

National Conference on Alternative IRB
Models:
Optimizing Human Subject Protection

November 19-21, 2006

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Executive Summary

Background

This report summarizes the findings of a national conference held in Washington, D.C. on November 19-21, 2006: “National Conference on Alternative IRB Models: Optimizing Human Subject Protection.” Its purpose was to enhance the protection of human subjects of research by encouraging the use of alternative Institutional Review Boards (IRB) models under appropriate circumstances. Planners shared a belief that the changing nature of research involving human subjects, particularly investigations involving multi-institutional trials, has created an opportunity to be more innovative in selecting IRB models.

The conference was sponsored by the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), the Association of American Medical Colleges (AAMC), the American Society of Clinical Oncology (ASCO), and the Department of Veterans Affairs (VA); cosponsors included the Association of American Universities (AAU), the Council on Government Relations (COGR), the Consortium of Social Science Associations (COSSA), the Department of Defense (DOD), the National Association of College and University Attorneys (NACUA), and Public Responsibility in Medicine and Research (PRIM&R). The Food and Drug Administration (FDA) also participated in planning the conference.

Framework for the Conference

Issues explored in the conference were identified by participants in a preceding workshop, “Alternative Models of IRB Review,” held in Washington, D.C. on November 17-18, 2005. Sponsors included OHRP, NIH, AAMC, and ASCO. This workshop was suggested by the Secretary’s Advisory Committee on Human Research Protections (SACHRP) in the fall of 2004 as a means of exploring the issues associated with the use of alternatives to local IRBs. Participants included IRB chairs, academic investigators, community-based researchers, attorneys, patients, ethicists, industry officials, and senior university and medical school research administrators.

Participants in the 2005 workshop identified significant barriers in selecting and implementing alternative IRB models. The 2006 conference explored each of these issues in depth. The first day of the conference featured panels and breakout sessions on the following subjects:

- Addressing issues related to liability
- Sharing authority and responsibilities
- Ensuring review quality, and
- Costs, timing, and loss of revenues.

On the second day, key issues distilled from participant reports were addressed from the perspective of specific stakeholder groups. Findings from both days are presented below.

Addressing Issues Related to Liability

What implications would the use of alternative forms of IRB review have for regulatory or civil liability? Session participants who explored this question concluded that risks will always be present for institutions engaged in research, regardless of whether an internal or external IRB is used. Cases involving civil liability are rare, but the number could increase as the number of trials grows. Findings of regulatory noncompliance are more common; therefore, regulatory liability is a more significant concern. Given the responsibility institutions bear under their Federal-Wide Assurances (FWAs), institutions are apprehensive about the potential consequences of decisions made by external IRBs. The structure of the institution's FWA has implications for liability; institutions may choose to include or exclude research funded by sources other than the Federal government. Institutions are concerned that decisions by external IRBs might be inconsistent with institutional policies and procedures, compromising the institution.

Institutions are also concerned about their own potential liability when they serve as the IRB of record for community-based research projects. If an institution extends its FWA to research not funded by the Department of Health and Human Services (HHS) and reviews research for community investigators, the activities of these investigators could place the institution at risk.

Under what circumstances would the various forms of alternative review be most appropriate from the perspective of regulatory or civil liability? Session participants concluded that certain types of research should be considered for external review. These include multi-site trials, areas requiring specialized expertise not readily available to the institution, research related to situations that require rapid response, research involving special populations, and research accomplished through practice-based or regional networks.

Define how local IRBs and external IRBs should share responsibility for regulatory liability in light of the belief that local institutions are responsible for oversight of all aspects of research performed in their institution. Sharing of regulatory liability is best specified in detailed agreements between institutions.

Sharing Authority and Responsibilities

How can shared authority and responsibilities best be managed to ensure appropriate control and accountability? Session participants concluded that sharing authority and responsibilities is enhanced by trust, transparency, and good communication in the relationship between the institution and the external IRB. Accreditation can provide a baseline assurance of quality.

Define how local IRBs and independent IRBs should share responsibility for research review and oversight. Include recommendations for how to deal with a catastrophic untoward event, an OHRP for-cause review, or an inquiry from a reporter. Stakeholder groups explored this question and concluded that most responsibilities cannot be divided using an "all-or-nothing" model; they are truly shared. Response to untoward events is a shared responsibility. The delineation of responsibilities is in part a contractual issue that should be clearly defined at the beginning of the relationship between the institution and external IRB. Further, the agreement

between the institution and the external IRB should address responsibilities for speaking to media representatives if a “catastrophic untoward event” occurs.

Ensuring Review Quality

What are the issues, barriers, and challenges involved in using alternative IRB models that are related to quality of review and the capacity to consider the local context of research?

Issues related to quality of review under traditional models include redundant reviews in multi-site trials, variability, delays, a loss of efficiency, and needless “tinkering” with consent forms. Also, local and institutional politics may detract from the desired focus on human subjects, introducing bias. Positive attributes of local review, however, include knowledge of local investigators, opportunities for mentoring, and superior knowledge of the local subject population in some instances.

Barriers to the use of the various models for independent review include resistance from the IRB or institution, the perception that other IRBs would not care as much as the local IRB about quality or other institutional priorities, concerns that bureaucratic checklists might be used at the expense of ethics, lack of trust, insufficient communication, and lack of awareness of alternatives.

How can shared authority and responsibilities best be managed to ensure appropriate control and accountability? Participants felt that multiple options for conducting alternative forms of review exist, and an “all or nothing” approach does not capture the range of possible options for review that are currently being created and explored. Examples of such options include collaborative consortia, facilitated local review, and risk management reviews. They observed that emerging information and communication technologies facilitate collaboration across a distance, reducing barriers to the use of independent IRBs or collaborative forms of review. Technology can facilitate information sharing within and across IRBs, increasing trust through transparency of operations.

Attributes of successful, alternative review models include good two-way communication, trust, exchange of documentation, a patient or subject-centered ethic, resources for investigator training and oversight, and provision for meaningful community input and participation.

Define how local IRBs and external IRBs should share responsibility for “local context.”

Session participants concluded that external IRBs have the advantage of being less vulnerable to institutional pressures when a protocol is submitted by an investigator with a questionable record. To ensure that local context is adequately addressed, institutions should convey their knowledge of local factors that affect human subject protection (such as knowledge of investigator reputation) to the external IRB.

Research subjects and advocates stressed that issues regarding local context arise more frequently than is generally recognized and should always be explored. They believed that subjects and their representatives should be involved throughout the research process to ensure sensitivity to local issues, regardless of the form of IRB review, and suggested that advocacy groups provide training to enable them to play this role effectively.

What empirical data are needed to assess risks and benefits of alternative forms of review, their impact on the quality of reviews and oversight, and related issues? Session participants agreed that data are needed to help everyone explore and assess the various forms of alternative

review and to help ensure they are used in ways that benefit all stakeholders. Appropriate metrics for assessing IRB performance suggested at the conference include:

- Turnaround time,
- The level of respect accorded to the IRB's advice and counsel,
- The reading level of consent forms,
- Member selection and attendance,
- The number of times protocols are amended,
- The resources available to the human research protection program (HRPP),
- How technology is applied, and
- The extent to which subjects are involved and understand the protocol.

Because of the importance of such research, participants recommended that HHS give OHRP the authority to issue grants to support research on human research protection.

Costs, Timing, and Loss of Revenues

What are the significant issues surrounding the costs of alternative forms of IRB review? How would the use of alternative forms of IRB review affect the timely completion of milestones in research oversight? Participants stressed that variability in the time required for multiple IRBs to review a multi-site study is a key concern to sponsors, who need to be able to predict the time needed for review and budget accordingly. However, participants felt there were insufficient data at present to answer either of the questions posed.

To gather needed data and facilitate comparisons among forms of review, participants suggested that meaningful data related to costs, quality, and timeliness of review should be collected using standard methodology. They stressed that a common taxonomy is needed to allow standardized data collection and comparison across institutions. Participants also observed that technology can make it easier to develop and use appropriate metrics to measure efficiency and timing.

Would the use of alternative forms of IRB review have a negative affect on funding of human subjects protection at the institutional level? Session participants concluded that in some cases, use of an external IRB might lead to a loss of revenue needed to support institutional Human Research Protection Programs. A particular concern is the availability of funds for education and training. However, they felt they lacked definitive data to answer this question.

The Role of Regulatory and Funding Agencies

Participants believed that regulatory agencies could do much to encourage institutions to use external IRBs when appropriate. They recommended that regulatory agencies give clear signals that alternative forms of review are acceptable. In addition, because of concerns about the potential for regulatory liability resulting from the actions of an external IRB, participants asked HHS to revise its policies regarding the responsibility of institutions for all work conducted under their FWAs. They suggested that HHS consider policies similar to those of the FDA, which ties regulatory liability to the organization responsible for the alleged problem. An alternate approach to alleviating institutional concerns would be for OHRP to include a statement in the FWA to the effect that when institutions use due diligence in selecting an external IRB, they will not be held responsible for

that IRB's decisions. The meaning of due diligence should be clearly defined so that institutions can demonstrate compliance.

Participants stressed the importance of harmonization among Federal laws and requirements to help institutions assure that their use of external IRBs is fully compliant. They called for clarification and harmonization among all regulatory requirements related to the use of alternative forms of IRB review, as well as clear guidance on the use of these mechanisms. Participants also urged HHS to harmonize the Health Insurance Portability and Accountability Act (HIPAA), which is administered by the HHS Office of Civil Rights, with the Common Rule. They viewed this as especially important for multi-site studies.

Some session participants also suggested that Federal agencies that sponsor research consider the use of incentives to encourage grantees to use alternative forms of reviews when they are appropriate.

Foreword

This report summarizes the findings of a national conference held in Washington, D.C. on November 19-21, 2006: “National Conference on Alternative IRB Models: Optimizing Human Subject Protection.” Its purpose was to enhance the protection of human subjects of research by encouraging the use of alternative Institutional Review Boards (IRB) models under appropriate circumstances. Planners had two primary goals:

- To optimize IRB access to appropriate ethical and scientific expertise for reviewing increasingly sophisticated projects, and
- To make the best use of scarce IRB resources.

Planners shared a belief that the changing nature of research involving human subjects, particularly investigations involving multi-institutional trials, has created an opportunity to be more innovative in selecting IRB models.

The conference was sponsored by the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), the Association of American Medical Colleges (AAMC), and the American Society of Clinical Oncology (ASCO), and the Department of Veterans Affairs (VA); cosponsors included the Association of American Universities (AAU), the Council on Government Relations (COGR), the Consortium of Social Science Associations (COSSA), the Department of Defense (DOD), the National Association of College and University Attorneys (NACUA), and Public Responsibility in Medicine and Research (PRIM&R). The Food and Drug Administration (FDA) also participated in planning the conference.

A foundation for the conference was laid by an earlier workshop, “Alternative Models of IRB Review,” held in Washington, D.C. on November 17-18, 2005. Sponsors included OHRP, NIH, AAMC, and ASCO. This workshop was suggested by the Secretary’s Advisory Committee on Human Research Protections (SACHRP) in the fall of 2004 as a means of exploring the issues associated with the use of alternatives to local IRBs. Participants included IRB chairs, academic investigators, community-based researchers, attorneys, patients, ethicists, industry officials, and senior university and medical school research administrators.

Participants in the 2005 workshop identified significant barriers in selecting and implementing alternative IRB models. The 2006 conference explored each of these issues in depth. The first day of the conference featured panels and breakout sessions on liability; shared authority and responsibilities; quality of review, including capacity to consider local context; and costs, timing, and loss of revenues. On the second day, key issues distilled from participant reports were addressed from the perspective of specific stakeholder groups. The closing plenary sought to define areas of consensus. The conference used breakout sessions, followed by plenary presentations and general discussions, to garner a range of perspectives.

I. Introduction

The framework for the conference was established by opening remarks from four speakers in a plenary session: Dr. Bernard Schwetz, the Director of the Office of Human Research Protections (OHRP); Dr. Robert J. Levine, the Co-Director of the Interdisciplinary Bioethics Center at Yale University; Dr. Lowell E. Schnipper, the Theodore and Evelyn Berenson Professor of Medicine at the Harvard Medical School; and Dr. Richard W. Bianco, the Associate Vice President for Research and Regulatory Affairs at the University of Minnesota and an Assistant Professor of Surgery. This session was moderated by Dr. Levine.

Welcome and Opening Remarks

Bernard Schwetz, D.V.M., Ph.D.

Director, Office of Human Research Protections

Dr. Schwetz stressed that in joining with other agencies to sponsor this conference, OHRP is by no means signaling a loss of confidence in local IRBs. Nor is it pushing institutions to use central or external IRBs. Rather, OHRP's interest lies in ensuring that models for IRB review that are selected are those that are most appropriate for the institution and its needs, as well as for the specific research.

OHRP is interested in learning why more institutions are not using the emerging alternative models for review. To this end, it cosponsored a workshop on this topic about a year ago; over 50 participants explored the pros and cons of alternative models and addressed the question of how to encourage the use of the models best suited for particular research programs. While the exchange of views at the 2005 workshop did not result in a mass movement from one position to another, attendees both expressed themselves and listened to others with different points of view. The barriers to the use of alternative models that were defined through their efforts provide the starting point for this 2006 conference. Areas of particular concern included:

- The legal and regulatory liability of the research institution and the local or external IRB;
- The need for agreements that clearly define shared authority and responsibilities, which are essential when problems develop;
- Ensuring adequate understanding of the local context when an IRB in a remote location is used;
- Assurance that the review will meet or exceed the standards of the institutional IRB;
- The relative cost of alternative forms of review;
- Accomplishing the review in a timely way; and
- The potential loss of resources that the institutional IRB needs to fulfill its responsibilities.

To explore these issues further, Dr. Schwetz noted that both sponsoring and cosponsoring agencies have reached out to key stakeholder groups. The result is a diverse group of attendees. He expressed the hope that participants will garner valuable information and return home having heard a variety of experiences and opinions. Sponsors and cosponsors are also looking forward to hearing stories of both successes and difficulties in using alternatives; in addition, some recommendations are expected to emerge from the conference, although they are not its primary purpose.

A Historical Perspective on Alternative IRB Models

Robert J. Levine, M.D.

Co-Director, Interdisciplinary Bioethics Center, Yale University

Looking back to the origins of the IRB, Dr. Levine reminded participants that, writing in 1978, the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research saw IRBs as an agency that would balance the interests of investigators with those of the subjects. The Commission wrote: “The ethical conduct of research...requires a balancing of society’s interests in protecting the rights of subjects and developing knowledge that can benefit society as a whole....[Review is required] because investigators are always in positions of potential conflicts of interest by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects....” It envisioned that the local committee would “work closely with investigators to assure that the rights and welfare of...subjects are protected and...that the application of policies is fair to the investigators.” The expected relationship with investigators, Dr. Levine pointed out, was a collegial one. The Commission also saw IRBs as “local committees...operating pursuant to Federal regulations and located in institutions where research...is conducted,” holding the view that “compared to the possible alternatives of a regional or national review...local committees have the advantage of greater familiarity with the conditions surrounding the conduct of the research.”

Initially, during the 1970s and 1980s, IRB membership was desirable; it was considered an opportunity for a professor or a student to make important contributions to the academic community. During this period, Dr. Levine said, senior and respected members of the faculty served on IRBs and students competed for coveted appointments to the committee. They were motivated by the wish to be of service to the discipline and to the institution, as well as a desire to be respected within the institution. Such motivated members, he said, are critical to the success of the IRB.

However, Dr. Levine said that motivation to IRBs was eroded as the credibility of IRBs was called into question. Governmental commissions and journalists have publicly portrayed IRBs as incompetent, and local IRB members have been held responsible by their colleagues for shut-downs resulting from compliance issues. Their prestige also suffered, he believed, when they were required to enforce questionable policies (such as the requirement to get informed consent from so-called “secondary” research subjects) and carry out energy-sapping, low-yield chores such as periodic reapprovals for ongoing research and the review of adverse event reports.

Another factor in declining motivation to serve on some IRBs is the fact that medical schools are in the throes of a severe financial crisis. Faculty members are required to generate revenue and may no longer see activities that do not generate revenue as sufficiently rewarding. This situation, in Dr. Levine’s estimation, could be the biggest threat to the motivation to be an IRB member.

Because of the twin challenges of maintaining credibility within the institution and of recruiting and retaining high quality members, Dr. Levine saw cause for concern about the well-being of the local IRB. In consequence, he sees more universities and other institutions turning to central review boards and other alternative forms of review. While he does not see this trend as likely to result in any measurable decrease in compliance with regulations, the speaker feared that something of “immeasurable value” could be lost in the process.

Clinical Cancer Research: The Role of Alternative IRB Models in Enhancing Progress

Lowell E. Schnipper, M.D.

Theodore and Evelyn Berenson Professor of Medicine, Harvard Medical School

Dr. Schnipper provided background on how the American Society of Clinical Oncology (ASCO) has reached the conclusion that alternative forms of IRB review must be used with greater frequency. He explained that advances in the understanding of cancer biology have led to a “sea change” in cancer medicine, resulting in an urgent need for “smarter” studies and a sharp increase in the number of research participants.

Historically, clinical cancer research used an empirical approach in which drugs were evaluated to find cures that worked by killing certain cells. This approach has resulted in significant progress in certain types of cancer. For example, 70 percent of pediatric cancers are now curable; curative therapy is available for several adult cancers, including Hodgkins and non-Hodgkins lymphoma, testicular cancers, some leukemias, and breast cancer; there has been a 20 percent improvement in survival rates for colo-rectal cancers. Despite these successes, significant progress has been slow for most prevalent cancers.

Recent advances in the understanding of cancer development and cell biology have highlighted the potential for therapies that interfere with the molecular mechanisms that drive the cancer process. We now know that cancer is a highly diverse disease and that it is characterized by distinct alterations that present “druggable” molecular targets. If these targets can be identified, strategies can be devised to interfere with the “locomotive” that propels cancer cell development, halting the cancer. However, any one of these targets could be expressed in only a small number of cancers. A further complication is that different cancers present different molecular targets (a function of the diverse pathways that drive them). Given the complex challenge of finding targets that will respond to drugs and the heterogeneous nature of most cancers, it may be necessary to collect samples from patients from many sites across the nation or even worldwide. Studies can then test agents against the cancers with the “druggable” target. Dr. Schnipper stressed that access to a large patient population, speed, and high-quality data are the essence of performing clinical research in this context.

An ASCO task force concluded that, for multi-site oncology trials, review by local IRBs is duplicative and time consuming; it will not allow researchers to meet the challenge of the changing nature of research successfully. Task force members interviewed representatives of institutions large and small and heard consistent reports that local IRBs were overwhelmed with volume and by the time-consuming requirement to analyze adverse events from multi-site trials. IRBs varied greatly in the expertise in oncology represented on the IRB; expert review, which ASCO considers critical, is not always available. Additional barriers to optimum IRB performance included limited funding and difficulties identifying members, both of which contributed to difficulties monitoring the implementation of clinical trials. ASCO also concluded that IRB reviews varied in quality, that investigators needed more education, that the process for reviewing potential conflicts of interest lacked uniformity, that informed consent review tended to focus on the document rather than the process, and that the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) should harmonize their research oversight.

ASCO is committed to modifying the system to ensure broad scientific expertise, promote efficiency, and support the “smart trials” that the next phase of cancer research demands. Consequently, the potential for centralized or regional forms of review has become a focal point for discussion. In the context of multi-site trials, alternative forms of review have the potential to reduce costs, eliminate duplicative review, enhance speed of review while retaining quality, help ensure consistency across trial sites, and offer concentrated expertise in specialized areas. The local IRB would then be able to focus its resources on monitoring the onsite trial.

In a 2002 policy statement on oversight of clinical research, ASCO highlighted a “tremendous opportunity to employ a centralized mechanism to provide ethical review by highly trained IRB members, allowing local IRBs to take advantage of the financial and time efficiencies that central review provides.” ASCO envisioned multiple Centralized Review Boards (CRBs) functioning as regional review boards, using a single protocol and consent form, and monitoring and evaluating adverse events (AEs) on a “global basis.”

Dr. Schnipper concluded by stressing that the infrastructure that protects human research subjects must adapt in order to support the potential for progress, ensuring both high quality science and ethically sound trials. This change is essential to take advantage of the unprecedented opportunities created by groundbreaking research to address a serious public health problem.

An Institutional Perspective on Alternative IRBs

Richard W. Bianco, Ph.D.

Associate Vice President for Research and Regulatory Affairs, University of Minnesota; Assistant Professor of Surgery

Dr. Bianco is the authorized Institutional Official (IO) for the University of Minnesota; in this capacity, he is responsible for oversight of research and IRB functions. He has also served as a member of the University’s IRB for 12 years, a period that included experience acting as Vice-Chair. His University has experienced a “dramatically intensified” level of pressure to “outsource” the review process, particularly for multi-center trials. Like other academic health centers, the University of Minnesota is seeking to increase the number of clinical trials it conducts; intense financial and time pressures drive the search for alternative, efficient forms of review. The difficulty in getting faculty to serve on the IRB is an additional incentive for change.

Both sponsors and faculty members have encouraged the use of central IRBs. A medical consultative committee convened by Dr. Bianco urged this strategy in the belief that it would result in quicker approval for proposed projects and foster consistent review of multi-center trials. Some faculty went so far as to assert that sponsors will not offer the university opportunities for clinical trials if it does not use Central IRBs. Unfortunately, there is a common misperception that using an alternative review mechanism is simply a matter of signing a form that will absolve the university and its faculty of further oversight responsibilities.

While Dr. Bianco does not believe that local systems of subject protection are significantly flawed, he does believe that improvements in structure, service, and efficiency are needed. While the “train has left the station” in regard to alternative forms of review, he would like to slow the train and take a careful look at options.

The University of Minnesota has developed metrics to show how much time is spent on each phase of the clinical trial application process. These data do not suggest problems that can be solved by using central IRBs. Dr. Bianco noted that:

- The time required to place an application on the IRB's agenda is largely determined by the quality of the application.
- The longest delay in IRB review is the time spent waiting for the Principal Investigator (PI) to respond to the IRB's stipulations.
- The longest delay in the entire process involves contract negotiation and financial administration.
- Significant delays can also result if a financial conflict of interest is disclosed.

Positive trends include increasingly professional local IRBs (a transformation aided by accreditation), integrated compliance programs, and service-oriented procedures and staff. At the same time, the speaker sees clinical researchers becoming less involved with protecting human subjects and reports a trend toward fewer physician IRB members and less experienced IRB members, which can lead to inadequate and extended review. Integrated programs may also be perceived as resulting in longer times for IRB reviews.

Additional institutional support is needed to increase the efficiency of the IRB review process and process an increased number of clinical trials. Given the importance of quality proposals in avoiding delays, services are needed to help investigators prepare sound proposals. Adequate scientific review before a proposal is submitted to the IRB is essential in order to free the IRB to concentrate on human research protection issues. Input from scientific panels and assistance in proposal development can help reduce review time.

Believing that patients and subjects can best be served by strengthening local oversight programs and by engaging PIs in human subject protection, the University of Minnesota is instituting an enhanced peer review process in 2007. The new process will use some of the procedures that make central IRBs effective to improve the institution's IRB. Key elements include the following:

- Senior faculty members (primarily research physicians) will be compensated for IRB service and receive a credit for this service in post-tenure review. Dr. Bianco explained that the financial incentive is used in order to make sure faculty members feel obligated to attend. These experienced members are less likely to "wordsmith" multicenter clinical trial proposals, resulting in needless delays.
- An extensive roster of alternates will be maintained, which will include senior faculty in training.
- The university will continue to develop and credential professional administrative staff.
- The university will also continue to develop and enhance electronic tools that facilitate the review process, such as common forms and tracking numbers.
- The IRB will meet weekly.
- At the same time, the University will develop and enhance cooperation with other accredited local and central IRBs, establishing reciprocity and affiliation agreements where beneficial. No review options are "off the table."

University leaders hope these procedures will result in better prepared proposals and quicker response to IRB stipulations, reducing two of the major contributing factors in lengthy reviews. The university's choice of approach reflects its concern that outsourcing could disconnect the PI from the human subject protection process and the belief that it makes more sense to move in the opposite direction – perhaps even making IRB service mandatory for all clinical investigators.

II. Addressing Liability Issues

The objective of this session was to explore the following questions: What implications would the use of alternative forms of IRB review have for regulatory or civil liability? Under what circumstances would the various forms of alternative review be most appropriate from this perspective? Panel presentations and the subsequent open discussion were moderated by Judith E. Leonard, J.D.

Opening Remarks by Panelists

Moderator: Judith E. Leonard, J.D.

Vice President for Legal Affairs, General Counsel, University of Arizona

Ms. Leonard opened the workshop with the reminder that many participants in the November, 2005 workshop on alternative forms of IRB review were convinced that institutional counsel would be opposed to the use of alternative IRB models and prevent their use.

Alexander E. Dreier, J.D.

Partner, Hogan and Hartson

Mr. Dreier highlighted relevant learnings from recent litigation involving human subject protection. He observed that litigation specifically related to the use of an “outside” IRB has not yet occurred, but the discussion might benefit from a look at general trends in litigation. While litigation has increased, he stressed that tort claims brought by injured research subjects remain relatively rare and often attract attention simply because of their novelty. Litigation could become more frequent as the number of clinical trials and the possibility of related injuries increase. It is also possible that patients’ expectations of experimental treatments may grow, leading to dissatisfaction. He noted that there is already a plaintiff’s bar that consists of lawyers who specialize in representing people injured in research trials.

When litigation does occur, the Principal Investigator (PI), who usually was the one who had the most direct interaction with the subject, is the most frequent target. However, since the PI seldom has “deep pockets,” the PI’s employer is often named. In the case of medical research, the hospital where the research is conducted is sometimes a target, but the subject’s lawyer could have difficulty developing a credible theory of liability if the hospital is not directly involved in study design or oversight. The sponsor is another preferred target, but the sponsor may be too removed from the direct cause of the alleged injury (unless there is a defect in device or drug that can be traced back to the commercial sponsor). While IRB members are sometimes named, they are often dismissed early from the case; plaintiffs have little success in suing them since the members have not themselves committed the act alleged to cause harm.

Typical grounds for liability usually do not apply to the IRB. There is no contract with the research participants, and the IRB does not make direct representations to human subjects. Courts are divided on the issue of whether an informed consent form (ICF) could be considered a contract, and if so, who the parties would be. Whether or not a fiduciary duty exists would vary according to State law, but this typically requires a demonstrated relationship of trust and responsibility; since it is

unlikely that the IRB would have met with a particular subject, this would be hard to prove. In a few cases, however, courts have found that IRBs do have a duty of care to research participants.

To date, courts have found the federal regulations do not create a private right of action; if an IRB acts in violation of the Common Rule, this should not independently create grounds for proceeding against the IRB or anyone else. Several courts found that no private right of action was intended by Congress, since it established OHRP as a means of investigating complaints.

Under various tort or contract theories, some courts have considered the possibility of institutional or IRB liability in specific cases. Examples of areas in which claims could occur might include a failure to ensure warning regarding research risks or failure to update the informed consent form. Possible claims could also derive from negligent training for the PI, negligent selection of the PI or study site, or negligent supervision of the PI or study site. However, Mr. Dreier believed it would be difficult to prove that any of these caused the plaintiff's injury. Areas in which PIs might be held liable include conflict of interest, fraud, or negligence.

Turning to the liability implications of using a nonlocal IRB, Mr. Dreier suspected that it would not be a critical factor in many cases; in each instance, it would be important to examine the specific factors that led to litigation. However, the quality of the IRB review definitely affects the likelihood of successful litigation. There are also aspects of the institution's relationship with an external IRB that, if not addressed, could lead to problems. These include the following:

- A communication lapse could result in problems such as a delay in responding to an adverse event.
- Conflicts of interest could arise with either an inside or outside IRB and should always be considered.
- Using an outside IRB might affect the institutional response to discovered problems in research. In particular, conversations between institutional staff members and those of the outside IRB would not be protected by attorney-client privilege, while an internal dialogue between the IRB Chair and the institution's legal counsel would be confidential.
- Underreporting or overreporting might occur.
- It is important to consider where the interests of the outside and inside IRB are aligned and where they diverge.

Diane Lopez, J.D.
University Attorney, Harvard University

Ms. Lopez focused her presentation on how to identify and minimize related liability risks related to the use of an external IRB. She noted that use of an in-house IRB does not eliminate risks, and it is possible that in some instances an alternative model might actually help to manage or reduce risks for specific studies. She identified some of the key questions she would ask if such an agreement were being considered:

- Will the quality of the external review be as thorough and complete? Is the institution accredited? Have you checked their references? Do they normally work with this type of protocol?

- What happens when there are problems? Who decides when and how to investigate? For example, who will investigate allegations of investigator noncompliance? Who decides when suspension is warranted? When will notice of potential problems be given to the Institutional Official?
- How are tasks coordinated between the external IRB and the institution? Who will accept responsibility for what in each situation to ensure quality and accountability? Critical attention should be given to “drilling down” and defining essential responsibilities.

In most situations, the speaker said, external institutions will present their own contract language to the institution. She suggested that institutions create an internal checklist for use in reviewing such a contract; it could be used to identify missing or unacceptable elements.

Ms. Lopez reviewed several contracts between institutions and external IRBs and was encouraged to find that none of them included provisions regarding indemnification. She said if such a clause were inserted in the contract, an important defense for the institution could be lost. Academic institutions are entitled to a cap on damages awarded for activities that occur in the course of performing their mission as a nonprofit entity. This is an important protection that should not be waived.

The speaker assured participants that few in-house lawyers, when approached with a request to establish a working relationship with an external IRB, will say “don’t do it.” It is more likely they will be willing to help establish a good working arrangement with an external review board if there is a good reason to do so.

Ara Tahmassian, Ph.D.

Associate Vice Chancellor, Office of Research, University of California, San Francisco

Dr. Tahmassian highlighted the strains that many institutions experience in the attempt to review multiple protocols using only internal IRBs. He estimated that institutions commonly have 2-4 panels, though many have as many as 8; each panel requires 14-18 faculty members who meet twice each month. Based on discussions with colleagues, Dr. Tahmassian estimated that a typical IRB requires 70-90 person hours of faculty time per meeting and 1,820-2,340 person hours annually. An institution with 3 IRBs requires 5,460 – 7,020 person hours of senior faculty time. He suggested that this level of effort is becoming unsustainable, especially for small institutions.

The speaker pointed out that under the current system, delays may result when essential expertise cannot be accessed readily by the local IRB. Studies are approved slowly and valuable research time is lost, with a negative impact on urgently needed protocols. It is not uncommon for a panel to review 12-15 protocols in a meeting, spending only 10 minutes per protocol. The current system, he suggested, is creating liabilities of its own.

The major reason for hesitation regarding the use of alternative models is the potential for liability, with the possible result of damage to the institution’s reputation. However, the speaker said the primary focus should be on protecting human subjects and, for medical trials, facilitating the introduction of novel diagnostic and therapeutic care. He was optimistic that a wealth of expertise is available that can be engaged to create models that meet these goals and also address liability concerns constructively.

In moving forward with a clear agreement that will minimize liability, institutions should clearly consider and address issues such as the following:

- **Division of responsibility:** Who is responsible for what aspect of the review, and in what order are reviews conducted?
- **Consistency of reviews:** How do we ensure consistency among different panels?
- **Who is the final authority?** The local institution must retain the authority to say “no” to a study approved by an outside IRB.
- **Understanding of local context:** How will critical information be shared or learned?
- **Institutional knowledge of investigator histories:** How will information on past difficulties be relayed?
- **Effective communications with the investigators:** How will information be exchanged in a timely way?
- **Effective communications with internal research support:** How are new or changed requirements communicated?
- **Training:** Who is responsible for designing and delivering training, as well as any refresher courses?
- **Faculty openness:** Will the faculty be as open with a third party as they are with colleagues?
- **Logistics and coordination:** How are other committee approvals coordinated?
- **Routine post-approval monitoring:** Who is responsible and how does reporting occur?
- **Incident investigations and reporting:** What control does the institution have over this process?

David Wynes, Ph.D.

Senior Associate Vice President for Research, University of Iowa

Speaking as an Institutional Official with experience using an external IRB, Dr. Wynes emphasized the importance of integrating the new IRB into the existing human protection program. He explained that when the University was considering the use of the Western IRB (WIRB), he attended its review meetings and met staff members. Like Iowa’s review program, the Western IRB is accredited, which gave some assurance of quality.

Managing the relationship well requires a clear agreement that identifies a specific body of work the institution wishes to delegate to the outside IRB. Often this involves industry-sponsored, industry-initiated clinical trials. The types of trials may determine the relationship of the external IRB to the Federal-Wide Assurance (FWA). For example, Iowa University’s FWA does not cover research that is not funded by the Federal government, though all research is reviewed through an equally rigorous process. Consequently, Western IRB is not listed under the institution’s assurance. Noncompliance would be dealt with as a business relationship between the two parties.

The university has delineated roles and responsibilities that reflect both human subject protection and the need to minimize liability. Ancillary committees within the university review protocols before they are referred to Western for issues such as conflict of interest. The University has provided standard subject injury language that WIRB knows should be in every consent form. The institution also provides standard language related to Health Insurance Portability and Accountability Act (HIPAA) requirements. Finally, he noted that the University reserved the right to keep any study in house. For example, when an investigator has had previous issues with compliance, the university might choose to retain and oversee the study to ensure these problems do

not recur. The university has outsourced 150 studies a year, reducing demands related to IRB review (but not staff time, since staff still have as least as many functions to perform in regard to the external IRB).

The university also works with the National Cancer Institute (NCI) using its “facilitated review” process. Under this process, the Central IRB (CIRB) must be listed on the institution’s FWA because the research is Federally funded. Consequently, the university must self-report when problems are identified. The institution monitors the external IRB’s performance by reviewing its minutes regularly and checking to ensure modifications are handled properly. The speaker also commented that through Individual Investigator Agreements, the university’s IRB sometimes acts as the IRB of record for other institutions through its FWA. Such agreements also make the university vulnerable to the consequences of actions by persons other than its own staff. Complexities related to liability may be expected to increase along with the number of alternatives used by the institution.

Summary of Discussion

A session participant asked attendees who had used alternative IRBs whether they had realized the expected benefits. One responded that his institution’s IRB was now able to spend more time on protocols reviewed internally, giving better consideration of risks and documentation of issues. Another reported dramatic improvements in the time needed to approve certain protocols, especially those requiring expertise not readily available within the institution.

Session participants addressed the question of what categories of research were good candidates for possible outsourcing. Suggestions included protocols involving diseases that develop rapidly in individual patients or in the population, protocols that involve or could be perceived to involve a conflict of interest for the institution, international studies, research involving prisoners, protocols related to pandemic infections and bioterrorism, and time-sensitive disaster-related studies.

A panel member cautioned that it is a questionable practice to send out the riskiest studies; some of these might be best handled in house. When a session participant expressed concern that faculty members might receive different treatment depending on what type of study they were conducting and which IRB reviews it, another panel member responded that any institution that has more than one IRB has already experienced such inconsistencies.

Session participants saw essential next steps as continuing dialogue to ensure appropriate choices and share information; clarifying the acceptability of alternative IRBs from a regulatory compliance standpoint; and educating university counsel members on liability issues and strategies.

Other concerns not discussed in detail included those related to the institution’s liability when it serves as the IRB of record for practice-based research networks. A participant also highlighted concerns about how HIPAA issues would be addressed in network situations; she expressed serious reservations about her university serving as the privacy board for another agency.

Conclusions and Recommendations

Ms. Leonard reported to the plenary session that the group had learned that civil litigation related to human subject injuries is rare, though it could increase in the future as the number of trials grows. Findings of regulatory noncompliance are more common and therefore a more significant concern.

Types of research various members felt might be considered for potential external review include the following:

- Multi-site trials, especially those that are industry sponsored. Multiple reviews may not add quality and do create delays.
- Areas requiring specialized expertise, such as international studies and rare diseases. In this case, there was some debate about whether more expertise could be accessed equally well by using an external board. There was no agreement on what these areas might be, as they would differ for each institution.
- Research needed to respond to national priorities such as epidemics and pandemics, or to situations such as disaster response in which many institutions must become involved quickly.
- Protocols in which subjects are special populations, such as prisoners, that require special expertise and representation from the affected community.
- Practice-based or regional research networks involving unaffiliated entities or practices.

A panelist pointed out that depending on how the institution chose to structure its FWA, industry-sponsored trials might or might not have been included. This has implications for liability. For government studies, the institution would be directly responsible for any violation of the FWA. For industry-sponsored trials, if those are excluded from the FWA, a violation would be addressed as part of the business arrangement between the institutional IRB and the external IRB as well as through potential regulatory action by FDA.

Group members generally agreed on the following advice:

- Use independent boards that are part of an accredited program.
- Engage in-house counsel in discussions regarding alternative boards – do not assume opposition.
- Educate counsel about use of external boards.

Recommended actions for the Federal government include revising HIPAA or the Common Rule with a view to harmonization between these requirements. It was noted that HIPAA compliance is particularly complex for multi-site studies. Members were generally supportive of a Federal agency such as NIH designating one responsible IRB for multi-institutional research, but urged that the human research protection program be accredited to enhance trust.

The group also noted the following unresolved concern: institutions continue to be concerned about the responsibility they bear under their FWAs for actions taken by external IRBs.

Further Discussion. There was no further discussion in the plenary session on liability.

III. Sharing Authority and Responsibilities

The objective of this session was to explore the following questions: How can shared authority and responsibilities best be managed to ensure appropriate control and accountability? Under what circumstances would the various forms of alternative review be most appropriate from this perspective? Panel presentations and the subsequent open discussion were moderated by Angela Bowen, M.D.

Opening Remarks by Panelists

Marjorie Speers, Ph.D.

Executive Director, Association for the Accreditation for Human Research Protection Programs (AAHRPP)

Dr. Speers set the stage for the discussion by giving several examples of IRB models in current use, observing that the question of shared authority and responsibility applies in each case:

- The organization has its own IRB and relies upon that IRB.
- The organization has its own IRB and relies upon the IRB of another organization for review of some or all protocols. (Many organizations have such an agreement in place whether they use it or not.)
- The organization relies upon a central IRB (for example, in the NCI model).
- The organization relies upon a lead IRB.
- The organization is part of group of organizations that form an IRB.
- The organization relies upon an external IRB.
- The organization uses some combination of these options to perform IRB functions.

As part of a human research protection program, the IRB's primary functions include verifying the following: the research is ethically justifiable; risks are minimized; risks are reasonable in relation to any anticipated benefits to participants and the importance of the knowledge that is reasonably expected to result; the selection of participants is equitable; consent will be sought and documented; the research plan makes adequate provisions for monitoring the data to ensure safety; and provisions are adequate to protect the privacy of participants and maintain confidentiality of data. These functions must all be addressed when authority and responsibilities are shared.

Specific requirements embedded in the regulations mandate that IRBs conduct an initial review of research, establish primary reviewer systems and expedited procedures for review, approve an appropriate consent process, handle notifications of investigators, carry out continuing reviews, keep minutes, and retain appropriate records. In addition, OHRP guidance requires that IRBs make determinations regarding research and exemptions, identify relevant materials for review, and document determinations and protocol-specific findings.

IRBs must determine procedures they will use in the following instances – all of which are to be communicated or negotiated when responsibilities are shared:

- Conducting initial and continuing review of research and reporting its findings to the investigator and the institution;
- Determining which projects require review more frequently than annually;

- Promptly reporting unanticipated problems involving risk to subjects or others;

Some Key Questions for Federally Funded Studies

- How will conflicts of interest be identified and managed?
- How will noncompliance be identified and managed?
- How will scientific review be handled?
- Who will assess resources needed to conduct the study?
- How will units communicate with each other?
- Who is responsible for ensuring compliance with State and local laws?
- Who determines and makes exemptions?
- How will unanticipated problems involving risks to subjects or others be identified, reported, and investigated?
- Who handles the reporting to IRBs, institutional officials, the federal agencies, and other stakeholders in the event of suspensions and terminations, unanticipated risks, or serious and continuing noncompliance?
- Who conducts monitoring following IRB approval?

- Promptly reporting serious or continuing noncompliance;
- Promptly reporting suspensions and terminations; and
- Verifying through a third party that no material changes have occurred since the last IRB review.

In clarifying responsibilities, Dr. Speers stressed the importance of differentiating between requirements that pertain to IRBs and requirements that pertain to the institution's human research protection program. Good communication

among all entities involved will be critical and should also be delineated in advance. She advised that business and IRB functions be clearly separated when dealing with an external IRB. Agreements about how responsibilities will be handled should be in writing and should address all the issues that are related to regulatory requirements.

Angela C. Wishon, J.D.

Assistant Vice Chancellor for Regulatory Compliance, University of Colorado at Denver and Health Sciences Center

Ms. Wishon described the IRB structure of the University of Colorado at Denver and the Health Sciences Center, highlighting the complex issues that arise in the relationships among the entities involved. Six legally separate entities, each with its own standards, are served by the Colorado Multiple Institutional Review Board. This Board, in turn, serves as the IRB of record for several institutions and maintains a variety of relationships with other IRBs. For example, it uses the Western IRB, an independent IRB, for industry trials, maintains a reciprocal agreement with the National Jewish Medical and Research Center, and conducts facilitated local reviews in connection with the central IRB established by the National Cancer Center. Ms. Wishon explained that the medical center conducts 3300 protocols each year, 14 percent of which are industry-funded clinical trials.

Tasked with establishing the agreement with the Western IRB, Ms. Wishon held discussions with key faculty members, many of which urged her to proceed with the agreement on the grounds that it would be more efficient or that failing to do so would result in a loss of possible sponsors. However, one Chair who was ethically opposed to the prospect of outsourcing this work resigned in protest. She stressed the need to work through issues arising from the organizational culture when an external IRB is introduced.

Several other important issues were highlighted. First, she noted that the Federal funder may not accept review by an external IRB; it is important to understand the regulatory provisions that might apply. Also, participating institutions that had already ceded their HIPAA-related Privacy Board responsibilities to the Colorado Multiple IRB had to cede them again to the external IRB. She noted that issues related to informed consent and privacy were especially critical to the hospital. In preparing the business proposal, it is essential to ensure the external IRB has the credentials required to understand the type of protocols to be reviewed – for example, experience with academic medical centers.

Don E. Workman, Ph.D., C.I.P.

Executive Director, Office for the Protection of Human Subjects, Northwestern University

Dr. Workman described Northwestern University's increasingly complex human research protection program. The university has several IRBs that serve multiple legally separate entities (resulting in complicated discussions of liability). Faculty conduct research at various sites and affiliates. Reciprocal agreements exist with some entities, and in some cases the university has found itself added to the assurance of entities it does not know.

How can shared authority and responsibility be managed best? The speaker made the following specific suggestions:

- Shared authority and responsibility will be better managed when a human subject protection program understands its own model and has already developed its organizational responsibilities along the lines of the five domains identified by the Association for the Accreditation of Human Research Protection Programs (AAHRPP): organization, research review unit, investigators, sponsored research, and participant outreach.
- The Federal-Wide Assurance (FWA) and sample IRB Authorization Agreements may be overly simple documents. Don't forget all that lies "behind" these documents and must be addressed in agreements.
- Alternative models for IRB review and oversight offer different and possibly better business process models; however, clear lines of communication and organizational structures are needed. Even within a university system, it is advisable to have a clear chart showing lines of communication and coordination.

The speaker suggested that alternative IRB models may be a useful way to manage institutional conflicts of interest. They may become increasingly appropriate to consider as the number of institutions engaged in the research increases and when the type of research under review is specialized. He stressed the need to empirically evaluate alternative models to determine what is most effective and efficient in different circumstances and to learn from what is and is not working. He also suggested that institutions would benefit from having access to other sample agreements or additional guidance on how best to delineate shared responsibilities. These should address relatively complex models as well as simple ones. The IRB selected should succeed in meeting the following provision of the Common Rule:

§46.107 IRB membership (a) The IRB shall be sufficiently qualified... to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

When this is the case, he suggested, investigators may even be motivated to return to the IRB for advice rather than viewing its members as “police.”

Brent C. Miller, Ph.D.

Vice President for Research, Utah State University

Dr. Miller spoke from the perspective of an Institutional Official coming from a university that conducts primarily social and behavioral research and that has relatively little experience with alternative IRBs. He noted that exploration of this topic is not generally high on the list of academic centers like his that conduct primarily nonmedical research.

The speaker recognized that duplicate reviews in multi-site investigations are often not required, may be expensive and wasteful, may have variable outcomes to the review process, and may be inefficient. His university became involved in the current controversy when the Student Wellness Center asked to participate in clinical drug trials and a member of the institutional IRB resigned in protest, feeling that the local IRB lacked the expertise needed to evaluate the proposed trials. The member also feared the commercial sponsor would be able to influence the outcome of the review and the research itself.

When his university uses an external IRB, it usually occurs as a local collaboration. This option might be selected when the proposed study involves a population at another site, when the university lacks equivalent expertise in the study area, or when the primary expertise to conduct and oversee the study resides at the other institution. An external IRB would be used only in cases in which a “crisp agreement” is possible that resolves questions of authority, accountability, and liability. In addition, the university must be confident that human participants are protected as fully as they would be using the local IRB.

Summary of Discussion

Participants began by exploring the potential for alternative forms of review and identifying instances in which they would be especially appropriate or inappropriate. One commented that either internal or external IRBs have the potential to provide equivalent protection; neither should be viewed as “less than” the other. In some instances, the best alternative might be to allocate the resources needed to bring a local IRB “up to speed” rather than contract with an external IRB. In other cases, such as in some community hospitals, the number of protocols per year is so small that it often makes more sense to use an external IRB. Also, most PI-initiated studies were considered poor candidates for external review.

Attendees generally concurred that use of a central IRB was often the best choice for large multi-site studies. Nevertheless, one attendee shared an instance in which the twentieth IRB to review a protocol caught a serious error. Another rejoined, however, that this example did not necessarily mean that redundant reviews were the best option for protecting human subjects; it might suggest that the 19 IRBs that missed the error needed more investment to bring them “up to speed.” Other examples of instances in which central IRBs are probably the best option include protocols that involve rare diseases or protocols that involve intervention agents for sudden outbreaks of a disease. Participants were in agreement that there is no one model that works for all situations.

While the group did not reach consensus on which IRB functions should and should not be contracted, participants suggested that the local IRB is usually in the best position to do training and certification, ensure its grants and contracts are consistent with approved protocols and procedures, and identify conflicts of interest. It should also provide information on local PIs and conditions. Either the local or central IRB may initially become aware of possible investigator noncompliance, but when this is suspected, both IRBs should be involved in follow-up activities. For example, in cases of serious suspected noncompliance, the Western IRB generally sends two staff members to the site to investigate and prepare a report communicating its findings to the local IRB and institution. The institution then involves its legal counsel and fulfills its reporting requirements. The external IRB may report adverse events (AEs) to the institutional IRB in the requested format and frequency.

While some members were concerned that the local IRB would not be able to participate effectively in monitoring if it did not do the protocol review itself, others explained that contracts could be structured to allow local concurrence or participation. One type of agreement has local IRB representatives review the same protocol as the external IRB, with the understanding that it may reject a protocol approved by the external IRB, but not the reverse. In facilitated review, a subcommittee of the local IRB may propose certain changes in the consent form or other aspects of the protocol to address local needs. Colorado University often sends representatives to its external IRB when its protocols are reviewed, and some collaborative models provide for local participation in centralized protocol review.

Participants also noted that sponsor support often plays an important role in human subject protection. Although program costs are often built into indirect costs charged to the sponsor, these are sometimes allocated to whatever functions caused trouble most recently and may not provide effective cross-the-board prevention. The moderator observed that in a recent study, a researcher was unable to determine the actual cost of institutional programs to protect human subjects because of inconsistencies in how these costs are computed and recorded. Participants agreed that effective collaboration and communication with sponsors, as well as other stakeholders, should be built into the review program.

Other specific points included:

- Metrics are needed to measure IRB quality.
- Model agreements addressing a variety of possible arrangements would be helpful to institutions.
- Clearer terminology is needed to delineate the various review options.
- It may be helpful in defining expectations to think of the external IRB as “another one of your IRBs.”
- While many IRBs have informal reciprocal agreements with other IRBs that are not delineated in writing, this is not a recommended practice.

Conclusions and Recommendations

Dr. Bowen summarized the group's deliberations in the plenary session. She noted that everyone accepted the concept that responsibilities would have to be shared if an external IRB were used; the institution's obligations cannot be signed away. They also agreed that coordination must occur at the outset and must include a crisp agreement that spells out who will be responsible for each action in each situation. Group members recommend that lawyers be involved from the outset and that agreements should be documented in writing. Investigators, sponsors, standing IRBs, and other stakeholders should all be represented as agreements are crafted.

Specific concerns to be addressed in the use of an external IRB include how adverse events and problems with investigator compliance will be addressed, how changes in the protocol will be made and approved, how investigators will be credentialed and trained, and what mechanisms will be used to assure compliance with applicable laws. Insurance and indemnification must be addressed, as well as who will maintain confidentiality and manage public relations. It is important to be clear on what the "inside" (internal) and "outside" (external) IRBs can say about each other in a public forum. Specific contact points must be identified, and communication and coordination procedures must be very clear. For example, the local site may become aware of a possible problem involving an investigator and need to engage the reviewing site in further investigation of the issue. It is important to ensure that decisionmaking will be independent of inappropriate influences.

The group did not develop a specific list of duties and responsibilities of the institution that might be transferred by contract. Many members had only limited experience in using external IRBs; also, it was felt by some that this would vary depending on the nature of the research and other factors. However, the moderator suggested that the primary reviewing IRB should retain the primary responsibility for investigating issues that arise locally in the course of the study and making any amendments required to the protocol. The local institution should also be involved in instances of investigator noncompliance and will need to fulfill the reporting requirements under its FWA, including reporting suspensions and terminations.

Group members also considered issues related to terminology, noting that the many different names for alternate forms of review are confusing and lack precise meanings. They preferred the use of the term "delegated IRB" for external IRBs. Some felt the term "commercial" IRB had perjorative implications and the term "independent" should be used instead.

In reference to quality, the group also noted a need for appropriate metrics to measure consistency of review and overall IRB quality. There was strong support for the accreditation process as a means of providing some assurance of the capacity for competent reviews.

Further Discussion. Conference attendees expressed particular concern about the issue of conflict of interest and how this might affect the choice of the best mechanism for review. Some participants expressed concern about the conflict of interest that might exist for IRBs funded by commercial sponsors and presumably engaged in trying to keep their business. However, Dr. Bowen, founder of the Western IRB, countered that only about one-third of Western's revenues come from commercially sponsored research. The remaining funds come from 150 institutions for which WIRB

is the sole IRB. Further, of its 137 Board members, only 15 are affiliated with Western; only one employee attends each meeting. A spokesperson from another external IRB stressed that the IRB membership consisted of 80 percent independent practitioners paid solely according to the time they spent on review. Dr. Bowen stressed that no evidence has ever come forward that would support the claim that an external IRB has been “bought.”

Other participants observed that every IRB has different sources of potential conflict of interest; this is certainly true of institutional IRBs. One noted that when reviewing colleagues, pressures and relationships may color the review; “firewalls” are needed by every review board. Another asked, “who is from a university that has never had an investigator allege that if the IRB does not approve the protocol, the sponsor or study will be lost?”

Several participants underscored the need for empirical data to inform judgments about alternatives. For example, while a movement toward alternatives has been noted, no one knows the “magnitude or velocity” of change. Another participant pointed to the need to find and share emerging “best practices” that could help institutions move forward.

IV. Ensuring Review Quality

The objective of this session was to identify the issues, barriers, and challenges involved in using alternative IRB models that are related to quality of review and the capacity to consider the local context of research. Panel presentations and the subsequent open discussion were moderated by Daniel K. Nelson, M.S., CIP.

Opening Remarks by Panelists

Moderator: Daniel K. Nelson, M.S., C.I.P.

Director, Office of Human Research Ethics, University of North Carolina, Chapel Hill

Mr. Nelson began by citing specific regulatory requirements related to community context and community representation:

- The IRB shall be sufficiently qualified through the experience and expertise... and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel (45 CFR 46.107[a]; 21 CFR 56.107[a]).
- The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (21 CFR 56.107[a]).
- Each IRB shall include... at least one member whose primary concerns are in nonscientific areas (45 CFR 46.107 [c][d]; 21 CFR 56.107[c]).
- Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution (21 CFR 56.107[d]).

While specific requirements are brief, existing Federal guidance expands on them and may even appear to discourage the use of alternative models. Notably, a 1992 report on “Local IRB Review of Multicenter Clinical Trials” posted on the OHRP Web site states: “Only the local IRB is familiar with the particular circumstances of its research setting and is in a position to weigh critical considerations like state and local laws, professional and community standards, institutional policies, and the needs of differing patient or subject populations. Thus, the local IRB is in the best position to ensure that persons deciding whether or not to enroll in research have the greatest level of accurate information necessary to make that decision. Each IRB must continue to review all protocols and informed consent documents with the greatest of care, regardless of any prior review at the national level.”

More recent guidance from July, 2000 on “IRB Knowledge of Local Research Context” states: “Institutions have a profound responsibility to ensure that all IRBs designated under an OPRR-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements. This responsibility endures regardless of the IRB's geographic location relative to the institution and the research. It is particularly critical where the research involves greater than minimal risk to subjects or vulnerable categories of subjects.” The same guidance requires the following information on local context to be taken into account: anticipated scope of the

institution's research activities; types of subject populations likely to be involved; size and complexity of the institution; institutional commitments and regulations; applicable law; standards of professional conduct and practice; method for equitable selection of subjects; method for protection of privacy of subjects; method for maintenance of confidentiality of data; language(s) understood by prospective subjects; method for minimizing the possibility of coercion or undue influence in seeking consent; and safeguards to protect the rights and welfare of vulnerable subjects.

Suzanne R. Pattee, J.D.

Vice President of Public Policy and Patient Affairs, Cystic Fibrosis Foundation

Ms. Pattee spoke both from her own perspective as a lifelong research subject and as a representative of the Cystic Fibrosis Foundation, a nonprofit organization founded by her parents to encourage and support the development of therapeutics for cystic fibrosis.

The speaker explained that the foundation has a Therapeutics Development Program that involves seventeen universities in four States in a network linked through a single Coordinating Center. The research program has an external advisory committee, a Patient Advocacy and Ethics Committee (on which the speaker serves), and a Data Safety Monitoring Board (DSMB). She emphasized the program's critical role in supporting clinical trials, since the disease is relatively rare and incentives are needed to encourage sponsors to conduct trials. She pointed out that the many years required to develop a new medication and make it available to patients constitute a significant percentage of the current life expectancy of persons with cystic fibrosis (to their mid-30s). From a patient's perspective, the ability to conduct multiple trials, access the small pool of prospective patient participants in diverse locations, and expedite review are critical.

Ms. Pattee said that from this perspective, delays in the review process associated with multiple local IRBs and the variable quality of their changes have raised concerns at the foundation. She noted that changes in the consent forms made by local IRBs are often not substantive; sometimes they even increase the reading level and introduce errors. She was confident that external IRBs and DSMBs could perform many of the functions of the local IRB with no loss in quality. She further stressed that in the case of a disease such as cystic fibrosis, the patients themselves are in effect a "community" regardless of where they live. The knowledge required for expert review is relatively rare and can best be accessed through a central review mechanism. Such disease-specific expertise is important in protecting human subjects and in understanding their needs and concerns. At the same time, she believed, central review can increase efficiencies by reducing delays, avoiding duplicative reviews, and reducing variation in consent forms.

At present, the Cystic Fibrosis Foundation is seeking to increase the number of clinical trials it conducts and to expand its network of trial sites and potential subjects. More care centers across the country – approximately 120 – are now participating in clinical trials. As the foundation seeks to achieve its goal of doubling the number of trial participants in the next three years, it looks to external IRBs as a means of increasing both the safety and the timeliness of these trials.

Stephen E. Sallan, M.D.
Chief of Staff, Dana-Farber Cancer Institute

Dr. Sallan spoke from his perspectives as a practicing oncologist, clinical investigator, research program manager, and a former IRB Chair who held this position for approximately 10 years. He explained that the Dana-Farber Cancer Institute is composed of seven institutions working under a single umbrella. The Institute reviews human subjects research for all these institutions; in November 2006, it was overseeing 1800 active therapeutic trials.

The speaker stressed the critical importance of understanding the science involved in a study. He maintained that when institutions are shut down as a result of regulatory compliance issues, the underlying flaw often lies in the science. The complexity of medical science in the cancer field demands breadth and depth of expertise; the Institute's Scientific Review Committee therefore includes not only scientists with expertise in specific fields, but also persons able to ensure that knowledge of biostatistics informs research design. The IRB includes clinical investigators, research nurses (a critical link between investigators and patients), research pharmacists, and cancer survivors, among others. These review mechanisms constitute what Dr. Sallan called "governance by doers" – oversight by people with hands-on experience in the types of studies being discussed. This type of expertise, he felt, transcends geographic location. In effect, for this type of research, cancer itself is the local context. Further, he suggested that the very meaning of "local context" has changed over the last 30 years. For example, the Internet has "flattened" our lives and made the concept of local context less relevant.

Dr. Sallan explained that IRB members at the Institute are generally people engaged in clinical research through its member institutions. Members sign up for three-year terms that are mutually renewable, and over 90 percent of them choose to renew. The Institute's experience has been that when researchers see the IRB as adding value rather than being obstructionist, they want to be part of it. The best protection for human subjects, he said, can only be assured by identifying good people and maintaining "eternal vigilance."

Peter Vasilenko, Ph.D.
Director, Human Research Protection Program, Michigan State University

Dr. Vasilenko observed that many local IRB members believe that their IRB is the "hardest" to satisfy and has the longest review time, but protects subjects better than any other; consequently, they cannot trust or rely on any other IRB. The speaker felt this view was generally false and closed the door to alternatives that might actually protect human subjects more effectively. He noted that some evidence suggests that multiple reviews may degrade rather than enhance human subject protection.

The speaker emphasized that a range of alternatives to purely local review is available, including collaborative reviews. Michigan State University, for example, has research programs in six different locations throughout the State. A collaborative, centralized IRB has been formed that has written agreements with each participating institution. Its 15 IRB members include representatives from many of these institutions. The Community Research IRB (CRIRB), which is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP), meets monthly, with phone-in participation by "remote" members; it is experimenting with Web conferencing and is close to being able to have a meeting via the Internet.

The CRIRB forwards its decision together with complete documentation of the study to all participating sites, and the local IRB Chair determines whether or not to “concur” with its decision. Everyone seeks to avoid re-review. There is a close personal relationship and partnership between the central IRB and participating sites. A group of IRB administrators meets twice a year to enhance the partnership and address administrative concerns. In addition, the CRIRB serves as the IRB of record for a number of other clients. The speaker reported that the quality of reviews has been outstanding. He said the joint expertise and perspectives brought together on the CRIRB provide for comprehensive reviews that many find more complete than those of their “home” IRB.

The important issue of ensuring sensitivity to local context has been addressed by including IRB members from participating institutions on the CRIRB, using local research collaborators, and communicating with or visiting partners when information is needed. Dr. Vasilenko felt that while concerns about local context are often cited as barriers to collaboration among IRBs, in many cases the underlying issue relates less to protecting human subjects than to protecting the institution’s local control.

The speaker cited a number of benefits of a collaborative approach to IRB review. These include:

- Avoiding inconsistencies in the consent process;
- Facilitating jointly sponsored training and educational activities;
- Conducting objective, nonbiased reviews free of local politics;
- Offering diverse reviewers with concentrated expertise in specialized areas;
- Eliminating duplication of effort;
- Stretching IRB resources;
- Increasing the efficiency and speed of review without sacrificing quality; and
- Stimulating collaboration and funding opportunities.

Dr. Vasilenko saw this type of collaboration as the “wave of the future.”

Stuart Horowitz, Ph.D., M.B.A.

Director, Miami Children’s Hospital Research Institute

Dr. Horowitz’s presentation focused primarily on practical means for addressing local context and quality issues when using an external IRB. He stressed the importance of regular communication, standard operating procedures, and developing various templates for informed consent as means of ensuring the institution’s concerns are met and quality is assured. Clinical Trial Agreements (CTAs) are another important tool for ensuring a common understanding of what will be done and how. The local institution should share its own conflict of interest management plan and carefully review that of the alternate review board. The speaker underlined the importance of accreditation to establish a reliable baseline for quality assurance.

The speaker suggested a number of considerations that should be taken into account when selecting a central or alternative IRB. These quality checks are based on the regulatory criteria for IRB approval of research. The local IRB should investigate how risk categories are assigned, whether this is done accurately, and whether the IRB is balanced in its assessment of benefits to participants. He advised reviewing the IRB’s standard operating procedures (SOPs) to understand how it reviews

protocols. It is also important to review the IRB's quality assurance program. There is no substitute, however, for actually attending convened meetings of the central or regional IRB at least once per year to understand their dynamics and staying in touch with the central/regional IRB by telephone. Dr. Horowitz also recommended reading the meeting minutes regularly.

The speaker saw consideration of local context as a shared responsibility that requires “push and pull” – a “push” from the local institution, which should share relevant and timely information, and a “pull” from the IRB conducting the review, which should seek the information it needs to do a responsible job. The local IRB should be prepared to share information from the institution's “rumor mill” – for example, the fact that there is a high turnover rate among the investigator's research coordinators and talk that he may be “cutting corners.” Tools for gleaning information on the local context include questionnaires on local attitudes, interviews with investigators and staff, regular site visits, representatives of the alternative IRB who live in the community or visit often, monitoring local media, collecting information from public records and databases to understand demographics, and researching relevant State and local laws. Teleconferences and videoconferences can be used to facilitate communication. The speaker suggested that the potential for local politics to contaminate the review process should be frankly acknowledged.

Before a protocol is sent for external review, Dr. Horowitz recommended that an internal suitability review be conducted.

Summary of Discussion

In the ensuing discussion, participants considered the question of what “local context” really means, both in the context of international research and research conducted within diverse urban communities. While some felt that a remote IRB would be less committed to ensuring community involvement and representation than a local IRB and far less likely to reach out to community members, others pointed to many means of eliciting meaningful community input from those affected, regardless of the IRB's location. Key points included the following:

- Today's technology allows seamless coordination across distances.
- Local consultants can be informative on issues related to local culture and concerns.
- Diverse communities may include dozens of subcultures and languages within a few miles.
- Patient advocacy can not only enhance subject protection, but also increase the quality of the protocol.
- The local community's involvement should be ongoing and involve each phase of the study, from design to receipt of results.
- The thinner the bonds between decision makers and subjects, the greater the risks to human subjects.

Participants differed on whether remote IRBs would strive to understand the implications of research from the subjects' point of view. One emphasized the importance of cultivating the same empathy toward participants one would have if they were family members. Another, however, felt a remote IRB could do this equally well. A participant recommended the use of risk management reviews as a means of ensuring that appropriate protections are in place, noting that such a review can be done regardless of location.

While supportive of collaborative review models, one participant questioned whether independent IRBs would share the same commitment to ethics as the local IRB; this individual stated, “you can’t outsource ethics.” One concern was that institutions using an external IRB would pay less attention to the important functions of mentoring and fostering a culture of ethics. Others rejoined, however, that there is no basis for questioning the ethics of independent IRBs or for assuming that functions such as mentoring will necessarily be lost or diminished. One participant emphasized the importance of the local IRB working closely with the remote IRB to ensure that ethical standards are maintained. Another pointed out that many local IRBs maintain that they themselves have been forced into a bureaucratic role; use of a local IRB alone, therefore, does not solve the problem. The question, “has compliance eclipsed ethics?” applies across the board. An unconvinced participant continued to assert that an external IRB would be more likely to pursue an efficiency-driven model in which subjects are not appropriately represented.

Several participants reinforced the importance of accreditation as a minimum guarantee of a quality review. Others added that responsibilities for quality control accrue to both the local and remote IRB; for example, forms provided by the local IRB must be accurate and consistent with internal criteria. Specific agreements should define institutional expectations. In this regard, while one participant reported increasing use of study-specific IRB authorization agreements, a speaker discouraged such “one-off” agreements in favor of ongoing communication regarding expectations and standards over time.

A number of people raised concerns about the quality of protection local IRBs can provide in multi-site reviews. One attendee who had prepared a model consent form reviewed by 85 IRBs, each of which was given the authority to edit the form, reported that over half these local sites had removed critical elements from the form, including failure to communicate the potential for death. Another participant who reviewed consent form changes made in 8 studies at 104 sites reported needless variations that added to delays but did not improve subject protection. Some persons stressed the advantage of access to specific scientific expertise in a centralized site as a means of ensuring quality and improving subject protection. One insisted that available data suggest that multiple local reviews result in the same or often less protection for human subjects. Others, unconvinced, called for more and better data to help assess review quality.

Other specific issues raised in discussion included the following:

- Effective strategies are needed to protect mobile subject populations. It is often difficult to continue research in such cases.
- Building trusting relationships can take a great deal of effort over a period of years.
- The involvement of senior institutional leaders is critical to build trust.
- Human subject protection cannot be enhanced without developing clear standards that define investigator responsibilities.
- A variety of types of expertise are needed on IRBs to inform decisions (not just scientific expertise).
- Funders and regulatory agencies must endorse the use of alternatives in order for institutions to use them with confidence.

Conclusions and Recommendations

Reporting to the plenary session on behalf of the group, Mr. Nelson highlighted issues with traditional models such as redundant reviews, variability, delays, a loss of efficiency, and needless “tinkering” with consent forms. He also noted that local and institutional politics may detract from the desired focus on human subjects, introducing bias. Positive attributes of local review, however, include knowledge of local investigators and opportunities for mentoring and superior knowledge of the local subject population in some instances (though this was controversial).

Barriers to the use of cooperative review models discussed in the group include resistance from the local IRB or institution, the perception that external IRBs would not care as much as local ones, concerns that bureaucratic checklists might be used at the expense of ethics, lack of trust, insufficient communication, and lack of awareness of alternatives.

Participants felt that an “all or nothing” conceptualization fails to incorporate the multiple options for review being created and explored. Examples of such options include collaborative consortia, facilitated local review, and risk management reviews. Participants noted that the environment has changed, facilitating such approaches through technology.

Attributes of successful models identified by participants include: good two-way communication, trust, exchange of documentation, a patient or subject-centered ethic, resources for investigator training and oversight, and provision for meaningful community input and participation. One collaborative model discussed in the group offered the potential for joint educational opportunities that raise standards across all member institutions.

Issues to resolve include a clear understanding of what “quality” really means in a review and how it can be measured. Also, some felt a clear signal is needed from regulatory agencies that alternative models are acceptable.

Further Discussion. A participant challenged the application of the Cold War adage, “trust, but verify,” to IRB relationships. He suggested that the emphasis should be on trust, which should be built and nourished through communication.

One attendee emphasized the seriousness of the lack of local knowledge on the part of an external IRB. For example, he argued, the contracted IRB might fail to understand what is and is not an appropriate incentive for participation in a given community. Another participant observed that one might anticipate striking differences in the acceptability of a particular procedure in different communities. Others responded, however, that mechanisms exist for conveying or gathering essential information on local context; also, institutional IRBs do not understand their own local context perfectly.

A pharmacist observed that laws and regulations may differ greatly from State to State and noted that for many protocols, IRBs would need to include representatives who are thoroughly familiar with applicable laws and regulations in the local areas where the protocol is implemented.

V. Costs, Timing, and Loss of Revenues

The objective of this session was to consider the following questions: What are the significant issues surrounding the costs of alternative forms of IRB review? How would the use of alternative forms of IRB review affect the timely completion of milestones in research oversight? Would the use of alternative forms of IRB review have a negative effect on funding of human subjects protection at the institutional level? Under what circumstances would the various forms of alternative review be most appropriate from this perspective? Panel presentations and the subsequent open discussion were moderated by Martin Charns, D.B.A., M.B.A.

Opening Remarks by Panelists

Felix Khin-Maung-Gyi, Pharm.D., M.B.A., C.I.P.
Founder and CEO, Chesapeake Research Review, Inc.

Dr. Gyi began by offering historical background on the topic. He noted that in the Federal Register of January 27, 1981, FDA adopted regulations establishing standards for the composition, operation, and responsibilities of IRBs that review clinical investigations involving human subjects (21 CFR part 56). During the public review required before issuing a final rule, questions were raised about the administrative costs associated with IRB reviews. FDA responded that costs such as travel expenses and meeting rooms could be paid by sponsor and institutions and estimated the cost of an investigation to be approximately \$100. It anticipated “little, if any, incremental costs to the agency.” The speaker noted that while we know today that review costs are far more substantial than anticipated, we still lack hard data on how specific factors affect cost.

Review costs to be considered include not only dollar costs to the institution and its IRB and to the investigator, as well as future potential income to both, but also nonmonetary costs such as the possible impact on reputation and public relations. Some costs, such as those related to technology and maintenance, are seldom built into the program. The speaker suggested that Federal sponsors in particular do not adequately fund the oversight required. For example, he noted that lack of a cost structure adequate to cover analysis of adverse events could have a negative impact on human subject protection. Participant protection programs need effective cost recovery programs, as well as accurate accounting procedures that capture both incoming revenue and costs.

Overarching issues of concern in this topic area include:

- Where are the costs? Are they being accurately addressed?
- Have we maximized process and administrative efficiency?
- Are revenues captured and allocated to the IRB appropriately?

He proposed that in the critical areas of costs, speed, and quality, “we have to choose two out of three.”

Moira A. Keane, M.A., C.I.P.

Director, Research Subjects Protection Program, University of Minnesota

Ms. Keane began with a caution against confusing speed and efficiency. She defined efficiency as implying that available resources have been maximized to provide an effective review. It is not possible to develop an algorithm for how long it takes to develop an appropriate risk-benefit analysis. However, data on local institutional performance and the performance of alternative mechanisms would be helpful in decision making, and these are not commonly available. We also lack data on the actual costs of institutional review.

Clinical trials involve a heavy work burden for the IRB office and members. Some economy of scale is likely for large portfolios, while small operations may have more significant burdens. Whatever the portfolio size, many institutions are challenged to cover the actual administrative costs of their IRBs. If revenue associated with specific studies is directed outside the institution while management and recordkeeping responsibilities remain, there is concern that the human subject protection program may be unable to meet its obligations.

The speaker saw the following questions as critical to explore:

- Why is it that local IRBs often perform less efficiently than alternative IRBs? What can be done to emulate what works for others?
- What are the costs and benefits associated with outsourcing some or all research review?
- What exactly is being sought through the use of alternative mechanisms? What are the goals?
- Will there be a dual system for review? Does this imply value judgments and different standards related to different kinds of research?
- Are some researchers placed at a disadvantage if alternative mechanisms are used? Are researchers doing commercially funded studies at greater advantage than those whose studies are investigator initiated?
- How do we assure that IRBs perform appropriately?
- How much local oversight is needed when alternative mechanisms are used?

The speaker saw a need for a precise vocabulary to describe alternative mechanisms. She suggested that institutions be flexible and open to explore these options, but move cautiously.

Jean-Louis Saillot, M.D.

Head, Pharmacovigilance Schering Plough

Dr. Saillot identified several key drivers in the current clinical research environment that are pertinent to the topic. He pointed to the increased complexity of product development and the longer duration of many development programs. In addition, he noted a clear trend toward large, multi-center trials and away from trials that can be carried out by a single institution. This change requires an effective infrastructure that will help to provide homogeneity across sites. Trials are also commonly conducted in multiple countries, challenging reviewers to balance local aspects of the project with global needs and issues.

The speaker observed that from the sponsor's perspective, efficiency, timeliness, and quality are important concerns, but cost is much less important. The cost of protocol review and monitoring

actually represents only a tiny part of overall product development costs. Sponsors have an interest in reducing redundant reviews and identifying the most promising paradigms; improvements in efficiency and timeliness may have a positive impact on product development and would justify a higher investment.

While rapidity of review is critically beneficial to sponsors, Dr. Saillot stressed that timing and quality of review are not mutually exclusive. In fact, he asserted that efficiencies gained by avoiding duplicative reviews should lead in improvements in both quality and timeliness. Reduced review loads should lead to increased focus, and more rapid and thorough reviews are the expected results. This would be helpful to multiple beneficiaries, including research participants.

Todd H. Wagner, Ph.D.

Health Economist, Health Economics Resource Center

Dr. Wagner, who has completed several studies of IRBs, has co-authored a study in which he and two colleagues estimated the cost of running an IRB (Wagner, Cruz, and Chadwick, 2004). Authors concluded that the average human subjects protection office cost approximately \$180,000 annually (in 2001 dollars). The average office processed 670 actions per year, including 74 full-board initial reviews (a number that would increase dramatically if adverse events were included). Each of these actions cost an average of \$1,115. However, Dr. Wagner noted that the standard deviation for actions was \$1,747, pointing to a wide variation in costs per action.

In reference to costs, the speaker said there was strong evidence that large economies of scale exist. He suggested that small IRBs consider contracting with a local IRB or creating a regional co-op, while medium and large IRBs should consider “farming out” protocols when the cost of internal review is greater than the cost of external review. Unfortunately, he said, most institutions do not have enough data on what their programs really cost to run to weigh costs accurately.

Dr. Wagner questioned whether a system that depends on volunteers receiving neither cash nor in-kind compensation can be sustainable. He felt that if creativity were allowed to work, prospective payment systems might be developed with built-in incentives that reward efficiency, innovation, and quality improvement. The downside would be if these gains in efficiency came at the expense of quality. This is a legitimate concern, but determining how best to see if quality is being maintained depends on finding ways of measuring it. Once quality can be demonstrated in acceptable terms, trust can be enhanced.

Currently, we lack critical data that would help institutions make the best possible choices. They need “process” data on how much time and effort are required to review various types of protocols. Data are critical for quality improvement; risk management; maintaining morale among IRB staff, administration, researchers; and providing a road map for system improvements. Sound data can help select evidence-based methods that will improve quality as well as achieve a more cost-effective system. The speaker looked forward to a time when it would be possible to predict the costs of reviewing particular types of research using different mechanisms more accurately, facilitating decisionmaking. Dr. Wagner used the analogy of a medical model in which there are accepted benchmarks for the cost of particular procedures and operations based on experience.

Summary of Discussion

An NCI program director asked panelists for more information on the amount of time IRBs spend reviewing adverse events. He was told that while some estimates suggest approximately 9 percent of an IRB's time may be spent reviewing AE reports, this estimate is based on surveys that rely on the respondent's recall. It is possible that the responses are influenced by recent events and are relatively unreliable. Dr. Gyi added that in general, IRBs do not collect and keep the type of records that would help determine how their time is spent.

In regard to costs, participants agreed that essential data were lacking. IRBs are largely a service industry dependent on volunteers. IRB staff members are frequently underpaid when their salaries are compared to other administrative staff working in other parts of the institution, such as grants administration. The frequent confusion between direct and indirect costs in accounting makes it difficult to see what funds are available to the IRB and how these funds are being spent.

Participants also reinforced the importance of metrics. Some felt that it was much easier to develop appropriate ways to measure cost and timeliness than to express quality in ways that allow comparisons. Dr. Charnes suggested that if it were possible to re-engineer the way services are provided, the "3-legged stool" that Dr. Gyi described (cost, speed, and quality) might be stabilized without trading off any of the "legs."

A participant asked about savings that might be associated with the transition to electronic systems. Ms. Mary Banks of Boston University Medical Center responded that her institution had moved to an electronic system two and a half years ago. It estimates approximately \$1,000 per week in savings related to copying expenses, filing, and transporting documents. It is now possible to measure how long it takes for protocols to get through the system and to know such metrics as how many protocols are waiting for review and how many adverse events have been processed. Review time has been decreased as well. In addition, now that project reviews are projected on a screen during the IRB meeting, reviewers are consistently arriving with completed reviews ready to present. Others noted that technology can also be leveraged to improve or facilitate communication across multiple sites, enhancing cooperation and promoting transparency. It also allows participation by consultants and members in remote locations. Electronic systems may also help members anticipate emerging needs.

In regard to timeliness, Dr. Gyi observed that the same pressures applied by sponsors to institutional IRBs are also applied to alternative IRBs. Dr. Sailot commented that lack of a reliable time frame is what hurts sponsors the most in multi-site studies; if the speed were known, it would make planning possible. The lack of uniformity is a major concern. IRBs have different application forms, for example. A member of a collaborative IRB represented in the group is currently analyzing the diverse applications and instructions that exist in participating institutions with a review to standardization. Some also felt the variability in communication from the IRB to investigators and sponsors detracts from efficiency: how are investigators to reconcile different directions from different participating sites? Despite these concerns, some local sites see "homogenization" as antithetical to quality.

Dr. Gyi commented that bottlenecks may be associated with sponsors, investigators, and administrative processes not directly associated with IRB review in itself; unfortunately, IRBs are the

last in the chain of events and often take the blame for actions beyond their control, such as incomplete proposals or time spent on legal review. A participant noted that no one is discussing outsourcing work related to processing grants and contracts. Members agreed that more dialogue is needed on the entire process to understand where delays occur most frequently and how efficiency might be improved.

Some participants were concerned about the potential loss of revenue to institutions if alternate forms of IRB review were employed. Dr. Saillot suggested that if sponsors understood what subject protection activities were being accomplished at the institutional level that required support and if associated costs were explained, it might not be a problem for many sponsors to allocate costs accordingly. This is impossible, however, when activities and related costs are not clearly identified. Another member commented that protocols that bring in considerable funding support for IRB functions are not always prime candidates to be contracted out. Finally, some participants underlined the importance of educating institutional officials regarding funding needs to ensure that costs are allocated to support crucial activities.

Conclusions and Recommendations

In the plenary session, Dr. Charns highlighted participants' concerns related to lack of data on the costs, quality, and timeliness of both internal and external IRBs. They felt that meaningful data should be collected using standard methodology to assist in decisionmaking.

Technology can make it easier for IRBs to develop metrics that help them assess efficiency and timing. It may also improve efficiency and timeliness of reviews. Technology can also facilitate communication across sites and between external IRBs and institutions. Further, access to information both within and across IRBs can help improve trust by increasing transparency.

Some participants saw external IRBs as a potential threat to the revenue that supports local IRBs and helps maintain institutional subject protection programs. They questioned how local IRBs could be compensated when responsibility is shared with external IRBs. A particular concern was the loss of revenue needed for education and training, which is currently generated from commercially sponsored studies.

Session participants observed that regulatory requirements related to the use of alternate IRBs should be clarified and harmonized. Institutions need both guidance and education on how to use varieties of external IRBs. This includes identifying ways that local context can be adequately addressed.

Participants understood that the lack of a reliable timeframe is what hurts sponsors the most. They underlined the importance of ensuring relative predictability of time, process, and outcomes from site to site as opposed to simply working "faster." Sponsors need to be able to predict the time needed for review and budget accordingly.

Further Discussion. Many plenary session participants were not convinced that a crippling loss of funding for the local human protection program was inevitable when external IRBs were used. Some felt that IRBs could retain funds by demonstrating the costs of administrative support and required training to administrators, then ensuring that an appropriate percentage of indirect costs remained at

the institution to support these functions. One participant stressed that the issue of how to fund the IRB function fairly should not be allowed to stand in the way of using the most appropriate model for review. Another thought sponsors would be willing to support local protection activities if their cost and value were demonstrated. One participant pointed out the irony of local IRBs worrying about the potential loss of funding for their programs while criticizing “commercial” IRBs for working for pay.

VI. Stakeholder Perspectives on Key Issues

Key questions arising from the work of the first day were formulated by the conference steering committee and presented to attendees for deliberation in stakeholder groups. Following these meetings, moderators reported findings in a closing plenary session, followed by an open discussion.

Turning Recommendations into Action: The Charge to Stakeholder Work Groups

Alan Fleischman, M.D.

National Institute of Child Health and Human Development

Speaking as a representative of the conference steering committee, which had met to analyze the experience of the first day and map the agenda for the second day, Dr. Fleischman proposed that the following assumptions underlie recommendations emerging from the first day of the conference:

- There is increasing use of alternative models for IRB review, including central and external IRBs, and academic institutions are developing partnerships with these organizations to share the responsibility for review and oversight of research.
- Demands for an efficient process must be balanced against the need to protect the interests of all research participants.
- Any recommendations must take into consideration the concerns of potential and current research participants.

Conference participants also identified a need to harmonize HIPAA and the Common Rule, a concern that OHRP is well aware of and seeking to address. Therefore, that issue was not earmarked for further exploration at this time.

Dr. Fleischman delineated the following key issues for stakeholder breakout groups to address on Day 2 of the conference:

1. Define how local IRBs and external IRBs should share responsibility for research review and oversight. Include recommendations for how to deal with a catastrophic untoward event, OHRP for-cause review, or inquiry from a reporter.
2. Define how local IRBs and external IRBs should share responsibility for regulatory liability in light of the belief that local institutions are responsible for oversight of all aspects of research performed in their institution.
3. Define how local IRBs and external IRBs should share responsibility for “local context” including:
 - knowledge of population, cultural norms, and other local context issues,
 - community engagement/involvement,

- knowledge of investigators' previous performance, and
 - knowledge of research context and whether the proposed site is adequate to meet the needs of the protocol.
4. Define what kinds of empirical data are needed to measure the real risks and benefits to subjects or participants, investigators, and institutions of centralized review of research protocols.
 5. Define what kinds of empirical data are needed to measure:
 - the impact of external IRBs on the quality of reviews and oversight;
 - the role, if any, of HRPP accreditation in facilitating centralized review; and
 - the role, if any, of accreditation and/or certification of IRB professionals and investigators in supporting alternative systems of IRB review.

Stakeholder Perspectives on Key Questions

Following breakout sessions in stakeholder groups, moderators reported each group's deliberations on each of the five questions.

1. Define how local IRBs and external IRBs should share responsibility for research review and oversight. Include recommendations for how to deal with a catastrophic untoward event, OHRP for-cause review, or inquiry from a reporter.

IRB Chairs, Members, and Administrators. Dr. Stephen Sallan, moderator for this group, highlighted primary conclusions. First, these stakeholders affirmed the utility of the following list of key responsibilities, as prepared by AAHRPP for human research protection programs seeking accreditation: IRB review; conflict of interest management; scientific review; adequacy of resources for the study; knowledge of and compliance with State and local laws; handling exemptions; handling of unanticipated problems involving risks to subjects or others; reporting to IRB, Institutional Officials, and Federal agencies; and post-IRB approval monitoring. They also affirmed the utility of AAHRPP's model of a comprehensive human research protection program as a meaningful starting point for considering roles and responsibilities. Group members stressed the importance of making model Standard Operating Procedures (SOPs) and contractual agreements available online at a widely publicized site. Finally, participants observed that social and behavioral research has not been widely discussed during this conference and deserves further exploration.

Institutional and Signatory Officials and Research Officials. Dr. David Wynes, moderator, reported that Institutional Officials were particularly concerned about the fact that OHRP holds institutions responsible for all compliance issues that occur under their FWAs, regardless of where the alleged violation occurred. The FDA model, in contrast, holds the specific component (reviewing IRB or investigator) responsible. They felt strongly that regulatory responsibility should rest with the reviewing institution and that alternative review boards should have FWAs as institutions do. When institutions report noncompliance on the part of a delegated review board,

they should be told, “thank you, we will investigate this further” – not, as is currently the case, that the institution is obligated to self-report noncompliance. Model agreements and Memoranda of Understanding should be available. Group members also discussed the “flip side” of the alternative IRB issue, which is the hesitation on the part of many institutions to serve as the IRB of record for community-based research, a concern similarly driven by potential liability for errors they cannot control or predict. Institutions are “getting it in both directions.” Re-evaluation of the dilemma in which institutions find themselves is recommended on the part of concerned Federal entities, especially OHRP.

Research Subjects and Advocates. Ms. Suzanne R. Pattee, moderator, said that participants recommended that subjects be given a toll-free number they can call for reliable information when untoward events occur.

Investigators and Sponsors. Dr. Carol Dukes Hamilton, moderator, said those present affirmed the importance of continued local-level involvement when an alternative review mechanism is used. Most responsibilities cannot neatly be divided in an all-or-nothing, either-or model, but are truly shared. This group also engaged in a discussion of how Federal sponsors can incentivize institutions to use Central IRBs when the Federal agencies strongly feel this option is appropriate. For example, Federal agencies could require institutions to demonstrate their willingness to use an external IRB as part of their application for funding.

Institutional Legal Counsel. Ms. Jeanine Ornt, moderator, reported that a written contract that clearly defines how responsibilities will be shared is the optimum strategy for protecting institutions. This group also felt it would be helpful to have access to model contracts that are more detailed and specific than are currently available on the OHRP Web site.

External IRB Administrators. Dr. Angela Bowen, moderator, said her group agreed that a specific plan for sharing responsibilities should be developed at the start of the relationship, including a plan for who will speak for whom and when in the event of a untoward catastrophe. The delegated IRB should be able to speak on its own behalf when it is under fire, but only after speaking first to the local institution. Whichever entity is specifically under fire in the press should generally be the one to respond to adverse publicity; however, coordination is essential. It is usually best if one party does all the talking.

Open Discussion. Dr. Levine concurred with external IRB administrators that in instances in which a newspaper story has suggested that a particular institution is responsible for particular lapses, the agreement should provide for the IRB or external IRB said to be at fault to have the first option to speak with members of the press.

2. Define how local IRBs and external IRBs should share responsibility for regulatory liability in light of the belief that local institutions are responsible for oversight of all aspects of research performed in their institution.

IRB Chairs, Members, and Administrators. Dr. Sallan emphasized the importance of ensuring that the patient remain the primary focus of concern when research oversight is discussed. Group members noted that when problems occur, flaws in the entire HRPP system must be carefully considered and addressed. Usually failures do not lie with a single individual or component; rather, HRPP system design did not provide for appropriate prevention and intervention.

Institutional and Signatory Officials and Research Officials. Members of this group stressed the importance of taking a comprehensive view of the institution's human research protection program and all its components. This allows the institution to perform the necessary self-evaluation to see how the pieces of the system fit together, what is working and what is not, and what components are most appropriate to delegate. This review should precede any discussion of contracts.

Research Subjects and Advocates. Ms. Pattee reported that her group believes there should be no barriers to the use of delegated IRBs when they are the best choice from the standpoint of human subject protection. Since institutional concerns about liability could be a barrier to making an appropriate choice, they proposed that OHRP policies be changed to assign responsibility for compliance violations to the party that committed the violation.

Investigators and Sponsors. Investigators remain responsible for investigator-level violations regardless of which IRB reviewed the protocol. Investigators are subject matter experts who should know how to organize and conduct the study. They "own" the protocol and meet with subjects face to face. Dr. Hamilton added that liability issues should be addressed proactively, since institutions are already losing grants because of their insistence on models sponsors may see as inefficient.

Institutional Legal Counsel. Participants noted that the term "responsibility" actually has two pertinent and separate meanings. The first refers to accountability and the second to consequences. They felt that the best way to address accountability issues is to delineate them in a contract developed with the participation of both lawyers and technical experts. They strongly felt that accountability should be specific to the party responsible for the actions in question. As for consequences in the event of a violation, they recommended including a statement in the FWA to the effect that if the institution exercises due diligence in selecting a delegated IRB consistent with applicable and specified standards, the delegated IRB is responsible for the actions it took in carrying out the duties outlined in its contract. They strongly felt that accountability should be specific to the party responsible for the actions in question. Institutions must be assured that their FWAs will not be placed at risk for actions they did not commit. Institutions typically will accept responsibility for the conduct and implementation of the research, but the reviewing IRB should be held responsible for problems related to a flawed protocol. In some cases, both the institution and the delegated IRB might be responsible.

Members felt that additional OHRP guidance would be helpful in removing impediments to the use of delegated IRBs. Specifically, they felt, OHRP should define what constitutes “due diligence” when contracting with an external IRB. Dr. Ornt suggested that SACHRP might help by making a recommendation supportive of such policies.

External IRB Administrators. Administrators of external IRBs viewed the problem differently from institutional administrators and their legal counsel. They were concerned about the potential ramifications of institutional shut-downs on their own operations. Dr. Bowen advocated that external IRBs should be treated as independent and separate entities from the institutions that have contracted for their services, and that an external IRB should not be held responsible for compliance failures on the part of the institution.

Open Discussion. A participant observed that relatively little attention has been given to liability issues in collaborative relationships among institutions within the same region or university. The audience member suggested that granting agencies could provide further guidance to encourage such collaborations.

3. Define how local IRBs and external IRBs should share responsibility for “local context,” including:
 - knowledge of population, cultural norms, and other local context issues,
 - community engagement/involvement,
 - knowledge of investigators’ previous performance, and
 - knowledge of research context and whether proposed site is adequate to meet the needs of the protocol.

IRB Chairs, Members, and Administrators. Participants felt that university IRBs often fail to recognize local concerns themselves, whether or not an external IRB is involved. “Community” should be considered from multiple standpoints, including geographic location, ethnic and cultural group, and the common experience of a disease or condition. To emphasize the importance of considering this dimension fully, a participant cited a multi-site study in which one site included members of a Native American population for which the epidemiology of the disease, the analysis of risks and benefits, and the health resources available to the community were all strikingly different from other study sites. Dr. Sallon felt that the investigator and the reviewing IRB should both be responsible for ensuring local issues are fully addressed when they are relevant to protocol design and review.

Institutional and Signatory Officials and Research Officials. Participants limited their discussion to issues of investigator performance and noted that an external IRB may be less vulnerable to pressures than an internal IRB in approving a protocol submitted by a previously non-compliant investigator.

Research Subjects and Advocates. Participants strongly encouraged early and continuing community involvement throughout the research process. Accreditation requirements should address this important element and institutions should recognize how helpful it can be to involve

potential subjects at each stage of research, from protocol development through analysis and reporting. Community involvement can make a huge difference in the willingness of subjects to participate. Advocacy groups can also help train community members so they can become more involved as subjects. Group members suggested certification of investigators to ensure their ability to involve and protect human subjects.

Ms. Pattee expressed concern that some conference participants appeared to believe that many studies do not have significant local context issues. She suggested that unless the question is asked, the existence of important issues may not be identified.

Investigators and Sponsors. Participants advocated for a checklist of issues that should be addressed as responsibilities are divided between local and external IRBs and felt that questions related to local context should be included. The group also discussed multinational studies, where the need to understand local context is magnified. In general, the analysis of local context might be best done by someone who lives in the area where research will be conducted. However, the concept of local community is not only geographic in nature.

Institutional Legal Counsel. Group members re-emphasized the importance of involving someone with technical knowledge, including knowledge of the subject population, as contracts with external IRBs are drafted. Dr. Ornt added that personal relationships with investigators can color institutional reviews, and consideration of investigator-related issues may be more fairly addressed by an external IRB that is not involved in local “politics.”

External IRB Administrators. Dr. Bowen commented that external IRBs have given thoughtful consideration to the issue of local context and see it as a major hurdle that must be addressed appropriately. Where research is conducted within an academic institution, the institution is often a vital link for the external IRB; however, the common “town and gown” separation may limit researchers’ knowledge of the subject community. The external IRB also needs knowledge of any problems the institution has experienced with particular investigators.

Open Discussion. Dr. Levine clarified his earlier comment that “something of immeasurable value may be lost” as alternative models are employed. He explained that nothing would be necessarily lost unless the institution’s entire human research protection program were to be discontinued as a result of contracted IRB review; in such a case, the loss would be very serious indeed. An important function of the program is serving as an institutional presence to remind people about the importance of applying ethics to research and providing a source of information about how this can be done.

Dr. Levine added that it is difficult to communicate cultural norms and that it is important to ensure that individuals thoroughly familiar with the community in which the research is carried out are included in the review process. He observed that communicating information about investigators might be difficult from the standpoint of confidentiality and wondered whether the institution might be opened to a lawsuit accusing it of slander. Another participant questioned this concern, however; he suggested instead that if the external IRB cannot be treated as one of the institution’s own IRBs, the institution should not enter into the relationship. Issues regarding confidentiality must be clearly articulated in the contract between the institution and external IRB, and provisions should ensure that information about investigators can be frankly communicated. This may be the most important aspect of local context. A second audience member concurred; he said such information might be

toned down in terms of the language used to express concerns (as compared to the way it might be presented in an institutional IRB meeting) but should always be conveyed clearly.

An audience member who participated in the NIH-funded HIV Vaccine Trials Network (HVTN) suggested this as a good model for how local context can be incorporated. Investigators are required to establish a Community Advisory Board (CAB) that is involved in each aspect of the project. In response to a question, the participant explained that the CAB probably did not have the power to veto a protocol, but could certainly exert public pressure. Although it requires time, patience, and energy to work with CABs, she asserted that doing so has been worthwhile. For example, CABs have contributed to development of the informed consent process and facilitated subject engagement. Dr. Fleischmann added that there are data to support the assertion that both recruitment and retention are positively impacted when subjects are engaged.

Dr. Levine commented that the desirability of community engagement was strongly supported by the reaction elicited by a specific 1986 protocol that involved the use of a placebo as one arm; the subject community strenuously objected – a reaction that, he said, can “look like a veto.” A participant reinforced the importance of local context by noting that in a study he was familiar with, alternative routes of administering insulin were received with particular enthusiasm by inner-city subjects who did not want to be seen on the streets carrying needles and syringes.

4. Define what kinds of empirical data are needed to measure the real risks and benefits to subjects or participants, investigators, and institutions of centralized review of research protocols.

5. Define what kinds of empirical data are needed to measure:

- the impact of external IRBs on the quality of reviews and oversight;
- the role, if any, of HRPP accreditation in facilitating centralized review; and
- the role, if any, of accreditation and/or certification of IRB professionals and investigators in supporting alternative systems of IRB review.

IRB Chairs, Members, and Administrators. Participants stressed the importance of eliciting feedback from subjects. Requirements such as annual IRB review should be tested through research. They agreed that the IRB’s turnaround time is a useful metric. Noting the requirement in the Common Rule that the IRB should be “sufficiently qualified...to promote respect for its advice and counsel” (45 CFR 46.107[a]), they also suggested using the level of respect accorded the IRB as a meaningful metric.

Institutional and Signatory Officials and Research Officials. Participants felt a grant program was needed to obtain more empirical data. Research should address the value of specific regulatory requirements on human subject protection and evaluate the impact of noncompliance. One option would be for OHRP to carry out such studies; however, OHRP currently has no authority to issue

grants. Participants suggested that SACHRP examine this issue and consider recommending to the Secretary of HHS that the agency accord grant making authority to OHRP.

While there is increasing interest in the use of alternative forms of review, there are obstacles to their use that remain to be overcome. Accreditation seems a step in the right direction. However, more data are needed to help everyone explore and assess the various forms of alternative review and to help ensure they are used in ways that benefit all stakeholders.

Research Subjects and Advocates. Participants strongly encouraged canvassing subjects for information on their experiences, including whether or how they were involved in the assessment of local context. Were subjects well informed about the protocol and given access to appropriate training when needed? Participants suggested that advocacy groups be involved to deliver training where needed.

Investigators and Sponsors. Group members focused on the need for a common taxonomy that would define domains and terminology to allow comparison across studies. For example, the type of study, the risk level, and review time should each be defined in standardized terms.

Dr. Wagner envisioned a data base where such information could be downloaded by researchers. It would also help administrators assess the strengths and weaknesses of their programs and component systems. Studies and researchers could be assigned identification numbers. Dr. Wagner speculated that researcher-related problems might surface as programs conducted by the same individual at different institutions were brought together for comparison. Of course, questions regarding confidentiality would have to be addressed. He noted that the current effort to develop electronic medical records addressed some parallel questions, and lessons learned from this effort might be helpful and informative.

Institutional Legal Counsel. Ms. Ornt suggested that focus should be placed on gathering knowledge that would help remove impediments to finding and using optimal ways of promoting research and the welfare of human subjects.

External IRB Administrators. Dr. Bowen said her group benefited from a presentation by Dr. Michael Klag of Johns Hopkins University at the November, 2005 workshop on this same subject. For example, in comparing the status of his institution's human research protection program before and after its shutdown by OHRP, Dr. Klag said the reading level on consent forms was now lower. Other parameters to track might include IRB member selection criteria, member attendance, the number of times protocols are amended after Board review, timeliness, and the nature and extent of resources available to the program. It is also helpful to understand how technology is being applied. The group suggested that AAHRPP would be an excellent organization to conduct this type of analysis and already has pertinent data that could be assessed.

Open Discussion. Dr. Levine noted that it is easier to measure process than outcomes, but it is the latter that really matter – for example, whether patients are better informed.

Closing Remarks

Bernard Schwetz, Ph.D., D.V.M.

Director, Office for Human Research Protections

Dr. Schwetz observed that the audience came with a wide range of opinions, and that diverse voices spoke and were heard. He stressed the importance of different stakeholders and groups expressing themselves on the issues and noted that approaches vary across the country. The IRB system was built to allow flexibility to adapt to specific circumstances.

While there were numerous messages of caution, the Director also heard messages that spoke of success in using alternatives and conveyed a level of confidence that these are working. He highlighted the following key points:

- If an IRB is not doing a good job, the choice of model will not change this. Those that are doing well will continue to do well using most models – and vice versa.
- There are situations in which the IRB is also the Human Research Protection Program. In such cases, outsourcing doesn't make sense and would leave the institution in a vulnerable position.
- The language used to describe alternatives needs to be "tightened up." The term Central IRB, for instance, means different things to different people.
- There is a need to reach out to institutional counsels and provide additional information needed for their increased understanding of alternative models.
- The issue of trust is paramount.
- It is clear that meaningful empirical data are needed to improve the process; it is important to keep pushing for studies that address processes of review and can provide such data.

OHRP will consider further the messages that were directed to them and determine what guidance or other responses may be helpful. OHRP wants to do what it can to ensure that the system is working in a way that provides maximum protection and ensures that institutions are free to choose the best model for each set of circumstances.

Dr. Schwetz expressed his thanks to the organizing committee, sponsors and cosponsors, to Dr. Levine and Dr. Fleishmann, to all moderators and speakers who contributed to the discussion, and to the audience members.

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Attachment: Models of IRB Review

Prepared by NIH Program on Clinical Research Policy Analysis and Coordination (CRpac)

Models of IRB Review		
TYPE	DESCRIPTION OF MODEL AND EXAMPLES	TYPICAL USE
Local IRB review - single site study	Institutionally based IRB reviews research at own site	Academic institutions; private research institutions; government agencies conducting own research
Local IRB review - multi-site study (no central IRB)	In multi-site research, each site has own IRB review, independent of other sites	Multi-site studies, public or private sponsors, where each site has own IRB (e.g., federally funded or pharma studies using academic sites)
IRB cooperation – multi-site studies	Participating IRBs share resource materials, SOPs, informed consent documents, and other information to facilitate work on multi-site studies Example: IRBNet	Multi-site studies where individual IRBs may benefit from the experience and resources developed by others. May be particularly valuable for complex or high-risk studies
Institution relies on IRB of another academic institution – single site study	For a given study, an academic institution turns to the IRB of another academic institution, perhaps because the latter has more appropriate expertise	Institution lacks resources or expertise to conduct own IRB review
Independent IRB review - single site or multi-site studies	A single independent IRB conducts review on behalf of one or more sites, which accept the independent review (no local review by each site) Example: Western IRB (WIRB)	Drug, device or biologic research conducted under IND; some non-product-oriented academic research, as well
Facilitated central IRB review - multi-site studies	Facilitated review whereby local IRB or representative accepts central IRB review, modifies it, or conducts full review Example: National Cancer Institute Central IRB (NCI CIRB)	Certain studies conducted with support from NCI

Models of IRB Review		
TYPE	DESCRIPTION OF MODEL AND EXAMPLES	TYPICAL USE
IRB reciprocity – single site or multi-site studies	Different sites form consortium; participating institutions agree to accept review by the existing IRB of any other participating institution; shared SOPs are developed Example: Multicenter Academic Clinical Research Organization (MACRO)	Institutions that have resources, motivation, and common interest to form a consortium
IRB consortium	A group of research institutions form a new entity to manage, audit, and monitor clinical research, including IRB review Example: Biomedical Research Alliance of New York (BRANY)	Institutions that share common attributes and seek to outsource IRB review and trial monitoring
Multiple IRBs review protocol – domestic	A national and regional IRB review the same protocol concurrently Example: Indian Health Service	Studies requiring extra oversight, particularly where inclusion of certain communities or knowledge of local context is especially important
Multiple IRBs review protocol – foreign single site studies	Multiple IRBs review research at a single foreign site, e.g., local IRB abroad, an IRB at a collaborating U.S. grantee institution, and possibly an NIH Institute IRB	International research, for example, some National Institute of Allergy and Infectious Diseases (NIAID)/ Division of Acquired Immunodeficiency Syndrome (DAIDS) studies