IBCs IN A CHANGING RESEARCH LANDSCAPE

A Policy Conference
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Meeting Summary

Introduction

When first drafted over 25 years ago, the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*) established Institutional Biosafety Committees (IBCs) as the cornerstone of institutional oversight of recombinant DNA research. At that time, recombinant DNA technology was a nascent science developed largely in the laboratories of major academic research institutions, where most of these committees were initially housed. A typical IBC was staffed by employees of a university or medical school, with faculty and institutional officials serving as the majority of its members. Since recombinant DNA research was limited to bench science, IBC review and concern focused primarily on the containment of genetically modified microorganisms in the relatively closed system of the laboratory setting.

Recombinant DNA technology has evolved dramatically in the years since. Many of the potential negative environmental and human health consequences that were originally feared of activities using these techniques never materialized, in part due to the responsibility exhibited by scientists in adhering to the *NIH Guidelines* and to the NIH process of public review embodied by the Recombinant DNA Advisory Committee (RAC). As public anxiety lessened and understanding in this field of science expanded, so did the settings and applications in which these techniques were employed. The commercial potential of recombinant techniques led to a burgeoning biotechnology industry and the expansion of this area of research out of the laboratory into clinical trials.

Given their mobility, when humans became recipients of recombinant DNA products, new questions were raised about the nature of containment, laboratory and clinical safety surveillance, and monitoring. Further, as clinical applications have continued to develop from Phase I into Phase II and even Phase III studies, the landscape for human gene transfer research has evolved in much the same way that other fields of clinical research changed decades ago. This includes the increasing prevalence of multi-site trials and the use of non-academic sites that lack the traditional infrastructure for the creation and maintenance of institutional committees, such as IBCs.

It is largely as a consequence of this changing landscape in which human gene transfer trials are occurring that IBCs are now taking on new forms, just as Institutional Review Boards (IRBs) did a number of years ago. There is increasing demand for centralized IBC review for multi-site trials as well as commercial IBC services for smaller clinical sites. Consequently, there has been

an emerging use of independent IBCs and other arrangements where the IBC is convened and staffed "off-site." While centralized and commercial IRB arrangements have been accepted for some time, it is less clear whether IBCs should follow the same paradigms. Arguably, the risks and benefits of research to human subjects can be considered by IRBs at a geographic distance. IBCs, on the other hand, must take into account such matters as containment, physical plant, facilities, and training of personnel, which requires direct and detailed knowledge about the site where the research is taking place.

In addition, as with nearly all areas of research, human gene transfer trials are increasingly a collaborative endeavor. The participation of multiple investigators and clinical settings in a single project challenges traditional or simple notions of what entities may constitute a "site" or "institution" for the purpose of IBC review, surveillance, and accountability.

The *NIH Guidelines* do not offer a definitive view of independent and off-site IBCs, nor their role in multi-institutional collaborations. The *NIH Guidelines* state that an institution conducting recombinant DNA research with NIH support must "establish" an IBC, but do not stipulate the means for doing so or what the location of the IBC must be. For human gene transfer trials the *NIH Guidelines* state that, before research participants can be enrolled, IBC approval must be obtained "from the clinical trial site," but leave some ambiguity about the definition of a clinical trial site and the relative physical locations of the site and the IBC.

In considering and attempting to clarify these matters, the NIH sought to take into account not only the proper functioning and siting of IBCs (per both the letter and apparent spirit of the *NIH Guidelines*) but also acknowledgment that the research environment has changed considerably since the requirements for IBCs were first developed. The challenge is to maintain the effectiveness of IBCs while not impeding the progress of research through requirements that may be inflexible or outmoded.

Thus, on December 7-8, 2001, the NIH Office of Biotechnology Activities (OBA), which implements the *NIH Guidelines*, convened a policy conference to revisit the expectations, roles and responsibilities of IBCs in the oversight of recombinant DNA research – especially human gene transfer research. The goals of the event were to explore such questions as:

- Are the IBC requirements as articulated in the *NIH Guidelines* still sound?
- Have the requirements kept pace with the changing landscape of clinical research?
- How do new clinical research and IBC paradigms and the *NIH Guidelines* mesh?
- What does the "I" in IBC mean?
- What does it mean to "establish" an IBC?
- What is the nature of local oversight?
- What is the "site" for purposes of IBC approval?
- In what ways should IBCs reflect community concerns?
- How should IBCs relate to Institutional Review Boards (IRBs)?

To ensure that broad and diverse perspectives were brought to bear on these questions, the meeting was free of charge and open to all who wished to attend. Staff, chairs, and members of the IBCs were specially targeted in efforts to publicize the meeting. In addition, a discussion

"Roundtable" was assembled to bring together representatives from industry, academia, the investigator community, biosafety officers, patient groups, and the federal government.

The first day of the event was primarily educational in orientation. A series of presentations was given to bring all participants up to the same level of knowledge and understanding with regard to the history and fundamentals of IBCs, open issues relative to the role and institutional accountability of IBCs, and challenges faced by IBCs in the current research context. The second day of the event entailed a Roundtable exploration of some salient questions relative to the characteristics and expectations of IBCs, along with discussion of a set of hypothetical cases that illustrated some of the emerging IBC arrangements.

This report is a summary of the two-day policy conference. It presents major points made by each speaker and highlights salient issues raised in the ensuing discussions.

Opening Address: "The Changing Landscape of Research with Recombinant DNA"

Former NIH Director Donald Fredrickson, M.D., drew on his recently published memoirs, *The Recombinant DNA Controversy*, in recollecting the development of the *NIH Guidelines* and specifically the concerns that led to the creation of IBCs. Dr. Fredrickson was NIH Director at the time that the seminal 1975 Asilomar conference took place and subsequently when the first version of the *NIH Guidelines* was produced a year later. He described the evolution of guidelines and regulations governing the protection of human subjects in research and specifically touched on the development of formal institutional requirements for the review of human research protocols by an independent body, now known as an Institutional Review Board. The gradual acceptance by the scientific community of IRBs as a means of ensuring the protection of research subjects laid the groundwork for the subsequent establishment of IBCs.

The NIH did not wish to regulate the conduct of recombinant DNA research. Moreover, the Asilomar conference was in many respects predicated on the preference that scientists responsibly oversee the risks of their own research. Compliance with codes of safe conduct was nonetheless viewed as important and IBCs were envisioned as a means to ensure monitoring of this field of research. IBCs were also viewed as a reasonable mechanism for allowing public participation in the oversight of recombinant DNA research. As such, they became an important element of the expanding oversight of science.

Session I - The Origins Roles and Responsibilities of IBCs

W. Emmett Barkley, Ph.D., Director, Office of Laboratory Safety, Howard Hughes Medical Institute, described the "History and Origins of IBCs in the NIH Guidelines: Asilomar Revisited." An active participant and biosafety expert at the Asilomar conference, Dr. Barkley recalled how scientists accepted the need for principles to guide the planning and safe conduct of recombinant DNA experiments. Asilomar marked an era in which laboratory safety would become an essential consideration in the experimental design of recombinant DNA research, guided by the principle that safety practices should be commensurate with the estimated risk. The participants at the Asilomar conference concluded that investigators should be responsible

for conducting risk assessment, informing laboratory staff of potential hazards, assuring staff competency in safe practices, and exercising caution in the conduct of their research.

In addition, the organizers of Asilomar believed there was a need for institutional review of recombinant DNA experiments and for institutional certification of physical containment in research laboratories. Further, they recommended that a knowledgeable committee conduct containment reviews through an efficient process that took local circumstances into account.

In response to Asilomar and calls from Congress and the public, in June 1976 the NIH developed an initial set of guidelines, using the IRB as the model for institutional oversight. Pertinent to today's policy discussions is the fact that central IBC review was viewed as acceptable at the time, Dr. Barkley said. In general, the original roles and responsibilities of the IBC were to provide advice on institutional policies; create and maintain a safety reference resource; certify that appropriate physical containment and training were in place; and develop a P4 safety and operations manual. IBCs were not charged with conducting scientific review.

The original IBC membership requirements included experience and expertise in scientific disciplines germane to recombinant DNA technology, as well as biological safety and containment practices. IBC members could be from the institution or consultants, but the committee was expected to possess or have available to it the competence to determine the acceptability of its findings in terms of applicable laws and regulations, community attitudes, and health and environmental considerations.

In 1978, the *NIH Guidelines* were revised, redefining IBC responsibilities to emphasize independent determination of required safeguards, exercise of delegated authority for approving certain experiments, and oversight of facilities, practices, and training. There was also a change in focus from "biohazard" to "biosafety" in the IBC activities.

Finally, in 1979, the NIH *Laboratory Safety Monograph* was published in response to requests for greater specificity in describing the practices, equipment, and facilities appropriate for the safe conduct of recombinant DNA research. It is a biosafety reference document that provides guidance to IBCs and tabulates its duties and responsibilities. The next major amendment to the *NIH Guidelines* of consequence to IBCs was Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants.*

Jack Keene, Ph.D., IBC Chair and Chairman of the Department of Microbiology, Duke University Medical Center, addressed "The ABCs of IBCs: The Nature of Today's Institutional Biosafety Committee." Dr. Keene described the factors affecting the changing landscape in which IBCs now operate, including

- locations outside of traditional medical centers,
- the increasing role of the private sector in human recombinant DNA research,
- the use of non-institutional and regional IBCs,
- intentional releases of microorganisms into the environment,
- the increasing use of recombinant virus vectors for gene transfer, and

- rapidly evolving research needs and controversies, including stem cell research and the threat of bioweapons.

Despite these changes, IBCs continue to have many of the key responsibilities originally that envisioned for them. These include ensuring adequate containment, conducting expert review and monitoring, informing the public of research plans, and providing a means of communication among researchers and healthcare providers. Long-range research goals that are facilitated by having an IBC include the abilities to conduct potentially hazardous research under controlled conditions, safely investigate disease processes, design new experimental organisms, and devise novel biological vectors. IBC review is appropriate prior to the initiation of research, at regular intervals during the activity, when a change in protocol occurs, and when new technologies are introduced.

Dr. Keene noted that, particularly with smaller committees, it is often difficult to meet the strict membership requirements for IBCs, as specified in Section IV-B-2-a-(1) of the *NIH Guidelines*. The wide variety of activities for which IBCs are responsible can demand expertise beyond that which can be provided by a group of only five individuals (the minimum number of IBC members per the *NIH Guidelines*). Larger committees may often be appropriate, since IBCs have quite a breadth of responsibilities, including:

- Examining experimental protocols that are submitted with grant applications,
- Evaluating the expertise of the principal investigator and staff to conduct the work,
- Evaluating the potential dangers of the work,
- Evaluating the biological containment plan and facilities per the *NIH Guidelines,*
- Determining whether additional expertise should be consulted,
- Determining whether health surveillance of laboratory staff is necessary,
- Requesting additional information from the principal investigator,
- Approving or disapproving the protocol, and
- Handling exceptions and exemptions.

IBCs must also recommend or require protective procedures, assigning protocols to appropriate levels of biological risk and physical containment specifications. In addition, IBCs may evaluate containment devices and procedures developed in response to its recommendations.

Amy Patterson, M.D., Director, NIH Office of Biotechnology Activities, spoke to "The NIH Office of Biotechnology Activities and IBCs: Promoting Synergy in rDNA Oversight." Dr. Patterson noted that OBA and IBCs are key components of a matrix of organizations involved in oversight, biosafety surveillance, and human subjects protections. For non-clinical research, this entails the agencies falling under the Coordinated Framework, and includes the U.S. Department of Agriculture, the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration, all of which have regulations governing some aspect of this work. For human gene transfer trials, the Office of Human Research Protections and IRBs have an additional role to play.

Dr. Patterson described some of the basic requirements that IBCs must fulfill under the *NIH Guidelines*, which include filing initial registrations, annual reports, and updates to committee

files as membership and other changes occur. There are presently about 450 IBCs registered with NIH. Over half (52 percent) are located in universities/medical schools; 27 percent are based in industry; 10 percent are housed in hospitals or clinics; 7 percent are in government facilities; and 4 percent are in private research institutes. It is interesting to note that the number of hospitals and clinics registering IBCs with OBA is growing steadily, a reflection of their increasing prevalence as sites for gene transfer trials. As these statistics illustrate, the registration process is important because it allows OBA to get a census of the field and to determine where recombinant DNA research is taking place. It also assures OBA that an appropriate mechanism of institutional oversight is in place and provides OBA with a point of contact when issues arise.

In addition to this form of compliance-based interaction, OBA interacts with IBCs in other ways. IBCs, for example, serve as sentinels in the field by which safety concerns and policy issues are raised and then discussed at a national level. OBA also serves as a resource for IBCs by virtue of its medical and scientific staff, who can respond to queries about interpretation of the *NIH Guidelines* and other matters. OBA also disseminates information of great relevance and importance to IBCs, such as the outcome of RAC discussion of protocols, data on human gene transfer trials, reports and minutes of safety symposia and policy conferences, and more. The establishment of a Gene Transfer Safety Assessment Board, the redesign and augmentation of the existing human gene transfer database, and additional scientific and policy symposia will all serve to enhance this role.

Dr. Patterson closed by noting the challenges that IBCs face in the current research environment and by describing the policy issues that OBA is studying relative to those challenges. She asked that conference participants provide (1) their comments about expectations of IBCs, (2) views about how OBA should handle registrations of "non-traditional" IBCs, and (3) opinions about how the *NIH Guidelines* should address IBC requirements.

Session II - IBCs and Institutions

Kenneth I. Berns, M.D., Ph.D., Vice President, Health Affairs and Dean, College of Medicine, University of Florida, addressed "Empowering IBCs in the Institutional Setting: Providing Resources, Assigning Authority, and Ensuring Accountability." A primary step in empowering IBCs, he noted, is to convince the faculty of the value and worth of biosafety review. There is a fine balance between ensuring safety and not impinging on academic freedoms.

Resources for IBC review can be committed in several ways, including to the institution's IBC, or externally to a proprietary IBC. The University of Florida uses a proprietary IBC for its commercially funded trials and an internal, institutionally based IBC for NIH-funded studies. In addition, academic IBCs often conduct reviews on behalf of external organizations, such as companies, other academic institutions, federal and state agencies, and private research foundations. Berns noted that the advent and growth of independent IRBs may be a harbinger of future trends for IBCs.

Institutions can provide resources to their own IBCs through staffing, provision of faculty as subject experts, and funding. Institutions can accord IBCs the authority to ensure not only compliance with the NIH Guidelines, but also enforcement of pertinent institutional policies and oversight of biosafety concerns. IBC staff can conduct lab inspections and programs of education as part of this responsibility. It is essential that IBCs be autonomous and accountable to both the institution in which the research is conducted as well as the federal funding and oversight agencies.

Kenneth Dretchen, Ph.D., Director, Office of Regulatory Affairs and Chairman, Department of Pharmacology, Georgetown University Medical Center, described "The Relationship of IBCs to IRBs and IACUCs: Their Respective Purview, Roles, and Responsibilities." He noted that IBCs are but one functioning unit in a complex web of regulatory activities at a research institution. He described the numerous units that might have research oversight responsibilities in a large academic research institution, including the office of regulatory affairs, the office of research assurance and compliance, the IRB, the IBC, the Institutional Animal Care and Use Committee (IACUC), the Radiation Safety Committee (RSC), the Research Integrity Committee, the Conflict of Interest Committee, the Office of Environment, Health, and Safety, and the animal housing facility. Each unit has different roles and responsibilities and reporting mechanisms. At Georgetown University Medical Center (GUMC), oversight is coordinated in part by cross-referencing on forms used in processing research proposals and by cross-representation of members on oversight committees. In addition, GUMC has an on-line database of research projects that is accessible to all these committees.

While some have commented that IRBs and IBCs have overlapping roles, Dr. Dretchen observed that their different mandates would preclude combining their functions into a single committee. However, their reviews can nonetheless be coordinated. Communication among administrative personnel is essential, Dr. Dretchen added, noting that his office has oversight of the activities of these two committees, as well as the IACUC and RSC. A combination of electronic tools, program orientation and review, monitoring to ensure compliance, and disciplinary action when noncompliance is found serve to increase safety for human subjects, health professionals, laboratory personnel, and the public. Dr. Dretchen proposed that, rather than having a "smokestack" approach whereby each committee relates independently to an oversight agency, their processes be instead integrated and interdependent.

Session III – The IBC Review Process: Open Questions Concerning Its Nature and Scope

Louis V. Kirchhoff, M.D., M.P.H., Professor of Internal Medicine and Epidemiology, University of Iowa College of Medicine, spoke about "IBCs and Continuing Oversight of Research: What is the IBC's Role in the Assessment and Ongoing Surveillance of Biosafety Risks." Dr. Kirchhoff observed that the IBC should conduct ongoing surveillance of all work involving recombinant DNA, including *in vitro* studies, experiments involving animals, and human gene therapy trials. In all of these situations, new registration documents need to be filed when there are changes in vectors or DNA inserts. In addition, reports of serious adverse events in human gene therapy trials need to be reviewed by physician members of the IBC who are trained in primary care subspecialties such as internal medicine, pediatrics, or family practice. The IBC also should review periodically its surveillance process with the goal of identifying

weaknesses that need to be corrected. Finally, the IBC must be prepared to respond to violations of the NIH Guidelines, both in terms of complying with administrative requirements for reporting such violations to the OBA as well as implementing measures designed to preclude such occurrences. In carrying out surveillance functions, IBCs face a number of challenges, not the least of which is getting investigators to report fully on their activities. Compliance with recombinant DNA requirements tends to be more problematic than in other areas, such as the use of radioactive materials and experiments involving animals, where investigators cannot obtain what they need for their experiments (i.e., radionuclides, animals) without fully disclosing what they plan to do. Moreover, in the latter two cases, investigators may have a higher appreciation for the risks of their work. The need for surveillance by the IBC is particularly important in human gene transfer research and in research involving the creation of transgenic whole organisms. Dr. Kirchhoff proposed expanding the categories of recombinant DNA research that are exempt from IBC scrutiny to allow more concentrated attention on these latter areas.

Terry Kwan, a community member of the Harvard University and Dana-Farber Cancer Institute IBCs, addressed "The Role of Community Members: Whom Do They Represent and What Do They Bring to the Review Process?" Ms. Kwan underscored the importance of appointing lay individuals as the "non-institutional" members of the IBC. They bring perspectives and challenge assumptions in a way that scientifically trained individuals typically do not. She added that if an institution is having difficulty recruiting community members for its IBC, then this may be a reflection of a larger public relations problem. Good sources of lay members are science teachers, and leaders and board members of non-profit organizations. She added that "busy people will do it if you make it interesting and meaningful."

Ms. Kwan outlined the characteristics of effective community members, including an interest in and understanding of the methods and goals of science, rudimentary knowledge of statistics and probability, familiarity with the surrounding community, integrity and strong ethical values, self-confidence, common sense, and absence of a personal agenda. Such members play a vital role in compelling the use of comprehensible language, adding local context and a real-world point of view, and independence from the academic research world. Lay members must balance protecting confidentiality with the public's right to know.

Session IV – Clinical Research: Addressing New Organizational Paradigms

Katherine High, M.D., Professor of Pediatrics and Director of Research, Hematology Division, Children's Hospital of Philadelphia, provided her perspective on "The Academic IBC in the New Clinical Research Context." Dr. High stated that, in human recombinant DNA research, the IBC at the Children's Hospital of Philadelphia (CHOP), which she chairs, is called on to assess novel therapies using recombinant DNA, including gene transfer (both *in vivo* and *ex vivo*), oligonucleotide strategies, DNA mismatch repair, and stem cell therapeutics. The scope of the review includes issues relating to recombinant DNA and RNA study agents, risks to health care workers and the public, as well as to the individual subject. Design of the clinical study is not the focus of the review but IBC members nonetheless need a working knowledge of pre-clinical safety and efficacy studies to conduct risk/benefit assessment. For example, they must be able to assess the likelihood of generating replication competent virus, either in production or

in vivo, the risks of horizontal transmission of study agents, and the risks of vertical (germline) transmission.

Education of health care workers at follow-up facilities is a relatively new issue that CHOP has had to consider. For example, while a research participant might receive a gene transfer intervention at CHOP, in many cases, patients return home to their local clinical treatment facility for follow-up and routine care. In one instance of this sort, OBA advised that the CHOP IBC oversee the biosafety risks of treating patients and handling samples at an outside hemophilia clinic. One concern, for example, was the possible spread of viral vectors to health care workers at the local facility. In response, the CHOP IBC advised health care workers at that facility to use universal precautions. When semen samples were positive for viral DNA, raising the specter of both horizontal and vertical transmission of DNA, CHOP advised subjects to use barrier contraception. This example of collaboration between an academic medical center and a local clinic highlights the challenges of defining the "site" for purposes of IBC review and biosafety oversight.

Steven Kradjian, Executive Director, Regulatory Affairs, VICAL Incorporated, addressed "The Needs and Responsibilities of Industry." Mr. Kradjian began by characterizing the evolution and present state of human gene transfer research. Whereas, all human gene transfer research used to be in Phase I trials, increasingly this research is moving into Phase II and even Phase III. As trials move into these latter phases, multi-site trials and the use of non-academic sites become increasingly prevalent features of this area of research. Twenty percent of VICAL trials take place in non-academic sites without their own IBC, and this share is expanding.

VICAL has its own IBC, which has traditionally reviewed internal research and manufacturing processes. Outside members outnumber VICAL employees on the committee, and the committee includes no one from the management team. Institutional IBCs also have a role to play in the testing of VICAL products. They conduct biosafety reviews for studies conducted in academic centers, reviewing the protocols and product information provided by VICAL. Non-academic sites without an IBC must establish an IBC to qualify for the study. VICAL often assists in the establishment of a local IBC by identifying a commercial provider of IBC services, who provides and trains local technical and medical reviewers, and instructs the site how to register the IBC with OBA.

Mr. Kradjian proposed a schema for determining the best means of employing various forms of IBC review. First, he distinguished between the matters that are of concern in Phase I versus latter phase trials. In Phase I, the product and its human applications are often untested, and IBCs must consider appropriate review and containment levels. By Phase II and III, the product is generally well characterized and containment issues have already been dealt with. At these junctures, compliance with Appendix M of the *NIH Guidelines* is the major consideration for IBCs.

Given these characteristics, Mr. Kradjian proposed that local IBC review at academic centers occur for Phase I human gene transfer trials employing novel products or novel approaches, especially those where public RAC review is likely. Centralized or remote IBC review, however, may be acceptable for Phase II or III trials, especially where these protocols are likely

to be exempted by RAC and entail containment at a BL-1 or BL-2 level. In these latter stage trials the safety issues are sufficiently characterized and the operational issues sufficiently large as to warrant a more flexible model of review, he said.

Cynthia Dunn, M.D., Vice President of Operations, Western Institutional Review Board, described "IBC Review in the Context of New Settings and Multi-Site Trials: The Western Model." Her organization, which has long offered commercial IRB services, has recently begun offering commercial IBC services, as well. Under this program, Western offers central administration of IBCs that it establishes for each research site. Many sites share core expert members, but each site also has at least two local members unique to that site. The IBC is accountable to an institutional official at the site, who must register the IBC with OBA and who receives reports from the IBC. Voting members of the IBC include clinical staff, a lay member, and biosafety or infection control experts. A representative from the trial site is non-voting and scientific or clinical members form the core IBC members. Dr. Dunn said that the IBCs serve as resources for the site, conduct protocol evaluation and site assessment, and review the consent forms because the IRBs often are not familiar with Appendix M of the *NIH Guidelines*. In addition, the IBCs assess adverse events and amendments to protocols. Meetings are posted and open to the public. Dr. Dunn believes this IBC model can provide the benefits of both "on-site" reviews and central coordination. Central coordination provides greater access to expertise, encourages best practices for compliance and consistent oversight, and minimizes conflicts of interest because the majority of members are non-affiliated.

General Discussion

Opportunity for audience participation was offered at several junctures during the first day of the meeting. A number of themes were raised.

Membership and staffing - Several conference participants raised concerns about difficulties in recruiting individuals to serve on IBCs. Also, given the growing number of human gene transfer protocols coming before IBCs, some questioned whether many committees have the clinical expertise needed to assess human safety issues. In addition to concerns about basic and clinical applications of recombinant DNA, other safety issues are often brought to IBCs, such as the proper handling and registration of agents that might be used in biological warfare or terrorism. These additional review responsibilities must be considered when funding, staffing, and appointing IBCs.

Stages of protocol review - Commenters sought clarification about the proper order of various stages of protocol review, including review by scientific merit review bodies, the IRB, the IBC, and the NIH Recombinant DNA Advisory Committee. Dr. Patterson reminded participants that RAC review no longer involves a recommendation regarding approval of human gene transfer trials; instead, the RAC process occurs early and serves to inform decision making by the IBC and other bodies.

NIH Guidelines – Several participants suggested that OBA could disseminate information on exemptions from the *NIH Guidelines*, possibly by posting the status of various agents and their

exempt status on the OBA website. A user-friendly version of the *NIH Guidelines* as a whole would be especially appreciated, several participants commented.

Professional education and guidance - Participants agreed that there is a need to educate investigators through face-to-face professional development on the requirements of biosafety compliance. One issue that surfaces in reviews and investigator-IBC interactions is containment. Several participants urged OBA to revisit the laboratory monograph in this area.

Adverse event reporting - Participants asked for clarification of whether RAC should receive information from the IBCs regarding serious adverse events. Others pointed to the need for IBCs to communicate with the IRB about these events and expressed uncertainty about the relative roles of these two committees.

Effectiveness – To promote effectiveness, IBCs need standard operating procedures and performance benchmarks. Cross-communication between IBCs, IRBs, and IACUCs is essential to their functioning optimally. Also, participants urged more communication up from the IBCs to RAC and OBA. In addition, means of promoting IBC networking would be useful.

Policy Roundtable–Characteristics of IBCs

On the second day of the conference, Roundtable participants and audience members considered a series of structured questions (Appendix A) concerning the expectations, roles, and responsibilities of IBCs. Some of the specific topics of discussion included the following:

- ensuring accountability of IBCs to the institutions they serve;
- enhancing public access to IBC meetings and information regarding IBCs;
- understanding and meeting community concerns;
- conducting appropriate safety surveillance procedures;
- following containment procedures at all facilities;
- ensuring representation of local knowledge on IBCs; and
- ensuring that safety training becomes an institutional priority.

In addition, Roundtable and conference participants discussed a series of hypothetical cases (Appendix B) involving IBCs that allowed discussants to consider their views about the roles of these committees within the context of actual examples. The following section summarizes these discussions.

Accountability

Because it is the responsibility of the institution that is conducting the research to establish the IBC and to accord it proper authority, it follows that the IBC should be directly accountable to that institution. Although the institution must ensure that the IBC understands what constitutes regulatory compliance, the IBC itself must ensure that it complies with the pertinent rules and regulations and must assume responsibility for obtaining the needed expertise and resources.

Several participants discussed the characteristics that make an institution accountable for IBC review. Because the *NIH Guidelines* were designed to apply to institutions that receive NIH funds for recombinant DNA research, those institutions have long held certain responsibilities in this regard. However, the research environment has changed—with more private funding, industry-academia-government collaboration, and multi-site trials. Consequently, while the *NIH Guidelines* speak to the responsibilities of NIH-funded institutions, other institutions may nonetheless have a key role and responsibility for the integrity of the trial. In light of this, some participants suggested that the *NIH Guidelines* need to be reconsidered as to how the accountable institution is defined.

The IRB and IACUC models of review require that an institutional official provide an assurance to the federal government that the institution is in regulatory compliance. This exact mechanism does not exist for IBCs. However, the original *NIH Laboratory Safety Monograph* says that "the IBC should be established by the highest administrator in the institution," implying that an institutional official should be accountable. Some participants suggested that there is a need to revise the *NIH Guidelines* as they pertain to clinical research in order to clarify the role of the official with IBC oversight responsibility and to distinguish that individual from the institutional official who signs the federal assurance for the protection of human subjects in research (as per 45 CFR 46).

To ensure that IBCs have access to the necessary institutional records, the institution must have at least one person on site who understands the organization's relevant policies and procedures (e.g., handling of hazardous materials, pharmacy procedures), participants agreed. In the Western model, each IBC has at least one individual – generally a nonvoting member - who is affiliated with the research site who can ensure or facilitate access to necessary resources and information.

As for institutional representation on the IBC, participants suggested that appointing a biological safety officer, an environmental health and safety official, or a research administrator would be the best way to enhance the effectiveness and institutional clout of the IBC. In the case of gene transfer studies, many participants emphasized that participation by a clinician or someone with expertise in infection control is essential.

Participants discussed a case example in which an experimental gene transfer trial would be initiated at an academic medical center receiving NIH funds. After the intervention, patients would be followed at a non-NIH funded oncology clinic 50 miles away. Participants stated that it would be reasonable for the academic IRB and IBC to have oversight of the trial, including the follow-up, at the oncology clinic, which would require rigorous communication and sharing of information between the two sites. Participants said that it is the responsibility of the principal investigator and the academic IBC to ensure that safety precautions are taken at the off-site location. The IBC, it was agreed, should ensure that the personnel at the secondary site have adequate expertise in biosafety.

In the event that a trial takes place at more than one institution, each with an on-site IBC, participants suggested that the second (or other) institution(s) might want to conduct a non-mandatory independent IBC review. The primary institution's IBC could be designated as the

lead IBC and could consult with IBCs at the other institutions. In any case, all sites must comply with the *NIH Guidelines* if they conduct any NIH-funded recombinant DNA research, based on the current wording of the *NIH Guidelines*. Research sites that receive no federal funding have no obligation to comply with the *NIH Guidelines*, although many do so voluntarily.

Finally, because of concerns about accountability and sufficient mechanisms for review and oversight, participants noted that some sites are not appropriate for clinical recombinant DNA research; the *NIH Guidelines* could help clarify the characteristics of acceptable sites, one observer suggested.

Accessibility/Availability

The *NIH Guidelines* encourage public access to IBC meetings. In some states, public universities are required to convene public meetings, but policies vary from institution to institution, particularly with respect to protecting patient confidentiality in open discussions of protocols. Several participants noted that the new privacy regulations proposed under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) might make it difficult, if not impossible, to divulge information publicly that would identify individuals, especially when adverse events are involved.

Other participants addressed the definition of "the public" and agreed that the press is a public entity. Many institutions, though, are now facing security concerns involving media reporting about the use and location of toxins and select agents in research settings. In general, participants agreed that the presence of non-institutional members on the IBC does not obviate the benefit of public access.

Community Concerns

Information about the perspectives of those outside the institution can provide valuable insight into how the community perceives the institution's attention to safety in its research activities. Trust is an important issue, especially in certain forms of recombinant DNA research where the risks and benefits remain uncertain. In considering the benefits of community participation, participants discussed how the institution and its research programs are enhanced when the community member of the IBC feels that the process has integrity. In addition, community members bring common sense and local sensitivities to the review process. Participants emphasized that non-institutional slots should not be filled exclusively with scientists and that the requirements in the *NIH Guidelines* for two such individuals should be viewed as a floor, not a ceiling.

Ensuring that community concerns are met is a more challenging task for industry, because its definition of community can differ greatly from that of the traditional academic medical center. For industry, notions of "community" can be diverse and constantly changing as a result of the rise in multinational corporations, frequent industry mergers, and the number of trials involving multiple sites. "Community" can also have a nongeographic meaning, encompassing certain patient groups, ethnicities, or classes of people who might be the subjects of the research.

Safety and Surveillance

Although the IBC must be assured that the institution is conducting safety surveillance, many participants believed that the committee could not undertake this function day to day. More often than not, this is more appropriately a responsibility of institutional staff. With regard to human gene transfer studies, several participants suggested that there is a need to more clearly define the IBC's function in this arena. In recent years, clinical activity in this area has become an additional IBC responsibility, but many committees lack the clinical expertise to review these studies, conduct surveillance, or assess adverse events. Some participants observed that Appendix M of the *NIH Guidelines* addresses human subjects protection issues that are already being attended to by IRBs.

Uncertainty remains about how IBCs should proceed when they receive reports of serious adverse events. This is especially true for IBCs that are unaccustomed to reviewing studies involving human subjects. Participants agreed that if serious adverse events are reported to an IBC, it should at the very least ensure that the reports are passed on to and discussed with the IRB.

Participants noted that it would be helpful to develop best practice guidelines for safety surveillance by IBCs that provide clear guidance about the relationship of these activities to those of IRBs and Data Safety Monitoring Boards (DSMBs). Participants were interested in knowing whether the DSMB model is helpful in considering the role of IBCs in safety surveillance. It was agreed that for multi-site studies, the use of site monitors might be a useful mechanism for ensuring that investigators at each site are in compliance with the IBC's recommendations.

Containment/Facilities

Participants discussed the importance of the community's perspective regarding containment issues. For example, a member of the community would be more likely to ask if a site has informed the fire department about how to handle an emergency or to express concern about construction issues than someone who is not a member of the community. Some participants noted that given the passage of the Patriots Act, it is especially important for individuals from the local community to become involved in laboratory safety activities, especially when select agents are involved.

Several speakers noted that the *NIH Guidelines* provide little direction on how to determine levels of risk and that it would be helpful if OBA could post on the Web the known hazards involved in working with various agents. One participant noted that the guidelines for xenotransplantation research provide a good model for determining and educating the community about risk.

The issue of containment becomes less clear in studies that involve patients who have been treated with vectors and sent back to their communities. Some participants suggested that a brochure containing both safety and contact information could be developed to send home with patients in the event that they require treatment by local health professionals. In addition, the

informed consent process should make clear what steps patients should take if they experience an adverse event after leaving the facility where the experiment intervention was performed.

Local Knowledge

Having knowledge of the skills and experience of the investigators who are proposing the research is essential to conducting effective review. However, this knowledge can also bias review. Bias might occur, for example, when untenured faculty members are asked to review the research of more senior investigators or colleagues at their institution. Nonetheless, a well-constituted IBC can balance the need for familiarity with the need for independent and unbiased review.

The *NIH Guidelines* do not specify how many IBC members must be employees of the institution, but participants noted that the intent of the original guidelines was to ensure that local knowledge was present on the committee. Participants agreed that, at the very least, the IBC should include a biosafety officer from the institution, especially given the requirements of Section IV-b-2-b of the *NIH Guidelines*. However, some participants suggested that institutional members should always be nonvoting members.

Training of IBC members

Many training programs are currently available for IBCs and investigators. However, merely training individuals to be aware of the regulations and the *NIH Guidelines* is insufficient. Focusing biosafety training solely on understanding the applicable regulations and guidelines may hinder some individuals from grasping the important concepts of good safety practices, the role of the biosafety officer, and the requirements of, for example, an industrial hygiene department. Safety issues and relevant training must become institutional priorities and cannot be left to the IBC to manage or oversee.

Recommendations About the *NIH Guidelines* and Future Initiatives

After working through the various exercises and case studies, Roundtable and audience members were asked to respond to the following question: "In light of the changing research landscape, what do today's discussions suggest for how the key roles and essential responsibilities of IBCs are reflected in the *NIH Guidelines*?**"**

Participants suggested that the NIH take the following actions with regard to IBCs, the *NIH Guidelines* and related matters:

- Provide a clear delineation between the review of basic recombinant DNA research and the requirements of Appendix M for clinical gene transfer studies.

- Harmonize and clarify the roles of IBCs and IRBs, drawing clear lines to distinguish their purviews and responsibilities. The goal should be to remove redundancy and gaps in review.

- Define more clearly the IBC's role in receiving, assessing, and reporting serious adverse events, and harmonize these activities with reporting requirements across the various agencies and institutes within the Department of Health and Human Services (DHHS).

- Articulate the surveillance responsibilities of IBCs and institutional staff.

- Incorporate into the *NIH Guidelines* a requirement to appoint an institutional official responsible for their implementation. In addition, OBA should consider developing a "biosafety assurance statement" that could be negotiated with registered IBCs, similar to that issued by the DHHS Office of Human Research Protections for clinical research.

- Define the term "clinical site."

- Encourage institutions to reward faculty for time and effort spent participating on IBCs.

- Develop a guide that describes the nature of exempt practices and good practices for exempt experiments.

- Review the *NIH Guidelines* and their IBC requirements as they might be applied to small privately funded clinical sites that are not affiliated with an academic medical center. OBA should encourage these sites to voluntarily comply and provide a way for them to do so.

- Simplify the *NIH Guidelines* and make them more user friendly. Separate the *NIH Guidelines* into several documents that focus on specific endeavors, e.g., large-scale laboratory work, studies in plants, animals, and humans. Such stand-alone sections would make it easier for investigators to identify their obligations and responsibilities. In addition, this approach would make the *NIH Guidelines* easier to modify over the years as science and the research environment evolves. The creation of an index and a flow chart outlining the steps in the review process would also be helpful.

- Provide education and training about the *NIH Guidelines* nationwide.