Conducting Risk Assessments & Determining IRB Level of Review – Part 2

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Former Executive Chair, Cedars-Sinai IRB’s
Associate Director, Common Disease Genetics Program
Associate Program Director, CTSI
Cedars-Sinai Medical Center

February 7, 2012
• The IRB at Cedars-Sinai
• Dealing with Genetics Research
• Avoiding Unnecessary Headaches
The IRB at Cedars-Sinai Medical Center

Three IRB’s that each meets every 4 weeks

- An IRB meeting occurs every 1-2 weeks
- IRB’s are not topic-specific

One specialized IRB, the SCRO-IRB, that reviews protocols involving human stem cells

- Meets monthly
# 2012 IRB Meeting Dates (Revised 12/8/2011)

Please note that before a submission can be forwarded to a listed meeting, it must first clear DEPARTMENT REVIEW, and undergo the mandatory PRE-REVIEW.

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<th>IRB #</th>
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Rapid Activation IRB

Processes protocols that require immediate review

• Compassionate use requests
• Therapeutic protocols for which there is an urgent patient need
• Early phase trials with a limited activation window

Use of this IRB is limited to urgent situations and circumstances where a study proposal or issue cannot wait until the next scheduled IRB meeting.
IRB Submissions are Web-Based, using Webridge

Also used for

- IACUC submissions
- CTSI-CTRC submissions
Welcome to Webridge, the online IRB & IACUC Submission, Tracking, and Review System

If you do not yet have a Webridge account (user ID and password), please click on the "Request Account" link above for instructions. If you already have an account, you may start using the system by clicking on the "Login" link above. Once you are logged into Webridge, you will be able to complete activities based on your role(s).

If you have any questions about Webridge, please contact the Office of Research Compliance and Quality Improvement at (310) 423-3783 or irb@cshs.org.

The WEBRIDGE system has been in production since July 23, 2004 for the IRB and August 17, 2006 for the IACUC.

IRB LIVE CHAT

Get real-time answers to your IRB questions by using the chat function in Webridge.

AVAILABLE: Monday - Friday, 9am - 5pm
Study Staff: Welcome to your Personal Workspace! Use the following guidelines to manage your submissions:

- Use the "Create" buttons at the left to create new studies.
- Respond to inquiries under My Tasks. The My Tasks tab shows those submissions where the IRB or the IACUC has requested further changes before your submission can be approved.
- The "IRB Studies" and "IACUC Studies" tabs shows studies you are associated with either pending or approved.

**Upcoming IRB Session**
Recent IRB Smartform Changes: Questions and Answers
January 18th & 25th, 2012, Davis 1004, 10:00 AM – 11:00 AM
RSVP to IRB@cshs.org with your preferred date

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### My Tasks

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# IRB

**IRB Studies will show up below 60-days prior to expiration.**

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Continuing Review: Continuation 2012 for IRB 9313

Study ID: Pro00009313
Date CR Approval Issued: CR00006127

Study Expiration Date: 3/31/2012
Study Begin Approval Date: 4/1/2011

Principal Investigator: LESLIE RAFFEL
IRB Primary Contact: SYLVIA VILLANUEVA

Meeting Date: Review Type:
Approved Number of Subjects to be Accrued: 5000 965
Subjects to be Accrued: 1/23/2012 9:39 AM PST

History

Activity
Created Continuing Review

Author
VERNE, ARLENE

Activity Date
1/23/2012 9:39 AM PST
Folder for LESLIE RAFFEL

Study Staff: Welcome to your Personal Workspace! Use the following guidelines to manage your submissions:

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GENETIC TESTING AND HUMAN SUBJECTS IN RESEARCH: THE DILEMMA FACING IRB’S
How does the IRB make sure that the appropriate protections are in place for human subjects, while still allowing important genetics research to move forward?
Genetics and Human Subjects Research - What’s All the Fuss About?

1. Concern for Discrimination/Stigmatization
   - Potential to identify individuals at risk before disease develops
     - Potential for insurance and/or employment discrimination
     - Risk of suicide/depression

2. Information obtained from one individual may have predictive value for other family members
   - May adversely impact family relations

3. Genetics is new and most people do not understand it
   - Fear makes for good news stories
   - We shun what we fear
Categories of Genetics Research Activities

1. Research involving collection of pedigrees (family trees)
2. Research involving recruitment of family members
3. Research involving collection of specimens for DNA isolation and storage
   – Sharing of specimens with other investigators
   – Long term storage of specimens
   – Dealing with potentially clinically relevant results
4. ‘Research’ that is really part of clinical care
   – Genetic testing that is only available in research labs
5. Research involving gene therapy
Pedigree collection:
Vital for the research, but does collection of information about family members who have not consented to participate constitute invasion of privacy?
The use of private information for the well-being of a patient is considered justified but in research, we are held to a higher standard.

The risk of a breach of confidentiality strictly for the benefit of research may not be justified.

Apply the standard of the 'minimally necessary' information for research.
Maintenance of confidentiality of family history information is paramount

- Investigators must provide the IRB with detailed descriptions of how the privacy of these records will be protected
- Consideration should be given to obtaining a Certificate of Confidentiality
- Some types of information (such as sexual orientation, drug use, abortion history) may be so sensitive as to be inappropriate to collect without the direct consent of all subjects
Certificates of Confidentiality are issued by the NIH to protect identifiable research information from forced disclosure.

They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding.

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.
Genetics in the Era of GINA
 Genetic Information Nondiscrimination Act

GINA makes it illegal for medical insurance companies and most employers to discriminate based on genetic information.

The law does not cover life insurance, disability insurance and long-term care insurance.
Recruitment of Family Members:

- Can investigators collect contact information for family members without their consent?

- If the IRB requires written information containing phone numbers for the investigators to be distributed to family members, with the family member initiating contact, what is the chance that anyone will call, even if they are interested in the research?

- Can the index case (proband) contact family members and obtain verbal consent to release contact information to investigators? What is the potential for coercion?
Many research studies involve long term storage of DNA samples or cell lines.

This may be very beneficial for the subject (multiple studies may be performed without the need to request additional samples) and the investigators (ability to perform ‘freezer studies’ to test new candidate genes, etc.)

But what types of safeguards are needed to protect subject privacy?

Who decides for what studies a given specimen can be used?
Permission to share my sample(s) with other researchers?

If you agree, your sample may be shared with other researchers, performing research on your condition or on other conditions. Please note your preferences below:

I give permission for the research team to share my sample with the individuals noted below:

- **YES □ NO □** Researchers at CSMC studying (state disease)
- **YES □ NO □** Researchers at other institutions studying (state disease)
- **YES □ NO □** Researchers at CSMC studying any disease
- **YES □ NO □** Researchers at other institutions studying any disease
- **YES □ NO □** In addition, I agree to be contacted in the future to receive information on other research studies investigating (state disease)
As part of this research, we will make your sample available to researchers at non-CSMC institutions who are studying the same disease as described in this consent form. Your sample will be shared with [insert name of institution(s)].

Insert applicable option:
The sample will be labeled with a unique study number that will link your identity so that only the research team can recognize you.

OR
The sample will not contain any information that could be used to identify you.
What about recontacting subjects?

• At the time that many studies are initiated, the likelihood of finding clinically relevant results in the near future is small.

• If such results are generated, what is the investigator’s:
  – Obligation to recontact study subjects?
  – Ethical right to recontact study subjects?

• What should the investigator do if the research turns up something that is clinically relevant, *but far different from what was expected*?
Exome Sequencing and Whole Genome Sequencing are Popular Approaches to Identifying Genetic Variants Associated with Disease

Suppose a new variant, not previously reported, is found in a research participant
*Should the subject be informed?*

Suppose that a subject participating in a study of asthma is found to carry a mutation that causes Huntington's Disease or a mutation in BRCA1
*Should the subject be informed?*
Willingness to receive results of testing performed as part of research

**YES □ □** I wish to receive information about the testing conducted on my sample

**YES □ □** I wish to receive general information about the study results. I understand that this will not include specific information on the testing completed on my sample.

**YES □ □** Should information that may be important to my health become available in the future, I would like to be contacted and given an opportunity to learn of this information. I understand that it is my responsibility to update any changes to my address information.
‘Research’ that is really part of clinical care

- Genetic testing that is only available in research labs

- Genetic testing that is clinically available but is performed in a research lab as part of the research
Research involving gene therapy
Gene Therapy holds the potential both for curing and preventing diseases that we will otherwise never be able to treat effectively.

Gene therapy is risky - the technology is new and there is much we still do not understand:

- gene regulation
- the impact of random vector insertion into the genome
- the impact of germ line insertions of recombinant DNA
Gene therapy protocols require additional levels of review, both locally and often at the national level as well.

Contact your IRB Office early in the process to be sure that you are following all of the necessary steps.
Genome Wide Association and Genome Sequencing

With modern genotyping and sequencing technology, investigators are routinely obtaining vast amounts of genetic information from the DNA of research subjects.

Making this data widely available is producing more rapid advances in understanding the genetic basis of many disorders.
The NIH Policy on Genome Wide Association Data

“...the NIH believes that the full value of GWAS to the public can be realized only if the genotype and phenotype datasets are made available as rapidly as possible to a wide range of scientific investigators”

*What about research subject privacy?*
The Fallacy: *Is DNA de-identifiable?*

Amy L. McGuire and Richard A. Gibbs

SCIENCE 312:370-371
APRIL 21, 2006

“....an individual can be uniquely identified with access to just 75 single-nucleotide polymorphisms (SNPs) from that person.”
Privacy in the 21st Century

How do we reconcile the expectations for health care and research privacy and confidentiality with the reality of an internet environment in which anyone can find out what you paid for your house, where you bank and how your friends are?

Do people have the right to expect privacy or is this an outmoded concept no longer relevant to modern society?
Research is held to a higher standard

Let the IRB know that you are cognizant of the unique issues in genetics research

Show that you have procedures in place to minimize risk of inadvertent release of information

Provide the IRB with a scientific justification for maintaining identifiable information
Have you provided a scientific rationale for the conduct of the research?

- Remember that there are lay members on the IRB, as well as scientists who may be unfamiliar with your research area
- Use lay language
- ‘Because I say so’ isn’t good enough
- ‘What’s the big deal, I just want to draw 10 ml. of blood’ does not mean scientific justification is unnecessary
Is selection of subjects equitable?

- What ethnic groups?
- Is pregnancy an exclusion?
- Are minors included?
- What about those with impaired cognition?

Provide a scientifically justifiable explanation for the inclusion or exclusion of specific groups of subjects - convenience is not sufficient.
Will subjects truly be giving informed consent?

- Consent must be free from coercion or undue influence - remember the problem of the therapeutic misconception when the investigator is also the treating MD

- Consent form must include all required elements - use lay language, include a complete description of procedures, risks, benefits, alternatives, and confidentiality protections

- Disclose any potential conflicts of interest
Are the proposed procedures justified by your stated research objectives?

- What are the potential risks to participants?
- What safeguards are in place to minimize potential risks to subjects?
- Have you justified your sample size?

The IRB must assess the risk/benefit ratio, even when the procedures are low risk.

If a study is underpowered or overpowered, the risk/benefit ratio will not be acceptable.
Have you adequately described data safety and integrity monitoring methods?

- Be sure your DSMP describes procedures for monitoring and protecting subjects
- Describe your plan for maintaining the confidentiality of study data
- This is particularly important with the advent of HIPAA
When in doubt, provide more detail, not less

• Most IRB staff and members are pretty savvy and will know when you are trying to slip something over on them

• If the IRB cannot follow what you are planning to do, they cannot approve your study and will table your proposal while sending you correspondence

• Spending the extra time to describe your study up front saves time in the long run
Be humble and recognize that your colleagues and you have limitations.
If we knew what we were doing, it wouldn’t be called research, would it?

Albert Einstein (1875-1955)