Secretary's Advisory Committee on Human Research Protections Meeting
December 11-12, 2003
Washington, DC

Summary Minutes

FRIDAY, DECEMBER 12

Additional Subcommittee Business

Ernest Prentice, Ph.D.

Dr. Prentice noted that thus far SACHRP members had decided to convene expert panels at the March meeting that would address (1) HIPAA issues and (2) central IRBs. He asked SACHRP to complete the decision-making for the March agenda before proceeding with further business. The following points were made:

- Dr. Khin-Maung-Gyi suggested that a panel on litigation, with a focus on liability, be added to the agenda. Mssrs. Adams and Barnes, Ms. Kornetsky, and Dr. Polan agreed, noting that there is a pressing need to relieve IRB members of anxieties about litigation so that they might better focus on the subjects' best interests. In addition, affording IRB members some liability protection should help reduce the general litigation-wary attitude common across clinical research.
- Some Committee members preferred convening only two panels to ensure that there was sufficient time for discussion and possible development of recommendations. Other members favored three panels.

Motion

Dr. Fisher proposed that:

- Two panels be convened at the March meeting. One will address HIPAA and the other will address litigation.
- Subcommittees, as available, will review (1)AEs and (2) central IRBs.

Action

The motion was unanimously approved.

Roselle Award

Mr. Barnes announced that Dr. Prentice was presented the Roselle Award for excellence in research animal care. He is only the second non-veterinarian to win this award.

International Research Issues Panel:

International Activities and Challenges

Melody Lin, Ph.D., Deputy Director, OHRP

Dr. Lin thanked SAHCRP, especially Dr. Polan, for their work selecting the panel. She explained that her PowerPoint presentation would set the stage for the reports by the other panelists: David Borasky would provide a perspective from the field and Helen McGough would offer possible solutions to the problems identified by the panel.

Various statistics highlight the growing prominence of international research. Examples include the following:

- Over the past ten years, NIH expenditures for international research have increased from less than $20 million to more than $120 million.
- The percentage of New Drug Application (NDA) submissions using foreign data between 1995 and 1999 increased three-fold to 27 percent.
- During the same time, the number of foreign human subjects participating in NDA clinical trials increased from 4,000 to 400,000 people.

In 2001, the DHHS Office of the Investigator General (OIG) issued *The Globalization of Clinical Trials*. The report found that: (1) many international research sites had limited experience with human subject protections, and (2) FDA was constrained in its ability to ensure that protections were provided. For instance, between 1990 and 1999, the number of FDA inspections increased from 22 to 64 while the number of investigators involved in overseas research increased from 271 to 4458. To remedy this situation, the OIG recommended that FDA obtain more information on the performance of foreign IRBs and conduct capacity building. The OIG also recommended that FDA conduct more sponsor monitoring and create a database for tracking foreign research.

According to 45 CFR 46.103(a), all institutions, domestic and foreign, engaged in HHS-sponsored international studies must provide research assurances. These are negotiated and approved by OHRP. The OIG promulgated two key recommendations for OHRP to address. The first recommendation, to exert leadership in protection at non-U.S. sites, is outside OHRP's jurisdiction. The second recommendation was to encourage accreditation directly and through cooperative efforts with FDA, NIH, and other organizations. This recommendation has informed OHRP's international mission, which is to:

- Build capacity for ethical review
- Increase awareness of requirements
- Assure compliance
- Ensure all HHS research follows ethical principles

OHRP's current focus is capacity building. The Office is providing workshops alone and in cooperation with other Federal agencies, the World Health Organization (WHO), and research institutions in the Americas, Asia and the former Soviet Union. Responses to the programs have been positive, and OHRP will continue to:

- Provide regional research ethics courses targeting institutions that conduct significant amounts of international human research.
- Network with other organizations to increase ethics training opportunities and to promote voluntary international accreditation.

Over time, OHRP will leverage resources to respond to the challenges of building infrastructure and sustainability and to maximize program impact.

Perspectives from the Field: The Realities of Developing Country IRBs

David Borasky, CIP, Office of International Research Ethics, Family Health International

During the past 50 years, the United States has created a research ethics infrastructure that includes regulations, oversight mechanisms, the IRB system, and the professionalization of the field. During that time developing countries faced a series of political and economic crises that made developing a research ethics infrastructure a low priority.

However, beginning about five years ago, institutions in developing countries began developing and using IRBs. This was primarily in response to foreign research requirements, including the HHS regulation mandating that international institutions participating in research sponsored by the Department have IRBs and obtain FWAs. Although most overseas institutions are moving towards compliance, they often do not have the training or information--such as manuals, checklists, and SOPs-- necessary to do so. They also do not have the technology to access this information on-line.

Other compliance challenges include the following:

- The "best and brightest" researchers are chosen for the IRBs. Because these are the scientists with the heaviest workloads and the broadest research involvement, their IRB meeting attendance is poor and they do not provide an unaffiliated, disinterested voice for review.
- Many IRB members are uncertain about their priorities and focus on scientific methodology while giving ethics short shrift.
- The IRBs often lack:
  - Qualified community representatives
  - Administrative staff trained to manage timely document flow, retrieval, and storage.
  - Policies to ensure consistent and timely review.

In addition, the foreign institutions generally receive guidance in completing the IRB requirements from the U.S institutions that received the research funds. Often these American institutions are not certain of the relevant laws or equivalency regulations. This lack of information, coupled with the need to move expeditiously, can create problems. For example, some international IRB members report that they have been guided in ways treat requirements as "bureaucratic formalities."

Mr. Borasky reviewed a case study in Uganda that highlighted many of the problems experienced by developing nations attempting to comply with IRB regulations. Based on these experiences, Mr. Borasky concluded that developing countries need the following forms of assistance to establish and sustain IRBs that meet Federal requirements:

- Mentoring from U.S. partners, possibly conducted with support from NIH Enhancement Grants.
- More oversight and guidance from Federal agencies with the required expertise such as OHRP and FDA.
- Training in IRB administration and review; this might be provided by PRIM&R and Applied Research Ethics National Association (ARENA)
- Strategies to generate revenue such as allowing IRBs to charge review fees.

Capacity-Building in International Research: Challenges and Practicalities
Helen McGough, Director, Human Subjects Division, University of Washington
International clinical research programs sponsored by HHS and FDA usually are structured so that the domestic institution receives the prime award and is responsible for ensuring that reviews occur at all sites. The foreign institution, usually a subcontractor, is required to provide ethical review before research can be conducted.

U.S. institutions usually have established and experienced IRBs, but this may not be the case among foreign subcontracting institutions. The lack of an IRB, or inconsistencies among them, can cause serious problems. These include:

- Duplication of reviews
- Lateness of reviews
- Non-Compliance (e.g., no quorum, no continuing review, no amendment review, the appearance or existence of conflicts of interest)

WHO has been offering forums, supported by OHRP, to help resolve these issues. Other resources for problem resolution are the NIH Fogarty International Center, the Center for AIDS Research (CFAR) and PRIM&R. Other options for resolving problems could include certification such as that offered by ARENA, or accreditation, which is currently being discussed by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

In addition, successful strategies for resolving these problems have been identified by institutions conducting international research. For example, the University of Washington (UW) has successfully involved in-country researchers and IRB members in creating and presenting tailored curricula and workshops. Activities that promote mutuality--one-on-one meetings with key staff to solicit their guidance prior to the sessions, the use of interactive materials, and the inclusion of mock IRB sessions--enhanced the impact of the activities.

In the future, UW workshop topics will be expanded to include other responsible conduct of research (RCR) topics such as conflicts of interest, data management and ownership, and research misconduct. In addition, more formal workshops are being planned for IRB members and institutional administrators concerning infrastructure issues such as:

- Resource availability
- Policies and procedures
- Membership recruitment, retention, and voting
- FWA and IRB registration

Two other future directions for UW include: (1) expanding in-country site visits to include IRBs and (2) providing fellowships and other mentoree opportunities for host IRB members, chairs, and staff.

In her conclusion, Ms McGough noted that finding funding resources for IRBs is particularly important; as well as charging fees for reviews, IRBs might include overhead rates for infrastructure costs in their contracts.

Discussion of the Panel Presentation on International Research Issues

Dr. Lin responded to questions:

- OHRP offers foreign institutions six options from which to choose one set of FWA procedural standards.
- The Secretary of DHHS has delegated the responsibility for decisions about equivalence to OHRP.
- OHRP has developed a report on international equivalence that addresses patient protection criteria. The next step is to assess foreign SOPs and guidelines to determine whether they meet these criteria.

Mr. Barnes explained that overseas institutions not conducting HHS-funded research do not need FWAs. In fact, the institutions may not have equivalent protections and do not need to provide any assurances until and unless an FDA application is made. Ms. McGough observed that UW encourages, and sometimes requires, participating overseas sites participating in research with no IRB and FWA requirements to provide similar documentation and activities.

The FDA's jurisdiction does not extend beyond the United States, Dr. Lepay noted. He added that the FDA can conduct only retrospective reviews when the investigator submits his or her FDA application after the research study is completed. The inability to look at IRB activity in real time can be very limiting.

Mr. Barnes noted that European studies must comply with national or European Union codes. He asked if panelists had had any difficulties complying with the European Data Directive for importing information. Ms. McGough said that her experience has been largely positive, but it does not include tissue transfer requests.

Dr. Prentice commented that the International Conference on Harmonization (ICH) and the Declaration of Helsinki requirements are more comprehensive than those required by 45 CFR 46. He asked whether the panelists felt that the international codes were burdensome. Ms. McGough replied that UW does not find them burdensome--the University conducts a relatively large amount of overseas research, accepts the need for meeting the requirements, and has become efficient in completing them.

Accreditation could help resolve problems regarding human research protections, Dr. Prentice noted. Dr. Lin agreed, but said that HRPPs in most developing countries were not close to meeting accreditation requirements. However, she also noted a few countries have included involvement in the research and development of medical devices in their plans for economic growth. These countries are more sophisticated and diligent in establishing their HRPPs.

Dr. Polan asked for clarification regarding the requirements for developing IRBs in foreign institutions when conducting international studies that are not sponsored by HHS or FDA. Ms. McGough replied that the home institution IRB could be used in these cases and the overseas IRB structure did not have to be developed.

In her experience, Dr Polan reported, most U.S. investigators are not informed about international research requirements. She asked the panelists for input on this problem. Many institutions offer training, Ms. Lin replied. Although it is not required by OHRP, it is mandatory for investigators who have received NIH international grants. Ms. McGough observed that the level of investigator education supplied by granting agencies varies widely, but that institutions are increasingly offering training. Dr. Borasky added that his organization has offices in 36 countries and identifies a leader in each to be the IRB "point person."

Dr. Carome explained the international FWA choices. An ethical standard must be selected from three options: the Helsinki Declaration, Belmont report or "other." The institution also must choose one of six sets of procedural standards to apply, one of the options being 45 CFR 46. Ms. McGough suggested that the host and domestic institutions should be given the flexibility to operate under the same ethical and procedural standards.

The following additional points were made:

- Ms. McGough stated that:
  - DHHS should continue to allocate resources for sustainability and capacity building.
  - At present, especially when there is not HHS or FDA involvement, domestic IRBs might help host sites develop Boards and supporting infrastructure.
- Dr. Lin noted that there might be OHRP guidance available to assist institutions in providing education concerning overseas research. However, this has not yet been posted.
- *Ex officio* member James Shelton, U.S. Agency for International Development (USAID) asked the panel to keep in mind that:
  - Socioeconomic gaps exist between foreign researchers and study subjects that can create research challenges
  - USAID has found limited value added when requiring IRBs as part of the health projects that they sponsor.

Dr. Hauser asked whether Federal funds were supporting clinical research overseas that did not include human research protections. Mr. Borasky replied that this probably was occurring. However, many organizations and agencies, including those represented by the panelists, were working to end this situation. Ms. McGough added that the problem highlights the need for prompt and collaborative reviews in which all the parties involved learn how to resolve review issues in culturally appropriate ways. Dr. Jones observed that investigators, even those well informed about domestic research protections, should be trained about international issues. She also suggested providing external assistance to institutions not conducting a great deal of overseas research.

Mr. Adams asked about the availability of funds for host institutions. Panelists replied that support is available from the NIH Fogarty International Center and the Burroughs-Wellcome Fund. Funding and training also are available from Harvard and Yale Universities. However, additional support is needed.

Dr. Fisher asked how SACHRP could best respond to the panel's comments and craft appropriate recommendations concerning international research. She noted that it seemed important to ensure that SOPs were in place that facilitated patient protection. In addition, she suggested that SACHRP's guidance should address moving towards higher ethical standards while maintaining flexibility, ensuring sustainability, and addressing the challenge of outsourcing research to foreign nations.

Suggestions for SACHRP Activity

Dr. Prentice asked the panel to make requests that SACHRP could use as the basis of recommendations for meeting international challenges.

- Dr. Min requested additional support for collaborations between OHRP and other organizations. This would enable the Office to leverage its resources, build greater capacity, and further promote international human subject protections.
- Mr. Borasky asked that OHRP provide clear guidance on equivalence protections and how these can be use by the domestic institutions.
- Ms. McGough agreed with Dr. Min and Mr. Borasky, and added that a cross-agency survey of activity would reduce duplication and increase collaboration.
- Dr. James Shelton suggested addressing informed consent issues; these include making certain potential participants understand the "informed consent" concept and developing language that does not unreasonably limit participation.

Action

Dr. Polan will begin drafting SACHRP recommendations. Mr. Barnes will help draft the section on informed consent.

AE Reporting Issues: Panel #1

Reporting Requirements for AEs: An HHS Regulatory Perspective
Michael A. Carome, M.D., Associate Director for Regulatory Affairs, OHRP

No AE reporting requirements are stipulated by the HHS regulations for the protection of human subjects. However, there are provisions of 45 CFR Part 46 relevant to AE reporting. Dr. Carome reviewed these provisions and explained that to comply with requirements, investigators must report unanticipated or unexpected serious adverse events (SAEs). Investigators and IRBs collaboratively determine which AEs meet this description; HHS anticipates that only a minority of AEs will meet the criteria. Once these AEs have been identified, they must be reported promptly to the appropriate institutional officials, the head of the supporting department or agency, and OHRP. However, "promptly" has yet to be defined. Dr. Carome concluded that, from the OHRP perspective, ensuring that serious unanticipated or unexpected AEs are reported is most important.

FDA's Adverse Event Reporting and Review
David A. Lepay, M.D., Ph.D., Senior Advisor for Clinical Sciences, FDA

FDA regulates, but rarely sponsors, clinical research. FDA uses the international guideline ICH E2a definition of AEs:

- Any untoward medical occurrence in a patient/subject administered a pharmaceutical product and which **does not necessarily have a causal relationship** with this treatment.
- Any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of a medicinal product, but **not necessarily related** to the medicinal product.

SAEs are those that are considered serious by medical judgment. Among them are events that result in: death, new or prolonged hospitalization, a disability/incapacity, a life-threatening event, and/or a congenital anomaly in the offspring of a subject. Unexpected AEs are those that:

- Have not been previously observed.
- Are more severe or have greater specificity than the AEs predicted in the investigator brochure or study plan.

FDA regulation is rooted in the "Good Clinical Practice" (GCP) system for sharing review responsibilities among investigators, IRBs, industry, and Government.

- Clinical investigators are required to document AEs and make both progress and safety reports to the research sponsor. Investigators also have the main burden of responsibility for reporting any unanticipated problems involving human subjects to their IRBs. Although the language concerning investigator responsibilities is broad, FDA uses a narrow interpretation, which can lead to difficulties harmonizing review efforts with other organizations.

- Sponsors are responsible for promptly reviewing information for a wide range of sources related to a study's safety and determining whether AEs have occurred that are associated with unreasonable and significant risks. If these have occurred, the sponsors must discontinue the study and notify FDA and all the IRBs and investigators involved via written Investigational New Drug (IND) Safety Reports. In addition, the sponsors' annual reports to the FDA must include a summary of the written reports and other information about AEs.

- The lead IRB has specific responsibilities for reporting in writing to other participating IRBs, FDA, and appropriate institutional officials concerning any unanticipated problems involving risks to human subjects or others. Continuing reviews of the study must be conducted at intervals appropriate to the degree of risk, but not less than once per year.

- The FDA is responsible for reviewing safety-related documents for the IND and works primarily with the sponsor to take any appropriate actions. If human subjects are or would be exposed to an unreasonable and significant risk of illness or injury, the FDA can impose a "clinical hold" that may stop the study. The agency continues to be responsible for safety reporting and review beyond clinical investigations and throughout product marketing.

- Parallel requirements exist for the medical device industry.

IRB Review of External Adverse Event Reports (AERs): The City of Hope Model
John A. Zaia, M.D., IRB Chair

Before beginning his presentation, Dr. Zaia explained that his focus is limiting the number of external AERs sent inappropriately to IRBs. He also thanked Gwyn Okey for her assistance with the presentation.

FDA IND regulations require that sponsors notify FDA and all participating investigators of any adverse experience **associated** with the use of the investigatory drug that is both **serious** and **unexpected**. FDA regulations also require investigators to "follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and the FDA of **any unanticipated problems involving risks** to human subjects or others…" The HHS regulations are similar, but the report must be sent to the Department or Agency head rather than the FDA. Appendix M of the NIH requirements for gene transfer studies requires investigators to submit "a written report on **any serious adverse event that is both unexpected and associated with the use of the gene transfer product…"**

The lack of harmonization leads to an unintended burden on IRBs because principal investigators (PIs) receive, and send for IRB review, large numbers of AERs from sponsors about subjects external to the institution. The AERs can be categorized as:

1. Expected, serious, unrelated to study interventions
2. Expected, not serious, unrelated to study interventions
3. Expected, not serious, related to study interventions
4. Unexpected, not serious, unrelated to study investigations
5. Unexpected, not serious, related to study interventions
6. Unexpected, serious, related to study interventions

In general, due to a lack of clarity about how these categories should be defined and used, PIs send AERs unnecessarily to IRBs.

The burden on IRBs is compounded by the lack of information in the external AERs. The majority do not include sufficient information for the Board to make a judgment regarding any required actions. In addition, the IRB does not function like a Data Safety Review Board (DSMB); therefore, it lacks information on the number of study subjects, the number with similar AEs, and any preexisting factors that might have contributed to the AEs.

To reduce the burden, Dr. Zaia recommended using the City of Hope (COH) model. PIs use the three AER categories (expected, serious, related to the intervention) to categorize AERs for DSMB review. This Board refers the AERs to IRB with their comments. The IRB (1) records and files minor AERs, (2) provides a modified review of SAEs for which minor modifications were recommended, and (3) conducts full-scale reviews for SAEs for which major changes were recommended. When an institution is unable to provide DSMB reviews, Dr. Zaia suggested that the PI should be provided with the data reporting the number of subjects who have: (1) been treated according to the protocol and (2) have suffered similar AEs. The PI should incorporate the data in his/ her report to the IRB.

Externally Occurring SAE Reports: Washington University in St. Louis School of Medicine IRB

Patricia Scannell, Director, Human Studies Committee, Washington University in St. Louis School of Medicine

Ms. Scannell confirmed Dr. Zaia's findings. Washington University in St. Louis School of Medicine has four subcommittees established to conduct SAE reviews. The number of external SAE reports coming to the IRB has grown to 206 each week, compared to 30 local SAEs per week. Problems with the external SAE reports include:

1. Insufficient data
   - Often no denominator
   - Lacking substantive medical information
   - Blinding makes it impossible to know whether the SAE was related to the study drug
2. The reviewer lacks knowledge of the disease and its treatment that can be applied to ascertaining risk.

As a result of these problems, the IRB and its staff are putting forth a large effort to achieve results that are unproven and probably of little benefit. In addition, IRB resources are not optimally focused on tasks that will protect human subjects.

To rectify this situation, the School of Medicine has developed an electronic submission process for SAE reports. The new process, which will be Beta tested in January, 2004, requires PIs to take a set of actions to protect research participants.

- The PI must determine whether anything stated in the SAE report increases the risk to the subject population. If the report does not increase the risk, it is archived. If it does, the PI must choose among options for the IRB's consideration: suspend study enrollment, revise the consent form, compose a letter to participants, modify the study, or take other action.
- The PI also must determine whether the SAE provides new information that is unanticipated and is of such magnitude/frequency to require modification of the consent form. If so, an IRB review will be conducted.
- Supporting documentation, revised consent forms/protocols, and amendments for all SAEs must be submitted to the IRB for archiving.

In this new process: (1) the Data Monitoring Committee (DMC) provides input to the PI who makes determinations and forwards appropriate information to the IRB, and (2) responsibility for expert assessment of SAEs and for advising the IRB rests with the DMC and PI. As a result, the IRB's formerly unrealistic workload becomes manageable and keenly focused on human subject protections.

Discussion of the First Panel Presentation on Adverse Events

Dr. Prentice observed that the presentations by Drs. Carome and Lepay did not refer to any requirement that IND safety reports generated by AEs that occur at external sites have to go to every IRB involved in a multi-center clinical trial. He added that part of the rapid increase in AERs reflects the growing utilization of multi-site trials and, hence, the proliferation of subjects. He asked Drs. Carome and Lepay for guidance regarding the increasing number of external AERs.

Dr. Lepay observed that some investigators do not understand AE reporting requirements, as has been demonstrated in several recent FDA-sponsored public meetings. Additional guidance may help remedy this situation, but other causes for this confusion also must be considered. For example, IRB SOPs may not be useful to investigators or may reflect IRB misunderstandings of the regulations. Education may be needed for all the participants involved in the AE reporting and review process. Dr. Carome added that the extensively detailed reviews undertaken by IRBs are not mandated by HHS regulations. He also noted that the Department has initiated efforts to identify the actual issues feeding into the AE reporting burden experienced by IRBs.

Dr. Prentice suggested that DSMBs could be created to analyze safety reports submitted in FDA-regulated research and send the documents to IRBs as appropriate. He asked whether FDA could provide sponsor guidance to implement this idea. Dr. Lepay responded that this might be an appropriate DSMB responsibility in some cases but that their workload also must be considered. He deferred further comment on these Boards until after SACHRP heard from Susan Ellenberg, a DSMB expert participating in the afternoon panel.

DMCs might be useful in reducing the burden on IRBs, Dr. Lepay suggested. However, IRBs need to better understand DMCS and make more effective use of them, including embracing their recommendations without requiring reviews of individual reports. Dr. Lepay explained that properly operating DMCs are an invaluable resource because members: (1) review reports in real time and (2) develop decisions based on predetermined statistical formulae and their own medical, statistical, and scientific expertise. He also observed that the FDA will soon finalize its DMC guidelines.

Ms. Kornetsky asked whether the definitions of SAEs could be better harmonized. Dr. Lepay explained that FDA is eager to expand its efforts to harmonize definitions, but faces many challenges. These include harmonizing the criteria used to define serious and unexpected AEs in biomedical studies with those used in social/behavioral research. Another challenge is balancing adherence to the Common Rule with international standards. However, progress is being made worldwide in harmonizing pharmaceutical and biomedical SAE definitions and criteria; perhaps this work can become a model inspiring further progress.

Ms. Kornetsky observed that:

- Current IRB procedures may not be suitable for multi-site trials.
- Independent DSMBs or other data safety entities are needed to gather information related to human subject protections and provide it to IRBs.

Ms. Scannell and Dr. Khin-Maung-Gyi agreed with Ms. Kornetsky. However, other SACHRP members raised questions about whether DMC advice would be accepted by IRBs.

Dr. Carome observed that addressing the growing number of external AEs seems to be the greatest challenge for IRBs. He reported that OHRP sees both the UW and COH

strategies as more than adequate. Dr. Prentice noted that neither program provides a second review of the PIs analysis; however this has been judged as acceptable. He added that these approaches are significant steps in reducing IRB workload.

Dr. Zaia said current problems are technical/scientific, not legal, and are the result of insufficient information being provided to IRBs. This information could be obtained from research sponsors without engaging DSMBs. Ms. Scannell commented that IRB procedures could be open to legal challenges via civil suits. Dr. Zaia observed that legal problems would be alleviated if sponsors were provided with guidance about what is required from them. Dr. Lepay noted that the FDA welcomes SACHRP input on guidance for sponsors.

Mr. Barnes added that the lack of harmonization among the regulating agencies leads to confusion and concerns regarding legal liability. To avoid law suits, sponsors tend to over-report and are reluctant to make recommendations. IRBs and PIs also often adopt a similarly motivated cautious approach. To resolve this situation, Mr. Barnes suggested that SACHRP become involved in making "threshold decisions" that define the parties responsible for various levels of information evaluation and reporting.

Robert Hauser asked whether all studies involving greater than minimum risk should have sponsor-supported DSMBs that conduct timely analyses and report their findings to the PIs and IRBs. Dr. Lepay deferred his response until after the afternoon session, but he suggested that DSMBs would not be needed for every clinical trial. Dr. Zaia commented that employing a revised, smaller DSMB would be very helpful, as would requiring a sponsor function in data safety review. Ms. Scannell added that IRBs need the expertise provided by DSMBs, but the formal DSMB structure and procedures are not always necessary.

Dr. Fisher suggested short- and long-term solutions to the IRB problems with external AERs. In the immediate future, SACHRP should facilitate efforts that:

- Enable IRBs to obtaining improved and possibly standardized information.
- Clarify the sponsoring agencies' responsibilities.
- Promote more specific communications from the sponsors to PIs and IRBs.

To help resolve more complex issues: (1) uniform definitions need to be developed, with a particular focus on "unexpected events" and (2) the role and composition of DMCs should be clarified and funding support identified. Dr. Fisher added that SACHRP should encourage a focus on ongoing tracking to provide a cumulative picture of successes and gaps in human subject protections.

In response to Dr. Fisher's comments, Ms. Scannell noted that: (1) investigators must get immediate alerts about SAEs and (2) IRBs need assurance that alerts are sent promptly to all appropriate parties. Dr. Zaia added that unexpected/expected AEs may be the most critical concept to define and that sponsor input would be needed on this issue.

Dr. Prentice thanked the panel, and provided comments based on his own experience:

- Resolving external AE problems is critical; local AEs are being satisfactorily addressed under current requirements.
- The University of Nebraska Medical Center takes a cautious approach to AE review: PI analyses are forwarded to the AE subcommittee of the IRB for review.
- External AE problems will only be resolved when FDA ensures that pharmaceutical companies use DSMBs for real-time data evaluations and send this information to the PIs to incorporate in their reports.

AE Reporting Issues: Panel #2

Drug Industry Perspective

Peter K. Honig, M.D., M.P.H., Merck Research Laboratories

Dr. Honig explained that the pharmaceutical industry faces inter-related issues concerning clinical trial AE reporting:

- AERs are most valuable in aggregate, but are provided to regulators, PIs, and IRBs as individual case safety reports (ICSRs).
- Sponsor behavior is driven by regulatory compliance; sponsors default to the lowest global common denominator (i.e., the most conservative approach).
- The current regulatory system was designed when clinical research was more localized and IRBs were more able to manage the volume of reports and more fully comprehend their content.

He suggested that the system should evolve in a timely manner so it can continue to ensure human subject protections.

Collecting and reporting AE information is critical for proper monitoring of human subject safety. Collection and report procedures are regulated by the ICH E2A (Clinical Safety data Management: Definitions and Standards for Expedited Reporting) and E2B (Data Elements for Transmission of ICSRs). Documents published by the Council for International Organizations of Medical Science (CIOMS) also are pertinent in collecting and reporting AE information. Merck is committed to complying with all relevant requirements, and staff is educated and updated about them through the company's AE Training and Auditing of Investigator Sites Program.

As appropriate, Merck convenes DSMBs to ensure that human subjects are appropriately protected. When deciding whether to use a DSMB, Merck considers the nature of the medical condition under evaluation, the size of the trial, the level of safety/efficacy uncertainty associated with the investigational product, and other factors specific to the study. Although the FDA has no DSMB requirement, Merck's policy is to use DSMBs for blinded studies.

Pharmaceutical companies face challenges in responding to different AE reporting requirements. For example, international research can require complying with ICH GCP, CFR, and European Union AER directives. To reduce these challenges, Dr. Honig recommended that regulatory organizations:

- Harmonize the expectations/interpretations of existing regulations with a focus on maximizing the impact of ICH principles.
- Seek opportunities to develop global consistency in AE collection.

- Evaluate the communication of important safety information from clinical trials; all parties involved in the trials should be encouraged to provide feedback for the evaluation.

Device Industry Perspective
Barbara Westrum, Director, Corporate Clinical Affairs, Medtronic, Inc.
Ms. Westrum thanked SACHRP for the opportunity to present the device industry perspective, but she cautioned that it is difficult to generalize across this field. She explained that industry regulatory provisions are included in 21 CFR 812. The regulatory focus is Class III devices, which are considered the highest risk. However, Class II devices are coming under increasing regulatory scrutiny.

There are significant differences between the device and pharmaceutical industries. Among the paramount differences is that the device industry is composed primarily of small companies whose products have short life-cycles (generally less than two years).

In addition, device and drug trials differ in significant ways that impact AE issues. AE attribution in device trials requires consideration of multiple factors, such as: investigator skill, procedure vs. device issues, maturity of the technology, device malfunction, and local vs. systematic effect (pharmacokinetics).

She recommended that SACHRP review "unanticipated" AEs because concern about them is a key industry driver. IDE regulations to do not formally define "unanticipated" AEs; these are prospectively identified in the investigational plan, protocol, and consent documents. FDA uses these definitions to monitor the study and assess the risk/benefit relationship as the study progresses. If the risk/benefit profile changes or new AEs are detected, the investigator may need to modify the protocol and/or consent documents and/or take other actions. An "unanticipated" AE is defined under 21 CFR 812.3(5)(s) as:

> "… any **serious adverse effect** on health or safety or any life-threatening problem **cause by, or associated with, a device,** if that effect, problem, or death was **not previously identified in nature, severity, or degree of incidence** in the investigational plan or application (including a supplementary plan or application), or any **other unanticipated serious problem** associated with a devices tat relates to the rights, safety, or welfare of subjects."

At present, companies use a standard AE reporting system in which the investigator reports to both the IRB and sponsor, and the latter prepares comprehensive progress reports that are sent to the IRB, investigator, and FDA. Increasingly, sponsors are coming to rely on a Clinical Event Committee (CEC) and/or DMC to adjudicate AEs on a case-by-base basis. However, safety reports only are written for AEs falling outside the range of what would be expected, either in terms of type or frequency. Comprehensives reports including numerators and denominators, are sent to FDA at least annually.

Expedited reporting is used for unanticipated AEs. A 25-day time period is scheduled for moving from the initial investigator report to notifying the IRBs and investigators that the study involves unreasonable risk and must be modified or terminated.

At present, the three key AE issues facing the medical device industry are:

- Timely reporting by investigators
- Inconsistencies in terminology
- The reporting of all AEs regardless of device/procedure relatedness.

Timely reporting issues revolve around the lack of investigator knowledge and training, time and effort burdens, staff turnover, and lack of inter-institution coordination. Terminology problems derive from different classifications of "severity," inadequate device descriptions in coding dictionaries, lack of coordination when multiple agencies oversee a study, difficulties in comparing literature across the field, and unclear IRB requests. The unnecessary reporting of AEs creates burdens for the sponsor, investigator, and IRB. Recent studies indicate that when all AEs are reported:

- Only about 5-25 percent of the AEs are serious and device or procedure related.
- Sponsors and sites expend two or three times the effort and resources to sift through the AEs.
- There is a risk that reactions to serious AEs will be delayed.

Sponsors are taking a variety of actions to address these issues. These include:

- Making agreements with FDA concerning requirements
- Taking a conservative approach for studying novel techniques
- Conducting careful risk analyses of potential AEs
- Training investigators and research coordinators
- Adopting severity classifications
- Verifying that investigators are submitting IRB reports
- Using medical advisors, CECs, and DMCs

In addition to implementing these ideas, sponsors are expanding their monitoring of studies and developing more clear expectations of IRBs. Specifically, sponsors are encouraging IRBs to train investigators on institution-specific policies and AE reporting requirements, develop clear approval letters, and use terminology consistent with regulations or standards. Sponsors also would like IRBs to support their efforts to secure investigator compliance, and review/acknowledge their annual progress reports.

In her conclusion, Ms. Westrum recommended that meeting participants rethink AE reporting. She suggested that: (1) definitions be standardized, (2) additional training and education be provided, and (3) standards be developed collaboratively by industry, IRBs and the medical community. Additionally, she encouraged participants to structure flexibility in reporting requirements, especially regarding: risk-based approaches, systemic reactions vs. localized therapy, novel vs. well-characterized technology, and patient risk priorities.

NIH Perspectives on AE Reporting: Looking to the Future
Amy Patterson, M.D., Director, Office of Biotechnology Activities, Office of Science Policy, NIH

NIH's mission is to discover new scientific knowledge that will improve human health. To that end, NIH funds, conducts, and oversees biomedical research. Patient safety and reporting are critical issues that cut across NIHs' functions. The Institutes are concerned about the diverse reporting requirements and formats that investigators must address in ensuring subject safety. Keeping track of multiple sets of requirements and managing the related workload are challenges for clinical researchers.

NIH has convened a Working Group on AE Reporting to address the diversity in AE reporting requirements. The Group surveyed the NIH institutes, centers, and sections (ICS) and found wide variation among and within the ICS with respect to: AE definitions and severity grading, expedited reporting timeframes, and reporting formats. The Group concluded that:

- These variations are obstacles for PIs, IRBs, and sponsors.
- NIH could make an important contribution were it to promote coordination and harmonization efforts.

The Group's report has been incorporated into the NIH road map. Harmonizing AE reporting requirements has been given a high priority in the clinical research (CR) policies and procedures re-engineering effort. Some progress already has been made in addressing conflicting AE reporting requirements for gene transfer research. Before January 2002, PIs had to report to NIH **all** serious AEs **immediately**. This was at variance with FDA requirements. The current harmonized requirement states that possibly associated unexpected events must be reported within 15 days or within 7 days if the event is fatal or life-threatening. It also includes uniform scope, timeframe, and definitions for safety reporting across FDA and NIH.

In addition, the re-engineering effort includes developing standards and models for electronic submission of safety and clinical research information. A new Web-based national gene transfer database, the Genetic Modification Clinical Research Information System (GeMCRIS), is scheduled for piloting in December 2003. GeMCRIS will serve as an analytic tool for NIH and FDA, facilitating the evaluation and analysis of safety information from all gene transfer clinical trials and providing database reports that can be routed to diverse user groups including IRBs, local DSMBs, and investigators. Over time, GeMCRIS will have broader utility, such as being adapted for use as an AE reporting system for NIH intramural and extramural clinical research.

NIH also plans to develop other components of a Web-based suite of tools for clinical research. All of the tools are being developed with input from the IRB and research communities as well as Federal agencies. SACHRP's input is welcome. .

Clinical Trial DMCs: Roles, Practices and Policies
Susan S. Ellenberg, Ph.D., Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA

Dr. Ellenberg explained that a DMC is a "group of experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial." The DMC provides many advantages: rapidly identifying

safety problems, pinpointing logistical issues, evaluating the continued feasibility of the trial as designed, and determining if trial objectives have been met and the trial might be terminated earlier than planned. In addition:

- As an interim monitoring system, the DMC helps ensure that internal study deadlines are met.
- The committee structure helps ensure that objective reviews are conducted and that uniform standards are applied.

Any challenges to objectivity or confidentiality of data can be averted by appointing members with no conflicts of interest or reasons for preferring a specific outcome.

Traditionally DMCs were used for trials with mortality/major morbidity endpoints. DMCs appear only once in U.S. regulations--they are required for emergency research studies in which the informed consent requirement is waived. However, there has been recent regulatory agency interest on the national and international levels:

- International regulatory groups have begun mentioning DMCs in their guidance materials.
- NIH, which used DMCs selectively for many years, is now utilizing them more frequently.
- FDA is completing a revision of its DMC guidance document.

In addition, DMCs are increasingly being used in industry-sponsored research. FDA has posted a Website for sponsors that provides guidance on establishing and operating DMCs: www.fda.gov/cber/gdlins/clindatmon.htm

Although all trials need monitoring, not all need DMCs. Trials for which DMCs might be established are those that:

- Might be stopped early for reasons related to efficacy
- Raise special safety and/or ethical concerns

Studies for which DMCs are less likely to be needed are:

- Phase 1or 2 trials with no expected unusual safety concerns
- Short-term trials of treatments to relieve common symptoms in fundamentally healthy populations
- Trials with no ethically compelling reason to stop early even if efficacy results were definitive

There are disadvantages to establishing DMCs. These include the increased complexity of trial management, higher costs, and the loss of sponsor and investigator expertise in trial monitoring. Thus, absent ethical imperatives, other, simpler monitoring approaches usually are acceptable.

Investigators, sponsors, and DMCs have specific responsibilities in conducting AE reviews. The investigator has front-line responsibility for identifying and reporting AEs. The sponsor reviews the reported AEs in real time and reports to the FDA and investigators as required. The DMC reviews comparative safety data at regular intervals and may review individual reports of particular concern. Based on this review, DMC recommends protocol changes to enhance participant safety.

The IRB also should be involved in trials with DMCs. The Board should assess the monitoring plan and DMC members' qualifications. In addition, the IRB may receive notification from the study sponsor regarding DMC decisions.

Dr. Ellenberg concluded her presentation by reiterating her four key points:

1. DMCs have become an important component of human subject protection systems.
2. Responding to the increasing use of DMCs, regulatory agencies have begun developing guidance documents.
3. DMCs help ensure the safety of trial participants while maintaining the integrity of interim study results and avoiding bias.
4. DMCs and IRBs have complementary roles in human subject protection.

Discussion of the Second Panel Presentation on AEs

Dr. Prentice complimented NIH on the development of GeMCRIS, which he has had the opportunity to preview. In response to questions about applying the GeMCRIS model for collecting data across the pharmaceutical industry, panelists explained that large drug companies already have sophisticated database systems and that the Federal Government is not likely to request that these be supplanted. Dr. Honig added that:

- The ICH 2B standards and data elements have been adopted and worldwide electronic transmission of ICSRs from industry to regulatory agencies is underway.
- It would not be a big step to develop a portal for investigators.

Dr. Ellenberg noted that both governments and industry are participating in the HL-7, which should lead to a more complete standardization of terminologies.

Mr. Barnes asked how: (1) CECs compare to DSMBs and (2) industry avoids conflicts of interest. Ms. Westrum explained that CECs look at each event individually and in detail with the goal of classifying the event. This information is given to DMCs in aggregate form as needed. In her experience, most companies have strict conflict of interest guidelines for CECs as well as DMCs. In addition, although investigators may serve on CECs, they recuse themselves when their own work is being reviewed.

Ms. Kornetsky observed that the groups developing conflict of interest guidelines should keep in mind that there are very few qualified experts on some topics. Guidelines should be written that balance the needs for objectivity and expertise in specific fields. Dr. Ellenberg noted that the FDA draft guidance for DMCs does encourage the development of conflict of interest guidelines, but it is impossible to obtain 100 percent independence in all cases.

Two questions were asked by Mr Barnes of Ms. Westrum and Dr. Honig. These were:

1. What criteria are used by industry when establishing monitoring systems?
2. Does the FDA oversee this?

Ms. Westrum responded that FDA requires the submission of comprehensive data monitoring plans. Medtronic's plans are compatible with the FDA's guidelines about the appropriate use of DMCs. The company establishes DMCs for: very high-risk trials,

studies of novel technologies having significant potential risk for morbidity or mortality, and/or large studies with overwhelming ethical issues linked to outcomes.

Dr. Honig explained that the pharmaceutical industry uses similar guidelines applied on a case-by-case basis. Merck generally conducts separate training for national and international investigators regarding AE reporting, but uses a standardized curriculum. A review of training compliance across 138 sites found that the number of unreported SAEs was less than two percent. However, Merck also found evidence of under-reporting of SAEs, largely because of the paperwork burden on PIs or their transfer of the responsibility to untrained protocol coordinators. Attempts are being made to rectify this situation through ongoing monitoring and education.

Ms. Westrum stated that AE reporting in the medical device industry is defined by the regulations of the countries involved in studies. The industry educates investigators and monitors compliance, but many studies require unique training. This problem is further complicated by the lack of standard terminology across American and European agencies. As a result of these issues, the industry has learned to be flexible and adaptable in getting information to the people who need it.

Dr. Polan asked about AE reporting standards in developing countries. Ms. Westrum explained that these countries follow either the European or American standards, often depending on the study. In general, the Declaration of Helsinki is accepted as a minimum standard. However, Ms. Westrum did not know whether developing nations, on a country-by-country basis, complied with the Declaration. Dr. Honig commented that these nations generally have adopted the ICH standard for pharmaceutical research.

Dr. Prentice noted that there is "wiggle room" in the ICH requirements regarding sponsors expeditiously reporting AEs to IRBs, investigators, and any other concerned parties. Dr. Honig speculated that the "wiggle room" exists as a way to accommodate the varying requirements of different regulatory agencies and the levels of importance they assign to different groups. The European clinical trial directives, as compared to those followed in the U.S., regard the sponsors and ethics committees as the most important "consumers" of AE information and view the IRBs and investigators as less important.

Dr. Khin-Maung-Gyi asked Dr. Honig if it was reasonable for SACHRP to ask sponsors to provide guidance to investigators regarding the key information that should be included in a report. Dr. Honig replied that the industry is compliance-driven and will respond to FDA requirements.

Dr. Jones asked Dr. Honig about encouraging aggregate reports. Dr. Honig explained that CIOMS VI encourages the development of program-specific periodic reports for studies of various products. However, he added, this procedure would reduce, but not eliminate, AE issues.

In response to questions about the NIH automated system, Dr. Patterson noted that:

- IRBs would be able to analyze aggregate data if some modifications were made. However, there also would be some legal restrictions on system access.
- Information about the system is being disseminated to institutions via the NIH listserv and a joint FDA/NIH press release. PRIM&R will be asked to help notify IRBs. SACHRP's suggestions about other dissemination opportunities are welcome.

Before concluding the session, SACHRP members thanked the panelists for their frank and informative presentations.

Public Comment

Gary Chadwick, Pharm.D., M.P.H.

Dr. Chadwick said that IRB restraint saves OHRP from a paperwork "landslide" because 45 CFR 46.103(b) could be read as requiring IRBs to pass AERs to the Office. He asked SACHRP clarify this section of the requirements.

Dr. Chadwick also suggested that SACRHP:

- Issue a recommendation stating that IRBs are no longer responsible for reviewing individual external AEs. Instead, HHS should follow the FDA model, leaving AER review to investigators and sponsors except when the reports are submitted to help justify consent form or protocol changes. This system would reduce the current IRB workload while ensuring that the Board reviews serious and unexpected AEs.
- Consider including ICH requirements for IRB reviews in a future agenda.

Summary of the Day's Activities and Future Business

Ernest Prentice, Ph.D.

In his wrap-up of the day's activities, Dr. Prentice noted that it was important for SACHRP recommendations for resolving problems to be translated efficiently into solutions. He also said that:

- International issues are not a regulatory burden for IRBs. Dr. Polan, with assistance from Mr. Barnes on HIPAA issues, will draft and circulate a platform with possible issues to pursue. This may be discussed at the next SACHRP meeting.
- One topic that can be quickly resolved concerns equivalency standards. OHRP requirements for equivalency standards need to be obtained and recommendations made about disseminating this information to the IRB and research communities in a clear, unambiguous way.
- SACHRP is committed to helping to resolve AE issues for the biomedical community. The Committee needs to think about the issues; forming an AE Subcommittee will be discussed at the next SACHRP meeting.
- Dr. Khin-Maung-Gyi and Ms. Kornetsky will identify speakers for a panel on litigation, not central IRBs.
- Fifteen minutes may not be sufficient time for panelist presentations or question and answer sessions. SACHRP members should provide Catherine Slatinshek with their ideas about the panel structure.

Drs. Prentice and Schwetz thanked OHRP and SACHRP, respectively, for their commitment and hard work. It is this dedication that will enable SACHRP to have a significant impact on the field.

Secretary's Advisory Committee on Human Research Protections
Meeting
December 11-12, 2003
Washington, DC

LIST OF ACTIONS TAKEN
Friday, December 12

March SACHRP Meeting

- Two panels will be convened. One will address HIPAA and the other will address litigation. Dr. Khin-Maung-Gyi and Ms. Kornetsky will identify speakers for a panel on litigation, not central IRBs.
- The formation of the AE Subcommittee will be discussed.
- SACHRP members should provide Catherine Slatinshek with their ideas about the panel structure. Fifteen minutes may not be sufficient time for panelist presentations or question and answer sessions.

Subcommittee Topics

Subcommittees, as available, will review (1) AEs and (2) central IRBs.

SACHRP Recommendations Regarding International Research

- Dr. Polan will begin drafting SACHRP recommendations. Mr. Barnes will help draft the section on informed consent.
- OHRP requirements for equivalency standards need to be obtained and recommendations made about disseminating this information clearly to the IRB and research communities.