

POINTS TO CONSIDER: A Work In Progress

Version: June 9, 2003

This is a compilation of issues, points, instructions, and pointers that have been raised in past reviews. *It is not intended to be an outline or to be comprehensive.*

APPLICATION INFORMATION

- ✓ Select the review process

Process	Submit:	Allow time	
Exempt	2 copies	48 hours	rare - establish the exemption being claimed
Expedited	2 copies	72 hours	Allowed if there is less than minimal risk and involves only procedures on the list.
Full Board	6 copies	3 weeks	required if NIH money or source is involved.

- ✓ Review the IRC Checklist for Submission of Request for Acquisition or Use of Biological Specimens.
- ✓ Write a protocol for submission. Although the major points below should be included, use of this document as the outline of a protocol does not work. This is not an outline. *Remember that no IRB member is as expert in your field as you are.*
- ✓ Fill out appropriate forms – (**FORMS ARE IN 4-41**) The forms were sub-divided for better usage. Each has been revised for biological specimens applications.

Expedited review request	Establishes that the application can be reviewed using the expedited process and provides a synopsis of important issues.
P.I. Application	One person must be responsible for the conduct of a study; this form tells the IRB about that person and the facility to be used.
Secondary Acquisition	The IRB must establish that (a) the sample was gained ethically and that (b) the use does not contravene any stated purposes

WHY HAVE IRB REVIEW?

"The high research value of human biological materials does not override the rights of individuals to protect themselves from possible adverse consequences of the research use of such materials." (NBAC Draft Report, p 124)

"Where identifying information exists, however, there must be an unambiguous system of protections to ensure that risks are minimized and that the sample's source's interests are protected."

History, Fear and Unmet Expectations – Many of these words are imbued with stigma.
Recombinant DNA – Eugenics – Control of powerful technologies – Cloning – Cures – Genetic Therapy.

IRC – Points to Consider

THE TOP HOT TOPICS

- CONSENT Was consent given? For what? Was it documented? Is a sample form available? Would the donor be surprised to learn about your use of the specimen? Might the donor disagree with your access to or use of the specimen? Is consent waiver possible?
- PRIVACY Who knows who the donor was? Where is the code held? Who can break it? How and when? When is the code destroyed irreparably? Is the same anonymous, de-linked, de-identified or what?
- RIGHTS By what right has the sample passed from the donor to the acquirer to the user?

SOURCE OF REGULATORY REQUIREMENTS

- ✓ You need to give the IRB enough information to know which regulations must be applied.

NIH CHTN	45 CFR 46	Research" is defined as a "a systematic investigation ..designed to develop or contribute to generalizable knowledge". "Human Subject" is defined as a "living individual about whom an investigator ... conducting research obtains: (1) or (2) identifiable private information. ...".
FDA	21 CFR 50 21 CFR 56	If samples are to be used to develop a product such as a diagnostic device the study should comply. 2/28/97 - Proposed Approach to Regulation of Cellular and Tissue-Based Products
Federal	HIPAA	If identifiable patient records or samples are involved.
State	Privacy rules Consent rules	Many states have rules regarding protection of patient privacy. It is the responsibility of the site to know their own state requirements.
Institution	Internal Rules IRB policies	Many institutions have institutional and IRB rules about secondary use of diagnostic or pathologic specimens. Any acquirer from an institutional source should be sure that institutional rules have been followed.
International	ICH	

PROTOCOL ISSUES TO BE CONSIDERED

Any complete protocol should address the circumstances under which the specimen was obtained, the trail of handling from the acquirer to the user and the purposes for which it will be used. Every protocol will, however, put emphasis on different areas. **This is NOT an outline.** It makes a terrible outline.

A. INTRODUCTION There should be an overview describing what is being done and why. It should be in language accessible to all members of the IRB.

- ✓ When the IRB reads the application, will they receive a coherent picture of what you want and why?
- ✓ When you have written your application, consider an unbiased assessment from an uninvolved friend.
- ✓ To do research is a privilege, not a right. It is not a scientists' absolute right to have access to samples; it is a right limited by ethics, laws, public perception and common sense.

A simple overview should be given. It should include a purpose, rationale, parties involved, and control points in the handling of the sample plus some information on how this study fits into the larger scientific environment.

IRC – Points to Consider

- Design: What is the goal of this study? Why is it being done?
What part of this study is IRC's IRB being asked to review?
Acquisition only (Which, if any, IRB[s] were involved?)
Use only (Which, if any, IRB[s] will consider the acquisition?)
Both
- Risks To individual donors -
Is it "less than minimal risk"?
Were financial, privacy and economic risks considered too?
To the class that the individual is part of
Is there any possible stigma or financial risk?
How "identifiable" is the sample and any accompanying information
- Benefit To individual?
To the class that the individual is part of?
To the company? (basic vs. applied)
To science??

B. TISSUE ACQUISITION ISSUES An IRB needs assurance that the original acquisition of the tissue was ethical.

- ✓ If an IRC investigator is getting the samples, our IRB should have a protocol, should review the consent document, and should understand the eventual use and any restrictions on that use. This will be the heart of your application.
- ✓ If an IRC investigator is acquiring the sample from a secondary source, our IRB should be assured that the acquirer is IRB approved and that the consent purpose contemplated the secondary use. Information about the acquisition may or may not be available. If it is not available, other assurances and documentation of approval from the original IRB *may* suffice.

1. Why did the initial collection occur?
 - ▶ Diagnostic specimen - waste from pathology or reference lab
 - ▶ Specimen in private collection
 - ▶ Volunteer donors
 - ▶ Retained from subjects in a research study
 - ▶ Was the sample existing as of the date you submitted the protocol?
 - ▶ Pharmacogenetics
2. Consent (If the sample is from a repository you may need their assurances. If you are obtaining the sample, the consent form will need review.)
 - ▶ Process
 - coercion if in therapeutic setting?
 - coercion if employees?
 - ▶ Elements
 - Specificity of purpose of end user (broad or general)
 - ▶ Storage of consent form
 - location, confidentiality, access?
 - ▶ Ability to refuse
 - now or withdraw sample later?
 - Was sample donation an integral part of study participation?
 - Was refusal perceived as a real choice?
 - ▶ Restrictions on use? (**critical point**)
 - Did the donor limit use? (consider religious issues, purpose as explained to the donor, etc.)

IRC – Points to Consider

Was future re-sale considered?

- ▶ Was consent reviewed by an IRB - was it waived? was documentation waived?
- ▶ Examples of language found in some consent forms with evaluation. The IRB considers consent form language in terms of lay understanding.

Consent Form statement	Critique
Purpose: "to examine, to retain for science or education or to dispose of."	None of the three verbs include to give or to sell to an outsider.
"... will not be used for commercial purposes."	A commercial company is presumed to have a commercial purpose.
"... will not be sold ..."	A transaction that is solely to cover the costs of collection is considered a sale.
"... will not be used for any genetics research..."	This would include both basic and applied genetic research
"... will be destroyed."	This is clear. It cannot be used.
"... will be used by an outside drug or biotechnology company for their basic research which might, some day, produce a product..."	This is clear. It is likely it can be used.

3. Ownership and Financial issues
 - ▶ Compensation to donor subject
 - ▶ Compensation to collector
 - ▶ Compensation to handler
 - ▶ When does "ownership" transfer at each step?
 - ▶ Is someone donating so that others can profit?
 - ▶ Cost to donor. Is the donor paying for the testing?

4. Risks
 - ▶ Physical risks from donation
 - ▶ Loss of privacy
 - ✓ Financial risks if status became known
 - ✓ Insurance issues
 - ✓ Stigma in community
 - ▶ Employee status?
 - ✓ Information available to employee health or human resources?
 - ▶ Family relations
 - ✓ Feedback of information could alter family dynamics.
 - ▶ Biosafety
 - ✓ What is the protocol for sample analysis in the event of an accidental needle stick?
 - ✓ Is there any need to return to the donor?

5. Benefits
 - ▶ Direct medical impact
 - ▶ Knowledge without known action to take
 - ▶ Assist to community of which donor subject is a member?

6. Adherence to source institution rules
 - ▶ Name of institution
 - ▶ Institutional compliance
 - ▶ Documentation
 - ▶ Foreign country collection and use (and discussion of their rules from that era and now)

7. Involvement of middlemen
 - ▶ Need to see their source documentation regarding institutional commitment
 - ▶ How do they assure the basics are considered?

IRC – Points to Consider

- ▶ Differences by type of organization
 - ✓ private, for profit
 - ✓ not for profit (NCI)

C. THE SAMPLE ITSELF

As various kinds of samples are viewed differently, the IRB must know about the types of samples being sought.

1. Population (similar to "eligibility" criteria and often on your requisition form)
 - ▶ Characterization (by disease, age, ethnicity, race, gender)
 - ▶ Size of population
 - ▶ Healthy or in treatment
 - ▶ Potential pregnancy/fetus
 - ▶ Relationship to person/site requesting donation - employees?

2. Type of specimen (There could be emotional, safety, religious differences)
 - ▶ Stem cell
 - ▶ Sputum
 - ▶ mature tissue
 - ▶ mucous membrane scrapings
 - ▶ Fetal
 - ▶ Cord blood
 - ▶ skin
 - ▶ hair

3. Amount needed
 - ▶ Repeat sampling?
 - ▶ Amount of blood
 - ▶ Is there enough left for pathology?

4. Identity Linkages: (CRITICAL)
 - If repository ____ Unidentified or ____ Identified
 - If research ____ Unidentified ____ Unlinked ____ Coded ____ Identified
 - ▶ Nature of possible links. Why maintained?
 - ▶ Where is linkage maintained - if at all?
 - ▶ Anonymity protection
 - ▶ Follow the track of one sample to illustrate identifier route
 - ▶ Other information needed
 - ✓ storage of CRF (case report form)
 - ✓ link of CRF to sample
 - ▶ Were there an accidental needle stick, would there be any return to the source?
 - ▶ Is demographic information in a small sample sufficient to identify one person?

5. Demographics - Information available
 - ▶ What information is attached or linked to the sample?

6. Packing and Shipping
 - ▶ Speed (freshness)
 - ▶ Safety
 - ▶ State laws for contaminated substances

7. Storage
 - ▶ Potential length of time in storage (changes of rules over years?)
 - ▶ How identified in storage
 - ▶ How is the consented use or purpose linked to the sample?
 - ▶ Backup protection at storage area? Emergency energy back-up

IRC – Points to Consider

D. RESEARCH PROJECTS - END USE

The IRB must be assured that the purpose is consistent with the donor's consent, that protections are continued and that use is consistent with "community" and "local" values.

1. Source of sample.
 - ▶ Repository or bank - already stored specimens
 - ▶ Repository or bank - specimens acquired to fulfill requisition. (include requisition)
 - ▶ Access to primary source - direct relationship with donor

2. Consent – Is this use allowed or precluded by the donor's stated intent or is the donor intent unknown? (see table above)
 - ▶ Consent was waived at the donor institution by their IRB
 - ▶ clinical sample with no written consent
 - ▶ Consent was obtained – the purpose is inconsistent with the study purpose
 - ▶ Consent was obtained – the purpose is not inconsistent with the study purpose
 - ▶ Consent was obtained – the purpose included this study purpose
 - ▶ If the sample is to be cloned or used in recombinant technology, were those words used?
 - ▶ If there will be any commercial value from an individual sample, the IRB must be notified.

3. Origination of request for sample
 - ▶ Who establishes request?
 - ▶ Who maintains control of ultimate use?
 - ▶ How is use - in accord with consent - controlled?

4. Specificity of study goals
 - ▶ Genetics
 - ▶ Very broad or very specific purpose?
 - ▶ End Points - How will you know when enough is enough?
 - ▶ Basic science -
 - ▶ Applied research - development of a product

5. Specificity of study design

6. Data requirements / needs
 - ▶ Longitudinal data
 - ▶ Clinical or diagnostic data
 - ▶ Identifiers

7. Financial return
 - ▶ To company from what?
 - ✓ patent? product?
 - ▶ To subject or class of subjects?
 - ✓ direct payment?
 - ✓ donation to class or to something on behalf of the class
(e.g., donation to contraceptive planning for use of stem cells.)

8. Disposition
 - ▶ What will happen to the sample when the user is finished?
 - ▶ Samples destroyed?
 - ▶ Will anyone else have access to samples?
 - ▶ Will anyone else have access to data?
 - ▶ What identifiers will be available to a secondary recipient?
 - ▶ Is there any sale or resale?

STUDY CATEGORIES

(Triage Categories taken from presentation by Barbara Handelin 8/00)

1. Family Studies

- Recruitment issues:
 - Who is doing the recruiting? PI and/or family members?
 - Is there likely to be coercion by means of family relationships and dynamics?
- Family Dynamics issues:
 - Guilt within family
 - Non-familial relationships revealed
 - Reproductive choices forced upon subject or family member?
- Rights –
 - Right not to know
 - Right not to be stigmatized within the family/community
 - Right to refuse to have pedigree published

2. Gene Modification studies

- Involvement of children
- Pre-clinical studies
 - Relevance of information
 - How used in consent information
- Gene delivery vehicle
 - Synthetic
 - “Live” – viral issues
- Genome effects
 - Permanence
 - Germline
 - Somatic
 - Normal evolution

3. Population Association Studies (e.g., fishing expeditions)

Types

- Discovery of new markers
 - Disease predisposition
 - Drug responsiveness
 - Disease progression
 - Differential diagnoses
- Polymorphism discovery
 - Genome-wide search
 - Disease targeted
 - Population frequency
- Clinical trials (used within) (have IBC and RAC approvals been sought)
 - Drugs
 - Diagnostic testing

Issues

- Privacy
 - Links
 - Confidentiality
- Stigmatization
 - Individual
 - Group
- Reporting requirements/restrictions
- Future use/misuse



***IRC* – Points to Consider**