Navigating Clinicaltrials.gov

Responsibilities, requirements, and regulations relating to studies registered under Carilion Clinic's Clinicaltrials.gov account

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Agenda

- Brief Overview of the Clinicaltrials.gov Website
- Applicable Clinical Trial (ACT) vs. Non-ACT
- Voluntary Submissions
- Registration How-To & Guidance
- Maintenance & Results Reporting
- Violations and Penalties

What is ClinicalTrials.gov?

ClinicalTrials.gov is a website and online database of clinical research studies and is maintained by the National Library of Medicine (NLM), an institute within the National Institutes of Health (NIH).

The purpose of ClinicalTrials.gov is to provide information about clinical research studies to the public, researchers, and health care professionals.

A limited review of the information provided by sponsors and investigators is performed by the NLM; however, the NIH and other U.S. government agencies do not review or approve the safety or scientific merit of all studies listed on the website.

ClinicalTrials.gov:

•Relies on sponsors or investigators to submit and update information about studies they are conducting

•Lists up-to-date information on clinical research studies and provides study results, regardless of outcome

•As of July 2023, the database includes over 450k studies that take place in all 50 states and over 200 countries

•Provides sponsors and investigators a place to publicly share information about clinical trials and the results of those trials in a way that supports laws, regulations, and policies requiring them to do so.

Major milestones related to ClinicalTrials.gov and how information in the database has changed over time

1997 — U.S. passed a law to create ClinicalTrials.gov

The Food and Drug Administration Modernization Act of 1997 required the National Institutes of Health (NIH) to create a database of clinical trials that have an investigational new drug application (IND) to test investigational drugs for serious and life-threatening diseases.

2000 — ClinicalTrials.gov launched for the public

NIH and the Food and Drug Administration (FDA) worked together to create the website, ClinicalTrials.gov.

2005 — Medical journal editors required that sponsors and investigators make clinical trials available on public databases

The International Committee of Medical Journal Editors (ICMJE) required that sponsors and investigators make their clinical trials available on ClinicalTrials.gov or other similar public databases if they want to publish trial results in a medical journal.

2006 — World Health Organization (WHO) created policy

The WHO policy stated that all clinical trials conducted anywhere in the world have certain information made available on ClinicalTrials.gov or other similar public databases.

2007 — U.S law required more trials and information on ClinicalTrials.gov

The FDA Amendments Act of 2007 (FDAAA) expanded the information that sponsors and investigators must submit to ClinicalTrials.gov, including:

- More types of trials
- More information about trials
- Results for certain trials, which led to the results database

2008 — ClinicalTrials.gov results database launched for the public

The ClinicalTrials.gov results database includes this study information:

- A description of the group of participants who joined and completed the study
- Findings from the study, including safety information

2017 — Department of Health and Human Services (HHS) Final Rule applied

The rule further explained what needs to be submitted under FDAAA, such as which trials, what information about them, and when. It expanded the types of trials that must submit results information.

NIH policy required NIH-funded clinical trials to be listed on ClinicalTrials.gov

The policy stated that sponsors and investigators are expected to submit NIH-funded clinical trials to ClinicalTrials.gov and report results information.

2018 — U.S.required public posting of informed consent forms

The revised Common Rule (45 CFR 46) required sponsors and investigators of government-funded studies to post a consent form to ClinicalTrials.gov or Regulations.gov.

Applicable Clinical Trials (ACT)

Defining which studies are mandated to be registered on ClinicalTrials.gov

Defining what is considered an Applicable Clinical Trial

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 <u>at least one</u> 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 <u>other than</u> a Phase 1 trial of a drug and/or biological product or is the study <u>other than</u> 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."	☐	☐

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22.

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

Additional Clinical Trial Definitions

ICMJE

- 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 cause-and-effect relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include 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.

NIH

- All clinical trials funded wholly or partially by NIH. Includes phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions. Applies to NIH-funded clinical trials where applications or proposals are received by NIH on or after the policy's effective date (Jan. 18, 2017). Applies to NIH-conducted clinical trials initiated on or after the policy's effective date.

Timeline of Record Creation

What	Who	When	Where	Why
Interventional Clinical Trial Observational Clinical Trial* Expanded Access	Responsible party: Sponsor (holder of IND/IDE) Principal Investigator** Sponsor-Investigator	ACT: within 21 days of enrollment of 1st participant ICJME & other medical journals: Prior to enrollment of 1st participant	Protocol Registration and Results System (PRS) https://register.clinicaltrials.gov/	Trial transparency Avoiding duplication of efforts Collaboration Advancing science Ethical principles

*ACT primarily limited to pediatric postmarket surveillances of a device product
**The sponsor may designate a principal investigator as the responsible party if the PI meets all of the following requirements: is responsible for conducting the study; has access to and control over the data from the study; has the right to publish the results of the study; and has the ability to meet all of the requirements for submitting and updating clinical study information.

Do I need to submit?

Drug Clinical Trial Under an IND

- ACT?

Yes

- Responsible Party?

Sponsor (IND holder)

- When does this need to be registered by?

21 days after first enrollment

- Do results have to be reported?

Yes

Behavioral Intervention with no drug or device

- ACT?

No

- Responsible Party?

Likely PI

- When does this need to be registered by?

Prior to 1st participant if publishing

- Do results have to be reported?

Not under FDAAA but may fall under other requirements

Phase 1 Drug Trial funded by NIH

- ACT?

No but must be registered

- Responsible Party?

Sponsor, PI or Sponsor-Investigator

- When does this need to be registered by?

21 days after first enrollment

- Do results have to be reported?

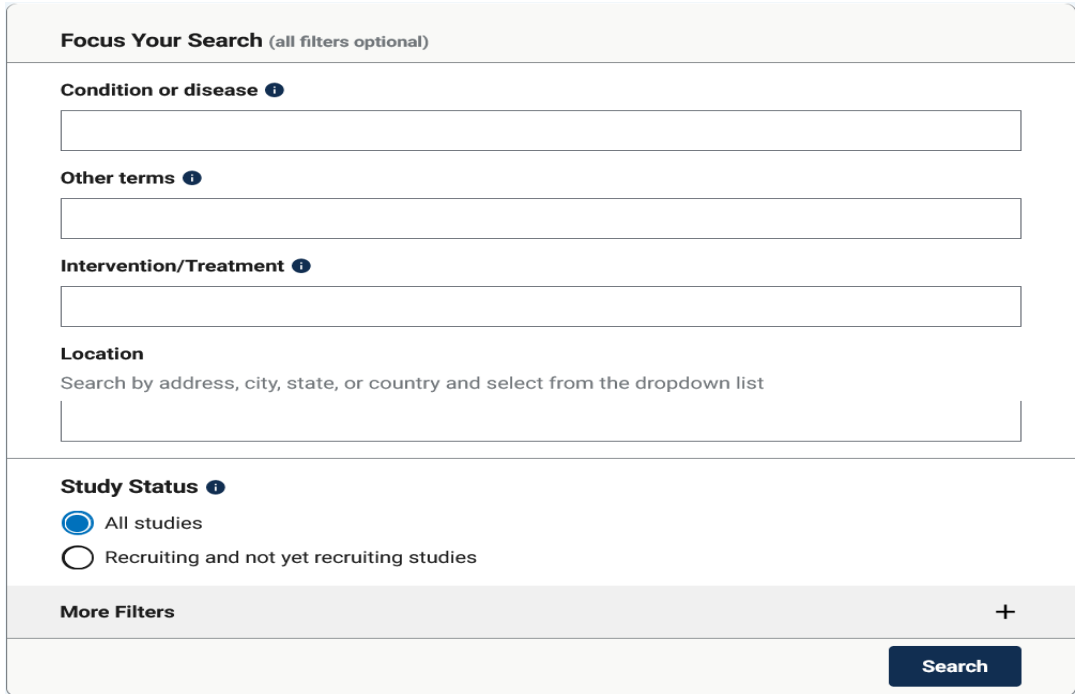
Yes

How will I know my study needs to be registered?

Carilion Clinic IRB Outcome Letter:

Clinicaltrials.gov: The study meets requirements to be registered on Clinicaltrials.gov. Please ensure you are familiar with all the requirements of Section 801 of the Food and Drug Administration Amendments Act (https://clinicaltrials.gov/ct2/manage-recs/fdaaa), as there are consequences for not registering, including potential fines. You must register this clinical trial prior to enrollment of the first participant. Please contact research@carilionclinic.org for assistance with the ClinicalTrials.gov Protocol Registration and Results System (PRS).

Clinicaltrials.gov Website: https://www.clinicaltrials.gov



To register or not register, that is the question

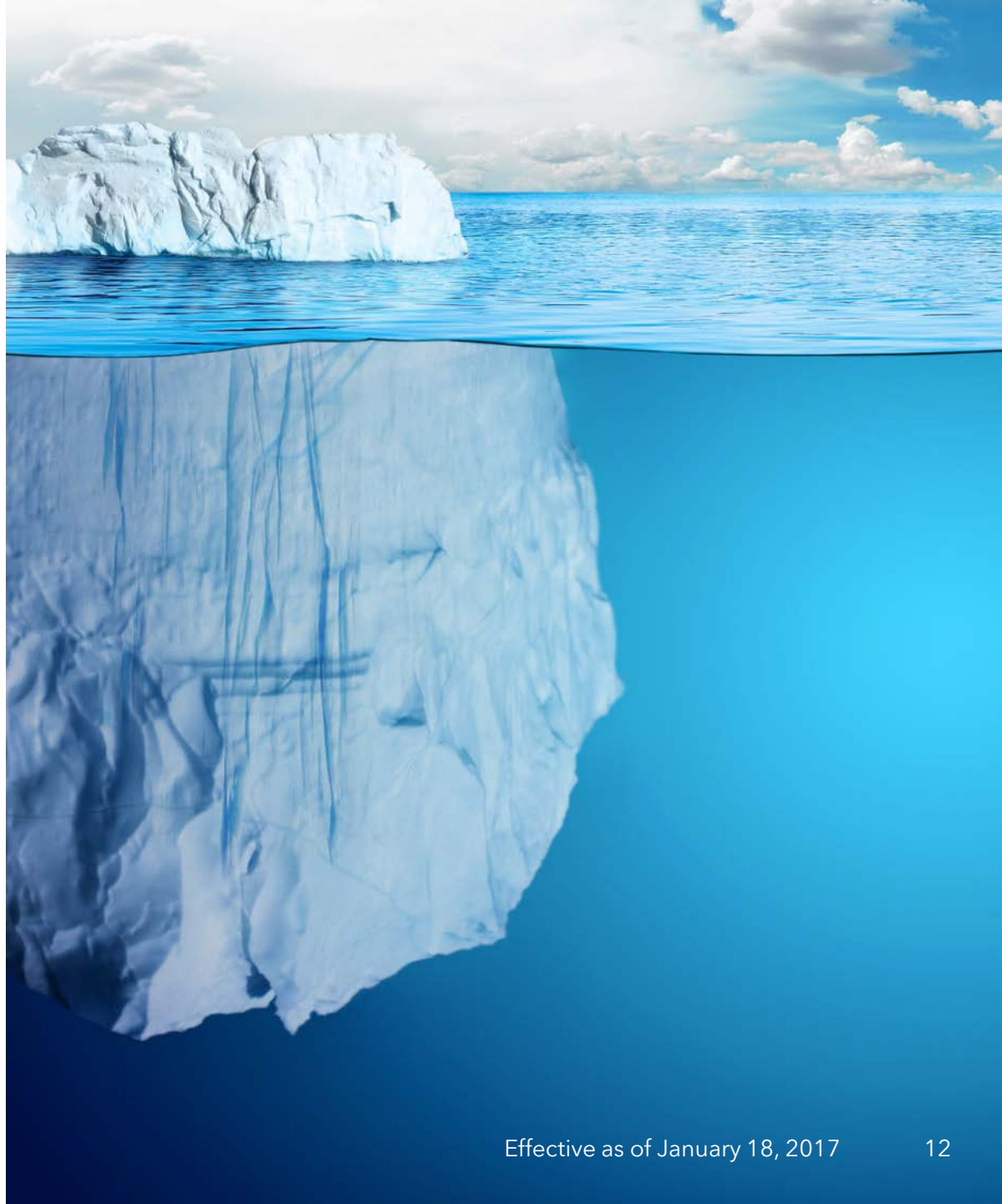
The following are examples of the types of studies that are not subject to the registration and results submission requirements of section 402(j) of the PHS Act:

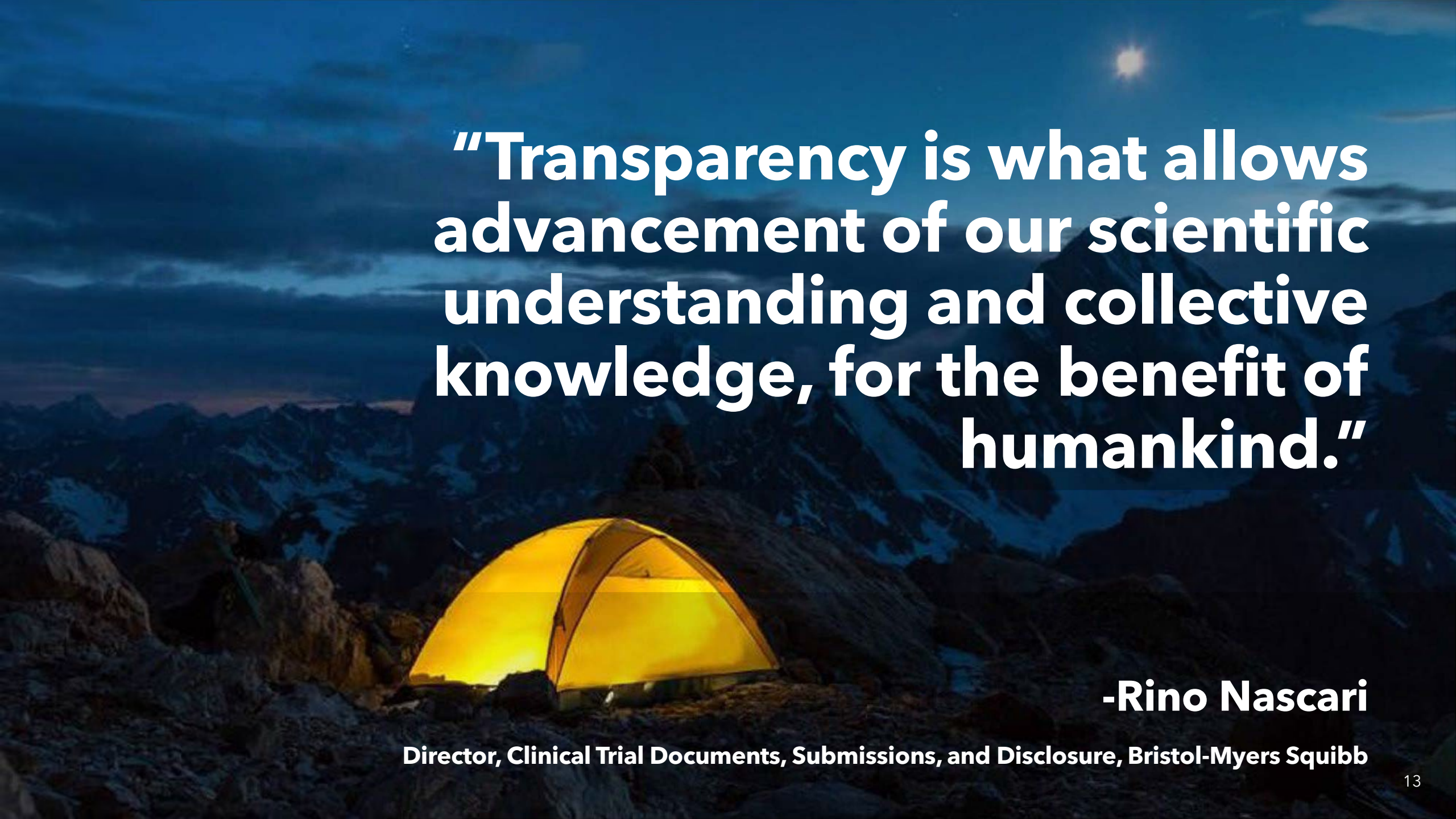
- Phase 1 trials of investigational drug products or biological products, including studies in which investigational drug products are used as research tools to explore biological phenomena or disease processes
- Small clinical trials to determine the feasibility of a device product or a clinical trial to test prototype devices, where the primary outcome measure relates to feasibility and not to health outcomes
- Trials that do not include drug, biological, or device products, such as behavioral interventions
- Noninterventional (observational) clinical research, such as cohort studies

Note: If a responsible party voluntarily submits clinical trial information for a clinical trial that is not otherwise subject to the registration and results submission requirements, the responsible party may have to comply with certain requirements under section 402(j) of the PHS Act and its implementing regulations.

Warning if you decide to pull the trigger and voluntarily submit

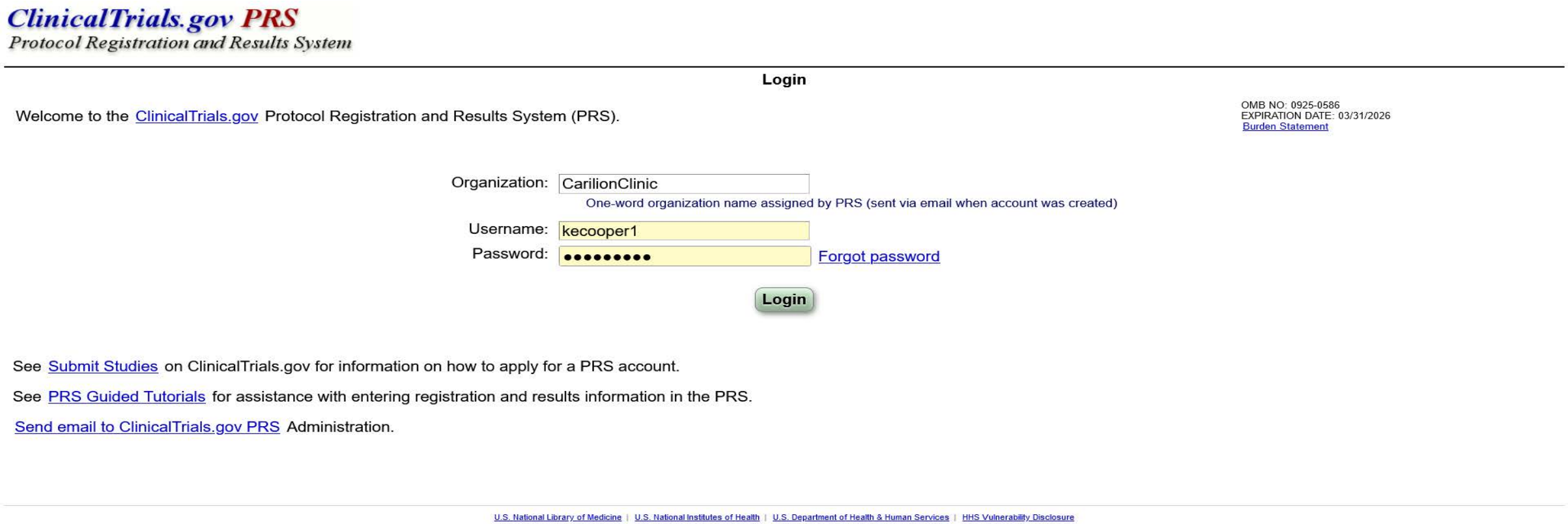
- Voluntary submissions may cause "triggered" trials; applicable trials required to be submitted under PHS Act section 351 or under section 505, 510(k), 515, or 520(m) of the FD&C Act in an application or report for licensure, approval, or clearance of the drug or device for the use studied in the clinical trial.
- Requiring the submission of information for "triggered" trials helps prevent selective voluntary submissions of results information from clinical trials that only show positive results for a particular product, but not from those applicable clinical trials that show negative or uncertain results for the same product (79 FR 69648).




“Transparency is what allows advancement of our scientific understanding and collective knowledge, for the benefit of humankind.”
-Rino Nascari
Director, Clinical Trial Documents, Submissions, and Disclosure, Bristol-Myers Squibb

How to Register

Log in to https://register.clinicaltrials.gov/



Quick Start Guide

1. **Change your password** - If you have not already done so, select Change Password from the Accounts menu on the Home page and complete the form.

2. **Create a record** - A study is registered in the ClinicalTrials.gov system by creating a protocol record. Select New Record on the Home page (either from Quick Links or the Records menu). Fill in a series of data entry pages.

Tip: Data is saved as each page is filled in, so that you can "Quit" at any time, saving the record for later completion using the "Modify a record" instructions provided below.

3. Mark the record as Entry Completed - After filling in the last data entry page, the Protocol Section page appears with all of the information provided. Review the information for accuracy and completeness, and use the Edit links to address ERROR messages, if any.

Return to the Record Summary page to see current status of the record. Follow instructions in the Next Step box to finish the registration process, using the Entry Complete button to indicate that data entry is done. Your organization's PRS Administrator will Approve and Release the record for PRS Review and processing by ClinicalTrials.gov. **The record should be available on the public site within 2-5 business days of Release by the administrator.**

EXCEPTION: If you are designated as the Investigator and Responsible Party for a record, you have the authority (and responsibility) to Approve and Release the record even if you are not an administrator. Open the record and follow instructions in the Next Step box on the Record Summary page to perform these steps at the appropriate times. More information on Responsible Party is accessible from the Edit Sponsor/Collaborators page.

4. Modify a record - After initial registration, a record can be modified at any time (except when the record is locked for PRS Review). The Record List on the Home page lists all of your records along with status information for each record. Open the record that you wish to update. The Record Summary page for that record appears. Use the Edit link(s) on the left to modify the desired section of the record.

When a record's status is Entry Completed, Approved, Released or Public, and the record is modified, the record status is automatically reset to In Progress. Remember to mark the record as Entry Completed when finished editing. Your organization's PRS Administrator will Approve and Release the modified record as described above.

5. Keep records up to date - Study records for active studies should be reviewed and modified, as needed, at least once every 12 months. Some data elements must be updated sooner (e.g., within 30 days of a change) based on the requirements in Section 801 of FDAAA and 42 CFR 11.64. **Pay special attention to recruitment statuses, location, and contact information**, as the accuracy and timeliness of this information is extremely important to patients and health care professionals. Update the Record's Verification Date (in the Protocol section, Study Status module) to confirm that the record has been reviewed.

6. Check for problems - The Record List on the Home page includes a Problems column listing issues for each record. To address problems open the record and make the necessary changes, following the instructions in the Next Step box near the top of the Record Summary page.

Registration Information

Protocol:

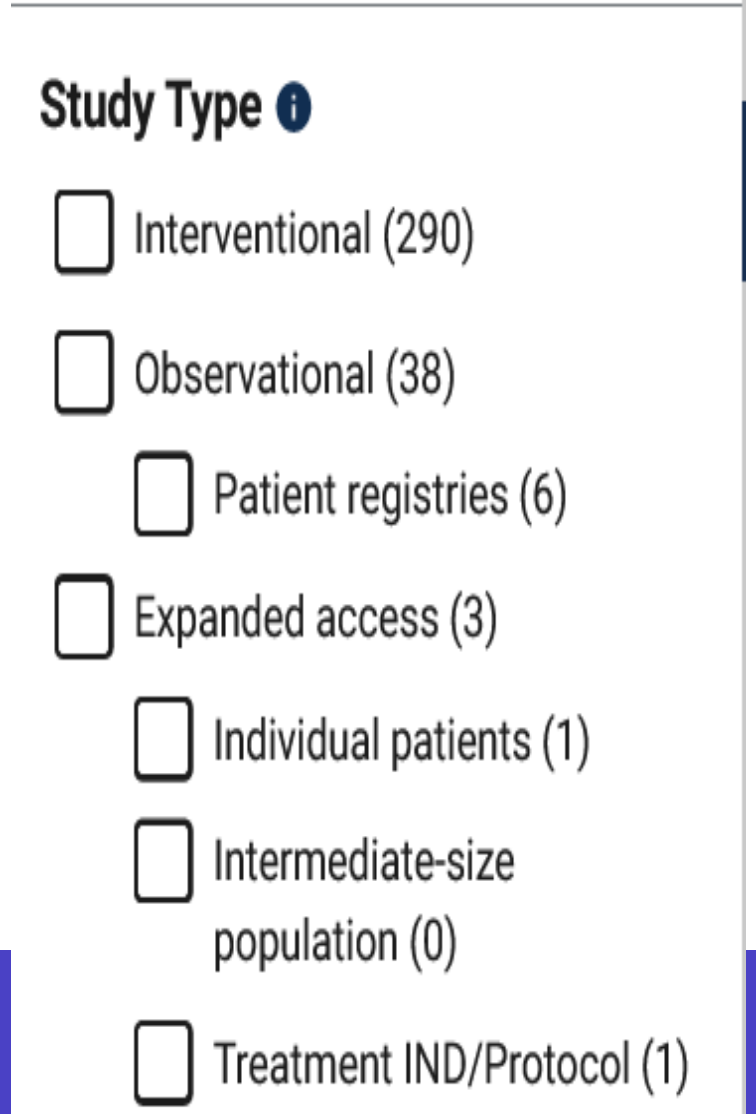
- *Study Description
- *Study Design
- *Conditions and Keywords
- *Arms/Groups/Interventions
- *Outcome Measures

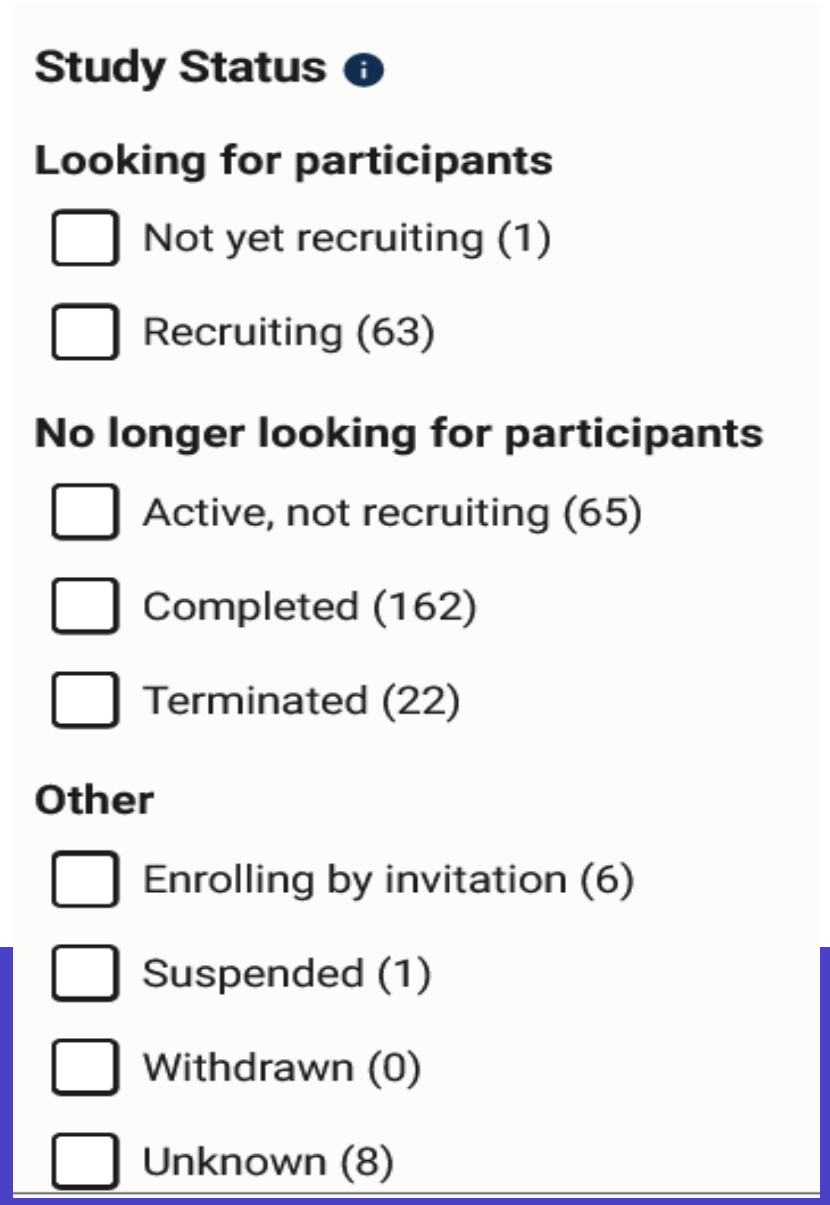
Recruitment/Site Information:

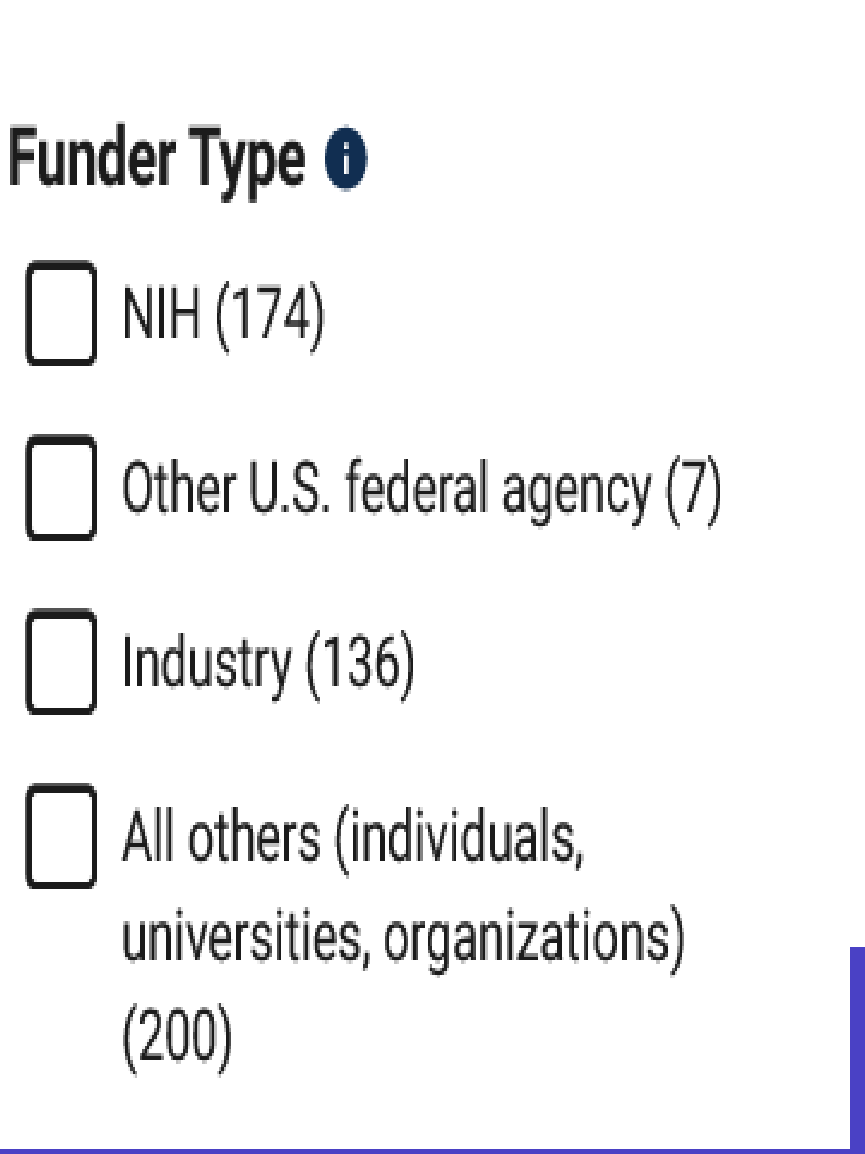
- *Eligibility
- *Locations and Site Contact Information

Collaboration Information:

- *Sponsors and Collaborating Sites
- *IPD Sharing Statement
- *References







Carilion Clinic Studies Currently on Clinicaltrials.gov

When to update record

If there are changes to the study, the changes must be updated on the ClinicalTrials.gov website within 30 days.

- These changes include:
  - Protocol amendment
  - Change in contact information
  - Change in status of recruitment or enrollment

- Even if there are no changes, the study record must go through verification at least every 12 months – this will require the Responsible Party to confirm the accuracy of the record and resubmit for PRS review.

- Record can be edited at any time by clicking on the “Modify” button & re-releasing the record for PRS review and publishing changes to the website.

Results Reporting

- Generally, the results of an Applicable Clinical Trial must be submitted by the Responsible Party no later than 12 months after the study completion date – the date the final subject completed their participation/final collection of data.
- Under the final rule, results information submission could be delayed for up to 2 additional years from the date of submission of a certification that either (1) an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or (2) that approval will be sought within 1 year after the primary completion date of the trial for a new use of an approved, licensed, or cleared product that is being studied in the trial (81 FR 64983).

Good Cause Extension Update

The Director of the NIH may extend the deadline for submission of results information for an ACT if the responsible party submits a written request that demonstrates good cause for the extension. An extension request must be submitted via the Protocol Registration and Results System (PRS) **prior to the date** (i.e., the day before) that results information would otherwise be due and must include a description of the reasons that the responsible party believes constitute good cause to justify an extension and an estimated date on which the results information will be submitted. The Director will review the extension request and notify the responsible party via the PRS as to whether the request demonstrates good cause and has been granted.

Civil Money Penalties

Civil money penalties may be assessed under 21 U.S.C. 333(f)(3)(A) of $10,000* for

(1) failing to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank

(2) submitting false or misleading information to the ClinicalTrials.gov data bank,

(3) failing to submit the required certification to FDA, or

(4) knowingly submitting a false certification to FDA.

If not corrected within 30 days additional $10,000 a day violation continues until corrected.

*Currently up to $13,327 initial and per day penalties

Opinion > Second Opinions

FDA Has Neglected Clinical Trial Transparency — Plus $45 Billion in Fines

— It's time for more aggressive enforcement of the law

by Megan Curtin, Navya Dasari, Justin Mendoza, MPH March 21, 2023

NIH toughens enforcement of delayed clinical trials reporting

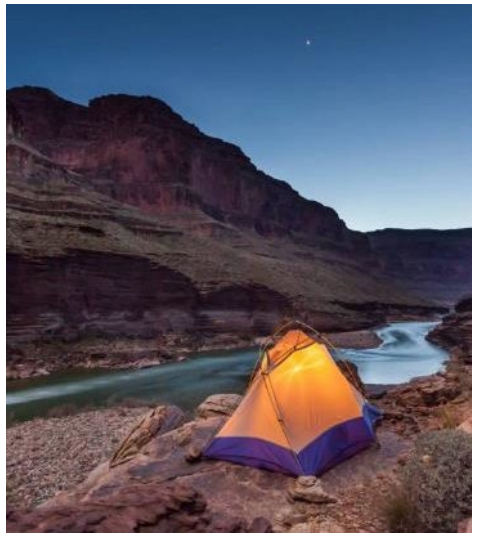
Agency says it has brought more than 200 tardy investigators into compliance since July 2022

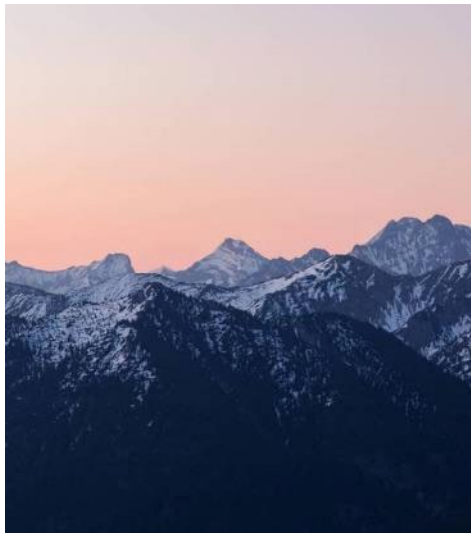
NIH Fails to Enforce Rules for Reporting Clinical Trial Results

A review by the US Office of Inspector General found that only about half of the scientists running clinical trials funded by the NIH in 2019 and 2020 appropriately recorded their findings in a federal database, as is legally required.

Summary

Carilion Clinic's mission is to improve the health of the communities we serve. Investigators at Carilion Clinic fulfill this mission by adhering to the regulations, policies, and ethical standards necessary to successfully conduct clinical trials and providing the results of these trials to the greater community.





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https://register.clinicaltrials.gov

Thank you!