

Human Subjects Protection Update

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New ClinicalTrials.gov Oversight at Boston Children's

ClinicalTrials.gov is the national registry of federally and privately supported research studies conducted in the United States and around the world. The U.S. National Institutes of Health (NIH), through its National Library of Medicine (NLM), has developed this site in collaboration with the Food and Drug Administration (FDA), as a result of the FDA Modernization Act, which was passed into law in November 1997.

ClinicalTrials.gov was developed as a tool to improve transparency and reduce duplication of effort across the research community. It is also the law and a requirement for publication for many journals.

Current effort at Boston Children's Hospital

We believe it is important to comply with the requirements of clinical trial registration, and to support our researchers in their obligations. BCH has recently added an additional resource to advise and support investigators in registering their clinical trials. Christina McCarthy our Regulatory Affairs specialist will assume a leadership role in assisting investigators. Not all clinical trials need to be registered, and investigators at Children's may not be responsible for registering all trials in which they are participating. However, there are instances where our PIs are responsible for registering clinical research. In these cases when it is determined that a BCH investigator is responsible for registration, a new policy will be implemented in July, that if the BCH investigator is responsible for registration, the IRB will not release IRB approval until the trial has been registered and the registration number included in the IRB application.

The following question and answers provide addition information about ClinicalTrials.gov, what needs to be registered, and how the oversight system will be implemented BCH.

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1. Why is the clinicaltrials.gov oversight system being implemented at BCH at this time?

Registration with Clinicaltrials.gov is not a new requirement. It has been the responsibility of investigators and sponsors to register trials as required. Until now the IRB application has included questions to prompt investigators to register as required, however, there were no resources for oversight assistance. The hospital has hired a regulatory affairs specialist to assist in these responsibilities, therefore we are now able to provide oversight and provide direct assistance. We are aware that over the past few years there have been two investigators who were not able to publish their research in journals of their choice because their trials were not appropriately registered. We now have the ability to implement a new oversight system to help investigators avoid these types of situations.

2. Why do I need to I register my trial?

- A. It's the law.** Most prospective clinical trials involving regulated drugs, biological products, and devices must be registered on ClinicalTrials.gov. The Food and Drug Administration Amendments Act of 2007 (FDAAA or US Public Law 110-85) was passed on September 27, 2007. The law requires mandatory registration and results reporting for certain clinical trials of drugs, biologics, and devices.
- B. You want to publish.** The International Committee of Medical Journal Editors (ICMJE) requires registration in a publicly available, searchable system. ICMJE doesn't require registration in ClinicalTrials.gov, but in any of several international registries, WHO, or European Studies registry. ClinicalTrials.gov is just the most obvious, easy and logical for our researchers, since they may have to post there for government reasons anyway.

New ClinicalTrials.gov Oversight at Boston Children's Hospital Continued

3. What studies need to be registered and is there a timeframe for registration?

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. Here is a summary of both requirements:

- FDAAA requires registration for “**Applicable Clinical Trials**”:
 - Interventional studies (drugs, biologics, devices)
 - Phase 2 – 4 (not phase 1 drug; not small feasibility device)**
 - US FDA jurisdiction (e.g., IND/IDE or US 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)

** The following are also not applicable clinical trials: observational studies; single patient expanded access (treatment IND)

- ICMJE registration is required for prospective studies that:
 - Assign subjects to one or more health related interventions to evaluate the effects on health outcomes
 - 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

4. Who is responsible for registering?

For ICMJE requirements, anyone can register, but the author is responsible for ensuring complete registration.

For FDAAA, the **Responsible Party (RP)** is defined as:

- The IND/IDE holder, OR
- If no IND/IDE:
 - The industry, cooperative group, consortium or other external sponsor that initiated the study, OR
 - If initiated by a principal investigator
 - The grantee institution OR
 - If no external funding, the PI

We recognize that this can get quite confusing. For additional information in assessing who must register a clinical trial, please contact Christina McCarthy at Christina.mccarthy@childrens.harvard.edu or at X4-2777, or visit <http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf> for more information.

New ClinicalTrials.gov Oversight at Boston Children's Hospital Continued

5. I heard that the drug company sponsor will register the trial, how do I know if I am responsible for registering the trial?

If your study meets any of the criteria listed in question 3 it is always a good idea to talk with your collaborators as to who is going to register. In general drug or device companies are responsible if they are the regulatory sponsor and are conducting the trial, however if the study is investigator initiated and you hold the IND you would be responsible. Also in a multicenter consortium trial, the investigator or coordinating center may take responsibility for registration but it is always a good idea to ask. We realize this may not always be clear and if it is not you may contact Christina McCarthy to discuss. The important thing is not to forget to ask the questions and follow through as appropriate.

6. How will submission of my research protocol in CHERP be used in the ClinicalTrials.gov oversight?

Beginning in July, IRB approval for your research study requires information about clinical trial registration. The protocol application will include revised questions to help you determine if the research requires registration. If your research fits the criteria for registration you will need to determine if you are responsible for registration. The protocol application questions are structured to specify who will assume responsibility for registration. If it is determined you are responsible for registration, the IRB will not release final approval until registration is complete and the registration number is listed in the protocol application. We have added an additional ancillary review within CHERP so that the regulatory affairs specialist is automatically notified based on the way you complete the protocol. If there are questions, or the information is incomplete you will be contacted.

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

The following are the consequences of non-compliance:

- **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

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

We recommend that you register, however please be aware that it is uncertain whether the FDA or the ICMJE will recognize or accept a late registration. To assist you we have now included questions about ClinicalTrials.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. If there are any questions you may also contact Christina McCarthy for assistance.

9. I've heard about results reporting. Is that required too?

Yes. FDAAA requires reporting of results and adverse events for a subset of studies. Results reporting is not mandated as part of the ICMJE requirements. **At this time we do not intend to enforce results reporting as a component of IRB review process.**

However, please be aware that you may be obligated by law (FDAAA) to submit results and adverse events on the ClinicalTrials.gov website. If you have registered a study, you must understand whether you have additional result reporting obligations.

Results Reporting Required for:

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

When:

- 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

New ClinicalTrials.Gov Oversight at Boston Children's Hospital Continued...

*Note: The Primary Completion Date may be well before you think the study is over. There may be additional follow-up that continues for years, but ClinicalTrials.gov wants results data submitted within a year of the final data collection for the primary endpoint. **That means getting to work on analysis and reporting quickly.** For help with understanding the results reporting requirement, or for issues with posting results please visit <http://clinicaltrials.gov/ct2/manage-recs/how-report> or contact Christina McCarthy at christina.mccarthy@childrens.harvard.edu or at ext.4-2777.*

10. How do I register my study on the ClinicalTrials.gov website?

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>

Step 1: Obtain an Individual User Account

In order to obtain an account under the Boston Children's Hospital organization, please contact Irine Breytburg at irine.breytburg@childrens.harvard.edu or at ext. 3205.

In order to generate an account, please provide Irine with the following information:

- 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.

Continued on the next page.

11. I heard that if I register my trial with clinicaltrials.gov I need to include a specific statement in my informed consent. Is that correct?

Yes, this is correct. If your research meets the criteria for ClinicalTrials.gov registration under FDA regulations the FDA does mandate that the following specific language be included in the consent. This language is optional for trials other than FDA regulated trials that meet criteria for registration. 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.”

12. Where can I go for more information?

The ClinicalTrials.gov website provides detailed information on how to register trials as well as how to post results. You can find information and FAQs at: <http://clinicaltrials.gov/ct2/manage-recs>

In addition, Christina McCarthy will be presenting a primer on ClinicalTrials.gov registration requirements on the following dates in CLS12: July 16th from 12:30p-2p and July 24th from 11:30a-1p. All are welcome to attend.

Facilitating Protocol Submissions Through CHERP:

1. Using The “Review Status” Tab

Do you want to know the status of whether ancillary reviews are complete for your protocol?

Click on the “Review Status” tab below the study dashboard to locate detailed information about ancillary review (AR) status (whether an AR is outstanding, if a review must be complete to obtain final IRB approval), Scientific Review and Department review Contacts, and detailed statistics about the initial new study review process.

The screenshot shows the 'Review Status' tab selected in the dashboard. A red arrow points to the 'Review Status' tab. Below the tab, there are sections for Scientific Review Coordinators, Primary Department Reviewers, Assigned Department Reviewer, and Ancillary Review. The Ancillary Review section contains a table with columns for Ancillary Review, Review Received, and Last Notified Date. Below this is a 'Review Statistics' section with a table showing various review stages and their durations.

Ancillary Review	Review Received	Last Notified Date
CTD		1/25/2014 8:43 AM
Drug Device	2/9/2014 7:41 PM	1/25/2014 8:43 AM
Laser Committee	2/18/2014 10:15 AM	1/25/2014 8:43 AM

Review Statistics:	Date Entered State	Date Exited State	Time Spent in State
Draft	11/7/2013 9:37 AM	11/11/2013 8:51 AM	95 hours 14 minutes 34 seconds
Scientific Review	11/11/2013 9:51 AM	12/3/2013 2:42 PM	533 hours 51 minutes 11 seconds
Draft	12/3/2013 2:42 PM	12/13/2013 11:02 AM	238 hours 19 minutes 38 seconds
Dept-Div Review	12/13/2013 11:02 AM	12/13/2013 11:15 AM	12 minutes 51 seconds
Analyst Review	12/13/2013 11:15 AM	12/18/2013 1:12 PM	73 hours 57 minutes 28 seconds
Analyst Review Feedback	12/18/2013 1:12 PM	1/23/2014 9:57 AM	908 hours 45 minutes 3 seconds
Analyst Review	1/23/2014 9:57 AM	1/25/2014 8:43 AM	46 hours 45 minutes 21 seconds
Assigned to Meeting	1/25/2014 8:43 AM	2/18/2014 1:56 PM	389 hours 12 minutes 58 seconds
Post Review	2/18/2014 1:56 PM	2/14/2014 4:23 PM	98 hours 27 minutes 42 seconds
Report of Action Review	2/14/2014 4:23 PM	2/19/2014 8:39 AM	112 hours 15 minutes 53 seconds
Post Review	2/19/2014 8:39 AM	2/19/2014 2:53 PM	6 hours 13 minutes 24 seconds
Full Review Feedback	2/19/2014 2:53 PM	2/25/2014 4:24 PM	145 hours 30 minutes 52 seconds
Follow-up Review	2/25/2014 4:24 PM	2/26/2014 1:03 PM	20 hours 39 minutes 39 seconds
Assigned to Meeting	2/26/2014 1:03 PM	3/18/2014 2:45 PM	288 hours 41 minutes 29 seconds
Post Review	3/18/2014 2:45 PM	3/13/2014 3:08 PM	72 hours 23 minutes 17 seconds
Report of Action Review	3/13/2014 3:08 PM	3/14/2014 9:36 AM	18 hours 28 minutes 4 seconds
Post Review	3/14/2014 9:36 AM	3/14/2014 2:56 PM	5 hours 19 minutes 54 seconds
Full Review Feedback	3/14/2014 2:56 PM	3/20/2014 9:15 AM	138 hours 19 minutes 24 seconds
Follow-up Review	3/20/2014 9:15 AM		4 hours 59 minutes 2 seconds

2. How to Use a Reportable Event Form.

When do you need to submit a Reportable Event Form?

Researchers should create and submit a CHERP “Reportable Event” form to notify the IRB about problems with study conduct that meet the IRB 72-hour [Unanticipated Problem reporting criteria](#). Once the form is created, there will be prompts to identify the type of Unanticipated Problem (see categories 1.1 to 1.13 on Form), and then provide additional information about the nature of the problem, how it has been addressed, and what affect it may or has had on subjects enrolled in the study. See CCI/IRB Guidance titled [Unanticipated Problems Involving Risks to Research Subjects And Others Including Adverse Events](#) or contact the IRB with questions about submitting a Reportable Event or about the

3. Submitting Data and Safety monitoring Board Reports.

A Tip to Prevent Delays in the Annual Continuing Review and Approval Process

Does your study have a data and safety monitoring board (DSMB)? How often does the DSMB meet? As part of the continuing renewal process, the IRB is responsible for reviewing DSMB meeting updates. It is important to either include these updates, or provide a reason why none are available, if otherwise expected according to the approved DSM plan for the study. DSMB updates may be formal minutes, or a simple email from the DSMB. The “Data and Safety Monitoring” section of the CHERP continuing renewal SmartForm includes a prompt to attach any new DSM updates, as well as a link to the study’s approved DSM plan for easy reference.

4. Adding Non-BCH Employees to Protocols

Things to Keep in Mind when adding non-BCH Employees to Research Studies

Non-BCH profiles should not be created for research team members who are waiting for their BCH ID numbers and login accounts. If a study team member is a new hire and will be a BCH employee, a BCH CHERP profile must be created for that person. That person is able to complete CITI training while waiting.

Non-BCH collaborators **do not** need to be added to protocols when he/she is only receiving or reviewing completely de-identified data.

When adding a non-BCH employee to a research team, please include a description of that person’s role in the study. Depending on the research activities that this person will be performing, he or she might be considered “engaged in the research.” In that event, the IRB at that person’s home institution will either need to review the protocol or agree to rely on the BCH IRB review. Please contact your department’s IRB Administrator with additional questions about this.

Welcome Meghan Cashman!

[Meghan Cashman](#) has recently joined us as an IRB Administrator. She joins us from St. Elizabeth’s where she served as IRB Administrator for seven years. Meghan is a painter and has an MFA in Visual Arts from Boston University. She loves to travel and spending time at Salisbury Beach. Meghan’s number is (857) 218-4022.

She will be handling the following departments:

Emergency Medicine	Nursing	Psychiatry
Endocrinology	Orthopaedic Surgery	
Hematology/Oncology	Urology	



Please join us in welcoming Meghan to Boston Children’s!

Memo-to-File: from the EQuIP Office

The following are a few **Best Practices** identified during recent EQuIP Study Reviews*:

Use the Informed Consent Library to access current consent documents:

One of the most common deviations noted during study reviews is when subjects sign expired, superseded, or unstamped consent documents. The most effective way to prevent this type of consent deviation is to use the CHERP [Informed Consent Library](#) to access the most current IRB-approved and stamped consent forms every time the research team prepares to consent a new subject. Ensure all study team members are trained to verify the correct consent version and to use the [Informed Consent Library](#).

Track and Report Minor Protocol Deviations according to CCI/IRB policy:

Protocol deviations are considered unintentional events that depart from the approved protocol and are identified retrospectively. [Per CCI / IRB Policy](#), Investigators should promptly review identified deviations and assess whether minor or significant. Significant deviations require reporting to the IRB within 72 hours of awareness using the CHERP "Reportable Event" smartform. All other deviations should be documented, and reported in aggregate at the time of continuing review. How minor deviations are tracked/documented will depend on the type of research and what is most efficient and effective for the study team. Sample [Deviation Logs](#) are provided on the [EQuIP website](#). Investigators can also choose to create individual Memos to File, or include a descriptive column that can be abstracted from a larger study activity database to meet this requirement.

Follow the Study-Specific, IRB-approved Recruitment and Consent /Assent Processes:

There are many recruitment methods and materials a research team may use to reach out to potential subjects, such as mailings or scripted phone calls to eligible patients/families, posting flyers in specific locations, and placing advertisements in specific media. However, recruitment processes must be selected as appropriate for each study and IRB-approved prior to use. Likewise, methods for obtaining informed consent/assent can vary (e.g. in-person, phone and/or via mail, fax or email) and must be IRB-approved prior to use. Make sure everyone on your study team employs only IRB-approved methods and materials for both recruitment and consent processes by verifying what is described in the IRB-approved protocol and corresponding CHERP smartform sections.

* A confidential, full or partial review of on-going studies to ensure compliance with applicable regulations and policies and to evaluate study conduct, organization, record-keeping and documentation. The EQuIP office aims to help investigators implement tools and strategies to improve identified problem areas. Reviews may be voluntarily requested by PI/staff (e.g. to ensure compliance, during staff changes, to prepare for an external audit).

Visit the [EQuIP website](#) for more information and resource or call Eunice Newbert or Susie Corl at the EQuIP

Struggling with CHERP?

IRB Administrators are available to provide CHERP Refresher training for your department. This can include some tips and tricks that IRB Administrators have noticed may be helpful, or you can provide specific questions for staff to answer. We are available to provide training for larger groups, but CHERP Support remains available for individual questions. Please contact your department's IRB Administrator for scheduling, if you would like to request this training.

Clinical Research Center (CRC) Services

The **Clinical Research Center (CRC)** at Boston Children's Hospital is an interdisciplinary, academic and service research center that provides assistance and education to the clinical research community at Children's.

The CRC provides the following services:

- study design, power/sample size calculations, analysis approach, data management methods
- design case report forms/survey instruments, study manual of operations, randomization methods and lists
- project management and study coordination
- data set organization/analysis file creation, statistical analyses, interpretation of results,
- contribute to manuscripts/abstracts/presentations
- protocol design and implementation
- nursing, nutrition and specimen processing
- consultation for studies that have behavioral outcomes, psychometrician services

To request a free one-hour consult or request services, click <http://www.childrenshospital.org/research-and-innovation/research-centers/clinical-research-center>



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The [Office of Clinical Investigation](#) has been established to oversee the protection of human research subjects at Boston Children's Hospital. Children's is committed to safeguard the rights and welfare of all children, adolescents, adults and family members who volunteer to participate in research. To this end, the Office of Clinical Investigation upholds the principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research, as the cornerstone of our mission, organization and daily activities.

- Have questions or comments about any of the articles in this newsletter?
- Need advice about your research?
- Want to know more about human subjects protection at BCH?

Please don't hesitate to contact the CCI and one of our staff will be happy to assist you.