

**Human Gene Transfer
Protocols and Institutional
Biosafety Committees: Should
there be Streamlined Review
for Low Biosafety Risk
Protocols?**

Jacqueline Corrigan-Curay, J.D., M.D.

September 13, 2011



Overview

- **Role of Institutional Biosafety Committees (IBCs) in review and human gene transfer (HGT) trials**
- **Feedback from some investigators**
- **Using one IBC for multiple reviews – current options and challenges**
- **Are there low biosafety risk HGT trials for which a streamlined review process could be considered?**
- **Potential proposals for consideration**
- **Next steps**

Role of IBC Review in HGT Trials

- **Identify and manage biosafety issues raised by gene transfer agents**
 - Horizontal or vertical transmission risk
 - Safe handling and administration
 - Ensure that the informed consent incorporates information regarding risks that arise from the biological nature of the agent
 - Examine the preclinical animal data that supports the safety of the vector
 - Identify new biosafety issues through analysis of adverse event reports
- **For protocols that undergo in-depth public review by the NIH Recombinant DNA Advisory Committee (RAC), ensure that the RAC recommendations are considered**

IBC and IRB Review of Human Gene Transfer Research

IRB Review	IBC Review
<ul style="list-style-type: none">▪ Conducts risk/benefit assessment relative to individual research participants (physical, psychological, social harms)▪ Selection of subjects and the informed consent process▪ Data monitoring provisions to ensure the safety of subjects▪ Provisions to protect subject privacy and confidentiality of data▪ Injuries or any other unanticipated problems▪ Compliance with regulations	<ul style="list-style-type: none">▪ Recombinant DNA research for conformity with the <i>NIH Guidelines</i>▪ Potential risk to environment and public health (risks to close contacts, HCWs, and the community, as well as to individual research participants)▪ Containment levels per <i>NIH Guidelines</i>▪ Adequacy of facilities, SOPs, PI and other personnel training▪ Institutional and investigator compliance (e.g., adverse event reports)▪ Reviews trial design, biosafety and containment, and compliance with <i>NIH Guidelines</i>

Requirements for an IBC under *NIH Guidelines*

- **Expertise**
 - Expertise in assessment of risk to environment and public health
 - Knowledge of institutional commitments and policies, applicable law, professional standards, community attitudes, and environment
 - Biological safety and physical containment
 - Laboratory technical staff (recommended)

Requirements for an IBC under *NIH Guidelines*

- **Membership**
 - No fewer than 5 individuals
 - Appropriate rDNA expertise collectively
 - Plant and animal experts, biosafety officer as appropriate
 - Expertise in assessment of risk to environment and public health
 - **At least two local members not affiliated with the institution**

Nonaffiliated Local IBC Members- Who are They?

- **Representatives of community interests with respect to health and protection of the environment**
 - E.g., state or local public health official or representative from an environmental authority, or other local government body, persons with medical, occupational, or environmental expertise
- **Individuals who “represent community attitudes,” e.g. a teacher, clergy, community organizer, local resident**

Role of the Non-Affiliated Members of the IBC

- *NIH Guidelines* require non-affiliated members who can represent local interests because the risk tolerance for research may vary by community
- Provides mechanism for transparency/local public input
 - May be of particular importance for international trials to ensure their local and cultural norms are taken into account

Feedback from Some Investigators Regarding IBC Review of Multisite Trials

- **A number of HGT trials are conducted utilizing vectors for which there is considerable clinical experience and biosafety risks are well characterized**
 - This may be particularly true for “off the shelf” products, i.e. do not require reconstitution at the site, that are administered using standard precautions employed for licensed live vaccines, e.g. measles, mumps, rubella, yellow fever
- **A different transgene in the same vector may raise clinical safety issues but not necessarily new biosafety issues**

Feedback from Some Investigators Regarding IBC Review of Multisite Trials, cont....

- Multiple individual IBC reviews of low risk trials may add little benefit to protect public health and such reviews can be costly, e.g. setting up new IBCs, delays in initiating important research**
- A mechanism to streamline review of low biosafety risk trials is needed to facilitate research, especially for multisite trials**

Multisite Protocol Review Challenges – Hypothetical case

- **Sponsor receives NIH funding for multisite HGT trial**
- The trial will be conducted at 10 U.S. institutions
 - 9 institutions are located on the East Coast and have IBCs in place as receive NIH funding
 - One outpatient clinic in California does not have an IBC
- **The California clinic must establish an IBC and register that IBC with OBA**
 - The IBC in California must have 2 local unaffiliated members on the IBC

Hypothetical case, cont....

- **The California clinic can register one of the East Coast IBCs as its IBC of record provided**
 - The IBC meets the expertise and membership requirements described in the *NIH Guidelines*
 - Including two unaffiliated local members
 - Knowledge of local institutional matters such as training, SOPs, facilities
- **The protocol must also be reviewed and approved by each IBC at the nine East Coast sites prior to initiation, which can lead to delays due to varying schedules for IBC meetings at different sites**

Could a Single IBC Review this Protocol under the *NIH Guidelines*?

- **Yes, the IBC could be administered centrally, by one entity**
- **All 10 sites could register the same IBC for review of the trial, but**
- **To fulfill the expertise and membership requirements of the *NIH Guidelines* the IBC:**
 - 1) **must include two individuals for each site that are both unaffiliated and local to that site (a total of 20 unaffiliated, local members)**
 - 2) **The IBC must have knowledge of each trial site's facilities, SOPs, training and expertise of personnel involved in research and other local matters pertinent to that site**

Challenges with Using a Single IBC for Review of a Multisite Trial

- **The difficulty of obtaining local, unaffiliated representation on the IBC grows with the number of trial sites**
 - This may be a particular challenge for vaccine trials in foreign countries where there may be a number of rural clinics
- **With a multisite trial it is difficult for a single IBC to have knowledge of the local situation at each site**

Potential Characteristics of Low Biosafety Risk Protocols

- **Vectors**
 - Non-replicating
 - Non-integrating
 - Not expected to persist and shed
- **Transgenes/promoter**
 - Do not code for toxin?
 - Cytokine?
 - Uses an antibiotic that is used against human disease to regulate the transgene?

Potential Characteristics of Low Biosafety Risk Protocols

- Administration does not require reconstitution of the vector – i.e. off the shelf
- The target tissue is easily visualized, e.g. subcutaneous, intramuscularly, into a superficial tumor
- There is clinical experience with the vector
 - Number of trials, patient populations
- Protocol selected for in-depth public review by the RAC
 - IBC needs to ensure RAC recommendations considered
 - Selection by RAC may indicate unique safety issues

Potential Alternatives for Discussion

- **Develop mechanisms that facilitate a shared or central IBC**
 - Eliminate the need for local unaffiliated members when reviewing a human gene transfer trial that poses extremely low risk for public health and environment.
 - Allow institutions to share local non-affiliated members even if geographically distant?
 - Would there be different considerations for U.S. versus international trials?

Potential Alternatives for Discussion

- After an the initial review of the first or second trial using a product determined to have a low biosafety risk, provided there are no serious adverse events that led to any change in the recommendations from the IBC regarding the trial design, could the *NIH Guidelines* offer IBCs the option of conducting an administrative review?
 - How much clinical trial experience would be required?
 - How would an administrative review be structured?
 - If a trial is subject to the *NIH Guidelines* and eligible for administrative review but the proposed site does not have an IBC, what infrastructure needs to be in place to review the trial?

Next Steps

- **Establish a RAC Working Group to develop some proposals for consideration by the full committee**
- **Report out the Working Group findings at a future RAC meeting**