses,
Discussion	Limitations, generalizability, interpretation
Other Information	Registration, protocol, funding

Analysed (n=)
- Excluded from analysis (give reasons) (n=)

Analysed (n=)
- Excluded from analysis (give reasons) (n=)


National Library of Medicine
National Center for Biotechnology Information
PRS Login
ClinicalTrials.gov
Find Studies
Study Basics
Submit Studies
Data and API
Policy
About
My Saved Studies (0)
How to Search
How to Use Search Results
How to Search for Studies with Results
Constructing Complex Search Queries
RSS Feeds
Learn About Studies
How to Read a Study Record
How to Read Study Results
Glossary
Patient Resources
PRS Accounts
PRS Help Resources
ClinicalTrials.gov API
About the API
How to Download Study Records
Access Data in FHIR
FAQs
Clinical Trial Reporting Requirements
FDAAA 801 and the Final Rule
Protocol Registration Definitions
Results Definitions
Expanded Access Definitions
News and Updates
About ClinicalTrials.gov
Trends and Charts
Modernization
Selected Publications
Release Notes
Disclaimer
Terms and Conditions
Linking to This Site
Accessibility
disclaimer for details.
Focus Your Search (all filters optional)
Condition/disease
Other terms
Intervention/treatment
Search

Support and Training Materials

On this page

Protocol Registration
Results Submission
Quality Control Review

This page is a compendium of helpful resources, files and templates for data submitters.

Many of these items are informative in nature, while others provide instructional information for various aspects of the protocol/results reporting process or using the Protocol Registration and Results Reporting System (PRS).

Protocol Registration

Using the PRS

- PRS Guided Tutorials — Step-by-step instructions for registering a study, uploading study documents, and submitting results information. The tutorials include Quick Overview Guides, a PDF library, annotated figures for

ClinicalTrials.gov PRS
Protocol Registration and Results System

Message to ClinicalTrials.gov Staff

Before sending a message to ClinicalTrials.gov, try the following alternatives:

- Check the Frequently Asked Questions page for answers to common inquiries to ClinicalTrials.gov.
- Contact your organization's PRS Administrator for assistance.

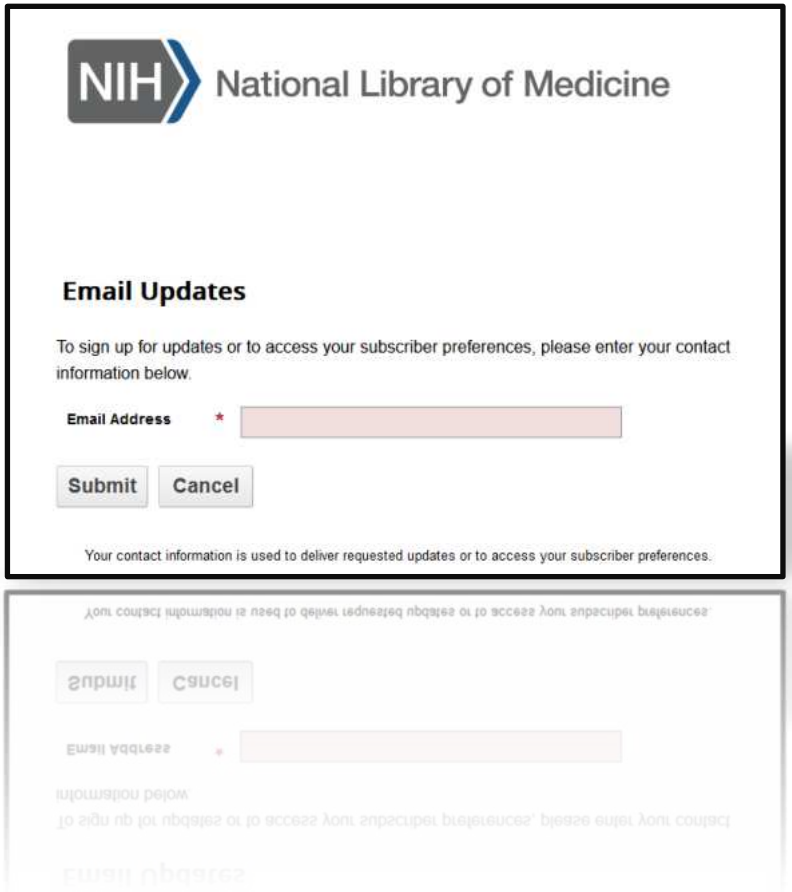
* Your Email Address: chennr@research.rutgers.edu; rutgersctgsupport@research.rutgers.ec

* Message:

Close

ClinicalTrials.gov listserve

- U.S. National Library of Medicine
- ClinicalTrials.gov & Train the Trainer
- ClinicalTrials.gov Hot Off the PRS!



Clinical Trials Registration and Results Reporting Taskforce

Monthly Conference call: 3rd Thursday 1 -2 pm EST

Mission: Focusing on the implementation of clinical trials registration and results reporting requirements that affect US academic health centers

Objectives:

- Understanding and applying the requirements;
- Identifying best practices in managing the requirements;
- Developing tools to assist regulatory support & investigators;
- Serving as a communication forum to support academia in meeting clinical trials registration/ reporting requirements.

Numbers of Members (as of 4/16/2024):

- 844 individuals, 279 organizations

Examples of our work:

- Template questions to identify ACTs (in IRB application)
- Administration and oversight benchmark survey
- Sample job descriptions
- Manual of considerations for protocol redaction prior to posting
- Forum for feedback to ClinicalTrials.gov staff at NIH

Monthly calls featuring representatives from

- ClinicalTrials.gov
- FDA
- OHRP
- Stakeholder/ interest groups

Additional Resource

TABLE 3—ESTIMATED BURDEN FOR REGISTRATION AND RESULTS INFORMATION SUBMISSION AT CLINICALTRIALS.GOV

Type of respondents	Number of respondents	Frequency of response	Average time per response (hours)	Annual hour burden
Regulated Submissions (Subject to this Rule)				
Registration	7,400	1 Initial	8	59,200
		8 Subsequent Updates	2	118,400
Results Information	7,400	1 Initial	40	296,000
		2 Subsequent Updates	10	148,000
Certifications to delay results submission	5,150	1	0.5	2,575
Extensic				500
Registra				704
sion.				
Results				1,350
Expande				426
				107
Sub				

OMB NO: 0925-0586
EXPIRATION DATE: 03/31/2026
Burden Statement

Public reporting burden for this collection of information is estimated to vary from 2.0 to 8.0 hours per response for registration, 10.0 to 45.0 hours per response for results information submissions, and 15 minutes to 2 hours for other submissions including certifications for delay, extension requests, and expanded access. These estimates include the time for reviewing instructions, searching existing data sources, gathering the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0586). Do not return the completed form to this address.

Takeaways 1/2

1. Study disclosure including registration and results reporting is an essential, integral component of the scientific method.

2. Notices of noncompliance from FDA, NIH and other entities will continue. Be prepared.

3. ClinicalTrials.gov Modernization is very needed and greatly appreciated.

4. Join the Clinical Trials Registration and Results Reporting Taskforce.

Takeaways 2/2

"We owe it to every participant and the public at large to support the maximal use of this [medical advances] knowledge for the greatest benefit to human health. This important commitment from researchers to research participants must always be upheld."

--- NIH Director Francis S. Collins, M.D., Ph.D.

Please complete evaluation.

Thank You!

N. Rebecca Chen
Rutgers ClinicalTrials.gov Administrator
Human Subjects Protection Senior Analyst
chennr@research.rutgers.edu