Requirements for Registration, Updating and Results Reporting for ClinicalTrials.gov

Karla Damus PhD MSPH MN BSN RN FAAN
Administrator, BMC/BUMC Clinicaltrials.gov and
Clinical Research Education
OHRA, CRRO, CTSI

damusk@bu.edu, 358 7382

BU Clinical & Translational Science Institute

Office of Human Research Affairs

CRRO Clinical Research Resources Office

Objectives

- Provide a brief history, scope and mission of ClinicalTrials.gov
- Explain the role of the ICMJE on the registration process and data sharing
- Discuss best practices and tips for registering, updating and posting results on clinicaltrials.gov
  - ✓Understand how to gain access to CTgov as a new user, start a new record, and add users
  - ✓Describe the role of the RP (responsible party) and institution/sponsor
  - ✓Present when and how to update/edit existing records
  - ✓Provide an overview of results reporting and submitting documents
- Discuss the penalties and enforcement for noncompliance

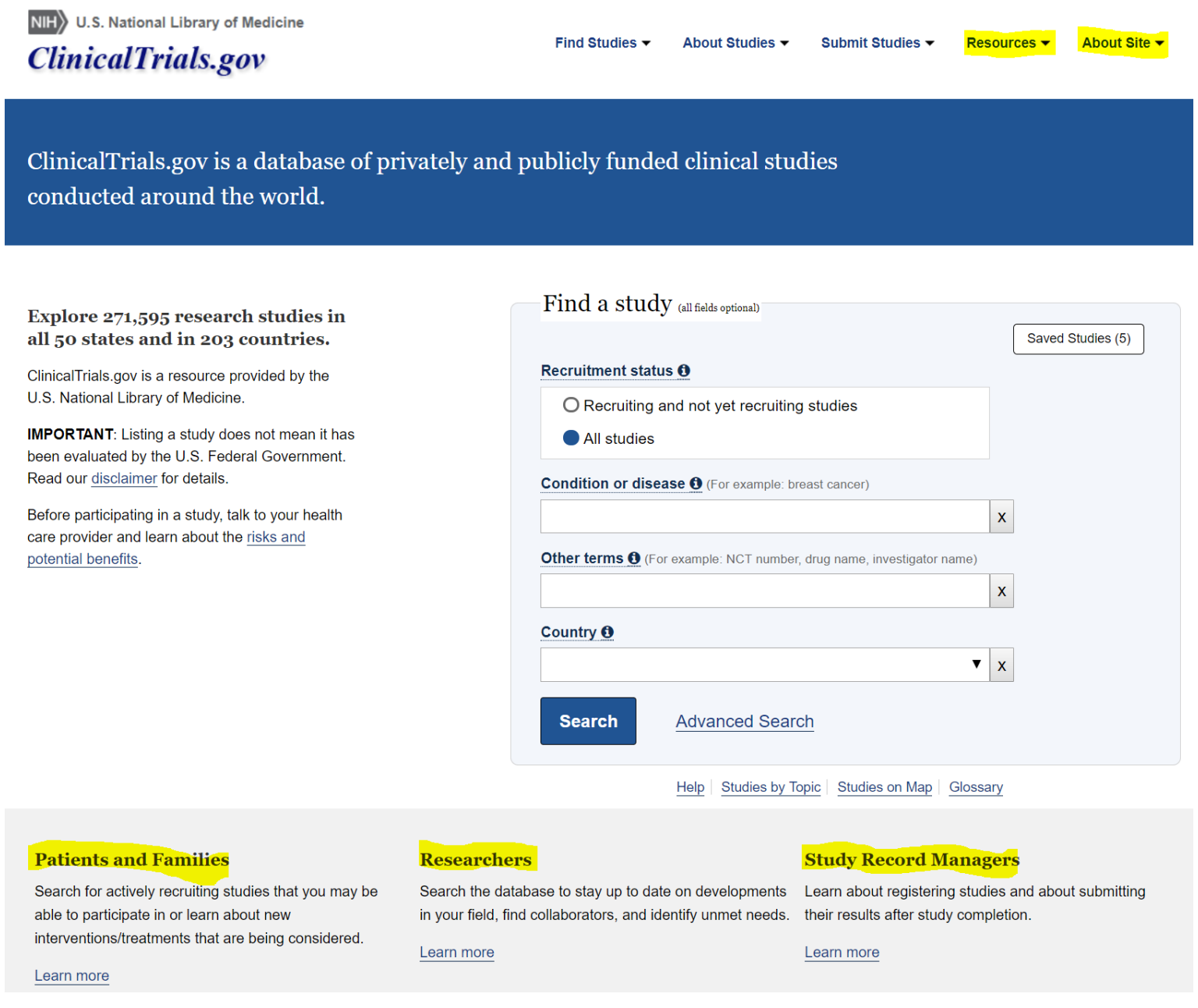
Why is Trial Registration Important?

- The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility because:
- There is a need to ensure that decisions about health care are informed by all of the available evidence
- It is difficult to make informed decisions if publication bias and selective reporting are present
- The *Declaration of Helsinki* (1964) states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".
- Improving awareness of similar or identical trials will make it possible for researchers and funding agencies to avoid unnecessary duplication
- Describing clinical trials in progress can make it easier to identify gaps in clinical trials research
- Making researchers and potential participants aware of recruiting trials may facilitate recruitment
- Enabling researchers and health care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers. The type of collaboration may include prospective meta-analysis
- Checking study design and outcome measures as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems (such as problematic randomization methods) early in the research process

What is ClinicalTrials.gov?

- ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. *It is searchable* like PubMed and also maintained by the NLM at NIH.
- Studies are generally submitted to the Web site (registered) when they begin, and the information on the site should be **updated throughout the study**.
- For some but not all studies, results are submitted after the study ends. This Web site and database of clinical studies is commonly referred to as a "registry and results database."
- ClinicalTrials.gov contains information about clinical studies in human volunteers. Most of the records describe clinical trials (also called interventional studies).
- A clinical trial is a research study in which human volunteers are prospectively assigned to interventions (for example, a medical product, behavior, or procedure) based on a protocol (or plan) and are then evaluated for *effects* on biomedical or health outcomes.

ClinicalTrials.gov

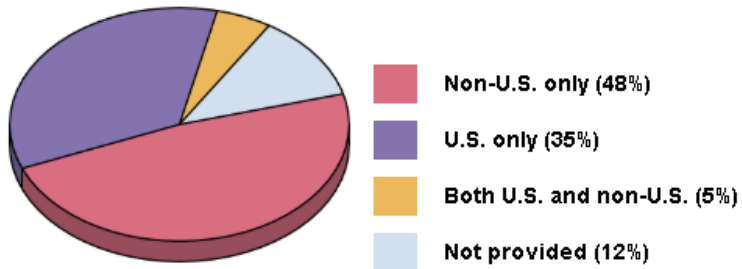


Locations of Registered Studies

The chart below shows the distribution of locations for all studies registered on ClinicalTrials.gov.

Percentage of Registered Studies by Location (as of January 14, 2019)

Total of 294,540 studies



Location	Number of Registered Studies and Percentage of Total (as of January 14, 2019)
Non-U.S. only	141,377 (48%)
U.S. only	102,158 (35%)
Both U.S. and non-U.S.	15,691 (5%)
Not provided	35,314 (12%)
Total	294,540 (100%)

Types of Registered Studies

The table below shows the number and types of studies that are registered and have results posted on ClinicalTrials.gov.

Study and Intervention Type (as of January 14, 2019)		Number of Registered Studies and Percentage of Total	Number of Studies With Posted Results and Percentage of Total***
Total		294,540	34,384
Interventional		233,588 (79%)	32,399 (94%)
Type of Intervention*	Drug or biologic	134,620	25,699
	Behavioral, other	73,298	5,817
	Surgical procedure	24,781	1,757
	Device**	29,246	4,100
Observational		59,614 (20%)	1,985 (6%)
Expanded Access		533	N/A

* A study may include more than one type of intervention, meaning that a single study may be counted more than once. Because of this, the sum of counts by type of intervention do not equal the total number of interventional studies.

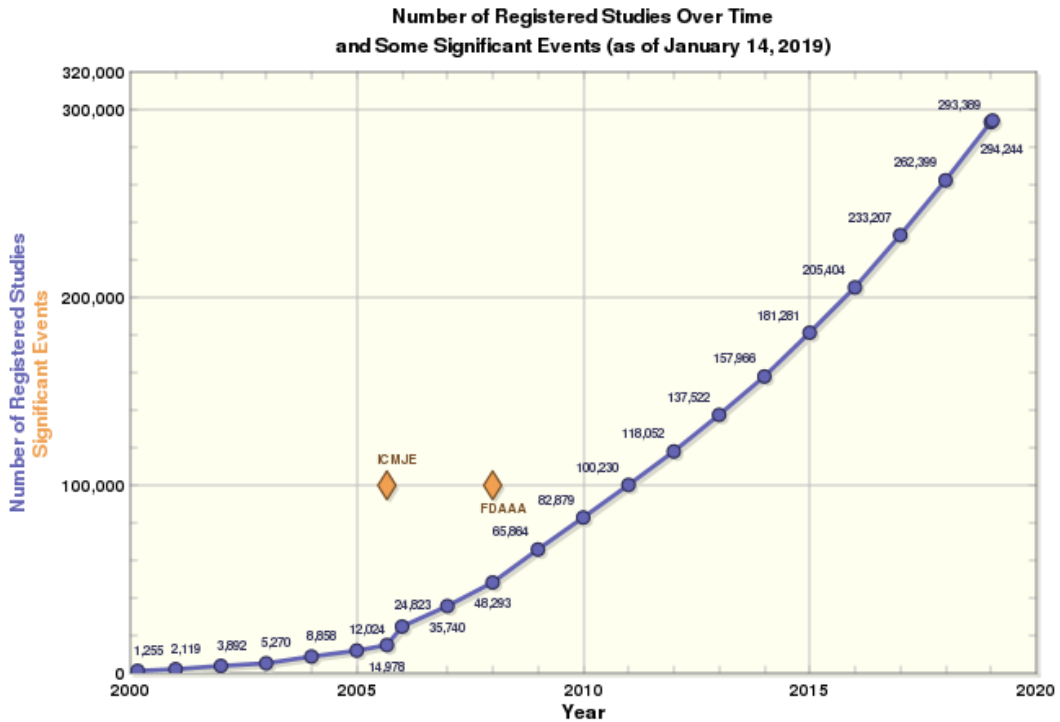
** A total of 805 applicable device clinical trials were submitted as "delayed posting" under the Food and Drug Administration Amendments Act of 2007 (FDAAA). That is, the Responsible Party indicated that the trial includes a device not previously approved or cleared by the Food and Drug Administration (U.S. FDA) for any use. These trials are not included in the counts of trials with at least one device.

*** Results are required to be submitted only for certain studies. For example, results submission is generally not required for observational studies; trials completed before 2008; and trials that include drug, biological, or device products not previously approved by the U.S. FDA for any use (if the Primary Completion Date is before January 18, 2017). See FDAAA 801 and the Final Rule for further information.

https://clinicaltrials.gov/ct2/resources

Number of Registered Studies Over Time

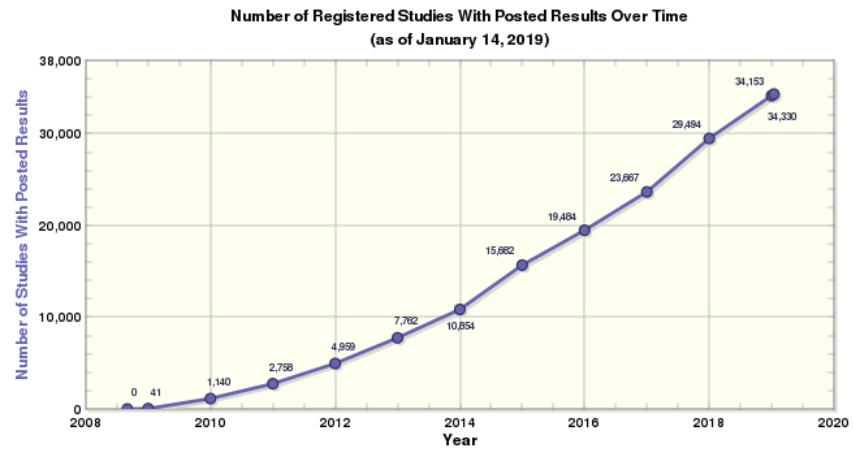
The graph and table below show the total number of studies posted on ClinicalTrials.gov since 2000, based on the First Posted date. The first version of ClinicalTrials.gov was made available to the public on February 29, 2000.



Source: https://ClinicalTrials.gov

Number of Registered Studies With Posted Results Over Time

The graph and table below show the number of registered studies with results posted on ClinicalTrials.gov, based on the Results First Posted date. ClinicalTrials.gov launched its results database in September 2008, at which time sponsors or investigators could begin submitting results for their registered studies. The results database was first developed to accommodate the results submission requirements outlined in FDAAA. See About the Results Database for more information.

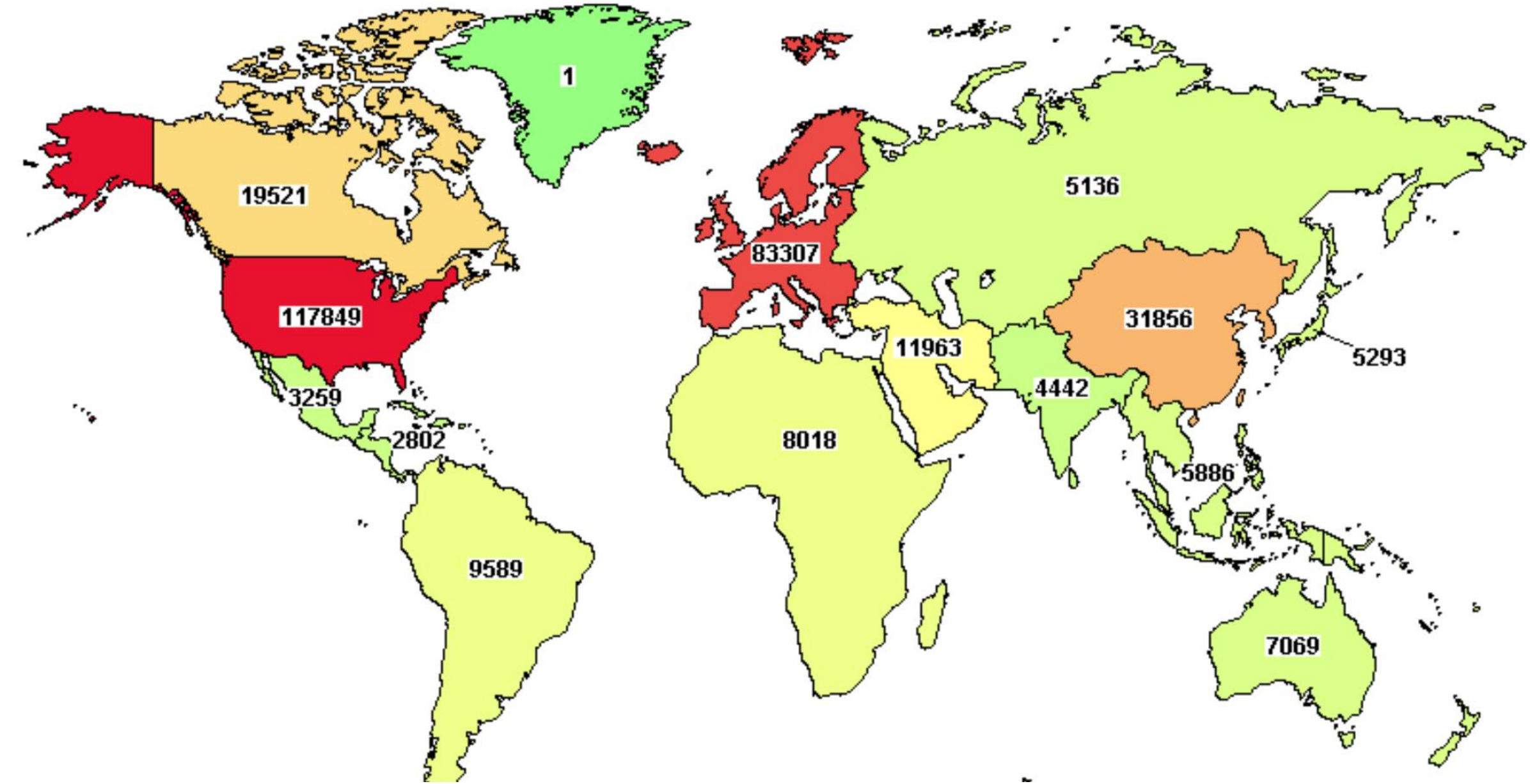


Source: https://ClinicalTrials.gov

Key:

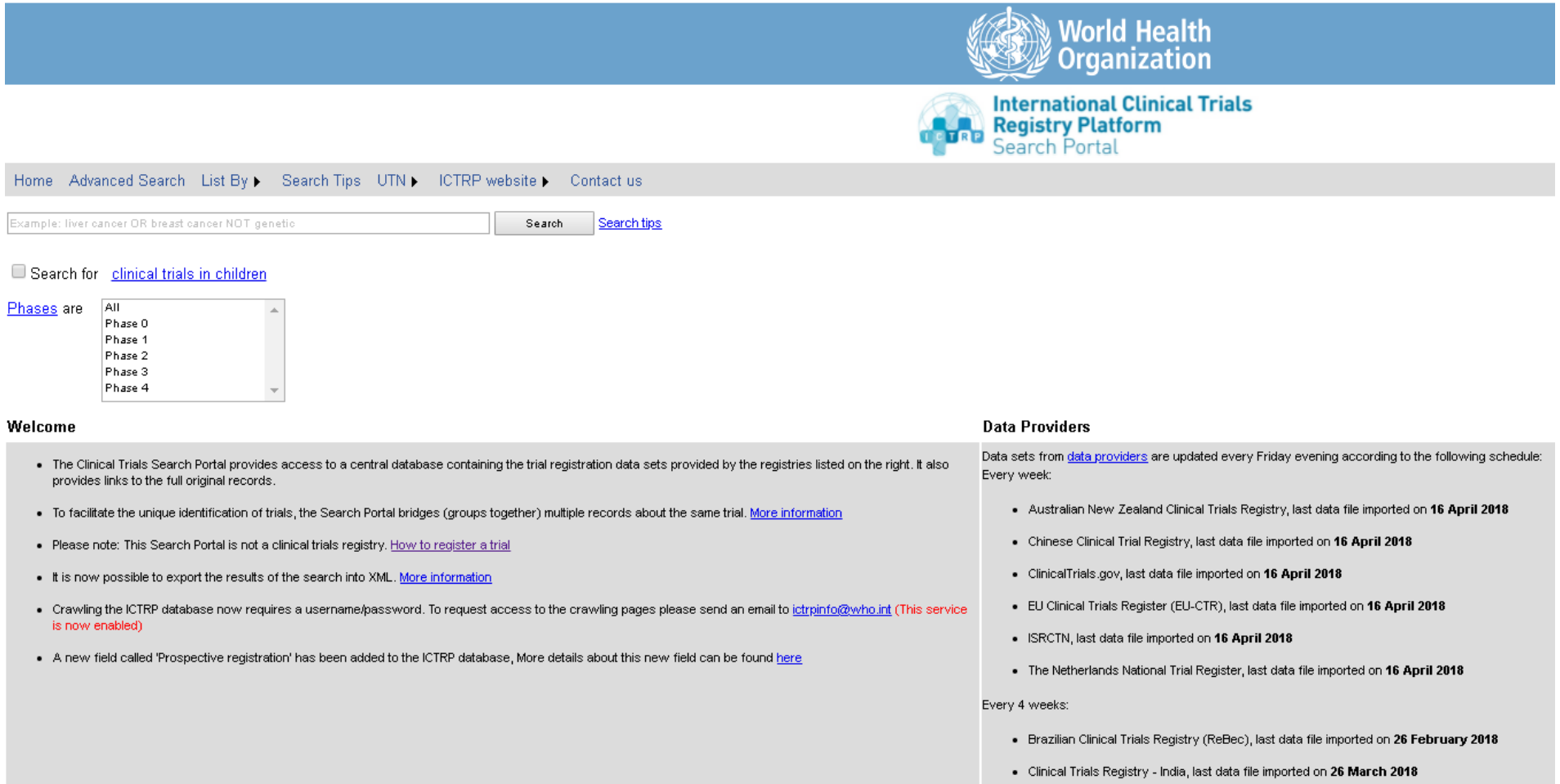
ICMJE: Indicates when the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication (September 2005)

FDAAA: Indicates when the registration requirements of FDAAA began and were implemented on ClinicalTrials.gov (December 2007)


1
19521
117849
3259
2802
9589
83307
5136
31856
11963
4442
5293
8018
5886
7069

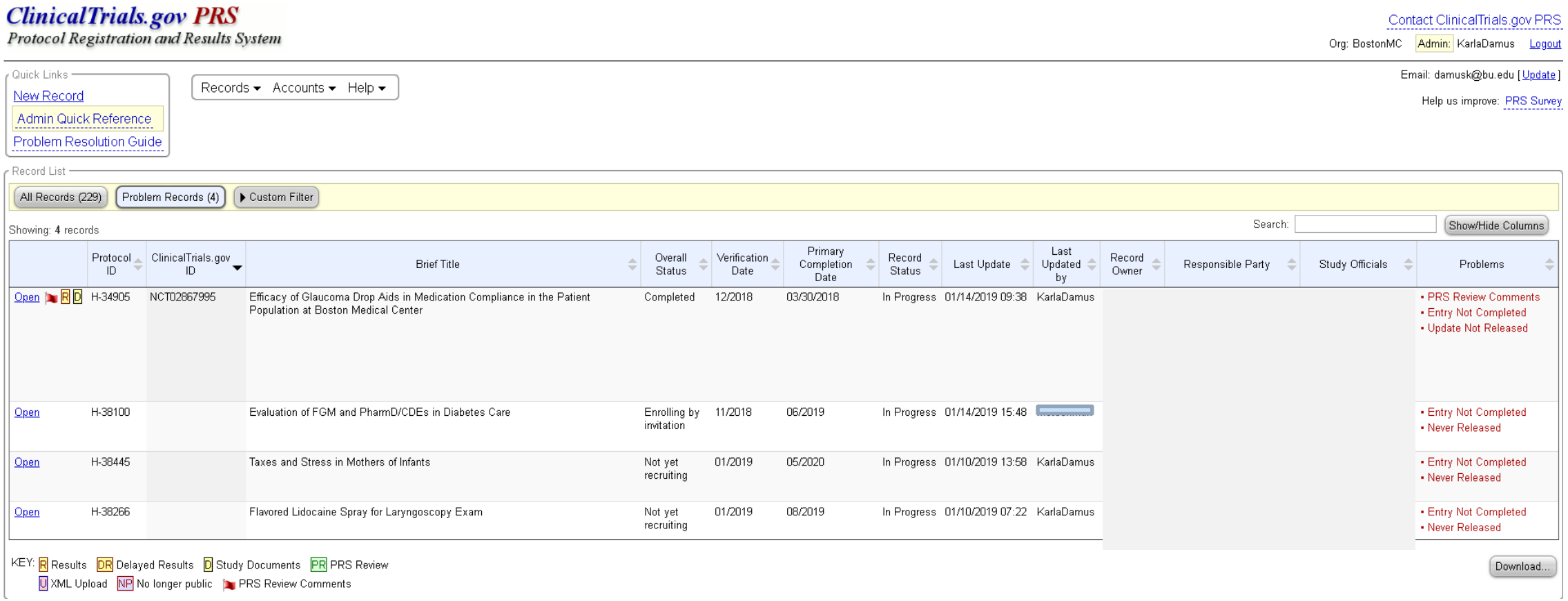
International Clinical Trials Registry Platform (ICTRP)

WHO ICTRP-The main aim of the WHO ICTRP is to facilitate the prospective registration of the WHO Trial Registration Data Set (24 items) on all clinical trials, and the public accessibility of that information.
UTN (Universal Trial Number assigned- similar to the NCT for the US ClinicalTrials.gov register/registry)



www.who.int/ictrp/

Register.ClinicalTrials.gov



BMC (BostonMC) 230 studies

BUMC (BostonU) 170 studies

CRC (BostonUCRC) about 60 studies-- PRS Administrator Cynthia Monahan (also CRC IRB Director)

BU Clinical & Translational Science Institute

CRRO Clinical Research Resources Office

ClinicalTrials.gov – Brief History

- ClinicalTrials.gov is a registry website maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH)
- ClinicalTrials.gov was launched in **2000** in response to FDA Modernization Act of 1997, which required HHS, through NIH, to establish a clinical trials registry
- In **2005**, International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication
  - In June 2007 the ICMJE adopted the WHO's definition of clinical trial: “Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.“
- In **2008**, ClinicalTrials.gov released its results database in response to the FDA Amendments Act of 2007 (FDAAA), which expanded the requirements to include result reporting for trials involving FDA regulated products
- Effective **January 1, 2014**, CMS required mandatory reporting of NCT on claims for items and services provided in clinical trials that are qualified for coverage under the Medicare Clinical Trial Policy (“Qualifying Clinical Trials”)
- In **2014** NIH expanded the definition of CTs

ClinicalTrials.gov – brief history (cont.)

- On **September 16, 2016**, HHS issued the final rule for Clinical Trials Registration and Results Information Submission, which clarified and expanded the registration and results submission requirements in accordance with FDAAA (the “Final Rule”)
  https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission

- On **September 16, 2016**, NIH published a Policy, which requires registration and result reporting of all NIH funded clinical trials (the “NIH Policy”) https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- The NIH Policy complements the Final Rule
- **Both the Final Rule and the NIH Policy went into effect January 18, 2017**
- Noncompliance enforcement began **April 18, 2017**
- Upgrades to the ClinicalTrials.gov system continue
  - **June 6, 2017**- ***IPD*** (Individual Participant Data) Sharing Statement module was added to the Protocol Section to document the plan for sharing and supporting materials.
  - **June 29, 2017**- The new ***Document Section*** requires uploading of the Study Protocol and Statistical Analysis Plan (SAP) as part of results information submission for studies with a Primary Completion Date on or after January 18, 2017. Informed Consent Forms (ICF) may optionally be uploaded.

What is a Clinical Trial Under the NIH Policy?

"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."

- Includes clinical trials that are not "Applicable Clinical Trials"
  - ✓Phase 1 trials of FDA-regulated drugs and biologicals
  - ✓Small feasibility studies of FDA-regulated device products
  - ✓Study of an intervention that is not regulated by the FDA (i.e. behavioral interventions)

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

NIH Clinical Trial Decision Tree

If **yes** to all of the following, registration and results reporting is required

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

Does not include observational and natural history studies

"NIH Policy on Dissemination of NIH-Funded Clinical Trial Information" Presentation to the Clinical Trials Registration Taskforce, December 15, 2016 by Sarah Carr and Valery Gordon
https://research.uic.edu/sites/default/files/Carr_Gordon_NIH.pdf

Is this a clinical trial?

The study involves the recruitment of research participants with disease X to receive either an investigational drug or a placebo. It is designed to evaluate the efficacy of the investigational drug to relieve disease symptoms.

1. ***Does the study involve human participants?*** **Yes**, the study involves human participants.
2. ***Are the participants prospectively assigned to an intervention?*** **Yes**, the participants are prospectively assigned to receive an intervention, the investigational drug or placebo.
3. ***Is the study designed to evaluate the effect of the intervention on the participants?*** **Yes**, the study is designed to evaluate the effect of the investigational drug on the participants' symptoms.
4. ***Is the effect being evaluated a health-related biomedical or behavioral outcome?*** **Yes**, the effect being evaluated, relief of symptoms, is a health-related outcome.

This study is a clinical trial.

Is this a clinical trial?

The study involves the recruitment of research participants with disease X to be evaluated with an investigational in vitro diagnostic device (IVD). The study is designed to evaluate how knowledge of certain antibody levels impacts clinical management of disease.

1. ***Does the study involve human participants?*** **Yes**, the study involves human participants.
2. ***Are the participants prospectively assigned to an intervention?*** **Yes**, the participants are prospectively assigned to an intervention, measurement of an antibody level, with the idea that knowledge of that antibody level might affect clinical management.
3. ***Is the study designed to evaluate the effect of the intervention on the participants?*** **Yes**, the study is designed to evaluate how knowledge of the level of an antibody might inform treatment.
4. ***Is the effect being evaluated a health-related biomedical or behavioral outcome?*** **Yes**, the effect being measured, how blood antibody levels inform treatment, is a health-related outcome.

This study is a clinical trial.

Is this a clinical trial?

The study involves the recruitment of research participants with disease X to test an investigational in vitro diagnostic device (IVD). It is designed to evaluate the ability of the device to measure the level of an antibody in blood.

1. ***Does the study involve human participants?*** **Yes**, the study involves human participants.

2. ***Are the participants prospectively assigned to an intervention?*** **No**, in this context the IVD would not be considered an intervention. The IVD is being used to test its ability to measure antibody levels, but not to test its effects on any health-related biomedical or behavioral outcomes.

This study is not a clinical trial.

Is this a clinical trial?

Prior to a study of the effects of interference on working memory and brain function, an investigator wishes to test the study procedures and adjust the difficulty of the memory tasks for a range of individuals. To do so, the investigator runs a few healthy volunteers through the procedures and adjusts and finalizes the procedures prior to initiating the formal study.

1. ***Does the study involve human participants?*** **Yes**.

2. ***Are the participants prospectively assigned to an intervention?*** **Yes**, the participants are prospectively assigned to different interference conditions.

3. ***Is the study designed to evaluate the effect of the intervention on the participants?*** **No**, the purpose of these preliminary or practice runs is to evaluate and refine the study procedures, not the effect of the intervention on the participants.

   This study is not a clinical trial.

Health-related biomedical or behavioral outcome

Definition: the pre-specified goal/s or condition/s that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.

Examples include:

- positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression)
- positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers)
- reading comprehension and /or information retention)
- positive or negative changes to disease processes
- positive or negative changes to health-related behaviors
- positive or negative changes to quality of life

Clarification-

- If procedures and tasks are being performed to measure and describe, but not to modify then the study is **NOT** a clinical trial
- Refer to case study # 18 a-f at: https://grants.nih.gov/policy/clinical-trials/case-studies.htm

Which Trials Require Results Information

- Applicable Clinical Trials (ACT) under FDAAA (The Final Rule)
  - Studies with a **Primary Completion Date** on or after January 18, 2017, results information required regardless of whether FDA regulated product has been approved, licensed or cleared for marketing
  - **Primary Completion Date** is “the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.”
- NIH-funded clinical trials initiated (enroll first subject) after January 17, 2017 that are supported from grants submitted after that date.

What is an ACT? Use The ACT Check List

Question	Yes	No
1. Is the study interventional (a clinical trial)? *Study Type* data element is "Interventional"	☐	☐
2. 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."	☐	☐
3. 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."	☐	☐
4. Do ANY of the following apply (is the answer "Yes" to <u>at least one</u> of the following sub-questions: 4a, 4b, OR 4c)?	☐	☐
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."		

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.

International Committee of Medical Journal Editors (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* are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioural 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.
  - The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

- The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

International Committee of Medical Journal Editors (ICMJE)

- The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering.
- Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.
- The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Registration and Results Reporting Requirements on ClinicalTrials.gov

Element	Final rule	NIH Policy
Intervention and phase type	Drug, biologic, device products regulated by FDA; *not phase 1*	All, including behavioral interventions; all phases
Timeframe-registration	Not later than 21 days after enrollment of the first subject At BMC/BUMC BEFORE IRB approval	Same
Registration data elements	Consists of descriptive information, recruitment information, location and contact information, and administrative data.	Same
Timeframe- results reporting	Not later than 12 months after primary completion date	Same
Results data elements	Includes participant flow, demographic and baseline characteristics, outcomes and statistical analyses, adverse events, the protocol and statistical analysis plan, and administrative information	Same
Effective Date	Jan 18, 2017; Compliance by April 18, 2017	Jan 18, 2017

Source: https://www.nih.gov/news-events/summary-table-hhs-nih-initiatives-enhance-availability-clinical-trial-information

ICMJE Policy (effective 2005 updated 2017). Registration required for all phases of clinical trials of all interventions with any funding source prior to enrollment of the first participant. Enforcement is refusal to publish.

ICMJE Data Sharing Policy

1. As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain **a data sharing statement**.
2. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in *the trial's registration*.
3. If the data sharing plan *changes after registration* this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.
4. Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt.
   - They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported.
   - Authors of secondary analyses must explain completely how theirs differ from previous analyses.
   - In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

- http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf

Responsible Party's (RPs) Obligations under the Final Rule and the NIH Policy

- **Register the clinical trial**
  - Final Rule + NIH Policy no later than 21 days after enrollment
  - **For ICMEJE prior to the enrollment of first participant**
    - *BMC/BUMC Policy Requires that all CTs be registered (obtain the NCT) before the IRB review will be completed*
  - For QCT (those that submit claims to CMS) prior to enrollment of first participant
- **Update the clinical trial (at least annually [prefer every 6 months] and as needed)**
  For Final Rule and NIH Policy update on at least once every 12 months (some information within 15 or 30 days of change-- recruitment status, Primary Completion Date)
- **Report results of ACT and NIH funded clinical trials**
  For Final Rule and NIH Policy, submit summary results, which includes adverse events information, *not later than 12 months after the Primary Completion Date* (delays allowed under certain circumstances)
- **Summary**

  ALL CTs must be registered and updated *as needed and at least annually*

  Results must be reported on all ACTs and any NIH grant with enrollment and funding after Jan 17, 2017

Required CT Results Information for ACTs and NIH Funded Clinical Trials

- Participant Flow
- Demographic and baseline characteristics
- Outcomes and statistical analyses
- Adverse event information
- Protocol and statistical analysis plan (new requirement)
- Administrative information
- Additional information for applicable device clinical trials of unapproved or uncleared devices

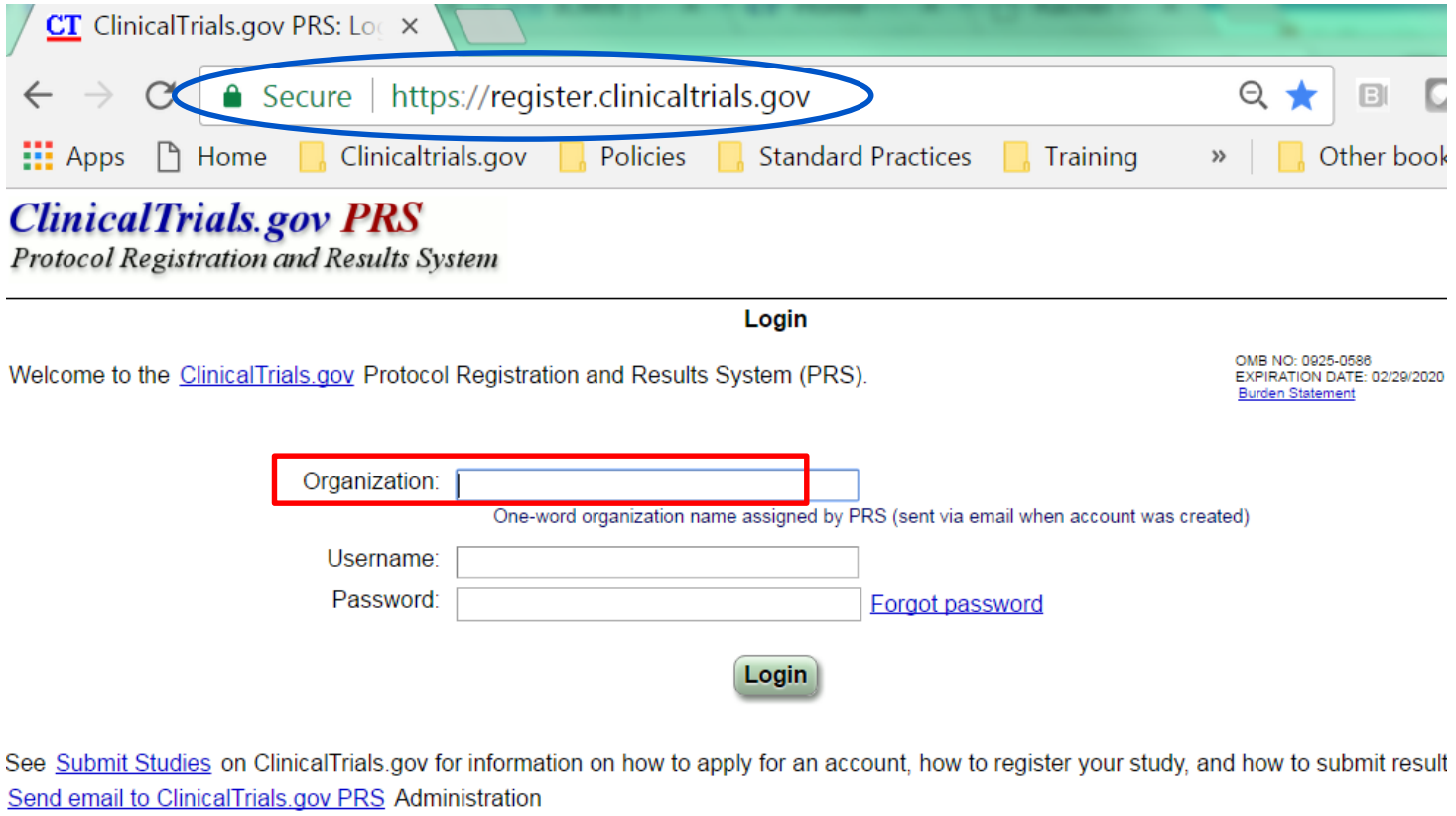
Review instructions and the templates before the trial starts to make sure the data is collected to facilitate compliance with the results information requirements

Navigating *register.clinicaltrials.gov*

(dashboard, protocol, results, and documents sections)

PRS- Protocol Registration and Results System

To obtain a ClinicalTrials.gov user account, contact your institutional CTgov administrator.
You will be assigned a username (case/space sensitive) and CTgov will email instructions on how to set your password. Your/the RP/PR's password can be reset as needed, just contact the PRS Administrator.
The organization name will be either **BostonMC** or **BostonU**



ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: BostonU Admin: KHDamus

Create New Record

To avoid duplicate or invalid registration of your study, check the following before proceeding with registration:

1. **Studies may only be registered by the Responsible Party.** The Responsible Party for a clinical study is the Sponsor, Sponsor-Investigator, or Sponsor-designated Principal Investigator who meets specific requirements.
   - When a study is subject to U.S. Food and Drug Administration regulations and conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND or IDE Holder is considered the Sponsor or Sponsor-Investigator.
   - When a study is not conducted under an IND or IDE, the entity or single person who initiates the study, by preparing and/or planning the study, and who has authority and control over the study, is considered the Sponsor or Sponsor-Investigator.
2. **Use the PRS account of the Sponsor or Sponsor-Investigator to register the study.** If the Sponsor has designated the Principal Investigator to be the Responsible Party for a study, that study must be registered using the PRS account of the Sponsor.
3. **Multi-site studies are NOT registered by individual sites.** If this is a multi-site study it must be registered only once, by the Responsible Party (IND/IDE holder or the person or organization who initiates the study and who has authority and control over the study) or its designated principal investigator (PI).
4. **Coordinate with all collaborators before registering.** If the study has multiple collaborators, contact the other organizations to confirm that the study has not already been registered and to notify them that your organization (or designated PI), as Responsible Party is registering the study.
5. **Refer to the ClinicalTrials.gov Review of Protocol Submissions document** for a description of items evaluated by ClinicalTrials.gov after protocol information is submitted.

Help Definitions

* Organization's Unique Protocol ID:	H-377777
* Brief Title:	Program to Reduce Obstetrical Problems and Prematurity Special Characters
[*] Acronym: (if any)	PROPP If specified, will be included at end of Brief Title in parentheses.
* Study Type:	(•) Interventional (or clinical trial) — participants assigned to intervention(s) based on a protocol ( ) Observational participants **not** assigned to intervention(s) based on a protocol; typically in context of routine care ( ) Expanded Access availability of an experimental drug or device outside of a clinical trial protocol

Continue Cancel

* Required
* § Required if Study Start Date is on or after January 18, 2017
[*] Conditionally required (see Definitions)

ID: H-377777 Program to Reduce Obstetrical Problems and Prematurity

Record Status

In Progress → Entry Completed → Approved → Released → PRS Review → Public

Next Step: Finish Protocol section *Entry Complete*

Record Owner:	KHDamus	Access List:	[] Edit
Last Update:	04/24/2018 05:18 by KHDamus	Upload:	Allowed Edit
Initial Release:	[Not yet released]	PRS Review:	[Not yet released]
		Public Site:	[Not yet registered]
		FDAAA:	Unknown (insufficient information entered)

Spelling Preview Draft Receipt (PDF RTF) Download XML Delete... Admin Only: Copy Protocol Change Owner

Open **Protocol Section**

Identifiers: [NCT ID not yet assigned] Unique Protocol ID: H-377777

Brief Title: Program to Reduce Obstetrical Problems and Prematurity (PROPP)

Module Status:

Study Identification:	✓
Study Status:	✓
Sponsor/Collaborators:	✓
Oversight:	Information is required
Study Description:	Information is required
Conditions:	Information is required
Study Design:	Information is required
Arms and Interventions:	Information is required
Outcome Measures:	Information is required
Eligibility:	Information is required
Contacts/Locations:	Information is required
IPD Sharing Statement:	
References:	

Document Section

Only certain studies need to have study documents uploaded.

- Full study protocol and statistical analysis plan -- required with results information submission for studies with a Primary Completion Date on or after January 18, 2017
- Informed consent forms - optional for all studies

Uploaded PDF/A Documents:

Results Section

Results submission is required by FDAAA 801 for certain applicable clinical trials of drugs, biologics and devices. Note: other clinical trials may need to have results submitted based on other funder or sponsor policies.

[Record must have a ClinicalTrials.gov ID (NCT number) before results can be entered.]

Delay Results For applicable clinical trials subject to FDAAA 801, results submission may be delayed (in limited circumstances) with a Certification or Extension Request.

For more information see: When Do I Need to Register and Submit Results?

ClinicalTrials.gov PRS
Protocol Registration and Results System

Home > Record Summary > Protocol Section

ID: H-37777 Program to Reduce Obstetrical Problems and Prematurity

Protocol Section

ERROR(S) in Protocol Section. See ERROR or information required messages below.

Record Summary Preview Edit All Help Definitions

Edit **Study Identification**

Unique Protocol ID: H-37777
Brief Title: Program to Reduce Obstetrical Problems and Prematurity (PROPP)
Official Title: Program to Reduce Obstetrical Problems and Prematurity in the Bronx
Secondary IDs: [U.S. NIH Grant/Contract Award Number]

ERROR: "" is not a recognized U.S. NIH grant/contract award number.
ERROR: Secondary ID is a required field.

Edit **Study Status**

Record Verification: April 2018
Overall Status: Enrolling by invitation
Study Start: April 10, 2018 [Actual]
Primary Completion: July 2020 [Anticipated]
Study Completion: July 2020 [Anticipated]

Edit **Sponsor/Collaborators**

Sponsor: Boston University
Responsible Party: Sponsor
Collaborators:

Edit **Oversight**

U.S. FDA-regulated Drug:
U.S. FDA-regulated Device:
U.S. FDA IND/IDE:
Human Subjects Review: Board Status:
Data Monitoring:

Information is required

Edit **Study Description**

Brief Summary:
Detailed Description:

Information is required

Edit Study Status

Help Definitions

* Record Verification Date: Month: April ▼ Year: 2018

* Overall Recruitment Status: Enrolling by invitation ▼

Before selecting Suspended, Terminated or Withdrawn see the Overall Recruitment Status definition.

Tip: Day is not required for Anticipated dates.

* § Study Start Date: Month: April ▼ Day: 10 Year: 2018 Type: Actual ▼

Date study is open for recruitment (Anticipated) or date first participant is enrolled (Actual).

* Primary Completion Date: Month: July ▼ Day: Year: 2020 Type: Anticipated ▼

Final data collection date for primary outcome measure.

* § Study Completion Date: Month: July ▼ Day: Year: 2020 Type: Anticipated ▼

Final data collection date for study.

Continue Back Quit

* Required

* § Required if Study Start Date is on or after January 18, 2017

[*] Conditionally required (see Definitions)

Definitions from CTgov

2. Study Status

Record Verification Date *

Definition: The date on which the responsible party last verified the clinical study information in the entire ClinicalTrials.gov record for the clinical study, even if no additional or updated information is being submitted.

Overall Recruitment Status *

Definition: The recruitment status for the clinical study as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical study has an Individual Site Status of "Recruiting," then the Overall Recruitment Status for the study must be "Recruiting." Select one.

- Not yet recruiting: Participants are not yet being recruited
- Recruiting: Participants are currently being recruited, whether or not any participants have yet been enrolled
- Enrolling by invitation: Participants are being (or will be) selected from a predetermined population
- Active, not recruiting: Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled
- Completed: The study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant's last visit has occurred)
- Suspended: Study halted prematurely but potentially will resume
- Terminated: Study halted prematurely and will not resume; participants are no longer being examined or receiving intervention
- Withdrawn: Study halted prematurely, prior to enrollment of first participant

Help: Study Status

Introduction

The Study Status module contains key dates and Overall Recruitment Status of a study.

Example

Study Status

Record Verification: December 2016
Overall Status: Recruiting
Study Start: December 18, 2016 [Actual]
Primary Completion: June 2018 [Anticipated]
Study Completion: January 2019 [Anticipated]

Data Entry Tips

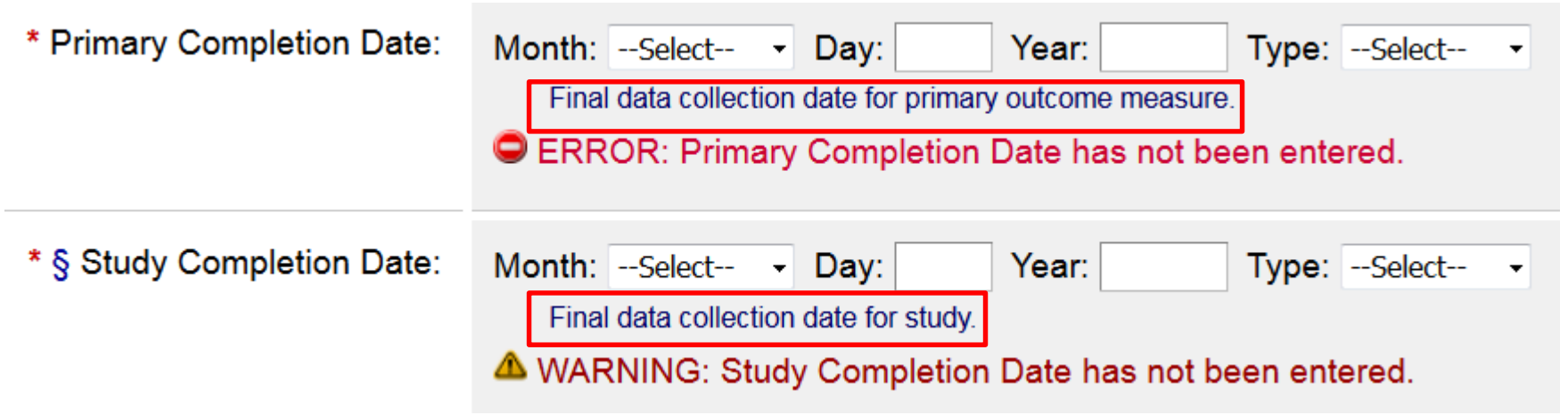
- Review a record for an Active (not completed or terminated) study and update the Verification Date at least once per year, even if no additional or updated information was submitted during that year. Note: some data elements will need to be updated more frequently.
- When Overall Recruitment Status is Recruiting, the Recruitment Status must be specified for each Location.
- When the final participant has been examined or received an intervention for the purposes of final collection of data for the Primary Outcome Measure, update Primary Completion Date and change Type to Actual.
- When the final participant has been examined or received an intervention for the purposes of final collection of data for the overall study, update Study Completion Date and change Type to Actual.
- When a study is terminated, update Primary Completion Date and Study Completion Date to reflect when data collection ended. Change Type to Actual for both dates.

Additional Resources

Protocol Review Criteria (PDF)

Interventional Study Protocol Registration Template (PDF)

Primary and Study Completion Dates



Completion Dates are based on <u>data collection</u>. They are NOT based on:

- data analysis
- publication
- IRB closure

If you use these as Completion Dates, you may have LATE RESULTS

If a date is 'anticipated' only provide a month and year. If a date is 'actual' you need to provide the full date.

Often the primary completion and the study completion date are the same but not always.

Remember to go back into the record and update all 'anticipated dates before they become in arrears or the it is an **error** and the record becomes a **problem record.**

ID: H-37777 Program to Reduce Obstetrical Problems and Prematurity

Edit **Conditions**

Conditions:

Keywords:

Information is required

Edit **Study Design**

Study Type: Interventional [Change...]
Primary Purpose:
Study Phase:
Interventional Study Model:
Number of Arms:
Masking:
Allocation:
Enrollment: []

Information is required

Open **Arms and Interventions**

Information is required

Edit **Outcome Measures**

Information is required

Edit **Eligibility**

Minimum Age:
Maximum Age:
Sex:
Gender Based:
Accepts Healthy Volunteers:
Criteria:
Inclusion Criteria:
-
Exclusion Criteria:
-

Information is required

Open **Contacts/Locations**

Central Contact Person:
Central Contact Backup:
Study Officials:
Locations:

Information is required

Edit **IPD Sharing Statement**

Plan to Share IPD:

Edit **References**

Citations:
Links:
Available IPD/Information:

Record Summary

ClinicalTrials.gov PRS
Protocol Registration and Results System

Home > Record Summary > Protocol Section > Outcome Measures

ID: H-37777 Program to Reduce Obstetrical Problems and Prematurity

Help Definitions

* Primary Outcome Measure:

Outcome 1
Title:
Description:
Time Frame:
× Delete Outcome

+ Add Primary Outcome

[*] Secondary Outcome Measures: (if any)

Outcome 2
Title:
Description:
Time Frame:
+ Copy Outcome × Delete Outcome

Outcome 3
Title:
Description:
Time Frame:
+ Copy Outcome × Delete Outcome

+ Add Secondary Outcome

Other Pre-specified Outcomes:

Outcome 4
Title:
Description:
Time Frame:
+ Copy Outcome × Delete Outcome

+ Add Other Outcome

Save Cancel

* Required
* § Required if Study Start Date is on or after January 18, 2017
[*] Conditionally required (see Definitions)

Group Activity

Editing Examples

Study Status Section

What is the record verification date?
How often do records need to be verified?
What is the overall status?
- What is the **overall status** if you have collected all study data on each participant but you are still analyzing identifiable data? ‘active, not recruiting’ or ‘completed’?

What is the difference between the **primary completion date** and the **study completion date**?
- Can they be the same date?
- What is the difference between the information provided for an ‘anticipated’ date and an ‘actual’ date?
- What would you do if you ‘anticipated’ that the ***primary completion date*** would be December 2019 but the ‘actual’ primary completion date turned out to be November 12 , 2019?

Once the **overall status** is ‘completed’ what other information needs to be added to the record?

Study Status Section

What is the record verification date? *From CTgov*- the date (month and year) on which the responsible party last verified the clinical study information in the entire ClinicalTrials.gov record for the clinical study, even if no additional or updated information is being submitted.

How often do records need to be verified? A minimum of once a year although CTgov prefers at least twice a year.

What is the overall status? *From CTgov*- the recruitment status for the clinical study as a whole, based upon the status of the individual sites. If at least one facility in a multi-site clinical study has an Individual Site Status of "Recruiting“ or “Enrolling by invitation”, then the Overall Recruitment Status for the study must be "Recruiting" or “Enrolling by invitation”.

What is the **overall status** if you have collected all study data on each participant but you are still analyzing identifiable data? ‘active, not recruiting’ or ‘completed’? If all study data has been collected on each participant then the study is ’completed’; you can continue to analyzed identifiable data for as long as you need to. “completed’ refers to recruitment not to the research study and is defined by CTgov as: the study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant’s last visit has occurred).

Study Status Section continued

What is the difference between the **primary completion date** and the **study completion date**? From CTgov-

Primary Completion Date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Once the clinical study has reached the primary completion date, the responsible party must update the Primary Completion Date to reflect the actual primary completion date.

Study Completion Date is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.

Once the clinical study has reached the study completion date, the responsible party must update the Study Completion Date to reflect the actual study completion date.

Can they be the same date? Yes and most of the time they are unless there is an intervention or data collection for secondary outcome measures that occurs after the primary outcome measures are collected eg a two year follow up survey or additional blood draw, BP, etc

Study Status Section continued

What is the difference between the information provided for an 'anticipated' date and an 'actual' date? An 'anticipated' date is the projected month and year when an event is expected. Do not provide a day, as if you provide just the month and year then the record will remain up to date until the end of the month (eg if you gave an 'anticipated' study start date of April 10, 2020 then on April 11, 2020 if it is not edited to 'actual' it will be an error. In contrast, if the 'anticipated date was April 2020, then the record is up to date until the last day in April but on May 1 an error message will appear unless the 'actual' date [which is a full date including the month, day and year] is entered.

What would you do if you 'anticipated' that the ***primary completion date*** would be December 2019 but the 'actual' primary completion date turned out to be November 12, 2019? Just go into the record and edit the primary completion date from December 2019 to the 'actual' date of November 12, 2019 and then release the record for PRS review. Remember if you make edits but do not release the record for PRS review is as if the edits were never made. You will see them on your institutional CTgov database/registry but they won't appear on the public clinicaltrials.gov registry until reviewed and released by CTgov.

Once the **overall status** is 'completed' what other information needs to be added to the record? You will need to go into the Study Enrollment section and change the 'anticipated' enrollment to the 'actual' enrollment as if the overall status is 'completed' you are no longer enrolling/recruiting participants for the study.

Outcome Measures

What three pieces of information are required for each outcome measure?

How many primary outcome measures and secondary outcome measures can you list?

If you are doing a study and depressive symptoms are to be collected using the Beck Inventory at baseline, 3mo and 6mo, propose an outcome measure title, a description and a time frame for the outcome measures

If you are doing a study and quarterly patient satisfaction is a primary outcome measure to be collected based on a survey, what title, description and time frame would you propose.

What would you do if your outcome measures change during the study?

Outcome Measures

What three pieces of information are required for each outcome measure? A title- a name of the specific outcome measure and how it will be assessed, a detailed description of that measure including how you would interpret results [eg are lower or higher scores more favorable], and the timeframe for collecting the outcome measure.

How many primary outcome measures and secondary outcome measures can you list? You can have as many of each as you need and you can also include additional pre-specified outcome measures. The number and types of outcome measures will be determined by your study protocol.

If you are doing a study and depressive symptoms are to be collected using the Beck Inventory at baseline, 3mo and 6mo, propose an outcome measure title, a description and a time frame for the outcome measures

Title- Change in depressive symptoms based on the Beck Depression Inventory

Description- The Beck Depression Inventory (BDI) is a 21 question multiple-choice self report questionnaire where each responses ranging in intensity from little or none to severe and are scored with a value of 0 to 3. The possible range of scores is 0 to 63. Standard cut-offs are 0 to 9= minimal depression; 10 to18= mild depression; 19 to 29= moderate depression; and 30 to 63= severe depression.

Time frame- baseline, 3 months, 6 months

Outcome Measures continued

If you are doing a study and quarterly patient satisfaction is a primary outcome measure to be collected based on a survey, what title, description and time frame would you propose. You would need a very specific title (eg Patient satisfaction based on a self report survey), a detailed description of the survey- number of items, range of responses (such as 1= strongly agree to 5=strongly disagree), the overall potential range of values and whether lower or higher scores are more favorable) and you would need to copy this outcome [using the 'copy outcome function] for each time frame (eg one for 3 months, one for 6 months, one for 9 months, and one for 12 months)

What would you do if your outcome measures change during the study? Since you are doing human subjects/clinical research changes in the protocol are expected so remember anytime a non-personnel amendment is submitted to your IRB to review the your CTgov record (and change the record verification date to that month and year) and make any needed edits including any affecting the outcome measures. If an outcome measure changes, edit it as needed which may involve changing the title, the description, and the timeframe or maybe just one or two of those sections. Then remember to always have the RP (responsible party)/PI or the sponsor release the record for CTgov PRS review.

Tips for Registering, Updating and Reporting Results on *ClinicalTrials.gov*

Some CTgov Tips

- All ERRORS and Major Comments (in pink) must be addressed in a timely manner
- You can ignore Warnings and Advisory Comments (in light orange)
- You can ignore Red flags on the overall record
- Do not use pronouns any where in the record (e.g. ‘the investigators’ instead of ‘our research team’)
- Use the ‘spelling check’ on the dashboard before submitting to PRS review
- Set up a tickler system for annual verification and for updating all ‘anticipated” dates
- Note the each time the record is released for PRS review a PDF is made and attached and a log of all traffic on the record

Some Additional Tips

- Each time you submit an amendment and/or the annual review to the IRB, revise your protocol, modify your outcome measures, or have other changes to the research (egg early termination of the study) go into your record and edit as needed
- If you have to report results meet with the PRS Administrator (months in advance) to review the tables, format and requirements for statistical testing.
- Before you begin to add results *check your outcome measures and make sure they are what you plan to report about as they flip to the results section*.
- Submit results as soon as possible and within a year of the primary completion date (records can become ‘late results per FDAAA’ during the review period)
- Respond to PRS Administrator comments promptly
- The public has full access to the posted information including changes that are made to the record so keep the record up to date, accurate and consistent with the research study.

NIH Policy for Noncompliance

- Requirements for clinical trial registration and results submission will be included in the terms and conditions of the award

- Must certify compliance with registration and results requirements in progress report forms

- Failure to comply with terms and conditions of award may provide basis for enforcement actions (45 C.F.R. 75.371 – Remedies for noncompliance for HHS awarding agency or pass-through entity)
  - Temporarily withhold payments pending correction
  - Suspend or terminate award
  - Withhold further awards for the project or program

NIH-Funded ACT and Final Rule Noncompliance

- If NIH-funded clinical trial is also an ACT, non-compliant with 42 USC 282(j) (FDAAA) and 42 CFR Part 11.66 (Final Rule)
  - HHS agency will verify compliance, and if not compliant, any remaining funding for grant or funding for a future grant to such grantee will not be released
  - If HHS agency will provide notice to grantee of non-compliance and allow 30 days to correct

- ACT (Applicable Clinical Trial)
  - Failure to certify compliance and failure to submit required information are violations of Food, Drug and Cosmetic Act
  - Civil monetary penalties of up to $11,800+/day
  - Institutions had until April 17, 2017 to become compliant

Resources

- https://clinicaltrials.gov/
- www.bumc.bu.edu/ohra/clinicaltrials-gov/
- www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- Zarin DA, et al. "Trial Reporting in Clinical Trials.gov– The Final Rule". NEJM 2016,375:20, 1998-2004. www.nejm.org/doi/full/10.1056/NEJMsr1611785
- Tse T, Bergeris A, Zarin DA. Lockbox for Registered Trials of Unapproved Devices. *N Engl J Med*. 2018 March 15;378(11):1064.
- Bergeris A, Tse T, Zarin DA. Trialists' intent to share individual participant data as disclosed at ClinicalTrials.gov. *JAMA*. 2018 Jan 23;319(4):406-8.
- www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information
- http://www.bu.edu/researchsupport/2017/08/31/new-nih-requirements-for-registering-nih-funded-clinical-trials-on-clinicaltrials-gov-and-for-good-clinical-practice-gcp-training/?utm_source=RR&utm_medium=email&utm_campaign=0917
- The hidden side of CTs-- https://www.youtube.com/watch?v=-RXrGLolgEc&feature=youtu.be

Site Specific Policies

Process AT BMC – BU Medical Campus

- Provide centralized support through the BMC – BU Medical Campus Office of Human Research Affairs (OHRA)
- Process is documented in a joint policy
- Studies to Register
  - NIH-Funded Clinical Trials (results information needed)
  - Applicable Clinical Trials (ACT) (results information needed)
  - Qualifying Clinical Trials (QCT) (those that submit claims to CMS)
  - Clinical trials Meeting ICMJE Definition
- Above studies should be registered in ClinicalTrials.gov concurrently with IRB submission
- NCT number must be provided to IRB and BMC CTO for trials using BMC clinical infrastructure

Process at BMC – BU Medical Campus

- BMC and BU Medical Campus each delegate PI as RP
- Departing PIs will need a transition plan for ongoing studies in ClinicalTrials.gov
- Registration through the PRS (Protocol Registration and Results System) institutional administrator
  - Karla Damus for both BMC and BU Medical Campus, if unavailable:
    - Fanny Ennever for BMC
    - Mary-Tara Roth for BU Medical Campus
- BMC non-compliance escalated to BMC Research Compliance officer then to BMC Institutional Official
- BU Medical Campus non-compliance escalated to Director, Human Research Protection Program, OHRA
- Training, education, and compliance monitoring will be provided by OHRA/CRRO/CTSI

Who is Responsible for Registering, Updating and Submitting Results?

- The Responsible Party is the awardee or investigator for NIH-funded clinical trial (subawardees and subinvestigators must coordinate with RP)

- When BMC or BU Medical Campus is the sponsor (no outside funding, NIH grantee) they will designate the PI as RP
  - To be the RP the PI must
    - ✓Be responsible for conducting the trial
    - ✓Have access to and control over the trial data
    - ✓Have the right to publish the trial results; and
    - ✓Have the ability to meet the ClinicalTrials.gov requirements for submitting and updating trial information

Supporting Researchers with the Process at BMC–BU Medical Campus

- Assist PIs in determining if their study is a CT and the type of trial
- Assist in registration, updating and reporting results
- Regular auditing and monitoring for compliance
- Training and education for RPs/PIs and research staff provided by OHRA/CRRO
  - Annually, present a CRRO Seminar on ClinicalTrials.gov
  - Integrate key information into CRRO trainings (PI and Fundamentals)
  - Educational venues developed for BMC/BU Medical Campus Research Professional Network (RPN) and the BMC Research Managers
  - Departmental presentations to research faculty on request
  - Website with ClinicalTrials.gov information, links, and resources (e.g. checklists, algorithms, templates, videos, publications)
  - CRRO consultations from the design of clinical trials throughout the registration, updating and results reporting process

Contact Karla Damus damusk@bu.edu, 358 7283

Contacts

Karla Damus
Administrator, ClinicalTrials.gov BMC/BU Medical Campus
358 7382
damusk@bu.edu

Fanny Ennever
BMC Research Compliance Officer
638-8874 fanny.ennever@bmc.org

Mary-Tara Roth
Director, CRRO
358 7679
mtroth@bu.edu