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So You Think Your Grant May Be Funded, Now What?
Tips for Efficient IRB Human Subjects Review and Approval

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Understanding IRB requirements

1. What is the IRB's mandate?
2. What is not in the IRB's mandate?
3. What types of studies require IRB approval?
4. What is the basis for IRB approval or continuation of a study?
5. What are the Investigator's responsibilities to the IRB?
6. What is the IRB looking for as it reviews a new research protocol?
7. What is the IRB looking for in an application for renewal of IRB approval?
8. What are Unanticipated Problems (UPs)? Do they include AEs and SAEs?
9. What is the relationship between the IRB and a trial DSMB (Data and Safety Monitoring Board)?
10. What is a Central IRB?

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1 What is the IRB's mandate?

The IRB's primary responsibility is <u>to protect human subjects</u>, and to ensure that all human research studies conducted at an institution are carried out ethically and in a manner that promotes the protection of participants in the research.

This is accomplished in part by reviewing <u>four types of submissions from Investigators</u>

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The 4 types of Investigator submissions

i) **initial Protocol review** for new studies

ii) **continuing renewal** for ongoing studies

iii) **modifications** to already approved protocols

iv) **reports of Unanticipated Problems** (UPs) that arise during studies

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Source of the IRB's mandate

The IRB operates under regulations of the US DHHS (specifically OHRP) and FDA.

DHHS: The US Department of Health and Human Services
OHRP: The Office for Human Subjects Protection of the DHHS
FDA: The US Food and Drug Administration

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2 What is not in the IRB's mandate?

- **It is not the IRB's mandate to protect the university or the investigators from litigation, or any other type of danger or harm.**

  Yes, by protecting human subjects, the IRB does protect the university and investigators from litigation to a degree. But that is not its formal mandate.

- **Minutes of all IRB meetings are forwarded to institutional officials (IOs). If the IRB sees warning signs that a protocol is approvable from the IRB standpoint but not a good idea for the institution, it alerts IOs at that point. Follow-up is the responsibility of the IOs, not the IRB.**

- **An institution may disapprove a study the IRB approves. However, an institution may not approve a study the IRB has disapproved.**

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3 What types of studies require IRB approval?

All studies involving human subjects which

> **i) meet the definition of research and human subject as outlined in the appropriate regulations and institutional policies**
>
> > *DHHS regulations apply to all federally funded research with human subjects.*
> > *FDA regulations apply to clinical investigations with human subjects that involve FDA-regulated drugs, devices, and biologics.*

OR

> **ii) are related to an investigational drug or have the purpose of getting FDA approval for marketing a drug or device.**

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4   Basis for IRB approval or continuation of a study

DHHS policies incorporating 7 criteria and 3 ethical principles (beneficence, justice, and respect for persons):

1. Minimize risk to human subjects (beneficence)
2. Ensure risk to subjects is reasonable and in proportion to the expected benefit (beneficence)
3. Ensure subject selection is equitable – no one group should be targeted for or excluded from research participation without appropriate justification (justice)
4. Ensure informed consent or assent, or a reason for exemption from it, is obtained for every subject enrolled (respect for persons)
5. Ensure informed consent or assent for every subject is documented appropriately, or reason for exemption from documentation of informed consent or assent is recorded (respect for persons)
6. Monitor data and safety (beneficence)
7. Protect the privacy and confidentiality of study subjects (beneficence)

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Key features of the DHHS regulations

- The NIH is part of DHHS, and follows the 7 principles above.

- The FDA has its own set of regulations. While there is considerable overlap with the DHHS regulations, and the 7 criteria outlined above are the same, there are differences in some requirements.

  – Comparison of FDA and HHS Human Subject Protection Regulations: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/educationalmaterials/ucm112910.htm#

- To receive federal money for research at Columbia, the University must obtain a federalwide assurance (FWA) from the OHRP. Columbia has agreed to apply these regulations to all research, not just federally-funded research, conducted by Columbia faculty, staff, and students,

- For non-government-funded research conducted at the University, the IRB is the primary oversight body. (The Clinical Trials Office and the IND/IDE Assurance Program are also involved.)

- Research that is affiliated with an institution that does not receive any federal funding for research is not required to comply with the DHHS regulations. Many institutions comply voluntarily. And to obtain FDA approval for marketing a drug or device, research must comply with FDA regulations.

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5 What are the Investigator's responsibilities to the IRB?

i) Conduct research according to the approved Protocol.

ii) Alert the IRB to UPs.

It is the study Investigator's obligation to ensure the IRB is notified about UPs within 5 business days, because UPs can jeopardize the safety of study participants.

iii) Report in on how the protocol is going by submitting renewals and alerting the IRB to any changes in the protocol.

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What does this mean in practice?

- **When you** <u>submit your original Protocol</u>**, specify in detail how the research will be conducted in a way that meets DHHS/OHRP/FDA requirements.**
  Submit your Protocol through RASCAL* <u>www.rascal.columbia.edu</u> in a timely manner. Reply to the IRB's responses and gain Protocol approval.
  *RASCAL is Columbia University's Research Compliance and Administration System

- <u>**Obtain renewals**</u> **in accordance with the IRB approval period (usually one year, but can be less or based on accrual).**

- **MEET YOUR OBLIGATIONS TO REPORT UPs (see below).**

- **Submit** <u>proposed changes</u> **to the protocol prospectively. Do not implement changes until IRB approval is obtained. An** <u>exception:</u> **a change needed to avoid immediate harm to subjects should be made. (But do not overreact.)**
  Changes without approval to avoid patient harm must be reported to the IRB after the fact.

- <u>**Close out the study**</u> **when i) it is completed, ii) it is closed by the sponsor or other entity, or iii) it will otherwise not be completed at the local site.**

- <u>**Maintain all required documentation**</u> **(e.g., consent forms, subject data, regulatory approvals) in accordance with applicable regulations and institutional requirements.**
  CRITICAL: BE PROACTIVE. DISCUSS

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6 IRB requirements in reviews of new Protocols

Note: MANY SUBMITTED PROTOCOLS ARE NOT ACCEPTABLE
They consist mainly of an expanded Background section, and a minimally developed plan specifying what will actually be done (in terms of obtaining consent, implementing an appropriate, detailed visit schedule, etc).

Submit a <u>well-developed plan</u>, with appropriate, fully specified sections, that describes exactly how the proposed research will be conducted, especially:

    i)   **How will informed consent be <u>obtained</u> (DHHS principle 4)?**
    ii) **How will it be <u>documented</u> (principle 5)?**
    iii) **How will <u>recruitment</u> be conducted so that enrollment goals are met?**

Advice from JLPT: Do not waste time reinventing the wheel. Build on what has been done. Use existing models from other investigators, mentors, etc. But understand everything you include: you are taking responsibility for it.

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8 IRB requirements in reviews of applications for renewal of approval

- **Assurance that the 7 approval criteria (see Item 4) continue to be met**
- **A report from the DSMB (or other DSM entity) that AE reporting is proceeding according to protocol**
- **A DSMB report on UPs**
- **Progress Report, if federally funded**
- **Confirmation that recruitment is meeting study goals**
    - *If not, it is unethical to continue to expose subjects to the risks associated with being in the study (DHHS principle 2.)*
- **Is the gender, ethnic, and racial makeup of the population being enrolled in line with what the approved protocol predicted? (principle 3.)**
- **Is the Investigator conducting the research according to the approved Protocol? This is required for renewal.**

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What are UPs? Do they include AEs (Adverse Events) and SAEs (Serious Adverse Events)?

UPs (Unanticipated Problems) are by definition reportable (i.e., must be reported) to the IRB.

A UP is an incident, experience, or outcome that is

i) <u>unexpected</u>

ii) <u>probably</u> or <u>possibly</u> related to participation in the research
AND
iii) suggests that the research places subjects or others at greater risk of harm

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Examples of UPs

- *Reportable* SAEs (Serious Adverse Events – see below)
- A higher-than-expected proportion of subjects is experiencing an *expected* SAE (see below)
- An inadequately protected computer or mobile device has been lost, e.g., a password-protected _but unencrypted_ mobile device with identifiable subject data.
- A study PI has departed with inadequate preparation for ongoing study oversight, placing patients at risk. (IRB now requires contact information for the second-in-command for some studies.)
- Risks or limitations in behaviors not adequately explained to or understood by the participant: psychological distress results
- Study data that includes identifiers has been accidentally released to parties who should not have access to those identifiers
- Correspondence sent to participants in a way that private diagnoses may be revealed (e.g. postcards or voicemails indicating involvement in an HIV study)
- Study staff have been exposed to needlesticks or other such risks

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Adverse Event Definitions (per FDA)

AEs (Adverse Events) are
- Any negative clinical events – can be anticipated or not. Very broad – see next slide

SAEs (Serious Adverse Events) are a <u>SUBSET of AEs</u>.
An SAE is an AE that
- **Results in death <u>or</u>**
- **Is life-threatening <u>or</u>**
- **Requires* in-patient hospitalization or prolong an existing hospitalization <u>or</u>**
- **Is associated with a birth defect or congenital abnormality <u>or</u>**
- **Causes permanent disability or incapacity**

*If hospitalization does not occur, the event is still an SAE

What is an adverse event?

- Definition: any adverse finding, temporally associated with drug use

- Adverse findings:
  - sign
  - symptom
  - abnormal assessment (lab, VS, ECG, etc)
  - cluster of signs, symptoms, abnormal assessments

FDA

What are <u>Expected</u> AEs?

- AEs can be expected because of
  i) <u>the nature of the disease being studied</u>
  For example, heart failure often leads to hospitalization

  or

  ii) <u>the nature or action of the study intervention (drug or device)</u>.
  For example, warfarin is known to be associated with bleeding.

  Your protocol should list the major expected SAEs

  Be clear which are
  i) for standard care components,
      and which are
  ii) for new interventions.

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Relationship between IRB and a trial DSMB (Data and Safety Monitoring Board)?

- **ALL studies (not just those that are NIH funded) must have a Data Safety and Monitoring <u>Plan</u>. The intensity of the monitoring varies according to the risk to the patients.**

- **Many studies that involve greater than minimal risk also require an independent Data and Safety Monitoring <u>Board</u> (DSMB) composed of experts relevant to the study. They regularly assess the trial and offer recommendations to the sponsor concerning its continuation.**

  A Phase I or single-site trial that involves greater than minimal risk may not require a DSMB.

- **High-risk phase III trials typically require a DSMB.**

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If there is a trial DSMB, what is the relationship between it and the IRB?

- Both are concerned with patient safety.
- IRB lacks statisticians, access to unblinded data, and ability to assess weight of evidence of SAEs. These are DSMB roles.
- Monitoring SAEs in real time is the responsibility of DSMB, medical monitor, or any other entity designated in the Data and Safety Monitoring Plan.
- DSMB also alerts IRB to observed trends in SAEs or UPs that may require revision of the protocol.
- At renewal, IRB reviews summary of reported UPs, looks for trends, and may request additional information from study team and/or DSMB to consider if a change to the protocol is required.
- IRB may require more detailed information regarding unexpected SAEs from the investigator when a study has no DSMB.

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9 What is a Central IRB?

Currently in almost all multicenter trials, the Protocol is reviewed and approved by the IRB at each site. So a trial which seeks to recruit at 100 sites needs 100 IRB approvals.

This system is time-consuming. There are pressures to move to one central IRB per trial (e.g. NINDS NeuroNEXT network).

The logistics of central IRB management are complex, and often as time-consuming as multiple IRB approvals. As the process for reliance on a central IRB is refined, this model may be attractive to more institutions.

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Overview of the IRB Process
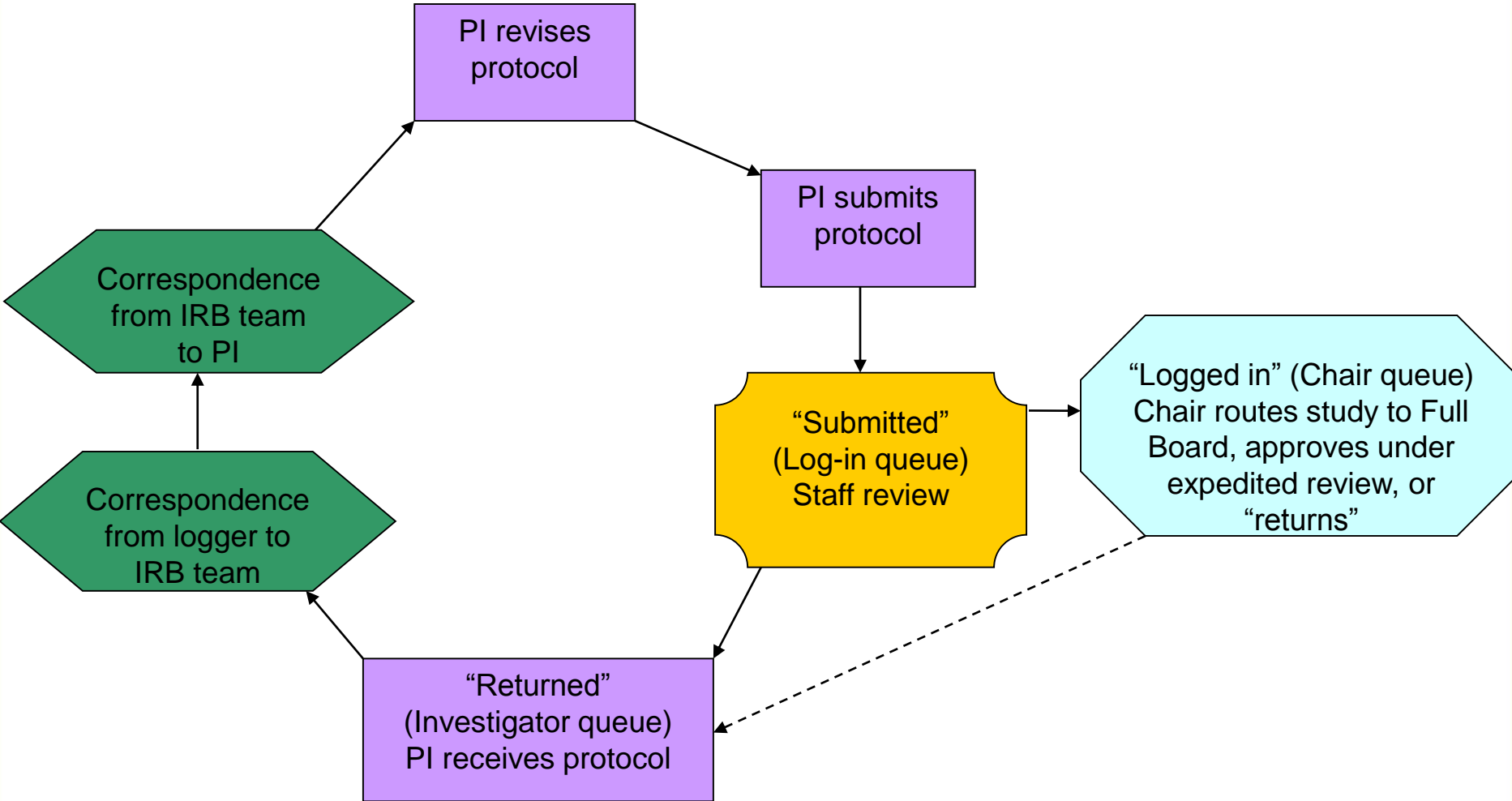
Overview of the IRB Process
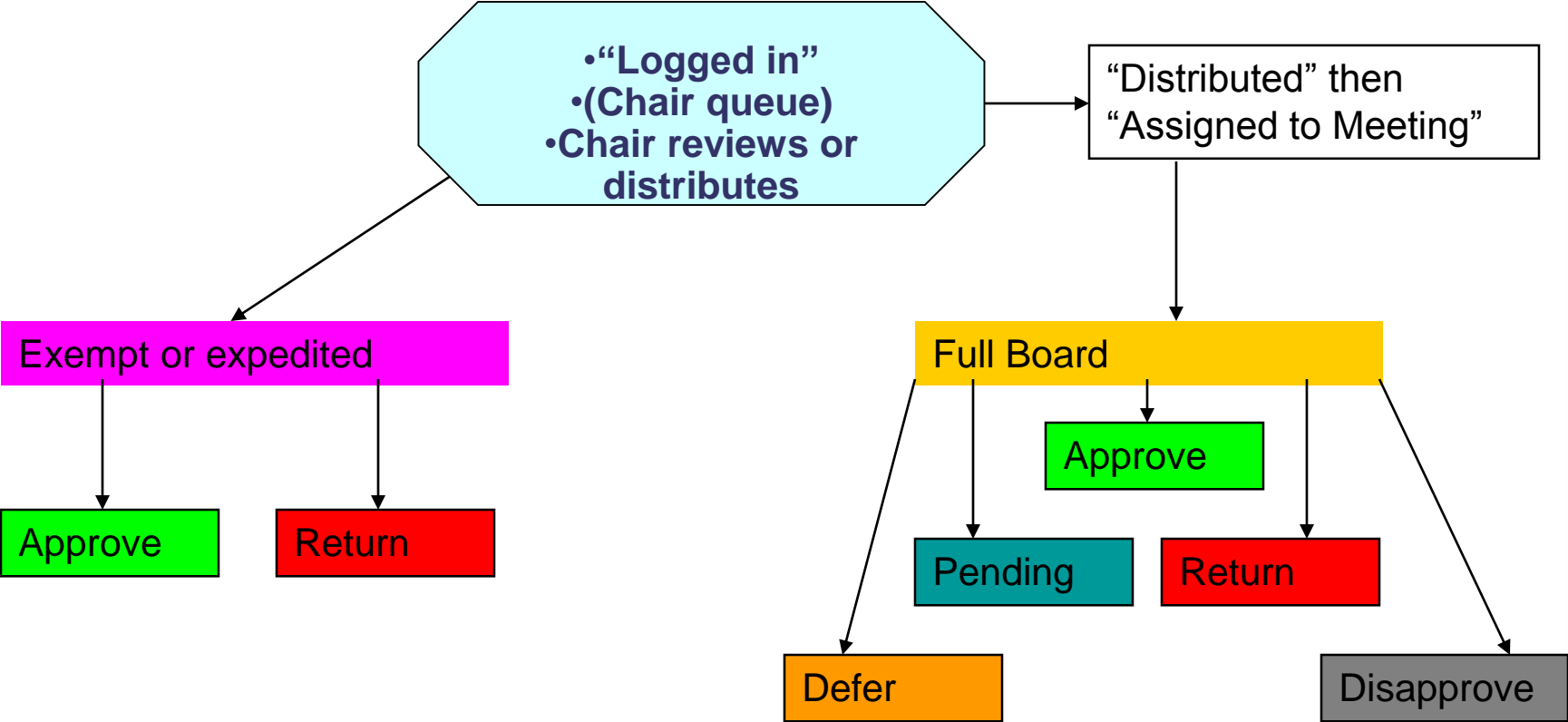
IRB Templates and Suggested Language

Visit the **Submitting a Protocol** and **IRB Policies/Procedures/Guidance** sections from the homepage of our website for access to IRB-created template and guidance documents including:

Submission Worksheets:
Analysis of Existing Data or Specimens
Informed Consent Process

Study Description help:
Study Description Sample Text
Abbreviated submissions

Suggested Language:
Consent Form Builder Sample Language
Incidental Finding Consent Template Language

Consent form Templates:
Minimal Risk Consent form template
Minimal Risk Consent form template for studies involving audio/video recording
Sample Short Form Consent Documents* (currently in 21 languages)

IRB Move Addendums:
English*
Spanish*

IRB Reviewer Forms (for reference):
IRB Reviewer Form
IRB Continuing Review Form

Other University resources for clinical research?

- **Clinical Trials Office (CTO)**
- **IND/IDE assistance program**
  A CTO program to assist investigators holding an IND or IDE at all stages of an investigation. See
  http://www.columbiaclinicaltrials.org/assistanceProgram.html

  IND: Investigational New Drug

  IDE: Investigational Device Exemption
- **CTSA**
- **BRIDGE**
- **SAC**

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Thank you!

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http://www.cumc.columbia.edu/dept/irb/documents/IRBStaffDirectoryexternal10.4.13.pdf

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