ClinicalTrials.gov

Background

Clinical Trials registration is public disclosure of key information of a clinical trial. The US Food and Drug Administration (FDA), the International Committee of Medical Journal Editors (ICMJE), and the World Health Organization (WHO) are just a few of the groups calling for clinical trials registration.

In 1997, the Food and Drug Administration Modernization Act (FDAMA) required registration of certain clinical trials in a national database, ClinicalTrials.gov. In 2007, the Food and Drug Administration Amendments Act (FDAAA) extended registration requirements and added results and adverse events reporting.

In addition, in 2005, the International Committee of Medical Journal Editors (ICMJE) implemented a policy requiring investigators to register interventional studies as a condition of consideration for publication.

ICMJE signatories:
- New England Journal of Medicine, Journal of the American Medical Association,

ClinicalTrials.gov is a registry of clinical trials operated by the National Library of Medicine that captures:

- Key summary protocol information before/during the trial
- Summary results and adverse event information of a completed trial

Boston Children’s Hospital (BCH) believes it is important to comply with the requirements of clinical trial registration, and to support our researchers in their obligations. Not all clinical trials require registration, and investigators at Children’s may not be responsible for registering all trials in which they are participating. However, there are instances when a BCH investigator is responsible for registering a clinical research study, either to meet the requirements of the law, or for journal publication requirements. In the case that a BCH investigator is responsible for registration, the IRB will not release approval until the trial has been registered and the registration number included in the IRB application.

Registration Requirements

FDAAA (the law) and ICMJE (journal policy) have different sets of requirements for what types of studies need to be registered and in what timeframe. Generally speaking, the ICMJE policy is much broader than the scope of FDAAA. Below is a summary of both requirements:
1) **FDAAA**

FDAAA requires registration for “**Applicable Clinical Trials**”:

- Interventional studies (drugs, biologics, devices)
- Phase 2 – 4 (excludes phase 1 drug studies, small feasibility device studies, observational studies, single patient expanded access studies)
- US FDA jurisdiction (e.g., IND/IDE or U.S. site)
- Studies initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007

**When:**

- Within 21 days of enrollment of 1st subject
- Update at least every 12 months (30 days for Recruitment Status and Primary Completion Date)

For more information regarding ‘applicable clinical trials’, see *Elaboration of Definitions of Responsible Party and Applicable Clinical Trials.*

2) **ICMJE**

**ICMJE** requires registration of any human research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Interventions include any intervention used to modify a biomedical or health related outcome (e.g. drugs, devices, surgical procedures, behavioral treatments, dietary interventions). Health outcomes include any biomedical or health-related measure obtained in participants including pharmacokinetic measures and adverse events.

**When:**

- Prior to enrollment of 1st subject

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**Who Is Responsible For Registration?**

1) **FDAAA:**

According to federal law, the ‘Responsible Party’ (RP) is responsible for registering and reporting results to ClinicalTrials.gov and is defined as:

- The Sponsor of the trial:
  - For studies, under an IND/IDE, the Sponsor is the IND/IDE holder (including Sponsor-Investigators)
  - For studies not conducted under an IND/IDE, the Sponsor is
    - The industry, cooperative group, consortium or other external sponsor that initiated the study, OR
If initiated by a Principal Investigator the Sponsor is

- The grantee institution* OR
- If no external funding, the PI

For additional information in determining who is responsible for registering, please reference Elaboration of Definitions of Responsible Party and Applicable Clinical Trials.

*Situations in which the “grantee institution” is the Responsible Party (and there is no IND/IDE)

For trials being conducted under a funding agreement or grant (e.g., NIH awards), the funding recipient is typically considered to be the grantee institution (i.e., BCH)). Per FDAAA, the grantee institution is considered the Sponsor and Responsible Party. In general, the Principal Investigator is in the best position to understand the research protocol, study results and adverse events. Per FDAAA, the Principal Investigator can serve as a Responsible Party if that individual:

- Is responsible for conducting the trial
- Has access to and control over the data from the clinical trial
- Has the right to publish the results of the trial
- Has the ability to meet the requirements

It is the policy of BCH to routinely designate the role of Responsible Party to the Principal Investigator.

Do I need to provide evidence of compliance with Clinical Trials.gov regulations to the granting or regulatory agency?

Yes, both the NIH and the FDA require that Investigators certify compliance with all ClinicalTrials.gov reporting requirements.

The NIH requires that Investigators list the clinical trial registration number, study title, and name and contact information of the responsible party on all progress reports involving an NIH funded clinical trial. For new trials, a statement confirming the study will be registered should be included in the Human Subjects section of the Research Plan.

The FDA requires that investigators submit FDA form 3674 with applicable trials conducted under an IND or IDE. The form and instructions on submission requirements are available on the FDA web site.

For additional details, please see Elaboration of Definitions of Responsible Party and Applicable Clinical Trials.

(2) ICMJE Registration:

While anyone involved in the clinical trial could register the trial, in practice this responsibility usually falls with the individual submitting the publication to the ICMJE journal, who is usually the Principal Investigator.
The Institutional Review Board Manual

Document: irbm_014_003_clinicaltrialsgov.docx

The Registration Process

Clinical trials are registered on ClinicalTrials.gov via a web-based data entry system called the Protocol Registration System (PRS). As a PRS user you are responsible for ensuring that the information you provide on your trial is correct, complete, readily understood by the public, and updated in a timely manner. The ClinicalTrials.gov website is located at: http://clinicaltrials.gov.

Steps to Register your Study on ClinicalTrials.gov

Step 1: Obtain an Individual User Account
In order to obtain an account under the Boston Children’s Hospital organization, please provide the following information to Irine Breytburg at irine.breytburg@childrens.harvard.edu:
- Full Name
- BCH User Name
- BCH Employee ID
- Email Address

Question 6 in the ClinicalTrials.gov PRS asks if your organization is already registered with the PRS (Protocol Registration System). The answer to this question is “YES”.

Step 2: Login to PRS
Once your account has been created go to https://register.clinicaltrials.gov/.
Complete the three fields on the Login screen. See example below:

Organization: Boston Children’s Hospital
Username: John Doe
Password: 1234

Step 3: Create a Protocol Record
A trial is registered in the system by creating a “protocol record.” Click on the Create link under Protocol Records on the Main Menu and fill in a series of data entry screens (note, you can copy and paste information into the requested data fields).

Step 4: Review the Protocol Record:
The Edit Protocol screen will appear after data entry is complete. Review the information for accuracy and completely and address any issues (ERRORS, ALERTS, WARNINGS, or NOTES) in the protocol record. You must address all issues for the registration process to be complete.

Step 5: Mark the Protocol Record as Complete
In order to fully register your study (and allow for approval and public release of information), you must be mark your record as COMPLETE.

Step 6: Keep your Protocol Record Up-To-Date
You must log into your account every 6 months to confirm or update the registration record. You will receive a reminder e-mail notification from clinicaltrials.gov once every six months to update your study information.
For additional information on how to register your study, please refer to the site How to 
Register your Clinical Study, and to the presentation ClinicalTrials.gov: A Review of 
Registration Requirements.

### Posting Basic Results

FDAAA requires reporting of results and adverse events for a subset of studies that are 
required to be registered on clinicaltrials.gov. Basic results posting is required for trials of 
FDA-approved drugs and devices. Results reporting is not mandated as part of the ICMJE 
requirements.

Specifically, results reporting is required for:

- Applicable Clinical Trials
- In which the study product is approved (for any use) by FDA

Results reporting is required within 12 months of Primary Completion Date (final data 
collection for primary endpoint). If product not approved by Primary Completion Date but is 
approved later, then results due 30 days after approval.

Submission of results is required within 12 months after primary endpoint 
completion date.

Delayed submission of result posting may occur due to:

- Seeking initial approval of investigational product
- Seeking approval for a new use
- Extensions for a ‘good cause”

In most cases at BCH, required studies will not qualify for delayed results submission.

According to ClinicalTrials.gov, the process of submitting results information to 
ClinicalTrials.gov is conceptually similar to preparing a manuscript for publication in a 
journal. An individual familiar with the study design and data analysis (such as the clinical 
investigator or study statistician) will need to be involved in order to accurately summarize 
the results information in the tabular format required by law and to ensure that the results 
are consistent with the ClinicalTrials.gov review criteria.

Scientific information is submitted as four separate modules:

1) Participant Flow
2) Baseline Characteristics
3) Outcome Measures and Statistical Analyses
4) Adverse Events*

Per ClinicalTrials.gov, the modules allow for the entry and display of information in a series 
of data tables with supporting notes but without narrative conclusions about the results. 
Summary results information may be submitted once data are available for one or more 
primary outcome measures and for each arm of the study.
Additional administrative information is required, including the study results point of contact and any agreement between the sponsor and principal investigator (PI) restricting the ability of the PI to discuss the results after the completion of the study.

*Adverse Event Reporting*

For studies requiring submission of results, the following information must be reported in the Adverse Events module:

- Serious Adverse Events and
- Other (non-serious) adverse events that exceed a frequency threshold of 5% in any arm of the clinical trial

Adverse events occurring with less than 5 percent frequency can also be voluntarily reported.

Some notes regarding adverse event reporting on ClinicalTrials.gov:

- Data should be tracked and reported in accordance with the procedures for data collection as defined in the protocol.
- Adverse Events are reported as summary data at the end of the study
- SAEs and AEs are presented in separate tabular format
- **This is not “real time” adverse event reporting while the study is ongoing**

For additional information on how to submit results for your study, please refer to the site *How to Submit Your Results*, and to the presentation *ClinicalTrials.gov: A Primer on Results Reporting.*

**Common Questions and Answers**

**I just received an email from ClinicalTrials.gov informing me that my record is “In Progress”. What does “In Progress” mean to me?**

NIH identifies the progress of clinical trials registration in stages. “In Progress” means that you are creating (or modifying) the record.

**I just received an email from ClinicalTrials.gov informing me that my record is “Completed”. What does “completed” mean to me?**

NIH identifies the progress of clinical trials registration in stages. “Completed” means you have finished entering the data for this study and the record is now ready for review.
I just received an email from ClinicalTrials.gov informing me that my record is “Approved”. What does “approved” mean to me?

NIH identifies the progress of clinical trials registration in stages. “Approved” means the Responsible Party has reviewed the record and has made any necessary changes.

I just received an email from ClinicalTrials.gov informing me that my record is “Released”. What does “released” mean to me?

NIH identifies the progress of clinical trials registration in stages. “Released” means the Responsible Party has released the record for posting to ClinicalTrials.gov.

Why can I not find my trial in ClinicalTrials.gov?

After a protocol record has been entered (or modified) and marked as ‘Complete’, it must be approved and released by the Responsible Party. From the time the record is approved and released, it normally takes between 2 and 5 working days for ClinicalTrials.gov internal quality assurance review and processing for publication on the ClinicalTrials.gov website. Records that contain Results may take up to 30 days. Please note that during the internal review by ClinicalTrials.gov administrators, comments may be generated that require you to edit your record prior to public release.

When will the "NCT number" for my trial be assigned?

The NCT number is assigned following quality assurance review, just prior to publication on ClinicalTrials.gov (see above). The NCT number then becomes visible in the Protocol Registration System.

Who is the “Oversight Authority” the ClinicalTrials.gov database?

a. If your study involves a drug, biologic or device and/or is conducted under an IND/IDE, the oversight authority should be listed as: United States: Food and Drug Administration.

b. If your study does not fall under the FDA’s purview, the oversight authority should be listed as: United States: Institutional Review Board.

What about collaborators?

List all collaborators applicable to a specific trial. If ClinicalTrials.gov does not have a match for a collaborator in their system, a link to ‘recognize it’ will appear.
I heard that if I register my trial with clinictrials.gov I need to include a specific statement in my informed consent. Is that correct?

Yes, this is correct. If you research meets the criteria for ClinicalTrials.gov registration under FDA regulations (FDAAA) the FDA mandates that the following specific language be included in the consent. This wording cannot be modified:

“ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”

This language is optional for trials other than FDA regulated trials that meet criteria for registration.

What are the consequences if I don’t register a trial that is required under FDAAA or ICMJE?

**FDAAA**
- Public notices of noncompliance and violations
- Withholding of NIH funds
- FDA sanctions
- Civil monetary penalties (up to $10,000/day)

**ICMJE**
- Cannot publish in journals following ICMJE policy, and other select journals

What if my study has already begun and meets the criteria for registering, but I have not registered?

We recommend that you register, however please be aware that it is uncertain whether the FDA or the ICJME will recognize or accept a late registration. To assist you we have now included questions about CliniclaTrial.gov registration on the continuing review forms. The questions will prompt you to consider whether your protocol meets criteria for registration however we will NOT withhold continuing approval until registration is complete. We ask that you voluntarily register.

What is the NIH Public Policy Access?

**NIH Public Policy Access** ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. To help advance science and improve human
health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication.

Is this policy the same as the requirement for registering clinical trials?

NO. These are two separate and unrelated requirements