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THE SABAN RESEARCH INSTITUTE

Basics of Ceded IRB Review

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Introduction

First, an apology.

I would like to tell you that I've put together a brilliant, arresting presentation that will keep you glued to your screen for the next hour, but alas I cannot.

There is no two ways about, ceded review is a complicated process and there is no shortcut to understanding it.

Even in HSPP staff meetings, there is an audible groan when it comes time to discuss ceded review.

We're going to start at the very beginning of not just ceded, but IRB review in general.

Introduction

As I was putting together this presentation, I was overwhelmed by how complex this process is, by how many variables are in play. Wide-spread implementation is still new enough that processes are constantly evolving, and it's not intuitive, particularly if you are not versed in the underlying principles of IRB review to start with.

I would like to tell you that I can give you every piece of information you will need to be an expert in ceded review in the next hour, but I outlined presentation in preparations for this one and it was close to 100 slides. I think we could probably spend 2 or even 3 hours here and not cover everything.

Instead, this will be the first of two presentations on the subject. I'm going to give you a high-level overview of the process along with much of the background information that will hopefully help you understand why things are the way that they are.

Introduction

My college Deebra Smith will be giving a second presentation in June that will focus more on the intricacies of CHLA's submission processes.

Some of this will be review for some of you, however there are people entering this discussion from a variety of starting points and it is important to define terms and provide the necessary background so that we all have foundational knowledge on which to build.

Many of the mistakes we see in the details of study submissions come from a failure to grasp the process as a whole.

My hope is that by laying out this information for you, you will be able to synthesize it to new situations as they arise.

So, buckle up, this is a long, densely-packed presentation. Please feel free to stop me if you questions along the way.

IRBs in the beginning…

We'll start with a brief review of Human Subject Protect as it relates to ceded review

You've all taken the CITI Human Subject Protection Course.

My hope is that you have a vague recollection of some of the serious lapses in research ethics that made IRBs and Human Subject Protection Programs necessary.

IRBs in the beginning…

Research like:

- Nazi research in concentration camps
- Tuskegee Syphilis Study
- Willowbrook Hepatitis Trials
- Stanford Prison Experiment
- Milgram Obedience Experiment
- Project MKUltra
- Numerous radiation and cancer experiments

IRBs in the beginning…

We all work in research, so the value of medical research should be obvious to us, but these studies make it equally clear, that oversight and review is necessary to prevent abuse.

Throughout the 1950's, 60's, and 70's, a series of laws were passed by congress to establish institutional review boards to review and approve research as a requirement for any institution receiving federal funding for research (think NIH).

IRBs in the beginning…

An IRB is an independent committee comprised of

- Doctors
- Scientists
- Administrators
- Community members
- Lay people

They meet periodically to review the ethics of proposed research studies.

The HSPP and our administrators help to facilitate this review by making sure everything the committee needs for its review is present in the application before they get started.

This is the point where most of you come in. You are who we're asking for that additional information to aid in their review.

IRBs Historically Speaking

For the first 20 years of IRBs, the vast majority of IRB review took place locally.

That means that if Dr. Jones at CHLA had an idea for a research study, he or she would submit an application to the CHLA IRB to review and approve their research.

This era was easy to understand. You work at CHLA or USC, they are your IRB. End of story.

The Evolution of IRB Review

In the late 1990's this model started to evolve in response to complex multi-center trials.

Under the old model, if the NIH selects 5 centers to conduct a new drug trial, 5 PIs submit 5 IRB applications to 5 IRBs, who do 5 separate, local, reviews, often identifying different problems at each site.

There are certain obvious inefficiencies in this model.

What is Central IRB Review?

After a long introduction, we arrive at the question that brought you here today.

In response to the complexity and inconsistency of local review for multi-center trials, someone got the idea of centralized IRB review.

Instead of 5 separate IRB reviews, one IRB collects as much information from the local sites as possible and then does a single IRB review for all sites.

All the other IRBs CEDE their review responsibilities to a single IRB. That's where the term comes from and with a few exceptions, that one IRB make all the necessary regulatory determinations for a study and shares those with all the sites.

In theory this cuts down on redundancy and increases efficiency. Why do something 5 or 10 times when you could just do it once?

Example of single IRB review

The HIV Vaccine Trials Network or HVTN is a large, on-going, NIH-funded, multi-center initiative based at the Fred Hutchinson Cancer Research Center in Seattle, WA.

It's been going on for more than 20 years, has reviewed more than 100 clinical trials for more than 70 study sites.

The COG CIRB is another example of a long-established single IRB review arrangement, where they review all studies for the Children's Oncology Group. It reviews studies for over 40 sites in the US, Canada, and Australia.

The NIH SIRB Mandate

With these types of arrangements in mind, in January of 2018 the NIH introduced a mandate requiring all new or competitively renewing NIH funded multi-center studies to utilize a single IRB model.

This forced IRBs and research institutions all over the United States to embrace the single IRB model on a wide variety of studies.

Nearly four years later, the research community is still struggling to establish best practices for the model.

The NIH SIRB Mandate

A couple slides ago, I said this single IRB review was more efficient in theory, because although the number of IRB reviews is obviously reduced, the unintended consequence of this new mandate was a dramatic increase in administrative tasks associated with single IRB review.

We now spend less time worrying about the risks of studies, but more time reminding people to upload the correct document to the application.

For example, in the old days we knew exactly what research was taking place a CHLA because we had reviewed and approved all of it. Under the new mandate, we had to work out new methods to track research.

We also had to figure out how best to communicate state, local, and institutional requirements to distant IRBs that couldn't be expected to be familiar with them, so they could take them into account for their reviews.

The NIH SIRB Mandate

There is also an issue of trust involved.

I worked at three IRBs over the past 14 years and I've working indirectly with hundreds over that time.

Every IRB I've ever worked with is convinced they're the only one that knows what they're doing.

It's hard to trust another IRB to do a good review, particularly when you know they won't be doing it exactly like you would.

It's even harder when you're a children's hospital because research involving children requires special care.

The NIH SIRB Mandate

We've seen refinement of the processes over the past four years.

Therefore, if you have an application that was approved a few years ago, it's likely that your administrator will request some changes to clean-up documentation in that existing application the next time you submit an amendment.

Improvements acknowledged, anyone who has submitted a ceded review application can attest to the fact that there are still quite a few bugs in the system to be worked out.

Who reviews what?

Who should be reviewing the study and why is one of the trickier questions faced by study teams and PIs in this brave new world.

The main options are:

- Local IRB (e.g. CHLA or possibly USC)
- Collaborating institution (UCLA, Seattle Children's Hospital)
- Independent IRBs (WCG, Advarra, etc.)

Who reviews what?

Some of the questions we'll need to ask in order to help you make this decision are:

- Who is funding the study? (unfunded, NIH, industry, etc.)
- What are the procedures and risks of the study?
- Where will the study be conducted?
- How many sites are there?
- Will all the sites be using the same protocol?

These are the decision points that help us determine what type of review is required and therefore who should be conducting that review.

Who reviews what?

For example, if the research is unfunded, there might not be the resources, or it may not make sense logistically to commit to single IRB review for a multi-center study without the NIH mandate forcing it.

Similarly, if the research is a chart review study, the administrative burden of single IRB review is likely greater than pursuing local IRB review across several sites.

This is knowledge that we don't expect you to have. You can come to the HSPP with these questions, and we will help to direct you towards the best review path for your study.

Who reviews what? – Local Review

If you (or your PI) are the recipient of an NIH grant for a multi-center trial, it's possible that CHLA may serve as the IRB of record for all study sites.

If you find yourself in this position, reach out to the IRB Director as soon as possible to discuss your options.

Due to the administrative burden of reviewing the research for all the study sites, we need to discuss if the resources are available at CHLA to conduct the review and if not, what your other options may be.

If you are considering a project like this, it's best to consult with the HSPP Director before submitting your grant application because we want to make the proposed budget reflect the necessary review costs. Failing to do so can leave you with very few options down the road.

Who reviews what? – Local Review

If we agree to serve as the single IRB for the study, this means we will:

Sign reliance agreements with each site to allow them the rely or cede IRB review to CHLA.

Gather local context information about unique conditions, requirements, and consent language for each site.

Use that information to generate consent forms and possibly recruitment materials for each site.

We will then review and approve that information and return the documents to you, the study team, to disseminate to other sites.

Who reviews what? – Local Review

We also review all amendments for those sites

And as necessary conduct annual continuing review. Documentation of which will also need to be disseminated to all participating sites annually.

Finally, we review all reportable events for the study. Even those that take place at other sites should be submitted to us as we are serving as the IRB for all sites.

Who reviews what? – Collaborating Institution

This is where a collaborator at another institution approaches an investigator at CHLA to participate in a study they're organizing. Their IRB will serve as the IRB of record for the study, so they will be reviewing for all study sites. This means the research they're doing, the research taking place at CHLA, as well as the research taking place at any other study sites.

The CHLA IRB will sign an agreement to cede IRB review to this institution.

They will review all of the consent forms, recruitment materials, etc. and approve them for distribution to sites.

Otherwise, this review happens similarly to local review, the biggest difference is that the review takes place somewhere else.

Who reviews what? – Collaborating Institution

We have numerous arrangements of this sort with institutions such as:

- CIRB
- Johns Hopkins
- University of Utah
- University of Michigan
- Seattle Children's Hospital

Who reviews what? – Collaborating Institution

The requirements in this instance are similar to the previously discussed local review, but roles are reversed.

Instead of CHLA serving as the IRB of record, we cede review to the other institution.

A reliance agreement is still required. Some institutions require an individual reliance agreement with CHLA that lays out the responsibilities of each institution in detail, however, most are now signatories to the SMART IRB.

A Brief Note about SMART IRB

SMART IRB is a confusingly named, but useful tool to facilitate single IRB and ceded review.

Rather than an IRB, as the name suggests it's actually a platform for managing IRB reliance agreements.

Before SMART IRB, almost all reliance agreements were study specific. When you wanted to start a new project, you had establish a reliance agreement with each of the other sites. This meant that the legal teams from both sites engage in negotiations about all of the minutiae of ceded review. The process took months, during which time the research was completely stalled.

A Brief Note about SMART IRB

SMART IRB introduced a single, universal agreement which hundreds of institutions around the country have signed on to eliminating the need for the laborious negotiations for each study.

Instead, now you can visit the SMART IRB website and if the institution you want to collaborate with is listed as a signatory, the universal agreement can be used.

The website also has agreements that can be printed out for documentation and while the documentation for each site is inconsistent as this time, it's possible to include things like local context information to further facilitate the ceded review process.

The site has gotten increasingly useful in the past years, and I expect it will continue to do so in the future.

Who reviews what? – Collaborating Institution

Circling back to collaborating institutions, when CHLA is ceding review to another IRB, we ask that you submit a ceded review application in iStar **before** submitting to the IRB of record.

The following documents should be submitted in that application:

- Protocol (does not need to be approved/final version)
- Reviewing IRBs approval letter(s)
- Reviewing IRBs consent and assent template(s)
- CHLA Site Specific Consent, Assent, and Addendum Forms (as applicable)
- CHLA Site Specific Documents (e.g. recruitment materials)

Who reviews what? – Collaborating Institution

We will review this application and the documents, let you know of any changes that need to be made and finally clear the application.

Then you will submit the documents that we cleared to the IRB of record, who will approve them.

Once you get the approved (hopefully stamped) documents back from the IRB of record, you will submit an amendment application for clearance to get the consents into EnCore.

Then you're ready to enroll.

Who reviews what? – Collaborating Institution

Once the study is fully cleared at CHLA we ask you submit the following amendments:

- Study personnel amendments
- Protocol amendment approved by the IRB of record
- Consent amendment approved by the IRB of record

We don't need to see:

- Changes to recruitment materials (unless they are specific to CHLA)
- Case report forms or other study instruments
- Reportable Events –
  - If an RE happens at CHLA, the study team should submit it to the IRB of record for review.
  - If an RE happens at another site and the IRB of record forwards the report to you. Keep it for your study records, but do not submit it in iStar

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

The last common option for ceded review is independent IRBs.

As the single IRB review model has become more prominent over the last couple decades, it has given rise to a new type of IRB. Unlike the IRBs of old that were associated with research institutions like the one we have here at CHLA, the likes of WCG and Advarra are independent, for-profit IRBs.

They don't do any research themselves. All they do is review studies. This focused approach allows them to do some things that aren't feasible at an institution such as CHLA, where research is only one of our many jobs which must be balanced against other priorities such as delivering top-flight patient care.

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

For example, as you likely know, CHLA's IRB meets once a week. Given the size of our institution, staffing levels, and the clinical responsibilities of our reviewers, once a week is a good fit for us.

WCG and Advarra can have daily even sometimes twice daily IRB meetings.

This arrangement has some clear advantages but, the disadvantages are a little less obvious.

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

The first disadvantage is cost. When the CHLA IRB reviews a research study, the cost to the study is little or often nothing. As an institution committed to research, the cost of review research is largely borne by the institution itself.

The cost model employed by independent IRB's such as WCG and Advarra mean that their services are often only available to industry-sponsored clinical trials when the sponsor can foot the bill.

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

I'm sure many of you have already observed one of the other major disadvantages in action. Independent IRBs don't posses the intimate knowledge of local laws, practices, and requirements.

For example, California state law requires that subjects sign a discrete research HIPAA authorization that is not a part of the consent form. This is a unique, California requirement and while we've written it into our contract with these IRBs, it is still implemented incorrectly on a regular basis.

When it ends up in the consent, we have to send it back and have it removed.

This doesn't happen with local CHLA review.

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

Similar to collaborating institutions, when CHLA is ceding review to an independent IRB, we ask that you submit a ceded review application in iStar **before** submitting to the IRB of record.

The following documents should be submitted in that application:

- Approved Protocol (required)
- Key information summary for main study ICFs (if no concise summary is in the main study consent template) (if applicable).
- CHLA Conflict Management Plan (CMP) (if applicable)
- Financial Conflict of Interest Consent/Recruitment statement (if applicable)
- CHLA Site Specific Recruitment and Subject Materials (if applicable)

Who reviews what? – Independent IRBs (WCG, Advarra, etc.)

We will review this application to ensure all documentation is correct, let you know of any changes that need to be made and finally we will clear the application.

Then you will submit the documents that we cleared to the IRB of record, who will approve them.

Once you get the approved consents back from WCG or Advarra, you will submit an amendment for clearance with

- Central IRB Approval/Certificate of Action letter(s)
- Central IRB approved CHLA consent and assent forms and site-specific recruitment and subject materials
- Updated and approved sponsor protocol

Then you are ready to enroll.

Who reviews what? – Collaborating Institution

Once the study is fully cleared at CHLA we ask you submit the following amendments:

- Study personnel amendments
- Approved protocol amendments
- Approved consent amendment

We don't need to see:

- Changes to recruitment materials (unless they are specific to CHLA)
- Case report forms or other study insturments
- Reportable Events –
  - If an RE happens at CHLA, the study team should submit it to the IRB of record for review.

Conclusion

With that we've reached then end of our (not so) brief overview of ceded review.

Deebra Smith's June presentation with focus on the details of each submission type including the resources and checklists that are applicable to each.

In the meantime, all the resources for ceded review (and all other review types) are available on the HSPP website and we are always available to answer your questions.