

CONTACT US:

2 Avenue Louis Pasteur
Suite 415
Boston, MA 02115
Tel: 617-355-7052
Fax: 617-730-0226

Human Subjects Protection Update Children's Hospital, Boston

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COMMITTEE ON CLINICAL INVESTIGATION

www.childrenshospital.org/research/irb

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CCRP*

[International Research: Avoid Non Compliance Important Consideration for Researchers](#)

The Committee on Clinical Investigation recognizes that the Children's Hospital Boston research community is conducting an increasing amount of research in international settings. It is incumbent upon all researchers to ensure that the cultural considerations of the host country/community are respected. This is partially accomplished by a requirement of local IRB review in addition to review by Children's Hospital.

Unfortunately the IRB has recently addressed two cases of serious noncompliance because investigators did not obtain local IRB approval before proceeding with research at the local site. The errors partially arose from failure to understand the challenges of conducting research abroad. Children's has previously established a policy that was developed to make clear what IRB requirements exist for such research:

http://childrenshospital.org/cfapps/research/data_admin/Site2206/Documents/cipp_081_024_International_Research_policy.doc

We now want to share with you some practical tips and key points to remember in planning a successful international research project

1. **Start early.**
2. **Expect delays.**
3. **Don't ever assume final approval is granted.**
4. **Communication is key.**
5. **Stay organized.**

Start Early.

CCI policy always requires local IRB review for any project that CHB investigators are conducting or supporting abroad. Investigators need to identify a local IRB to conduct review in addition to the Children's Hospital IRB. In cases where federal funds will support international research, the local IRB will also need assurance agreements in place with HHS. This will also take additional time if an assurance has not already been obtained. Obtaining IRB approval for an international research project takes additional time because the research is subject to approval from both the Children's Hospital IRB and the local IRB. The Children's Hospital IRB will require evidence of local review before releasing IRB approval. The Children's IRB has no influence over the local boards and they often require more time for review than here at Children's.

Plan ahead and start early when conducting international research.

Expect delays.

The path to IRB approval can take longer than expected. Some local international IRBs meet very infrequently and require applications to be submitted well in advance of the review. This is especially true in resource poor countries with little existing research infrastructure. Additionally, some local IRBs require full board review of all protocols. Others won't even accept your application without a letter that IRB review is complete at Children's Hospital.

In addition to determining the necessary and appropriate local reviews, the CHB IRB may want to consult with additional expertise on matters such as cultural context of the study performance sites as well as local laws applicable to the jurisdiction for research under review. Additional time must also be provided for translation of consent materials and other documents (IRB approvals, recruitment materials, etc.) into English so that the CHB IRB can review them.

Learn about the local requirements and timing for IRB review so you can try to accommodate potential delays.

Don't ever assume final approval is granted.

Your project cannot begin until you have received the formal, written documentation of final approval from all applicable IRBs. We also caution investigators not to purchase airfare or make travel or other date-specific arrangements until they have final IRB approval. We recognize that purchasing airfare, renting space and equipment on the ground and hiring local staff well in advance of travel dates can save money and time, however without final IRB approval from both sites you cannot perform your research.

Do not make travel arrangements on the basis of an expected IRB approval date.

Communication is Key.

Investigators are responsible for ensuring that study teams are up-to-date with regard to the protocol's status especially for studies conducted in multiple locations. International research often involves collaborators and research team members at the local site. This makes communication about IRB review and your research protocol essential. If you are the PI, it is your responsibility to make sure that there is a well understood line of communication at the local site. You are also responsible for ensuring compliance with IRB regulations, ensuring that the protocol is followed, promptly reporting adverse events, and staying abreast of changes to the study. While this can be a challenge due to time differences and language barriers, there are several tools (video-conferencing, email, secure file-sharing services) that can be used to make sure that everyone is on the same page, working from the same version of protocol and consents, and aware of key events such as IRB approvals for amendments.

Develop a clear written communication/ responsibility process for entire research team both locally and internationally

Stay Organized.

Managing a study at multiple sites, in multiple languages, making sure all the necessary approvals are in place, and making sure that all sites are working from the correct and current protocols and consent forms means that organization is very important. We recommend that you use checklists and study binders to stay on top of the paperwork and requirements so that nothing slips through. The EQulP website has some tools and templates that you can use for help with this aspect of study management. You may also contact the EQulP office for assistance in setting up clear written communication and responsibility plans.

The two recent incidents of noncompliance were unfortunate and could have been easily prevented. We hope that this information will assist other investigators in avoiding the same problems. Please feel free to contact the IRB office anytime you need assistance or have questions about international research.

New FDA Regulation for Informed Consents Regarding ClinicalTrials.gov

We would like to call to your attention a new FDA regulation (effective March 7, 2012) that requires 'applicable clinical trials' to include the following statement (exactly as stated,) in informed consent documents 'initiated' on or after March 7, 2012:

- "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at anytime."

This FDA regulation applies to all clinical trials that meet both of the following criteria:

1. Initiated on or after March 7, 2012

(the 'initiation' date refers to the Activation/Release Date on the final approval letter and the Activation Date documented in the footer of approved informed consents; please note this only applies to the initial study review of 'applicable clinical trials') **and**

2. Meet the criteria for registration on ClinicalTrials.gov

(these are "applicable clinical trials" as defined below)

This FDA regulation will not be applied retroactively. Therefore, informed consent documents with an Activation/Release date before March 7, 2012, do not need to be amended to include the required statement, and subjects do not need to be re-consented.

"Applicable clinical trials" are studies that meet the criteria for registration on ClinicalTrials.gov and defined as: controlled interventional trials (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation. This means that the trial has one or more sites in the US, involves a drug or biologic or device manufactured in the US or is

conducted under an IND or IDE.

A trial is an “applicable clinical device trial” if:

- the trial prospectively compares a device-based intervention subject to FDA regulation against a control in human subjects, OR
- the trial is a pediatric post-market surveillance trial

A trial is an “applicable clinical drug trial” if:

- the trial is a controlled clinical investigation other than phase 1 of a drug subject to FDA regulation

The IRB staff will take steps to help investigators apply this regulation as necessary. The required wording will be added to the English Informed Consent Template, and the CHERP Smart Form will be updated to include questions about ClinicalTrials.gov registration.

For “applicable clinical trials” currently in CHERP and undergoing initial IRB review, but not likely to receive IRB final before March 7, 2012 investigators are advised to amend their consent documents to include the required statement. The CCI/IRB staff will make every effort to remind investigators when this is necessary, however it is ultimately the responsibility of the investigator and sponsor to assure this language is included when applicable.

Frequently Asked Questions (FAQs):

Q. My study received initial conditional approval before March 7, 2012, and meets the FDA definition of an applicable clinical trial. Will the new wording still be required?

A. *It depends on the Activation/Release date for the consent. If the Activation/Release date is on or after March 7, 2012, the consent form will need to be revised to include the required wording.*

Q. My study received CCI final approval before March 7, 2012, and is registered on clinicaltrials.gov, but my consent document does not include the required wording. Do I need to submit an amendment?

A. *The FDA is not retroactively applying this requirement. If you wish, you may submit an amendment to add the language to the approved consent document.*

Q. My study received CCI final approval before March 7, 2011, and is registered on clinicaltrials.gov. When this is submitted for continuing review do I need to add this statement?

A. *No you are not required to add this statement. This requirement only applies to trials that were initiated after March 7, 2012. The initiation date is the Activation/Release date on your IRB approval letter and in the footer of approved consent documents.*

Q. My study already has CCI final approval, meets the FDA definition of a clinical trial, but is not registered at clinicaltrials.gov and the consent document does not include the required language. Am I required to register the study and include the language in the consent?

A. *You will not be required to add the language to your consent because the requirement is not retroactive. The study is required to be registered at clinicaltrials.gov. See the CCI Guidelines referenced below for information about registration.*

Q. Where do I include this statement?

A. *The regulations do not mandate where this statement appears. We are recommending that it be added right before the Consent/Authorization section at the end of the document.*

Q. My research is registered in clinical trials.gov although it does not meet the FDA definition of an

applicable trial. Do I need to include this language?

A. Under the FDA regulations you are not required to include this language, however if you feel this is information that may be useful for the research subjects, you may voluntarily include it. Please do NOT accidentally include this information if your trial is not registered, as this will certainly confuse research subjects who choose to search clinicaltrials.gov and cannot find the trial.

Reminder: Pharmacy Requirement for Dispensing Investigational Drug

As of February 1, 2012 for any new subject enrolled in a drug protocol, the pharmacy will verify in CHERP that consent was obtained prior to dispensing the drug. CHERP has been modified so that investigators and research team members can insert the required information for each subject. When you select a CHERP protocol, you will see a new activity titled "Enroll a Patient" on the left column. Once you select that activity you will be asked to enter subject information which includes, name, medical record number and date of birth (or any combination). A list of matching patients from the hospital's medical records database will appear. You will select the correct patient and enter the date the consent was signed. There is also a section where you can upload a scanned signed informed consent but this is not required. Subjects enrolled prior to February 1 will be "grandfathered" so you do not need to enter their consent information, however it is strongly recommended.

There is a detailed "How Do I" document with text and screen shots.

<http://chbshare.chboston.org/elibrary/isd/educate/cherp/cherp/How%20Do%20I%20Enroll%20a%20Patient%20into%20a%20Study%20in%20CHeRP.doc>. I

A question and answer information sheet may be found at

http://childrenshospital.org/cfapps/research/data_admin/Site2206/Documents/NewsletterJan2012.pdf

Welcome Susie Corl

We are pleased to announce the addition of Susan Corl to the EQUIP Office at Children's Hospital. Susan "Susie" Corl recently relocated from San Francisco, CA where she spent the past 5 years working in research quality assurance and Institutional Review Board (IRB) administration at the University of California, San Francisco Human Research Protection Program (HRPP). Before that she worked at the University of California, Los Angeles Office of the Human Research Protection Program as an IRB Administrator. Susie is originally from the Boston area, and received her BA from the University of Richmond, Virginia, and her MSW and MPH degrees at Boston University. Susie will be working with Eunice Newbert to further the efforts in education and quality improvement in our human subject protection program.