Kidney Disease Clinical Trials Task Force Workshop

March 7–8, 2002

Presentations

Dr. Eric Neilson, Morgan Professor and Chair, Department of Medicine, Vanderbilt University Medical Center, convened the meeting of the Kidney Disease Clinical Trials Task Force and introduced **Dr. Allen Spiegel,** Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Dr. Spiegel welcomed the participants and thanked then for coming to this important activity. Dr. Neilson stressed that the participants today would be thinking creatively about how to improve the quality of clinical trials offered by the National Institutes of Health (NIH) and the various members of the Council of American Kidney Societies (CAKS). They would put their various ideas on the table and propose a trial network that would be feasible and would work for a very positive triangle—the nephrology community, NIH, and industry.

The meeting's agenda included presentations on the various perspectives and aspects of developing and implementing a kidney disease consortium or network. The presentations are summarized below.

PRESENTATIONS

ASN Perspective

Dr. Roland Blantz, President of the American Society of Nephrology (ASN) and Professor and Head of the Division of Nephrology-Hypertension, University of California at San Diego, presented a brief background of the meetings and other events that led up to this meeting, beginning with the ASN Government Relations Committee's interest in development of a clinical trials consortium. Guidelines were developed at Renal Research Retreats in December 1998 and February 1999, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), ASN, and the Council of American Kidney Societies (CAKS). The common denominator among the retreat workgroups was to establish and maintain a permanent, cooperative, multicenter consortium devoted to clinical trials in renal disease. The consortium's overall goal would be to provide scientific evidence to significantly impact the diagnosis, delivery of care, and treatment and outcome for patients with kidney disease and related disorders. The consortium would have the following objectives:

- Conduct trials that would encourage innovative approaches to the diagnosis, treatment, and, hopefully, prevention of kidney disease
- Evaluate and improve the process of implementing clinical trials, such as patient recruitment, to complete studies more efficiently
- Provide centralized facilities for the coordination of unbiased data analysis and peer review
- Reduce the cost of clinical trials in kidney disease

With these goals in mind, the ASN Government Relations Committee, headed by Dr. William Mitch, Emory University, School of Medicine, developed a concept of a clinical trial consortium that would be

efficient and cost-effective. First, an organizational center at NIDDK would have the following responsibilities:

- Coordinate activities
- Evaluate applications from participating centers
- Establish criteria for those centers and evaluate them on a constant basis
- Construct study sections to evaluate new clinical trial proposals
- Distribute and monitor the funds for trials awarded to the participating centers
- Monitor the performance of the consortium of participating center
- Interact meaningfully with a centralized biostatistics center supported modestly by NIH dollars

The central office would be assisted by a steering committee and by peer review groups.

Secondly, the 20 to 30 participating academic and non-academic centers would be supported only through the clinical trials awarded from the centralized system. These would include federally funded, network-sponsored, and maybe even industry-sponsored trials. The criteria for center participation would be, in simplest terms, demonstrated expertise; sufficient patient material to be able to recruit patients; and evidence of institutional support—not necessarily total financial support but support at the local institution for continuing existence of a clinical trial center at that institution. The centers would not have to be homogeneous; some might contribute acute renal failure complications, some dialysis patients, and some large out-patient populations of persons with renal disease.

Thirdly, the consortium would include a centralized biostatistics center to confer legitimacy to centralized data analysis.

The ASN Clinical Sciences Committee and the Government Relations Committee estimated the total annual cost of this system at between $650,000 and $1 million. The central office, steering committee, and peer review groups would require between $300,000 and $400,000 annually. The maintenance of the biostatistics center might run from $350,000 to $600,000 a year. Additional funding would occur as additional trials came in individually from various sources. The participating centers would receive funds from their participation in individual clinical trials, but no constant dollar flow would occur from NIH.

The consortium, which would not duplicate an existing National Cancer Institute model, would provide opportunities for diversity of clinical trials, meaning study of small issues in large populations or of intensive issues in smaller, rare disease populations. The consortium would have minimal ongoing costs to NIH, but it would also have the imprimatur of NIH oversight and legitimacy for all of the trials. A centralized structure of rules and regulations for both federal and non-federal studies would also be present. The key element would be the separation of issues of recruitment, of patient availability, from the concepts of the study themselves, allowing ideas and the translation of basic areas to emanate from individual investigator groups that might not happen to have patient populations at their institutions to utilize. Finally, the NIH-funded biostatistics center and steering committee would provide centralized control over the entire process.

DKUHD Perspective

After thanking those present for coming and participating in this important endeavor, **Dr. Josephine Briggs,** Director, Division of Kidney, Urologic, and Hematologic Diseases (DKUHD), NIDDK, first listed the following tasks involved in implementing a clinical trial:

- Identification of the idea
- Planning and study design
- Subject protection and institutional review board (IRB) approval
- Patient recruitment and enrollment
- Study coordination and data collection
- Patient follow-up
- Analysis and reporting

Dr. Briggs traced the growth of NIH's clinical trials and studies in kidney disease from 1997 to what is projected for 2003. Beginning with the African American Study of Kidney Disease and Hypertension (AASK) trial and hemodialysis (HEMO) study, NIH is now funding an AASK follow-up cohort study, National Analgesic Nephropathy study (NANS), polycystic kidney disease (PKD) imaging, a Vascular Access Network, the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial, and the Chronic Renal Insufficiency Cohort (CRIC) study. A PKD intervention trial network, focal segmental glomerulosclerosis (FSGS) trial consortium, and R01 diabetic nephropathy pilots are planned for FY 2002–03. Also in FY 2003, is the possibility of a pediatric cohort longitudinal study and daily dialysis pilot trials. The NIDDK budget for kidney trials has grown from $14.5 million in 1997 to approximately $17.5 million in 2002.

Dr. Briggs stressed that even though NIDDK has grown from doing very few clinical trials, the Institute wants to do more, especially innovative work to slow the huge epidemic of end-stage renal disease. DKUHD held a two-day retreat to discuss the question "Could we achieve more by establishing a renal trial network or networks?." They also discussed the suggestion with Dr. Allen Spiegel, NIDDK Director. Questions raised are as follows:

- Should it be a broad network? Or focused networks targeting specific patient populations?
- Which problems, which patient groups would benefit from this approach?
- Did one network really make sense? Or, would it make more sense to have networks focused on dialysis patients, on children, and so forth?
- What do we hope to achieve?

As the division's scientists discussed the possible structure for the network, they kept coming back to this last question—What do we hope to achieve? DKUHD developed the following goals, with the first goal having the highest priority:

- Improve our ability to identify the best ideas and focus resources where there is the greatest likelihood of improving the nation's health
- Improve cost-effectiveness
- Improve training and career support for clinical investigation in nephrology
- Improve utilization of resources generated by our trials

Dr. Briggs emphasized that a major strength of such a network would be in training and career support and in the important collection of samples and data that are now largely mined by the steering committees of the trials but are potentially utilizable by a larger community. NIDDK is proactively improving the utilization of trial resources by forming a repository that will be completed this year and established next year, but a network might improve the renal utilization of all trial resources.

Dr. Briggs asked the group to focus also on goals—on what they hoped to achieve—as the basis of their discussions at this meeting. She stated that goal formulation was critical because goals may conflict. As one example, she said that improving cost-effectiveness should not be at the expense of appropriate training and career support for investigators doing the work.

In regard to interaction with industry, Dr. Briggs mentioned the importance of not only how to attract industry investment, but also how to learn from industry models and incorporate their structural refinements into the implementation of clinical trials. She asked what steps NIH could take to increase pharmaceutical investment in kidney disease, such as developing methods to facilitate their participation. Currently, Dr. Thomas Hostetter, director of the National Kidney Disease Education Program, in coordination with the National Kidney Foundation, is setting up a meeting with the Food and Drug Administration to discuss proteinuria as a surrogate marker in kidney disease. Greater clarity on outcome measures and algorithms for study design also may increase industry investment. On the other hand, NIH plays a critical role in sponsoring, with taxpayer dollars, the kind of trials (for example, drug comparisons, drug combinations) that are unlikely to be undertaken by the pharmaceutical companies.

Following Dr. Briggs' presentation, participants heard from representatives of groups with particular perspectives and experience in clinical trials in adult kidney disease, pediatric kidney disease, and end-stage renal disease (ESRD). The purpose of these presentations was to look at common threads and to offer ideas about the development of a structure for a clinical trial network, not to discuss areas of study for the network.

Clinical Trials in Adult Kidney Disease

Dr. Daniel Cattran, Professor of Medicine, University of Toronto, presented the regional data collection system used for the Toronto Glomerulonephritis (GN) Registry that has served as a template for a broader area. Dr. Cattran stated that the important points were the linking of the pathologists with the community of nephrologists in the area and the inclusion of all of the people in the region in the registry. This has ensured that the numbers of all the different types of primary GN are available in the registry. All patients who come in for a biopsy are asked to sign a consent form for their DNA, although all, of course, are not signed up for a clinical trial. Progressive cases are tracked. A central registrar actually goes to the physicians on a rotating basis and obtains the data, files it electronically, and keeps the nephrologists up to date through the registry. Initially, all patients who had biopsy-proven GN were tracked, but that

proved too expensive.

The registry is used to develop clinical trials, studies of the natural history of diseases, and basic investigational research. As an example, the group recently took their database of 500 to 600 patients with IgA nephropathy and completed a natural history study of these patients and also bootlegged on a study to look at cytokine expression from the DNA. The database was then given to centers in Scotland, Finland, and Australia, who used the same format and provided additional patients using the Canadian group's template for the disease.

In addition to the points made by the previous speakers, Dr. Cattran stated that patient contact and a feedback benefit to physicians was needed because recruitment is still the biggest issue for clinical trials. Physicians will not participate for the money alone. They want a benefit for their patients or something of value back for themselves from participating in an academic study—something unique and ongoing that takes the theory to their practice.

Dr. Cattran's other point was that in these relatively rare conditions, something is required that connects to the community and is very broad-based. These studies cannot be done in isolation, because the population base will not support it. These are long-term studies requiring three to six years. They need a population base, a focus, and clinical investigators who are actually practicing and know the community and the people that are interested.

Dr. Neilson, meeting chair, pointed out that in oncology centers, basically all patients are in some kind of trial. He suggested that a pool of patients with a variety of renal diseases would be valuable in a network. This would ensure that multiple trials could cost-effectively take place at the same time. Dr. Cattran agreed that this was a practical idea. In their registry, there are provisions about what can be done with the DNA tissue. However, it enables them to have a list of patients identified to contact for studies.

Clinical Trials in Pediatric Kidney Disease

Dr. Howard Trachtman, Director of Pediatric Nephrology, Schneider Children's Hospital, New Hyde Park, New York, illustrated the importance and differences of the pediatric nephrologist within the renal community as being a member of a clan of families, rather than a member of a single family headed by the adult nephrologist. He stressed that nephrologists share a common language and a set of problems. They think, talk, and act in a way that distinguishes them from other "-ologists." However, the pediatric nephrologist has some unique interests and issues that occasionally may clash with other clan members' goals. In a smoothly functioning clan, as in a well-designed and functional cooperative, each group must speak for itself, make its case, and convince the clan that its needs and interests should be addressed and satisfied. It is important to ensure that work goes to the most articulate, persuasive, and deserving members of the clan. From lessons learned from successful clans, Dr. Trachtman presented the following four major elements for the proposed consortium:

- Open, vigorous, fair competition among all nephrologists covering the entire gamut of ideas with the understanding that not all groups are capable of playing by exactly the same set of rules and that this must be accounted for in creating expectations

- Design of discipline-spanning studies to encourage cohesiveness of the group

- Promotion of the reputation of ASN and NIDDK as an endorsement to foster the work of clinical investigators

- Empowerment of and reliance on individuals who have demonstrated competence, commitment, and excellence in the conduct of clinical research

Fixed set asides for pediatric nephrology or splitting up clinical research funds will not serve the needs of pediatric nephrologists. Including a percentage of pediatric patients in an adult-initiated protocol will not work because each group is likely to have a different hypothesis and different specific aims. Instead, strong, vigorous, and open competition is needed. Pediatric nephrologists need to submit a steady stream of well-designed studies so that they will be supported in the same proportion as the entire pool of clinical researchers. These proposals should forcefully delineate the special needs of children and include arguments about the long-term benefit of understanding, preventing, and treating kidney disease in childhood. To accomplish this, it is important to appeal to the whole group of pediatric nephrologists to get involved in clinical research, extend repeated invitations to them to join the process, and make the competition user friendly because the broader the participation the greater the integrity and acceptance by the group.

Dr. Trachtman stated that two corollary lessons could be derived from the competitive clan. First, research priorities should emerge as a mixture of top-down directives and grassroots initiatives. Nephrologists will always mobilize as a whole in response to larger issues affecting the kidney, such as the recent concentration on diabetes-related research by NIDDK. In addition, the cooperative needs to be receptive to the ideas of smaller more discrete constituencies. Orphan diseases, more innovative ideas, off-beat therapies with less preliminary data, and proposals from less well-known institutions should be given consideration to make sure that the traffic in hypotheses and study design is truly state-of-the-art.

The second corollary is that the competitive spirit should not obscure relevant differences that influence the performance and output of specific groups within the clan. The quality of results should be the same, but the quantity must differ. Pediatric nephrology is challenged and limited by the lack of pediatric nephrologists, the number at each tertiary care center, the number of patients with specific diseases, parental reluctance to enroll their child in a protocol, and the lukewarm attitude of pharmaceutical companies to pediatric kidney disease. In addition, distinctive ethical standards apply to children such as the requirement that non-therapeutic research in which there is no direct benefit to the patient must not pose anything above minimal risk. Rigid adherence to productivity standards and uncompromising calculation of the financial return on investment undermines the ability of pediatric nephrologists to compete in the open market of clinical ideas. But, the clan is committed to the well being of the whole and is able to internally adjust expectations without sacrificing quality to ensure that each constituency is satisfied. This may mean extending the timeframe for completion of pediatric clinical trials, using novel experimental designs that keep the required sample size at a manageable level, performing at non-traditional clinical sites, and creating educational programs for parents and guardians to increase trust and acceptance of research in children with kidney disease.

Another lesson is that competition is not always the right answer. Sometimes the entire clan can work as a unit to tackle a problem. The challenge is how to assign everyone an appropriate role in the project to get the job done. A prime example is the Diabetes Control and Complications Trial (DCCT). This study enrolled 1,441 patients of whom 195 were adolescents. The protocol was purposely designed to include both children and adults. The outcome is striking. A paper in the *Journal of Pediatrics* in December 2000 verified the same outcome in adolescents as that reported in the *New England Journal of Medicine* in 2000 for adults, which documented the prolonged benefits of intensive therapy four years after stopping the trial. A unified protocol applied uniformly to adult and pediatric patients yielded important findings for all participants. This paradigm could be applied to hypertension, diabetic nephropathy, and polycystic kidney disease.

Dr. Trachtman said that the reputation and endorsement of such groups as ASN and NIDDK is invaluable. This is particularly relevant in clinical research where there are other sources of support that may be more lucrative but less credible to the general public. If a network is to be established to perform clinical research, it is important to reinforce the meaning of an NIDDK/ASN endorsement and build and sustain that reputation. Under their auspices, regional coordinating centers could be set up across the country—in the Northeast, the South, the Mississippi valley, the Midwest, the Southwest, the Pacific coast, and the Cascades. These centers could solicit proposals, focus on patient needs, and organize clinical trials. This would bring the stature of NIDDK and ASN out of Washington, D.C., and closer to each local investigator's home.

Once a clan has devised a way to handle a problem, Dr. Trachtman said, it assimilates the strategy into its routine operation. Hunters who have been successful in the past are sent out on all future foraging expeditions of the group. What matters is performance in the field. There is no need for re-credentialing as a hunter. Unfortunately, that is not the case now given the current regulatory process. Instead of building on past success, every new challenge is a start-up from scratch—selection of investigators, ethical clearance, and creating an infrastructure. Dr. Trachtman recommended that proven investigators be given the status of established clinical investigator, based on a formal application procedure incorporating strict rules about financial conflict of interest. He estimated that approval of 40 adult and 10 pediatric nephrologists to lead the centers would cost approximately $800,000 per year. That assumes they would receive 10 percent salary support from the NIDDK/ASN consortium with a peak allowable annual salary of $160,000. Even funding double that number of clinical researchers would cost $1.6 million dollars per year, a feasible figure, in his opinion, within the overall NIH budget. Doing this through the consortium might alter the mindset of the regulatory agencies and convince them that there are nephrologists—adult and pediatric—who are individuals of integrity, who have been effective investigators, and whose work should be expedited.

In summary, Dr. Trachtman pointed out that the needs of the individual investigator and the needs of the whole consortium need to be of equal concern and importance. He also recommended that nephrologists should never lose sight of the their place in a large subspecialty and should promote attitudes and strategies that will foster success by everyone. He emphasized that good clinical research is its own best reward and strategies that promote this will work to the benefit of all nephrologists—pediatric and adult.

Clinical Trials in ESRD

Dr. William Owen, Chief Scientist, Baxter Healthcare, and Adjunct Professor, Duke University School of Medicine, noted that collaborations have both opportunities and challenges. Clinical trials are often not cost-effective. Recruiting a sufficient number patients is difficult; patient care often changes substantially during a trial; and getting reimbursement for routine services can be difficult. Finally, the plethora of competing data collection initiatives can confound participation in trials.

Dr. Owen stated that NIH has basically focused on well-controlled randomized trials in ESRD, such as the hemodialysis study, which offers an example of some of the challenges. The trial is ending this year and the results will be presented this spring. Fifteen centers and one data-coordinating center have been involved. The population is a non-representative patient population, which is the bias, he explained, in using clinical centers that are affiliated academic medical centers. Industry has participated in a limited way, in a manner that has not presented a financial risk to the industry. Dialysis was provided, vitamins were provided, nutritional supplements were provided, and a urea monitor was available for a part of the trial. Two sets of practice guidelines were generated very early—the DOQKI clinical practice guidelines and practice guidelines from the New England Physicians Association, which have culminated in clinical performance measures by the Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration). Dr. Owen suggested that one of the questions for the group to consider in its

deliberations was comparison of observational studies versus randomization as in conventional trials like the hemodialysis study. Including the pilot phase, this study went on for almost a decade.

Between 1996 and 2000, there was a change in practice regarding the hemodialysis dose and the resultant rise in Kt/vs that may confound interpretation of new data.

Another challenge to doing ESRD studies, according to Dr. Owen, can be seen in a follow-up paper from Dr. Wolf's and Dr. Port's group in Michigan. Their study looked at anthropometric attributes, body mass index and its interaction with the dose of dialysis and the relative risk of death. The way the study design occurred, many patients in one group are not to be included. Again, this will affect the external validity of the trial.

As subjects for a consortium, Dr. Owen listed a number of items from a random survey he had conducted at a recent hemodialysis meeting. Among the most mentioned were timing of the initiation of renal replacement therapy; differences in outcomes by treatment modality—hemodialysis versus hemofiltration, peritoneal dialysis versus hemodialysis—for various patient segments; and interventional trials, such as nutritional interventions and cardiovascular disease interventions. After naming a number of current NIDDK trials and observational studies, Dr. Owen asked, "Why have these not been addressed by NIH and industry?"

Dr. Owen then presented "lessons learned" or being learned from his current role within the industry. First is intellectual property—inventions and patents have enormous fiscal value to industry. It is difficult to establish an invention record or obtain intellectual property in a clinical trial, and it is unlikely that a patent would be developed in a clinical trial that the competition will or will not use.

Second is time. Delays in trials are very costly, and that is especially true if something is patent-protected and the clock is ticking, and there is a lot of price sensitivity around it.

Third, in a clinical trial, a great principal investigator is needed, someone with expertise who has the ability to recruit patients. Unfortunately, many great scientists are not great trialists. They do not have the patients or they do not have trial experience.

The fourth lesson learned is the importance of marketing outcomes and messages. Industry is in business to make money and does not want to do a trial where the outcome is uncertain, where the trial does not support the company's product, or where it could support the competitor's product.

Fifth, industry is price sensitive to trends. They do not support a trial when the secular trend is already occurring, as in the HEMO study. Sales must be sufficiently large to quickly capture the expenditures of the trial. Industry does not support a trial whose results will only be marketable to a very small cohort.

Dr. Owen spoke of the advantages for industry in doing trials with NIH—the enhanced credibility and the scientific rigor—versus the disadvantages, which include the perception that using academic medical centers, using the NIH, can be slow and can drive up costs. There is also the concept that such research is science for science's sake, not for translation. On the other hand, industry can do the trial quickly, they have enormous resources, and they can translate that into clinical action very quickly, because their teams are planning the translation as the trial is being executed. This may create the perception that the trial work is self-serving, that profits are more important than science, and that the data presentation may be biased.

To partner with industry to a greater extent, Dr. Owen stated that certain considerations need to be made to align three components that are crucial to industry. Intellectual properties need to be protected, if at all

possible. Timeliness in execution of the study is very important. Selection of the investigators is critical.

The next presenters discussed implementation in a clinical center, administration and structure of NIDDK clinical trials, and determinants of costs in clinical trials.

Implementation in a Participating Clinical Center

Dr. Lawrence Appel, Associate Director, Johns Hopkins University, presented the perspective of the clinical center at an academic institution conducting multicenter and observational studies sponsored by NIDDK; the National Heart, Lung and Blood Institute; and the National Institute on Aging. Dr. Appel has been principal investigator for both investigator-initiated and Institute-initiated trials.

Dr. Appel listed the following principal investigator (PI) activities and functions common to all trials at academic centers, regardless of the number of participants:

- Prepare grant
- Design study
- Administer grant
- Recruit participants
- Conduct the intervention
- Monitor safety
- Collect data
- Interface with patients' personal physicians
- Present and publish results

Administering the grant requires a lot of the PI's time–staffing, preparing budgets, monitoring budgets, reporting to sponsors (including IRBs), and managing facilities. Dr. Appel highlighted the following three primary observations about the above functions that are applicable to fostering a kidney disease clinical trial consortium:

- Recruitment is costly, time-consuming, and frustrating, and it is not getting easier, it is getting worse.
- The costs of clinical trials are high, yet most grants do not cover core costs.
- Oversight of multicenter trials is inefficient and duplicative and diverts IRB resources from single center studies where there is substantially less oversight

In Dr. Appel's opinion, recruitment is the Achilles heel of trials and other observational studies. It requires dedicated recruitment staff and investigators to provide oversight and monitoring. The Health Insurance Portability and Accountability Act (HIPAA) guidelines will increase the cost and effort of recruitment, particularly in trials and in prevention studies that target subclinical disease, which is very

relevant for this group, because most people do not know that they have either an elevation of creatinine or an elevation in urea protein, which would make them eligible. This is going to have an adverse impact on future studies.

Dr. Appel stated that recruitment strategies depend on two major factors: the prevalence of the targeted condition and patient awareness. The problems come in trying to recruit people with subclinical kidney disease. To identify persons with clinical disease, like ESRD, the recruiter can go to a clinic, such as a dialysis center. Mass mailings may identify persons with hypertension as a risk factor for ESRD. However, to identify somebody with proteinuria and high creatinine, probably the best strategy is a clinical database as an enriched pool of potential candidates. However, HIPAA is going to be a problem for subclinical kidney disease, for CKD, in using clinical databases to identify individuals who meet core eligibility criteria.

Dr. Appel read the following excerpt from a November 20, 2001, letter from the American Association of Medical Colleges (AAMC) to U.S. Department of Health and Human Services Secretary Tommy Thompson about HIPPA restrictions: "The rule's restrictions on the use and disclosure of protected health information for research purposes and its limits on the retention of research data will seriously impair our ability to conduct clinical trials, clinico-pathological studies of the natural history and therapeutic responsiveness of disease, epidemiologic and health outcome studies, and genetic research." The letter's author also commented on HIPPA's onerous procedure requirements, ambiguous regulatory standards, and intimidating liability concerns. The letter concluded with the following statement, which Dr. Appel felt very relevant to establishment of a clinical trials network for kidney disease: "The rule is causing hospitals, health plans, and providers to question whether disclosing data for research purposes carries too great a compliance cost and liability risk to justify their continued sharing of 'de-identified' or identifiable data with unaffiliated researchers, even if the research is approved by an IRB." To do clinical trials, the network would require identifiable data to contact patients of unaffiliated researchers. When Dr. Appel was recruiting for AASK, less than 20 percent of the 64 participants came from Hopkins. Securing assistance and approval from other institutions, as he did for AASK, may be at jeopardy in the future under HIPPA.

Another disadvantage of a clinical database is that it is time-consuming and expensive. Dr. Appel presented some of the steps that cause the use of clinical databases to be time-consuming and expensive. These steps include identifying the database, dealing with the non-standardization in data entry and formats, acquiring separate IRB approvals of each part of the network before accessing the database, generating the files, and then determining eligibility and contacting the personal physician. Identifying either the physician or the patient can be difficult. Finally, the patient must be contacted and recruited. Conducting this effort and tracking it requires substantial effort.

In presenting his second observation—that clinical trials are expensive and most grants do not cover core costs—Dr. Appel gave the following reasons for these costs:

- Initial expectations are higher than for observational studies (follow-up rates of 95 percent vs. 80 percent require pursuit of that 20 percent of patients who do not show up for appointments, participant safety requirements that exceed those in clinical practice, etc.).

- Core activities such as recruitment and laboratory tests are expensive.

- Inherent inefficiencies are present such as the volunteer nature of the participants, the administrative burden, and regulatory requirements.

Most clinical trials are subsidized in multiple ways, although subsidies are disappearing as academic institutions deal with a bottom-line approach. The personnel aspect of clinical management is subsidized through the use of clinical fellows, research fellows on training grants, junior faculty on K-awards, individuals who may apply for a minority supplement, or the effort of paid investigators that is beyond salary. The facility is subsidized by the institution.

Other cost factors include (1) failure to accurately determine the amount of resources available and/or sample size before the trial design and request the needed resources in the grant budget, and (2) the requirement for uniform annual budgets whereas costs actually vary from year to year, with especially high costs during the recruitment period. Dr. Appel affirmed that a major benefit of a network would be a planning phase during which costs would be matched with resources for investigators, particularly those who are not normally responsible for budget development. Another benefit would be a provision in the planning phase to allow for modification of the sample size, if needed.

Dr. Appel's third observation was about the inefficiency and duplicative nature of oversight of multicenter trials. IRBs have the primary responsibility for clinical research, yet the system was designed well before the advent of multicenter studies. Today, the Data Safety and Monitoring Board (DSMB) and coordinating center are much better positioned for these functions.

In summary, Dr. Appel recommended the following actions:

- Modify HIPAA guidelines to restore access to clinical databases
- Develop a pre-grant process involving researchers and sponsors to set realistic budgets
- Through legislation, modify oversight of clinical trials by increasing responsibility of DSMBs and coordinating centers and decreasing responsibilities of individual IRBs

Current Administration and Structures

As a foundation for developing a renal network, **Dr. John Kusek**, Clinical Trials Program Director, DKUHD, NIDDK, provided an overview of the clinical trial organizations, structures, and support mechanisms that NIDDK currently has in place. Most of the clinical trials in NIDDK's rather large portfolio are supported by a cooperative agreement. Others are funded by an R01 or investigator-initiated grant. A large-scale trial in renal transplant recipients was originally an investigator-initiated grant and then was changed to a cooperative agreement. Dr. Kusek stated that of particular importance to the goal of the meeting is the fact that among these trials, there is a substantial network or group of investigators who have experience in pairing up clinical trials and epidemiological studies.

Dr. Kusek outlined the following major activities of these trial centers:

- Study design
- Trial implementation, including database development
- Recruitment
- Adherence
- Follow-up

- Quality control
- Data analysis and interpretation

Kidney clinical trials are supported by a range of organizational structures. The predominant model for large-scale trials, such as the Diabetes Prevention Program and Look AHEAD trial, is independently funded clinical centers, keyed budgetarily to the number of participants to be recruited. The centers are essentially independent units with a PI, study coordinators, data entry recruiters, and other personnel who support patient recruitment, intervention, and follow-up activities. They also typically have a data-coordinating center and a central facility. This approach has issues about flexibility when centers under-recruit, including the difficulty of how to move resources from one center to another.

Another model is a regional network established for a very well-defined initiative and target population, such as the one proposed for the FSGS trial. The FSGS network's regional clinical coordinating centers will recruit from medical organizations and individual physicians. They will be supported by a data-coordinating center. Another disease-specific example is the polycystic kidney disease network of independent, participating clinical centers that will probably become regional clinical centers where patients will be recruited and follow-up will be coordinated. This group will have a data-coordinating center and central facilities.

The hemodialysis vascular access consortium is a target-population model in which independent clinical centers incorporate other sites, such as additional dialysis units, to meet their recruitment goals as the sample size requirements are identified. Again, the consortium has a central data-coordinating center. The interesting feature about the vascular access consortium is NIDDK plans to run two clinical trials concurrently during the five-year life of the program. There are similar kinds of network structures in a number of trials, including urology, interstitial cystitis, and chronic prostatitis.

The capitation approach for recruitment and follow-up was used for pediatric kidney disease trials and will be used for the FAVORIT trial, which was converted from an investigator-initiated grant to a cooperative agreement. The PI at the initial clinical center will coordinate recruitment and clinical follow-up at 20 renal transplant centers in the United States. NIDDK is providing a stipend, a start-up fund, and a per participant payment for each participant randomized and followed-up. Capitation has worked well in the pediatric trials. NIDDK will be monitoring how well it works in a large-scale trial.

A variation is an investigator-initiated trial in Michigan in which independent clinical centers are supported via subcontracts through the parent grant. This program is heavily supported by industry and seems to be a highly effective and efficient way of doing that particular trial.

In his summary, Dr. Kusek reemphasized the goals that Dr. Briggs had presented—decrease costs, increase recruitment, shorten the time to complete trials, perhaps increase the number of trials to be performed, and get physician buy in or involvement in these trials in a wider community. In addition, hopefully, the trials will be incubators for new interventions; he suggested that pilot and feasibility studies might be one approach. Dr. Kusek said it is important to capitalize on existing resources such as the 100 different sites currently involved in NIDDK trials. NIDDK also would like to enhance collaboration with the private sector. Finally, training of clinical researchers in this environment needs to be fostered.

Determinants of Costs in Clinical Trials

Dr. Paul Eggers, Program Director for Kidney and Urology Epidemiology, NIDDK, presented the following sources of costs that affect clinical trials:

- Complexity of the trial (precise interventions, targeting a specific population, randomization, i.e., MDRD, FAVORIT perhaps)
- Number of patients to be recruited (MDRD=800; FAVORIT=4,000)
- Number of centers participating (effect of fixed costs as for study coordinator at 0.25 or 0.5. FTE; capitation can reduce some cost)
- Length of the trial (e.g., fistula access at 6 weeks vs. mortality in HEMO study, 11 years)
- Cost of the intervention used (often hidden; multivitamin vs. daily dialysis)
- Protocol costs (not ever low; particularly high in MDRD)
- Miscellaneous costs such as IRB approval and patient payments

As background for the group's discussion, Dr. Eggers presented slides showing the total costs, period and length of the trial, number of patients, cost per person, and cost per trial year for 10 selected NIDDK clinical trials. The data-coordinating center was included in the total costs and also broken out to show its separate cost and percentage of the total, which averages around 25 to 30 percent. The cost per person for the MDRD trial was approximately $75,000.

Three of the 10 trials had a limited or no intervention and were, in a classical sense, not a clinical trial. Interventions greatly affect the trial costs. In the FIND trial, for example, where there was no intervention, the cost per person was less than $6,000 for the whole trial. Again, in the FAVORIT trial where the intervention will be a multivitamin, it is expected that the per person cost will be low. Dr. Eggers explained that the cost per trial year, which he calculated by dividing the total costs by the length in years of the trial, might be misleading, because actual annual costs are not a flat line. The startup costs are high, then as enrollment is completed and data is being analyzed at the end, costs drop considerably.

Dr. Eggers pointed out that the examples in the slides of large, multicenter trials are very expensive kinds of trials that go on for 10 or more years. NIDDK does not consider in excess of $50 million or $5 million per year an unusual cost for these trials. In addition, the costs shown did not cover the entire cost of the trial.

To illustrate intervention cost, Dr. Eggers estimated the costs for drug and dialysis interventions used in seven NIDDK trials. He did not have figures for the urinary incontinence surgeries, which may have been covered by patients' insurance, or to estimate the lifestyle modification intervention in the Diabetes Prevention Program (DPP). DPP's lifestyle modification was primarily a patient behavior change and counseling support, which Dr. Eggers said could be an expensive intervention. In the AASK trial, the three drug therapies varied in retail cost from $125 to $851 per patient per year. Multiplying this by the number of patients gives the drug companies' cost. Dr. Eggers stated that typically, patients do not have insurance to cover drug costs and so these have to be picked up.

In the HEMO trial, HCFA (now CMS) allowed the same payment for each intervention, so the extra cost for a high flux or a high Kt/v was absorbed by the individual centers. This is an example of the hidden costs that occur in a lot of trials. In the vascular access consortium, the Aggrenox is fairly expensive over a two-year period, whereas the Clopidrogerel is a six-weeks intervention and is not quite so expensive. Dr. Eggers estimated daily dialysis at $30,000 per year, but the actual cost is currently unknown for the two therapies that will be used in this trial—overnight at home and in the center—that will include considerable training costs, which hopefully CMS will help cover.

The FAVORIT trial was designed with some innovative aspects. It is a large simple trial. The intervention is not terribly complex, and the follow-up is already fairly well designed. One of the problems in terms of recruitment is that all transplantations are on all kinds of therapies, so there is a huge amount of competition for these patients. Capitation will be used so the more patients recruited, the higher the payment, which, in a way, is a bit like paying for an outcome. It is an investigator-initiated grant application; therefore, it can start up faster than a Request for Application (RFA). It targets a captive patient population, which, Dr. Eggers noted, is one of the advantages in ESRD that does not exist in chronic renal insufficiency.

In response to Dr. Neilson's question regarding which DKUHD-sponsored trial did Dr. Kusek think demonstrated an optimal cost structure as a starting point, he replied that that was a difficult question because of several opposing elements. The investigator wants to carry out the project in a way that is well funded, with experienced study coordinators who know how to recruit. The independent clinical center model seems to be a reasonable approach to do that. A separate issue is determining the budget for the interventions and the trial. Drug costs are not the intervention; they are the vehicle for the intervention, along with counseling, and so forth. From the investigator's perspective, the independent clinical centers, if adequately funded, will provide PI support, study coordinator support, and presumably all the support for the necessary components, including carrying out the intervention.

Dr. Kusek continued to say that from an NIH perspective, and probably from the investigator's perspective, too, it is important to carefully adjust resources to performance. This can be very difficult when the Institute has established an independent clinical center and basically a good-faith effort is required, at least in the first year, with that budget. For the FAVORIT trial, NIDDK backed into the funding approach, realizing that there were lots of patients and not lots of money, so it was necessary to capitalize on existing clinical settings that could handle this seed money and follow through. If a structure can be flexible in relationship to recruitment and performance, Dr. Kusek felt independent clinical centers could be used.

Dr. Neilson agreed that a cost structure needed to provide for a data-coordinating center to support multiple trials, some salary support, and a form of capitation as a "pay as you go" means to allow for enrollment to expand the center's financial base and operation. He also felt that the group needed to consider that complexity in trial design can defeat the use of a single coordinating center to serve multiple trials and increase intervention costs. He suggested they find a balance between expensive and not-so-expensive concepts. Dr. Briggs added that cost-effective trials are probably going to be simpler trials. She cited several trials that NIDDK is comfortable with as budgetary models—the Hemolytic Uremic Sorbent Trial and FAVORIT.

PANELS

Panel 1. Data-Coordinating Centers: Their Roles and Costs

Dr. Gerald Beck, Acting Chairman, Department of Biostatistics & Epidemiology, Cleveland Clinic

Foundation, started off this panel by presenting the Cleveland Clinic's extensive experience in coordinating randomized, multicenter renal clinical trials, including the MDRD, AASK , CRIC, and Hemodialysis studies. Dr. Beck stated that the MDRD maximum budget was $1 million in a given year, which over 11 years would have been lower than the $28 million suggested by Dr. Eggers earlier in the day. Currently, his group is coordinating the Dialysis Access Consortium (DAC) studies. The consortium will involve seven centers, five currently, and has been undergoing a planning and development stage for a graft full-scale trial of 1,490 patients and a fistula pilot trial (50 patients) to be followed with a full-scale trial (1,228 patients).

Dr. Beck explained that these types of trials have a lot of phases, and they do take time. Typically, Phase I is Planning and Development, Phase II is Recruitment and Follow-Up, and Phase III is Close-Out, Final Data Analysis, and Reporting. Considerable work has to be done up front. Therefore, in funding studies, from the data-coordinating center (DCC) point of view, a lot of up-front funding to develop the protocol, set up operations, and set up databases is needed, in addition to the ongoing funding during the operation of these trials. Quality assurance procedures have to be put into place and this ties into IRB issues and informed consent. Compliance with regulatory requirements is becoming more complex and time-consuming for the DCC and the investigator. Center facility arrangements can vary a lot between the different trials. MDRD and AASK had a central GFR lab and a central biochemistry lab. The HEMO study had only a central biochemistry lab. Thus, the complexity of a given trial can drive up costs. Also, trials, such as AASK and HEMO, may have short- or long-term ancillary studies in addition. The DCC is very involved in logistical and administrative support throughout all phases of a clinical trial.

During Phase II, once the trial begins, the DCC monitors recruitment, collects the data, and may even be involved with patient management. In the HEMO trial, the DCC received information from the central biochemistry lab and electronically fed back patient prescriptions for the dialysis dose to the clinical centers. Depending on the specific trial, there are several complexities or levels of involvement such as centralized measurements and review, central outcome review, and interim analyses. Reports must be prepared for the steering committee, clinical centers, DSMB, and the sponsor. Another item is stored samples, such as urine and serum. These require funds to be maintained, access controlled, and managed after the trial is over.

Some activities such as ancillary studies and reports occur in both Phase II and III. In addition, the DCC has to have the expertise to develop new statistical methodology to handle certain aspects of the trial design or the data coming in. Protocols must be reviewed and stored specimens released. Then in the close-out phase, numerous papers and presentations must be prepared to report the analyses of the final primary results, as well as to provide feedback to the patients. A public-use database is usually created, maybe not right at Phase III, but a few years later when the main results have been mined and the data has to be archived. In a sense, the trial never ends for the DCC.

Dr. Beck named the following personnel resources as the basic minimum for a DCC for all trials:

- PI, co-PIs, and possibly a physician investigator at the DCC to provide on-site expertise
- Master's level biostatistician
- Statistical programmer
- Systems analyst
- Programmer analyst

- Financial administrator
- Study coordinator to interact with on-site study coordinators
- Administrative support

The mix of personnel resources changes across the phases. In the beginning, higher-level programming support is needed. Once the data starts coming in, more statistical support is needed to analyze that data, but less database support is required.

Dr. Beck estimated minimum basic DCC costs as approximately $0.5 million for Phase I and $0.75 million each for Phases II and III. He cautioned that these were Cleveland costs at a 48 percent indirect rate; the numbers might be higher on the East or West Coast. His figures include basic personnel costs, site visits, and meetings, but did not include costs for central facilities, consultants, or equipment.

In his list of challenges to set up a clinical trials network, Dr. Beck listed the following:

- Can multiple trials be done concurrently, or do they have to be sequential? This depends on patient requirements, whether different patients can be included, or whether they can be enrolled in subsequent trials after having participated in the first trial.
- Can common sets of core data be acquired or must the DCC reinvent the wheel every time? The data sets can be difficult to define and select.
- Is there adequate staffing at all the centers and the DCC.?

As a balance to the challenges, Dr. Beck listed efficiencies that can be gained. They are as follows:

- An ongoing experienced team
- Common core forms, databases, data definitions, QC procedures, analyses, and standard reports
- Cost-savings of an in-place organizational structure and central facilities
- Pre-trial planning and pilot studies by network to decide which trials to do next
- Pre-defined clinical sites for reduced startup times

For a chronic renal disease network, Dr. Beck suggested that the DCC work with NIDDK and the clinical investigators to plan new trials. This would include defining interventions and outcomes, inclusion and exclusion criteria, sample size and power, and even preliminary forms and databases prior to issuance of the request for application (RFA). They would also plan and carry out pilot studies if needed to determine whether a full-scale study was necessary. The DCC would design and carry out newly funded trials with the network of clinical centers, maintain the core database, maintain the clinical site roster, identify potential central facilities, and participate in other efficiencies.

Depending on what it was expected to do, Dr. Beck estimated that the network DCC might require approximately eight (8) FTEs, supplies, travel costs, and miscellaneous expenses for a total annual budget of approximately $138,000.

Dr. Donald Stablein, President, the EMMES Corporation, said his firm's first involvement in NIDDK renal work began with the Peritoneal Dialysis Registry of 25,000 patients over a five-year period in the 1980s, which, up to that time, was their biggest project in terms of patients. EMMES is a data management and statistical coordinating center, employing 120 people who work on clinical coordinating center activities. Most of their projects are funded by the various NIH institutes. They do some non-NIH projects and some that are registries or epidemiological studies. Although not focused in any particular disease area, the company spends most of its time on projects involving transplantation, infectious diseases, ophthalmology, and oncology. EMMES is currently serving 17 active projects, including eight that are for multiple protocols. These might be considered a network. Dr. Stablein remarked that staffing basically varied in relationship to the number of protocols and was very close to what Dr. Beck had described.

According to Dr. Stablein, regulatory issues are becoming an increasingly important activity for EMMES as it performs its DCC activities such as protocol development and data systems. Regulatory issues take up more of their resources and time than they did five years ago, which means more dollars are being spent on them. This becomes more of an issue in a trial focused on a product than in a dietary intervention or nutritional supplement trial because of the interface with the Food and Drug Administration (FDA) and compliance with government regulations.

In addition to performing its normal data-coordinating, statistical services, and other centralized services, the EMMES DCC also handles specialty services and subcontract support. These additional services vary by diseases. They may include a reading center where people look at photographs for an eye study, a specimen repository, drug shipping and packaging, and other tasks done by in-house staff. These trial-driven tasks need to be included in costs. If the trials had a separate center for drug packaging or a pharmacy center, the costs would not then be attributed to the DCC.

Dr. Stablein estimated that it cost approximately $150,000 last year to support EMMES data-coordinating center activities, which is equivalent to Dr. Beck's costs when his total is divided by the FTEs. This estimate includes labor, overhead, travel, and supplies, but not the drug packaging and other kinds of activities. About 40 percent of the work is done by protocol managers, data managers, and the like, which is slightly higher than what Dr. Beck described. This may be because EMMES is involved in more Phase I studies than in regulatory work. Or it may be that what the Cleveland Clinic terms statistical programming, EMMES calls data acquisition and monitoring. Dr. Stablein's estimate of statistical hours represents about 25 percent of the firm's level of effort. Another 15 percent is for computer professionals and administrative support.

Dr. Stablein explained that at Fred Hutchison Center or Harvard, there might be a very different view. These groups are very large coordinating centers, with thirty to forty people, rather than a median of five people, working on typical trials there. This illustrates that situations can be very different depending on the size, complexity, and number of trials being coordinated. According to Dr. Stablein, the following are other issues affecting network feasibility:

- Compatibility of study designs
- Match between research ideas, resources, and network objectives

- Effective working relationship with the data-coordinating center

As an example of when compatibility of study design requires a network, Dr. Stablein described an AIDS vaccine evaluation group. This ten-year project performed more than fifty or sixty trials—basically six a year—starting a new trial every two months, including many Phase I and II Trials. Each had very similar endpoints but used different products from different manufacturers and administered them to people in different ways, trying to elicit immune responses. In this case, only a network would have been efficient. On the other hand, a study that looked at swallowing problems in patients with Parkinson's disease and dementia in the first trial and speech issues in trauma patients in a different trial had very little in common. They were centered in the same funding agency, because the funding agency is responsible for communicative and sensory disorders, but it did not fit network needs.

As his final point, Dr. Stablein emphasized that there has to be a strong, effective working relationship between the data-coordinating center and the lead clinical center in the network.

Dr. Vern Chinchilli, Professor and Biostatistician at Pennsylvania State College of Medicine, offered a slightly different perspective. Dr. Chinchilli currently manages two data-coordinating centers for networks studying asthma. He perceives the following advantages to a trial network focusing on a particular disease category:

- Conduct of multiple clinical trials within the network
- Standardization of procedures and data collection forms across the trials
- Savings in labor, resources, equipment, and training
- Enhancement of the scientific team

Dr. Chinchilli felt this last point was subtle but very important because it takes a year or two for personnel to work together effectively as a team.

Challenges presented by Dr. Chinchilli included

- Strain on DCC and clinical centers to design, conduct, and analyze multiple trials simultaneously
- Competition for patients
- Possible confusion among research coordinators
- "Professional" patients who participate in multiple trials

Dr. Chinchilli pointed out that in a single disease network, patient criteria can be similar, although not overlapping, for two trials—an ongoing and a new trial. The clinical center could have patients who would qualify for either trial. The trial B clinical investigator then competes with the investigator for trial A, and the situation must be resolved at steering committee level, which can be a problem.

Another issue is that if there are subtle differences across protocols for simultaneous trials, the clinical coordinators sometimes get confused, especially if they are in a rush or under pressure. As a result, procedures may be not done incorrectly. One solution is to color-code the forms for the trials to help the

coordinators keep things straight.

Another major problem that Dr. Chinchilli has encountered is what might be termed "professional patients," people who like to enter trials, possibly for reimbursement or maybe just to be part of the trial. Since the investigator does not want the same set of patients in trial A as in trial B, there must be some exclusion criteria. For example, if a patient just finished trial A, they are usually required to wait a wash-out period before entering another trial, especially for pharmaceutical trials.

Dr. Chinchilli oversees two networks—the Asthma Clinical Research Network (ACRN) and the Childhood Asthma Research and Education (CARE) Network. ACRN is the older network, which was started in 1993 by the National Heart, Lung, and Blood Institute (NHLBI) to conduct multiple clinical trials in adult asthma. ACRN has six clinical centers and the coordinating center at Penn State. The network has completed six trials, is currently conducting three simultaneous trials, and is planning two more trials. DCC total costs are about $1.2 million a year. Over a 5-year period, NHLBI has committed approximately $24 or $25 million to the network. Therefore, total DCC costs come to about 25 percent of the total cost for the network, which is similar to what Dr. Eggers had said. Information about the DCC and the network can be found on their Web site.

Most of the ACRN trials are conducted over a six-month to twelve-month period. They have had 25 publications in major journals. According to Dr. Chinchilli, a network provides flexibility. For example, two trials (SOCS and SLIC) were conducted in tandem with a common six-week run-in period. At the end of the run-in period, the sicker patients were placed in the SLIC trial, and the milder patients were put in SOCS, so that with entry criteria that were mutually exclusive, recruited patients could be in one trial or the other.

Another example of the flexibility afforded by a network is the recently completed DICE trial, which had six treatment arms and six placebo arms. This was a little unusual in a single study, Dr. Chinchilli said, but it was done for blinding to compare six inhaled steroid medications that were approved by FDA when the trial began. Two other trials in progress (BARGE and SMOG) have allowed the group to develop a unique design called the matched crossover design. Patients in BARGE were screened based on their genotype for a particular type of chromosome. They were selected for two genotypes for which they were homozygous and matched according to pulmonary function during the baseline period. Then they were randomized together into a crossover design. So they were matched, he said, but it was like there were two separate crossover studies. The SMOG trial is recruiting smokers and non-smokers and matching them according to lung function and gender. They also were randomized together. A matched pair was then randomized together to a crossover sequence. These examples demonstrate the flexibility and capability a network has to try unusual things that would not ordinarily be possible.

NHLBI established the CARE network in 1999 to study pediatric asthma, presumably because they were very satisfied with the ACRN, Dr. Chinchilli said. CARE has five clinical centers and a data-coordinating center, again at Penn State. Its DCC total costs are about $1.2 million a year. Two trials are in progress and two more will be developed before funding ends in 2004, which could be extended if the initial effort is successful.

Discussion. The following questions and comments were made during the discussion following the above panel presentations.

Q. Given the potential cost savings in network sharing, how many trials can one network reasonably support at one time?

Dr. Richard Kaplan, Chief, Clinical Investigation Branch, National Cancer Institute, NIH, responded that

in the Cancer Cooperative Groups, nine or ten coordinating centers support approximately 500 clinical trials, of which about 170 are Phase III trials. Each coordinating center manages an average of 50 trials. Of course, the larger centers handle perhaps twice that and the smaller centers handle five or ten trials. They are broken down into various cancer disease groups.

Q. Can a single DCC support multiple networks such as an ESRD network, an acute renal failure network, and so forth? Multiple nephrology networks might be required because of the differences in types of patients to be enrolled in trials.

Dr. Beck responded that having different centers to respond to different renal diseases was possible. One DCC could support all of them. This would depend, of course, on the number of trials in the different areas. The DCC would have to enlarge.

Dr. Lee Hebert, Director, Division of Nephrology, Ohio State University Medical Center, stated that a single center efficiently conducting multiple trials simultaneously is possible. His group has five clinical coordinators running from eight to fourteen trials, of which three are usually NIH-sponsored and the rest are industry-sponsored. He had no doubt that they could run a network of renal centers.

Dr. Julia Lewis, Professor of Medicine, Vanderbilt University, commented that a major difference between NIH and pharmaceutical companies is the order of magnitude in the number of centers that participate in a trial. Industry, for example, manages 210 centers for a trial versus the AASK trial's 22. Industry usually must recruit far more patients to meet regulatory requirements. They also must make more site visits to monitor the trial. Some of the important complexities for the model being developed at this meeting are how regulatory requirements will be managed, how many participating centers will be managed, and how many regional centers can a steering committee be responsible for.

Dr. Beck agreed that the resources of a data center are very different for industry-sponsored trials compared to NIH trials. In industry, there is a need for more compliance and more monitoring.

Dr. Ravindra Mehta, Professor of Clinical Medicine, University of California, San Diego, cautioned that, although a single DCC can handle simultaneous trials, one of the problems is that in acute renal failure trials, for instance, there is a multidisciplinary team, not a single nephrologist. This reduces the level of control. Also, the type of data coordination activities can be very, very different. In addition, because of the multidisciplinary nature of the situation, there is also the possibility of competition with other non-nephrology trials because the providers are involved with other networks.

Dr. Melisa Cooper, Vice President, Bristol Myers Squibb, stated that industry could not afford to be less than efficient. To industry, the business of clinical research is the business of data management. To get an idea of the size of a typical industry effort, Bristol Myers Squibb conducts 300 to 500 clinical trials every year. Approximately 450 people staff their data management and statistical operation. Each statistician handles three to four protocols simultaneously in contrast to an earlier slide that showed that three-quarters of the time of one statistician is spent on a single protocol. The amount of data required by regulatory standards in the United States, as well as in other countries is immense. In addition to its in-house capabilities, her firm must outsource from 10 percent to 40 percent of their data management requirements. In designing the proposed network, efficiencies definitely can be gained by centralizing, but that will also depend on how the scaling up is done.

Q. Are the costs for a data center for a pediatric network the same as for an adult network? Are there differences in supporting two networks at one DCC site? Are there cost savings?

Dr. Vern Chinchilli said that there were cost savings in terms of training. When his group took on the

pediatric CARE network in addition to the ACRN adult network, staff had to be doubled. They worked on different networks because the pediatric nephrologists were very different from the adult nephrologists and the type of patients, criteria, and measurements were different. However, the ACRN group trained the new staff, which enabled the CARE group to start up quicker, creating a definite cost savings in the initial year.

Q. Dr. Chinchilli, please clarify the source of your annual budget based on your network experience.

Dr. Chinchilli replied that NHLBI supplies the annual $1.2 million core budget for the DCC. Additional funds may be granted for subcontracts such as for packaging drugs. For the clinical centers, NHLBI grants a core budget of $150,000 to $200,000 per year and the rest of their costs come from capitation.

Dr. Stablein later commented that he was not aware of any group that has staffed a network resource in the absence of a trial. The consortium will need to work with investigators to put together grants and to respond to questions.

Q. Dr. Chinchilli, what advantages have you perceived in working with a constancy of personnel?

The real advantage, according to Dr. Chinchilli, was the strong relationship that developed between DCC coordinators and the clinical centers, since these are the staff that basically implement the study. Having the same investigators was also an advantage.

Q. What are the duties of the DCC and the centers in the network? In particular, how would the DCC respond when an investigator wants to try a new steroid inhaler and asks if this is possible and what will it require?

Dr. Chinchilli explained that DCC has teleconferences with the clinical centers every two weeks, as well as in-person meetings approximately every two months. A great deal of time is spent arguing protocols. The steering committee must prioritize what trials will be done. Overall network approval is required. Also, the chair of the steering committee is not from any of the clinical centers, which keeps everything fair.

Q. What are your thoughts regarding general network construction? It seems that people could design and carry out studies without overlapping.

Dr. Richard Glassock, Professor Emeritus, UCLA School of Medicine, pointed out that Dr. Julia Lewis's earlier comment on the differences in needs between NIH and industry brought up a fundamental question on network design. An organization of renal networks to serve both NIH and industry would have to accommodate two contrasting trial styles. Given industry's concerns about time and dollars, the organization would have to be responsive to these issues to bring industry to the table. Industry has found that multiple sites are cost-effective. Also, industry tends to contract out its DCCs to get a competitive price rather than a cost plus arrangement.

Dr. Beck spoke about generalizing from a trial. NIDDK tends to employ academic medical centers that use only one kind of patient. Going out to broader community centers might bring in patients more quickly and provide different types of patients.

Dr. Jeffrey Fink, Assistant Professor of Medicine, University of Maryland School of Medicine, recommended that in designing the network provision should be made to encourage and promote clinical trials or studies, both at the observational and senior center level, to promote innovation. Doing so could lead to more meaningful and higher impact trials in later years.

Panel 2. Some Current NIH Trials Networks

Dr. Linda Wright, Deputy Director, Center for Research for Mothers and Children, National Institute of Child Health and Human Development (NICHD), NIH, presented the Institute's experience with its long-standing and productive Neonatal Research Network. The network has a very distinctive organizational structure, with a dual emphasis on productivity and cost-effectiveness. Dr. Wright suggested that its structure might provide ideas for the renal network model.

The goal of the NICHD Neonatal Research Network is to improve the outcome of all newborns; therefore, it seeks to address all the problems of newborns. According to Dr. Wright, the network's focus is on extremely small babies because they have the worst outcome, but there is a research interest in all neonates and their outcome. One of the network's problems is similar to that of a renal disease network—not a lot of patients are available to them in one place. The network has less than 30,000 extremely low birth weight preemies, and they are distributed among 400 to 800 neonatal ICUs, which causes an organizational problem.

Dr. Wright explained that Sumner Yaffe started the network in the 1980s when there were dramatic changes taking place in neonatology. At that time, no single center was able to award a trial and get the answer to a trial before a practice had changed. The network was created to fill the need for well-designed neonatology clinical trials. At the time, there was no sense of how to do a clinical trial that was shared by the field. Today, in response to the needs of large, randomized, controlled trials, the network has common protocols designed by PIs. Originally funded by R01s, the network is now using five-year cooperative agreements, which basically are a hybrid mechanism between a contract and a grant. The cooperative agreements are between NICHD, the clinical centers, and the data center. In 1985 the network had seven centers; by 2001, sixteen centers had been selected—and sometimes dropped—by the network. The network works with the data center at Research Triangle Park, but it has worked with different data center models and collaborates with numerous international studies. Dr. Wright stated that each data center has a distinct personality, organization, and working structure. She emphasized that a good match is critical.

The network steering committee, which meets four times a year as a group, is composed of the PIs from the sixteen clinical centers, the data center, and NICHD staff. There is also a multidisciplinary advisory board that reviews all protocols and helps keep things on track. In addition, a data safety and monitoring committee serves the entire network. The network is housed within NICHD's Pregnancy and Perinatology Branch. The group also holds subspecialty meetings, coordinator meetings, and training meetings. Training meetings occur at least once a year and at the start of a new protocol.

The network is overseeing a maternal lifestyle study, a group of young investigators studying inhaled nitric oxide, and a very large observational study at four of the clinical centers. Another group does follow-up exclusively. In addition, the network collaborates with other NIH institutes, industry, and other large randomized, controlled trials.

The network's annual budget is $5.2 million a year, with each center receiving an average of $300,000. The average cost per trial varies dramatically because some are short trials, and others are very complex. Trial costs vary between $500 and $1000 per patient. NICHD pays for research, but not "indirects" on patient care costs, and it does not pay standard care costs. Investigators often agree to standardize their care to reduce the cost of a trial. The PI has a significant up-front risk. The PI is given money up front based on his/her estimate of how many patients will be recruited. If the estimate is not met, the money is offset in the next funding period.

The network's funding mechanism grants a base budget to the PI of 0.1 FTE, a research coordinator full-time, and a half-time data entry person. Capitation costs are founded on the actual cost of conducting the trial, based on nursing time for start-up and training, estimated time per patient for data collection and patient care, research pharmacy costs, equipment costs, laboratories, and study drugs. NICHD normally pays for study drugs, but industry has been very generous.

The network database includes about 37,000 very low birth weight babies. Detailed information in the database helps generate hypotheses, as well as calculate sample sizes. The goal is to ensure that there is always a trial available for an open population. Babies can be randomized to more than one trial or network because they stay for an extended period of time.

Dr. Wright presented the following steps in the network's trial development process:

- Development of initial protocol by PI
- Submission to protocol review subcommittee (similar to an NIH review), who work with PI
- Concept clearance
- Approval and prioritization by steering committee
- External review by usually three specialists
- Appointment of trial subcommittee
- Development of forms and manuals
- Approval of IRB, advisory board, and data safety and monitoring committee
- Conduct of training and certification

The protocol review subcommittee, which looks at both the design and feasibility of the protocol, is a revolving committee made up of PIs from six centers, the data center PI, NICHD representation, and a chair. Ideas are also stimulated through workshops where leading epidemiologists discuss the Cochran Collaboration and priorities. Other workshops are with FDA, industry, and others. Members in each component of the network exert a lot of effort to make sure that the network is on track. A number of people are doing pilots to develop new studies to bring into the network. In setting priorities, members give the network priority as part of their cooperative agreement.

Dr. Wright offered the following "lessons learned":

- Choose the "right" PIs, that is, Pis who are energetic, well-seasoned, committed, and who have diverse expertise to provide collective wisdom and engage peers.
- Address important problems from the real world and within a reasonable time period (e.g., 18 months).
- Collaborate to obtain answers.

- Appreciate equipoise.
- Include lots of statistical expertise.
- Use appropriate therapies.

She suggested that it should take at least a year to get the show on the road. The "KISS" principle is important. Secure funding is needed. Databases are important and expensive. An independent data center is needed, not one funded through the PI's center. It is important to ensure that the cost/benefit ratio to the PI is in the right direction. They are interested in getting data without spending incredible amounts of time on organizational issues. Feedback and monitoring are necessary, and long-term follow-up should be considered.

Dr. Wright's list of challenges included the importance of equipoise, especially in trials of standard care. This can be nearly impossible for clinicians. To seize "windows of opportunity" can be difficult because the network is, in a way, like a big battleship that cannot change direction quickly if the field suddenly changes or someone else runs a big trial the group has been working on. It is a challenge to change clinical practice and see the value in negative trials. Finally, the network needs to be able to survive long recruitment periods and to abide by capitation funding.

Dr. Gordon Bernard, Professor of Medicine, Vanderbilt University, presented information on NHLBI's ARDSnet (the Acute Respiratory Distress Syndrome Network) and the industry-sponsored aPC (drotrecogin alfa [activated protein C]) study, which are organized similar to Dr. Wright's NICHD network.

For the activated protein C study, Dr. Bernard served as PI for the clinical coordinating center, not a data coordination center, and with independent publication rights. This study began around 1996 and involved a Phase II clinical trial to provide a go-no-go decision for a larger trial on the agent. There was a strict capitation payment at the clinical sites of $6,000 to $7,000 per patient. Industry's coordination costs were presumably enormous, because this was a very large trial. A large, multicenter trial like this requires about four or five years from start of Phase II through Phase III. Phase III, the PROWESS trial, included 11 countries and 158 sites. To coordinate the trial required around-the-clock phone coverage seven days a week by the Vanderbilt Coordinating Center (VCC).

Enrollment was approximately 2,300 patients with severe sepsis. Since this was a PI-initiated trial, the PI had authority and made decisions. In multicenter clinical trial networks, usually a steering committee with a disinterested chair must hold long, arduous discussions to make virtually every decision. The VCC Clinical Evaluation Committee is a concept used in a number of industry-sponsored trials to assess the quality of patients entering the study, especially when using numerous sites worldwide for which there is no prior knowledge of their quality. For this trial they asked the following questions: Were the patients really infected? Did they meet all the criteria for study? Did they have adequate source control and antibiotics? Was there adherence to the protocol?

The outcome being measured in PROWESS was sepsis-related death. Since 24 percent of patients with non-sepsis-related conditions that were possibly life threatening were being admitted, VCC amended the study early on to reduce these inappropriate admissions. This was important to the validity of the trial results for activated protein C versus the placebo.

ARDSnet, a comprehensive clinical trial coordination system with publication independence of the steering committee, had core budgets for the clinical sites and supported a full-time nurse coordinator and

about 20 to 25 percent of the physicians' salaries. In addition, depending on the study and required procedures, there was a capitation payment of $4,000 to $7,000 per patient.

ARDSnet originated in 1993 and initially was intended to investigate novel therapies (i.e., drug interventions). To give the attendees an idea of startup time, the first patient was enrolled about 15 or 16 months later, in 1996. This might have been a little bit longer than is typical, because early on it was realized, from the viewpoint of critical care, that the ventilator needed to be studied first. New sites were added in 2001. Operations will close in 2003, and there will be a new competition with everybody starting over at square one. The first trial, which was the first of its kind in critical care, was a success, and brought the network a lot of credibility. Dr. Bernard commented that it could be debated whether re-competition is efficient when the network is functioning well.

In the initial RFP, there were ten applications for coordinating centers, two were considered competitive by the scientific advisory committee, and one got final approval. There were 43 applications for clinical centers, 17 were competitive, and 10 got final approval, all major academic medical centers. In 1997, news came from an FDA-NIH workshop that the pulmonary catheter had a problem and might be contributing to mortality. NHLBI was the logical place to study this; therefore, ARDSnet added more centers to manage the additional work, the FACTT (Fluid and Catheter Treatment Trial).

The ARDSnet organizational structure consists of the NHLBI Division of Lung Diseases and a steering committee as the planning and oversight components. The operational ARDSnet elements are the clinical sites, the coordinating center, and the research labs. NHLBI sits on the steering committee and is very involved in the work being done. The committee is made up of PIs from each of the sites and a PI from the coordinating center. The committee receives and develops protocols with the initial work being done by the protocol subcommittee. A protocol review committee, an arm of NHLBI, submits the completed protocol basically for a "thumbs up-thumbs down" external review, and a data safety monitoring board reviews the protocol to ensure that it has built-in safety parameters. An executive committee manages the steering committee's day-to-day work.

Subcommittees perform a variety of functions. An institutional review subcommittee, chaired by a non-network member, handles non-performing sites such as those that have poor, are not recruiting well, or are slow to report data. Protocol committees review the different active protocols; a pathophysiology committee screens ideas about what to do with the banked samples; a natural history committee deals with information stored in the databases; and an ethics committee has been busy recently with issues surrounding surrogate consent and informed consent. A publications committee governs what information can be released and when and then reviews the publications. Recently a cost effectiveness group was added to look at the PA catheter because, in spite of the mortality issues, it is expected to be a major outcome and a cost-effective tool.

Dr. Bernard listed the following challenges to large-scale clinical investigations:

- Coordination is difficult and expensive; to justify this there must be a huge, unmet clinical need.
- Concept must survive preclinical, pilot trial hurdles.
- Clinical trials take years.
- Even the best studies and outcomes are scrutinized and criticized.
- Translation of study criteria to clinical practice is very difficult.

- Rapid adoption of even very successful new treatments is not a given.

Because of these challenges, the network decided it would only conduct Phase III trials for ideas that had already had some testing in the community in a randomized way and had shown they were feasible, reasonable, and had no major ethical issues with the randomization. As large trials were developed, it was decided that the network could "factorialize" other things on top of those trials and those factorials tended to be exploratory studies, Phase II studies, or less.

Dr. Bernard stressed that translation to clinical practice is still an issue after the trial is completed. When Eli Lilly finished the activated protein C trial, they spent hundreds of millions of dollars to get the information out quickly and positively to people who could use it. No funds were available to get the ventilator trial information out to critical care physicians. Some of these physicians pay attention to national meetings, but not all, he said. So rapid adoption of even very successful new treatments is not a given, even if everything else is done right.

Dr. Richard Kaplan, Chief, Clinical Investigations Branch, National Cancer Institute (NCI) spoke on the work of the NCI Cancer Cooperative Groups that were established nearly 40 years ago to do primarily Phase III trials. (NCI also has clinical trials networks on a smaller scale.) The cooperatives have both evolved considerably and remained the same, which is a problem. They have gone from investigator-initiated grants under NCI direction, to contracts, and now most are cooperative agreements. This was done largely because of regulatory issues for NCI's investigational drugs. These agreements have advantages. Projects and clinical trials remain investigator-initiated, but because they are cooperative agreements, they all have to be reviewed, protocol-by-protocol, by NCI. They are peer reviewed every six years. The agreements have enabled NCI to "wed" groups of trials and investigators. It has also allowed NCI to assist with standardization across clinical trials, to look at the whole system with important colleagues such as FDA and industry and to see what sort of efficiencies could be brought about.

Most cooperative groups are doing 50, 75, or even 100 trials at a time, of which there are 25 or 30 Phase III trials. This makes peer review a daunting task. The committees cannot dissect every detail. Basically they look at the scientific planning and the performance of a whole scientific package for a disease committee for a cooperative group over the previous six-year (previously five-year) period. Dr. Kaplan noted an important recent improvement: Any disease committee in any group that receives a score less than outstanding to excellent cannot be funded for more than three years and has to come back in for a site visit and re-review in three years.

There are now about nine big cooperative groups. There have been mergers and redistributions. The overall cost is in the range of $150 million, which is a reasonably large amount per patient, not an unrealistic amount per patient when it is divided up, but the infrastructure is very expensive. A key question from those outside the system always is, "How many do you need studying lung cancer? Or breast cancer? Or cancer X?" The answer is, nobody knows how many are needed. The answer is, all the good clinical questions need to be answered. Dr. Kaplan stated the latest challenge with this massive multi-headed enterprise has been to set up a system in which there is competition among all the groups to do studies that will be open to all of the groups. The groups are evolving more and more into entities that design and run trials. Most of the enrollment is currently carried out by about one-third of these. One of the issues is "Can we make the others more productive in clinical trials research?" Or should the rolls be purged and the resources concentrated on the one-third?

The cooperative groups are such a big entity that NCI has tried to use them to address things they were not originally designed to address, such as prevention research and genetics research. All the marriages have not been easy ones. The practitioners and the referrals often involve two different people. It has been a challenge to build new needs onto the old structure, he said. The cooperatives have had successes, as in the prevention trials, but some areas have not been so successful. It is difficult to get entities this large and this old to change their orientation. For one thing, the present medical environment encourages groups to develop studies that fit well into clinical practice patterns as they already exist, rather than to take on some of the more challenging questions of whether those patterns are reasonable or not. NCI is trying to build incentives for them to take on the more difficult questions. National promotion has been difficult in the past, because each cooperative group was distinct. One way NCI has tried to overcome this and promote effectively is to meld the cooperative groups into essentially one national effector, where anybody can put patients on any of the trials.

Dr. Kaplan commented that interactions with industry are obviously going to be a key part of the renal community's discussions. He spoke at some length on industry-related issues that have engaged NCI over the years. When the NCI clinical trials groups arose, industry essentially was not involved. For the first 30 years or so, NCI sponsored and developed most of the drugs that were ever registered. The last 10 years, NCI has become a minority developer of some of the important agents—something like 450 in oncology are being developed right now—and almost all of the really interesting ones are out there in industry. Developing the appropriate relationships between the NCI cooperative groups and industry has been a major focus. The speed of getting Phase III trials done is the number one criteria by far. Most companies have been scared off by the NCI cooperative group mechanism, in part because it has a reputation for the trials taking too long. One reason is they have been under funded and under capitated. NCI is trying to change that. Another reason is that they take a long time to get launched. This was because investigators were busy trying to satisfy themselves that these were the questions that they wanted to get answered. They only met together as groups two or three times a year, and there were long delays while they made up their minds. This is now being addressed. In several instances, from the presentation of a concept to activation of the trial has been under 90 days in a cooperative group mechanism, and they can now complete Phase III trials extremely rapidly.

Another obstacle has been the pricing clause for industry, which was a problem 10 years ago. Many companies have very different levels of sophistication in understanding how they can work with NIH or with NIH publicly funded resources. They don't know what NIH can offer, what the restrictions are, and what it will cost them or not cost them, and they do not like to lose control. They dislike that there is a data monitoring committee controlling their access to the data, rather than doing so themselves.

On the other hand, when NCI and industry meet and talk, a number of key advantages emerge. In those situations where industry knows their exact path to development, has a plan in place, needs a Phase III trial run quickly, and wants control of their own endpoints, there will not be coordination with the cooperative groups. However, the market is not very big in many disease areas, and it is not clear whether a new drug is actually going to be highly effective in that area. Figuring out what strategy would get the drug on the market and license it for a particular application is not always possible, and therefore, industry does not want to invest in its development along a normal industry pathway, even though they want to get the drug on the market. NCI can meet with them, explain that the cooperative can do the Phase II trials for them for free, co-file their IRB for free, handle all the regulatory burden, and if it works, they get the data and they can go with it. That is how NCI's industry interactions are basically set up. Sometimes these carry over even into the key licensing trials, but most do not. Still, it is very effective, because NCI can study combinations and even combinations of agents for two different companies at the same time. Dr. Bernard stated that for NCI, combinations probably are going to continue to be where the real impact of oncology is made. On the other hand, industry needs to collaborate with NCI because essentially, nobody else can do this.

Dr. Kaplan noted a lot of issues are related to the fact that the NCI groups collect less complete data than is typical in a regulatory trial under pharmaceutical sponsorship. However, in oncology, the FDA has agreed with the way they collect data, has endorsed it officially and unofficially, and has said to the companies, "If you work with the cooperative groups and the trial is not under your own sponsorship but under the cooperative group's management, a disinterested party, essentially, a non-conflicted party, we will accept the standards of cooperative group data collection and monitoring and auditing," which is a lot less intense. Dr. Kaplan said that some companies have been able to say, "We'll accept that. We'll back off on our normal requirements." In other companies, management sets requirements across so many diseases; therefore, the companies are not influenced by the oncology specialties or the special arrangements with FDA. They want to do more complete data collection, and that makes the use of the NCI-funded mechanism less attractive.

The cooperative groups are set up for Phase III trials, but the delays between interesting preliminary Phase II data in the real world and definitive Phase III data typically have been seven to ten years, completely unacceptable lengths of time. In response to this, NCI is encouraging the groups to do multi-institutional Phase II trials from the start. Since the groups are no longer primarily academic institutions—two-thirds are community institutions—then, if the trials are positive, it has been demonstrated that they are possible to do in the community and on a multi-institutional basis. This makes transition to Phase III quicker.

Discussion. A major point of discussion following these panel presentations concerned the fact that the patients in these networks are basically captive, critical, or intensive care patients with life-threatening illnesses for whom death is a fairly certain outcome, often within a short period of time. Most of these patients and their physicians are aware of this and, therefore, are more interested in participating in clinical trials. They are also generally being treated in large, disease-specific academic or community medical centers and, thus, are readily available for recruitment and participation in the trial. For the renal community clinical trials, this would not be the case for chronic kidney disease (CKD) patients. Even ESRD or acute renal failure patients (ARF), in critical care or receiving dialysis, are fewer in number, more scattered, and less likely to see themselves as being in imminent danger. One suggestion was that, given the recruitment problems, the network might best concentrate on trials in the area of ARF or ESRD, but the general recommendation was to consider all options, including prevention trials for chronic renal disease patients as well as looking at new therapies for those on dialysis.

In response to the assumption that cancer cooperative groups, for instance, have a tremendous advantage in patient recruitment, Dr. Spiegel quoted from an article on Senator Diane Feinstein's war-on-cancer bill, which states that only 4 percent to 5 percent of cancer patients (2 out of 10) participate in clinical trials; many do not because they are unaware that they have the option. For children with cancer, 60 percent are in trials.

Dr. Kaplan generally confirmed these numbers, adding that participation of children is as high as 80 percent, depending on the disease, because pediatric oncologists in major medical centers are treating almost all children with cancer. Adolescents tend to prefer adult oncologists. Adults, on the other hand, tend to be treated by oncologists spread throughout the community. These adult oncologists are highly competitive and have gotten out of the habit of participating in trials, except for the more lucrative industry-sponsored pharmaceutical trials. A higher percentage of participating patients are those at various NCI-recognized cancer centers or self-designated cancer centers.

Dr. Robert Toto, Professor of Medicine, University of Texas, Southwest Medical Center, asked Dr. Kaplan how funding was accomplished for trials where participating patients are from the community rather than at academic centers. This was an important point for the renal community network, especially

with regard to recruiting for CKD trials. Dr. Kaplan explained that NCI has the Community Clinical Oncology Program, which is a separately funded, competitive program. Investigators in the community who have clinical trial experience receive up-front funding in return for their guarantee to put 50 patients a year in treatment trials and others in prevention trials. Other community patients come from satellites to major centers, usually physicians who were formally in the center. These satellite groups receive up-front capitation payments based on their estimated accrual; this is needed so they can hire a data manager.

The following questions were also raised during this discussion period.

Q. Does having a network facilitate IRB approval?

Dr. Wright stated that the network does make IRB approval easier because a relationship is created with the local IRBs and they come to accept that the protocols have been carefully scrutinized and developed with the desired level of peer review and quality. Dr. Bernard's group has not gone to a centralized IRB arrangement. What they get from the network is an imprimatur that the question is reasonable to ask, which saves the IRB from grappling with that. Dr. Kaplan said that local IRBs generally accept NCI protocols; however, this does require a considerable effort and expenditure. NCI currently has a pilot program for a central IRB for 100 sites, with very strong support from the Office for Human Research Protection (OHRP). Four sites have already said they will accept the central IRB as the definitive review. NCI expects the others will also become comfortable with the system. The one problem is that the persons on the central IRB tend to conduct a tougher review and are less likely to accept a scientific design and proposed trade-offs than a local IRB. They often come back with improvements they want, even though the study has already been thoroughly reviewed by more than a dozen persons.

Q. What are the pros and cons between the 158-site study on protein C and the ARDSnet network studies?

Dr. Bernard replied that there are stark contrasts. For NIH trials, however, it would not be possible to pull together 158 sites around the world. There is a strong reluctance on the part of NIH to fund foreign centers. In ARDSnet, he has only recently managed to bring in one non-U.S. site, which is in Vancouver, Canada. Also, a network with a central coordinating center could not gear up to handle many sites and then gear down again within a reasonable period of time. Only a company with the kind of resources that Ely Lilly has can do that.

Q. Do you have specially dedicated panels to peer review the clinical trials?

Dr. Bernard responded that ARDSnet has a dedicated panel that reviews their proposals from the point of view of science, not competition; they rarely say "no," but sometimes give a qualified "yes." Dr. Kaplan said the NCI cooperative has dedicated panels, and they have said "no," causing some cooperative groups to fall out and new ones to be developed. Dr. Wright answered that his network has internal and external reviewers, and they also say "no" on occasion.

Q. What are your mechanisms for handling non-performers? Or do you just rely on contracts running out?

Dr. Kaplan explained that NCI has an institutional review committee that puts pressure on non-performers, although they do not have any really serious non-performance problems, just some below the mean. For these, they use a pressure-and-attention approach, including visiting them to assist them with their recruitment problems, to encourage them, and to establish a mutual professional relationship. NCI has only dropped one site over the years for recruitment and PI problems. Dr. Wright said his group does intense monitoring that includes site visits, detailed monthly spreadsheets on patient enrollment, and

monthly reports. Their only performance problem has been the 80 percent follow-up, which was probably funding-related.

Panel 3. Current Academic and Pharmaceutical Approaches to Trials in Kidney Disease

Dr. Edmund Lewis, Director, Section of Nephrology, Rush Medical College, Rush Presbyterian-St. Luke's Medical Center, opened his presentation by stressing the important contribution of a collaborative group to the leadership and collegiality necessary for successful clinical trials. Dr. Lewis described the collaborative study group he and Dr. Larry Hunsicker had formed to study the effect of ACE inhibitors in type 1 diabetic nephropathy. The study needed some 400 patients, which was more than had been required for the lupus trial they had conducted, so they expanded their initial group to 30 clinics. Dr. Lewis felt the clinics' organizational structure, although not a network, dealt with a similar range of activities and would work for the kidney disease clinical trials collaborative.

The organization was headed by an executive committee of senior physicians from the study group. These were the physicians with the most patients. They served on a rotating basis. The executive committee decided all the major issues, for example, what would be studied and what the protocol would be. Ultimately, all the investigators contributed to the protocol.

The clinical coordinating center, which included a central laboratory, was funded by NIDDK and housed at Rush. The NIDDK-funded biostatistics-coordinating center was initially at George Washington University. Bristol Myers Squibb agreed to fund the collaborating clinics. The NIDDK-industry funding levels were approximately 50-50. An independent patient safety monitoring committee included a representative from NIDDK. A clinical review committee of investigators reviewed events, clinics, and important issues, such as blood pressure control issues. This committee held meetings and interacted with the collaborating clinics, and they dropped some clinics for non-performance.

The clinical coordinating center's role was to work with the clinics on a daily basis. The center interacted with and trained the coordinators. It also constantly interacted with the biostatistics center and was responsible for the reports to the patient safety monitoring committee and, ultimately, to Bristol Myers Squibb. The group was generating data not only to publish in the *New England Journal of Medicine* (*NEJM*), but also to be utilizable, and in the right format, for Bristol Myers Squibb to present to the FDA. Dr. Lewis emphasized that in working with the pharmaceutical industry, it is also critical to be working with the FDA.

Dr. Lewis said that after the study with the well-defined type 1 population was successfully completed and published in *NEJM* in November 1993, the group wanted to study nephropathy in patients with type 2 diabetes, a more complex group to study. Unfortunately, NIH was not interested, although the group's submittal received a personal best priority score for Dr. Lewis. He also contacted a number of pharmaceutical manufacturers, including Bristol Myers Squibb, since his group had established an excellent rapport with them. Bristol Myers Squibb was willing to support another trial. The current structure is basically the same with the exception of the data safety monitoring committee, which is now appointed through Bristol Myers Squibb, although it is quite independent. There are also two very important subcommittees: a clinical monitoring committee with a permanent chair, Dr. Mark Pohl (blood pressure monitoring has been extremely important) and an outcomes classification committee, which is important for publication and FDA requirements.

Dr. Lewis pointed out that most corporations in the pharmaceutical industry are multinational. They need to enroll patients quickly, and to do that, they need a lot of clinics and must be active in a number of countries. For the study of type 2 diabetic nephropathy, the group expanded to 210 clinics in 21

countries, with a clinical coordinating center in the Pacific and another in Europe in constant contact with the Rush central coordinating center and the biostatistics center, which is now at the University of Iowa.

Dr. Lewis assured the group that the same organization could handle at least five studies at one time. They would have to expand staff and so forth, but the structure would work and is a current one in the field of nephrology. There is no need to reinvent the wheel, he said. He also recommended that the group continue to try to include industry, reminding them that these trials that were conducted jointly with industry were investigator-initiated trials.

Dr. Melisa Cooper, Vice President, Project Planning and Investment, Bristol Myers Squibb, prefaced her comments with the statement that the pharmaceutical industry is not only in business to make a profit but to return value to their shareholders. The average cost to develop a drug to the market stage, without the marketing cost, is approximately $800 million. She said that the reason it is that high is because the success rate for any one compound identified by the scientist at the bench is somewhere between 5 percent and 10 percent. Thus, only one out of ten to one out of twenty compounds actually makes it all the way through to FDA approval. The cost of just bringing one compound to the clinic, to do the initial Phase 1 studies, is somewhere between $30 and $50 million. With from nine to nineteen failures for every one success, the industry is spending approximately $500 million at this point. Another $270 million to $300 million is needed to complete the clinical trials necessary to secure approval. The company needs to be very strategic about what it is going to invest in research. It must buy down the risk before it increases or escalates the investment. The average time from when a scientist discovers a drug at the bench to getting FDA approval is 10 years, a very long period of time.

In responding to the question, "What sort of new trials would you support in association with the NIH?", Dr. Cooper answered that because of the up-front costs and the risk, Bristol Myers Squibb's usual approach has to been to work with the academic community and/or NIH only on studies after a drug has been approved. The company works with many experts in the area to understand the mechanism of action and to look for additional indications once the drug is approved, but before approval is given, the company generally does not conduct clinical trials with large groups in the academic community. Before approval, the firm's mandate has to be the safety of the patient, which is taken very seriously, she said. The reality is that the industry lives in an environment where the regulatory standards are incredibly high. It costs the industry nearly twice as much to conduct a study today because of all the quality assurance needed to ensure patient safety and the integrity of the data.

Dr. Cooper said that there are other unrecognized costs in direct supplies. Pharmaceutical development is the science of understanding how to synthesize and then scale up the manufacture of a drug. When talking about a small molecule, it might be $15,000 per kilogram and, depending on the potency of the drug, that translates to a certain amount of money. When talking about a biologic, it is tenfold higher, and to market a biologic, the cost to build a manufacturing production facility is in the range of $500 million to $1 billion, so there is a huge up-front investment.

To answer the question, "What kinds of trials are best left to the industry rather than the NIH?" Dr. Cooper said she preferred to focus on areas where there was a value for industry in working with NIH and the academic community. The first is leveraging patient groups. Access to patients is as much an issue in the pharmaceutical industry as it is in academia or at the NIH. That is why industry goes to so many investigators and physicians to conduct a study. She emphasized that this is clearly an issue for conducting nephrology trials right now, because of the way that the NIH is organized.

In addition to relying and collaborating on the scientific approach, the mechanisms of action of the disease, another area of huge value to industry is surrogate markers and outcomes. One of the biggest challenges to industry when it is conducting new trials is the discussions it must hold with the FDA and

other regulatory agencies about what is acceptable clinical proof that a drug is effective. Recent discussions at the FDA about proteinuria are a good example of that. Another area is in terms of assays. When working in a new area with a new target, a lot of time and effort has to go into understanding how you measure the target, not just proteinuria, but drug interactions and so forth, Dr. Cooper said.

Ultimately, there can be a huge value in bringing industry and the academic communities together to begin to reshape how clinical trials are done to meet everybody's expectations. One observation she had, after recent experiences, is "Why isn't there a separate renal division in the FDA? Why do we have to go to seven different divisions in the FDA to have a trial, to have a drug approved for patients with kidney disease?" That would be an interesting subject for further discussion.

One thing that industry does well, and they spend a lot of money on it, including commercials, is they do get information out to patients and physicians who are not aware of the availability of treatments. Obviously, there is a financial motive to that, but it is a very difficult thing to do, to change the practice of standard of care. This is an area that would be of benefit to NIH and the academic community.

Control of data and intellectual property is of immense value to industry because of a company's investment and the risks. The timeliness of the decision-making process and building consensus is of value to industry. The more groups a company must work with—the academic community; the government; and European, Southeast Asian, and American investigators—the longer and the more discouraging the decision-making process becomes because of the differences in standards of care and medical practices and because everybody strategically has a different intent when participating in these studies. These values would need to be considered and addressed for industry to work with NIH and the academic community.

Dr. Cooper said that, after listening to the prior discussions, she was struck by the lack of available effective interventions for patients who have renal disease, whether they have acute renal failure, chronic renal insufficiency, or are on dialysis. Because of this, she felt there probably is a huge opportunity to work on target identification more closely across the three groups in order to do the hypothesis testing that leads to drug discovery and clinical trials that effectively evaluate whether the drugs are of some benefit to patients.

Dr. Bradley Maroni, Senior Director, Anemia-Nephrology, Clinical Therapeutic Area Head, AMGEN, Inc., stated that the different pharmaceutical companies have a number of similarities in how they would approach cooperation with an NIH-academic collaborative. The companies also have different philosophies, and in that respect, his comments would be reflective of AMGEN's perspective. Dr. Maroni agreed with Dr. Cooper that industry must focus on trials that lead to registration and FDA approval. The time, money, and effort to get the approval means they must move very quickly, which makes it difficult to collaborate with NIH. Like Dr. Cooper, Dr. Maroni also saw the greatest opportunity for collaboration to be in the Phase IV, post-approval arena, where there are areas of mutual interest among the academic community, NIH, and industry, such as subsequent intervention and outcome studies.

Dr. Maroni suggested that another possible area would be orphan drug situations. Industry is not particularly set up to take on orphan drug indications. With access to the infrastructure at NIH that could be an area for collaboration as well.

In terms of what studies would be best left to industry, Dr. Maroni reiterated that these studies are the ones aimed at registering a drug for marketing approval or regulatory intent for a given indication. The issues here are timeliness, data ownership, and intellectual property, he said, adding that there also are

other trials that are driven by the commercial needs of a company. These trials would not necessarily be relevant for the general community or NIH, in particular, to support.

Dr. Maroni thought that the trials that NIH should focus on were studies to understand the natural history of a disease or disease mechanisms. These would be of more interest to NIH and the academic community than they would be to industry. Although this focus generally also applies to registries, epidemiology, and basic research, Dr. Maroni could think of examples where the company had been involved in non-industry collaborations in these areas.

From the point of view of a nephrologist, rather than AMGEN senior director, Dr. Maroni said he believed the basic, generic problem with clinical trials in nephrology is that many of the questions are complicated and not simple to solve. Intervention trials often have multifactorial etiologies, which, although not unique to trials, had been a challenge in the multicenter trials with which he was familiar.

He said other issues in NIH trials have to do with financing. Because of financial constraints, costs sometimes exceed the budgets available to do the trial, and the academic institution has to be very creative in how to contribute to those trials. This has implications in terms of the duration of the trial, the power of the trial, and the outcomes. Dr. Maroni said he was concerned that the renal community does not have the public or congressional visibility for CKD that cardiovascular disease and cancer have, obviously, given the numbers of patients.

Dr. Maroni did see an area where collaboration could work well for the three groups—industry, academia, and NIH—in their similar needs for data collection and management. To file their data sets with FDA, industry must build them from the ground up and ensure their validity. Given the rigorous regulatory requirements they must meet, industry has in place the infrastructure to do the data collection, data management, quality control, site audits, statistical analysis plans, and so forth for clinical trials. This data-coordinating center capability has a potential for some synergy of effort with a collaborative group in terms of sharing data sets, auditing the data, querying, and conducting additional analyses.

Dr. William Keane, Vice President, Clinical Development, Merck & Co. Inc., only recently left academia and affirmed the importance of creating a nephrology clinical trial collaborative. He stated that there is not just one way to perform clinical investigation, but there is substantial pressure on both industry and academia to perform trials in a more efficient and effective manner. Costs are enormous and the nephrology community must deal with this issue. From a pharmaceutical and industry perspective, there are a number of fiduciary responsibilities. There are issues of omission and commission. If industry does not do the right trials, if they omit to do a clinical trial, then an opportunity is lost, and that is a cost to the pharmaceutical industry. A host of regulatory issues drive labeling, drive indications, and are an incredibly complicated set of rules that are getting even more complicated.

Referring to the morning discussion on the need for growth of clinical trials, Dr. Keane said the pharmaceutical industry estimates that the need for patients is going to increase at the rate of 20 percent per year, which will result in intense competition for patients. Merck is looking at this issue and also asking "How can we do trials more efficiently and effectively within our academic institutions, so that we can actually participate more and more?"

Dr. Keane derived some interesting information from his firm's extensive databases. Merck's current patient recruitment challenges contribute to more than 40 percent of clinical trial delays, and these delays translate directly into a cost that has to be dealt with on a regular basis. Almost 90 percent of investigators overestimate their potential to enroll patients. Only about 20 percent of sites actually meet pre-specified endpoints; 80 percent do not, which means trials are not getting completed. More than 40 percent of the sites involved in Merck's clinical trials are one to six months behind schedule. In drug

development, that is $1 million per day. Multiplied by the number of clinical trials that a company like Merck does could mean a substantial amount of lost revenue. Finally, Dr. Keane said that investigator turnover due to under-performance is more than 50 percent. These realities must all be addressed.

Dr. Keane then presented the components of a large, randomized clinical trial life cycle that Merck would perform in approximately two years, with one year for development of the trial and one year for actual performance. The study design and protocol development and approval requires about 5 percent to 10 percent of the time. Another 5 percent to 10 percent would be spent in investigator and coordinator selection, patient enrollment, compliance, and resource development. Initiation of the study site, with such activities such as documentation, consent, IRB review, study drug, and training, requires15 percent to 25 percent. Study conduction and data capture takes from 40 percent to 70 percent over the entire life cycle, and data analysis from 5 percent to 10 percent.

Reviewing these components and the issues that concern industry, Dr. Keane said that protocol development and protocol approval, in general, takes the smallest amount of time available to the company. Merck is using numerous existing networks. One model is the Oxford Group, which just did a hypertension study for Merck under a grant given to that center. Another is Dr. Owen's collaborative at Duke University's clinical research center, which is under a Merck contract. The trial systems in pulmonary disease, asthma, and cardiovascular disease are much more mature than any trial systems that Merck has in nephrology. Having a network assists in improving the study design and protocol development and shortens time.

From a pharmaceutical basis, a great deal of effort and management goes into investigator selection in terms of how well a PI actually performs, how many patients the PI can recruit, and who the patients are.

The site initiation is another critical area in trying to get patients. The pharmaceutical industry is looking at different ways of approaching this problem, because asking centers to recruit patients is no longer effective. The company actually has to help the centers. Large patient databases based on disease spectrums need to be located to help investigators recruit. Merck also assists investigators within a network to create a kind of micro-network that will recruit patients on a timely basis.

Study conduction is an area in which electronic data capture systems and electronic clinical systems are going to grow rapidly. This is an area for possible collaboration in developing uniform systems to look at data, scrub the data to get a final file, and do data analysis with a clean data set, an enormously laborious task. It takes hours to go through this on an individual basis to attest to accuracy.

Finally, after data analysis is completed, publications and reports must be made. Industry recognizes that there is a problem in getting the publications out. Merck is creating a group of six doctoral-level people who will assist investigators in putting manuscripts together and in publishing the information.

Dr. Keane presented a matrix of clinical trials costs. For better centers such as Oxford, costs of study planning for an average 90-plus days to an optimal 48 days range from $270,000 to $135,000. Most of the effort is in the period of time when the first patient enters the trial to when the last patient leaves, which is almost two-thirds of the total time in a clinical trial. Again, the better centers in the network can reduce costs for this period by 40 percent to 50 percent, from slightly over $1 million down to $740,000. That translates into an enormous savings for Merck. A yearlong multiple-site trial with about 750 patients costs $2 million to $2.5 million dollars, just for the cost of the trial. Almost half (46%) of the cost is for conducting the clinical trial, getting the first patient in, the last patient out, and about 35 percent is related to dealing with the data and the data sets, evaluating the data, and doing all the necessary statistical analysis and reports. Improving the trial components has an enormous impact on the industry's willingness and ability to actually collaborate with others.

Dr. Keane assured the group that there are ways to streamline the clinical trial process for new technology. One area for collaboration is the electronic data system, from using hand-held palm devices to collect and electronically transfer the data, to development of accepted algorithms on how data can be scrubbed in order to look at sought-after areas and to validate the data. The statisticians cannot look at the data until there is a clean file. Industry also could play a role in collaborating to maximize site performance, which is something industry is interested in seeing happen. Merck is working with the AAMC to talk with the deans of medical schools to do that.

In conclusion, Dr. Keane emphasized that privacy issues are going to have a major impact on the conduct of clinical trials. From clinical, academic and pharmaceutical perspectives, the amount of data that has to be collected is enormous. A forum is needed for dialogue on how to modify the existing regulations. This is an important area for collaboration because there is only about a year to do this.

Discussion. Dr. Briggs opened the discussion by saying that she had enjoyed all the presentations and that NIDDK did not get enough opportunities to meet with the industry representatives present today. She asked if there were ways they saw of collaborating among themselves. She was aware that they hold roundtables and give funds to NIAID to do cooperative types of work, but wondered whether they would do epidemiological studies and mechanisms of renal disease, for instance, to determine targets. These studies are now done at NIH. Such cooperative work, some of which is now done by industry on a small scale, could be beneficial to industry and the rest of the community, too, if done on a larger scale.

Dr. Cooper said that, theoretically, the answer was "of course," but from a practical perspective, each company has very different strategic objectives and core competencies with respect to the disease areas they are invested in. When it comes to mechanisms of action, there might be some overlap, but probably not a huge amount. That is one obstacle. Another is the intellectual property issue, which is a very large obstacle across the pharmaceutical industry.

Q. Does the greater amount of information that needs to be collected by industry during a clinical trial in order to ultimately achieve FDA approval affect physician enlistment and patient recruitment.

Dr. Edmund Lewis answered that this did not make the situation more difficult. In fact, it probably made it easier because the FDA sets the standards so high for industry that it gave his group parameters that they might not have used otherwise and gave them requirements for standards. Biostatistics is so important in research that the requirements for industry—the amount of information required, the accuracy, and so forth—simply improved results and was good.

Q. How many of the studies have pure electronic data entry, not a paper case report form? Also, are there studies where there is no other source document other than the electronic case report form?

Dr. Keane responded "no" because a company like Merck is extraordinarily concerned that there be a paper trail. Pilot data is converted into electronic data systems. Dr. Keane has been involved in ways to do that—what kinds of trials, what kinds of data, how it can be done, how to evaluate the data, what kind of algorithms to use. This is an important, relatively new area that has received a lot of commitment from the people on top. Actually at Merck, it is brand-new. They will be assessing the effectiveness of several examples as to how effective they are in reducing time to a clean file and how cost-effective they are.

Dr. Maroni added AMGEN is just getting in to this, whereas in the HEMO trial, electronic data entry has been going on for years. He believes that there are potentials for efficiency and cost savings. However, AMGEN will not eliminate the paper trail. This will still be used for audits.

Dr. Cooper mentioned that the difficulty with electronic data capture is with the scalability and the number of centers or physician sites that the company is working with. For example, in the case of Bristol Myers Squibb's Phase I studies, the majority are conducted in one location, so they are entirely electronically wired between that location and their centralized database.

Q. One of the challenges mentioned in presentations about the synergies between industry and NIH network development is HIPAA regulations. Major issues with the IRBs, particularly in academic medical centers, will slow down the ability to conduct studies in a normal fashion. Currently at our institution, it takes us two to four months to get a study through the IRB. Obviously, industry, either from an economic or a drug development standpoint, cannot have as much patience as we do. I think that this is an important consideration where further dialogue might be very helpful. Is this an opportunity to develop a core IRB?

Dr. Keane voiced his agreement. Three models were presented earlier. One model is the individual institution, which is actually the slowest and most difficult to deal with. The second model is the network, which is intermediate in terms of the amount of time it takes to get approval. The third model is the centralized IRB, which has a lot to be said for it in terms of efficiencies and effectiveness, although there are some downsides. Merck has used all three models and prefers either the network or the central IRB. In this country, the centralized model has standardized forms and format that would help clinical trials in general.

Q. Dr. Lewis, do you have suggestions on how to cut costs for clinical trials, based on your experience with trials in both industry and academia

Dr. Lewis responded that in a closely knit network, some people offer their time for nothing. For instance, in his group, the clinical monitoring committee spent many hours discussing important issues. There is also a difference between giving somebody a pill or having an army of nutritionists count every calorie that somebody is eating, so trial design makes a difference. Dr. Lewis said he did think the industry model is a better model, because the clinics are getting seed money to put together their coordinators and other resources, and they are also getting paid on a per-patient basis, with bonuses at various milestones. Industry is not spending money hoping that people will perform. Industry is paying for performance. This is a very significant difference from NIH, where the center receives an annual grant and if it does not meet certain requirements, it receives telephone calls and so forth, but there is no way to guarantee that the clinic will ever perform.

Q. Dr. Briggs, what are the NIH requirements for having clinical trials outside the United States in order to have more centers?

Dr. Briggs said there were not insuperable barriers to international sites; a few NIDDK studies have Canadian sites. However, this does increase the time to approval because they have to go through a State Department clearance.

Dr. Ed Lewis added that in a model where NIH is paying for the data or clinical coordinating center and industry is paying for the clinics, it does not matter where the clinics are. In today's world, a company has to do international studies. To develop and implement such a model will require coordination.

Q. How do investigators propose studies to get industry to conduct trials that have a broader public health interest, are more of an academic-oriented issue, such as the Roy Collins study of a multivitamin cocktail versus placebo? Does industry actually decide whether they will pay for one hypothesis they are interested in and one they are not really concerned about? Perhaps this is a type of marriage that works.

Dr. Keane responded that Merck has recently completed two outcomes trials on the life cycle of a drug that were brought to them by investigators as hypotheses. One of the difficulties is that it is sometimes somewhat opaque about how and to whom to go to get answers for specific large clinical trials like that. A lot of these trials are done to support a specific franchise or a specific drug, as in the case of Zocor. Marketing is looking at all of these impacts in the field and how they can structure something that would be good for their ability to sell that particular drug. So it is timing. It is having the connections.

Dr. Ed Lewis pointed out that in one of his trials funded by Bristol Myers Squibb, one of the two drugs being tested was a Pfizer drug. Bristol Myers Squibb took a chance, especially since the study took a year longer than it would have taken otherwise. The investigators wanted very, very much to find out whether ARB's were renal protective as they were being sold as something that blocked the system, so they worked this out with Bristol Myers Squibb. Dr. Lewis stated that there is no reason why an investigator or a network cannot work something out with a pharmaceutical company. The main thing is the pharmaceutical company has to buy into the interest, and to a large extent, the investigator has to buy into theirs, and after that there are a great number of things that can be done with studies, even major things.

Dr. Cooper, who was the person at Bristol Myers Squibb who worked closely with Dr. Lewis and his group to secure the funding, added that such an arrangement depends on the strategic objectives and the core competencies of the pharmaceutical company. One of the things that Bristol Myers Squibb has always been very interested in is diabetes, and that is why they were able to partner so successfully on this, because that interest existed in the company, so it was of mutual benefit all around.

Q. Would the three representatives from the pharmaceutical industry to candidly present their views on the pros and cons of working with academic versus non-academic sites in a clinical trial? Also, which is less expensive—academic or community sites?

Dr. Maroni responded that this was a good question. The pro of academic centers is the prestige, the affiliation that goes with that. If they have a trial infrastructure and, in particular, if it is a challenging problem, and they have a large database of patients, this can simplify things. The downside can be dealing legally, getting the contracts through, working with the budgets, and of course, personalities can sometimes be an issue. On the community's side, the advantages are, if the trials are not rocket science, things can move more quickly and there are more sites available, which creates speed and efficiency because instead of 40 sites trying to get 30 people, there are 100 sites each getting 8 or 10 patients. The downside to that is that many of them do not have much experience, so a lot of hand holding is needed to meet regulatory requirements, which is why they are used mostly for Phase IV studies. Dr. Maroni could not say which type of site was less expensive, the academic or the community, since most of the work with community sites was for Phase IV trials.

Dr. Cooper said overhead costs associated with academic medical institutions are substantially higher. Compared to Harvard's 50 percent rate, a typical community physician's overhead is closer to 10 percent.

Dr. Keane added that Merck has a fairly hard line on overhead rates, but if the academic center has clinical experience and the capacity to get patients, Merck is willing to pay, but not the Harvard rate. Academic centers do tend to be very costly, not just in overhead, but in trial performance metrics. Merck looks at performance, which is why they have used so many networks, because they perform better in general. Another part of the answer is that there are different reasons for doing a clinical trial. One reason for doing a trial is to get experience out in the community with a particular drug. The private practitioners' clinics may be used to give them structured experience with the drug, which is part of drug development. To balance the issues, centers do have the expertise, the thought leaders.

Dr. Cooper added that, in all fairness, there are many academic centers that do an incredible job of

recruiting patients, and many community physicians who never recruit a single patient, so the 80:20 rule may not apply.

Q. One of the models will require industry interactions, given what needs to be accomplished in the next 10 to 20 years. Since the industry has biostatistic centers within its companies, is there a problem with the NIH having its own biostatistics arm? Would there be resistance from industry on that piece of the plan?

Dr. Cooper replied that she did not think there would be a problem because there are multiple examples of companies throughout the industry working hand-in-hand with data-coordinating centers and statistical centers that are located in academic centers, just as Bristol Myers Squibb has done.

This ended the March 7, 2002, presentations. Dr. Neilson reminded the breakout groups that they would be reporting the next day on their discussions. The breakout groups were made up of representatives of all the entities and perspectives present so that all groups would have some input. The goal was to get consensus for an organizational model to present to NIH for further discussion. It should be a structure that could be reviewed periodically and that would not become too colloquial. Dr. Neilson listed the following four items for the breakout groups to consider in evaluating their options:

- What are the types of things the group wants to study? These fall into two general categories—those that are preventive and those that are therapeutic management issues, particularly for acute renal failure and chronic renal failure. These are very different methodologies; some people may recommend that two kinds of networks should exist and co-exist around the same data coordinating center. It is important to account for the different types of interest.

- What kind of infrastructure can accommodate NIH, academia, and industry?

- What are the start-up costs for the proposed model? The experience of most of the networks is, that once established, other kinds of monies become available.

- How will performance be measured and adjusted within the network?

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