Kidney Disease Clinical Trials Task Force Workshop

March 7–8, 2002

Meeting Summary

The American Society of Nephrology (ASN) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) hosted a meeting at the Washington, D.C., headquarters of ASN on March 7-8, 2002, to discuss the development of an organizational structure that would foster kidney disease clinical trials and facilitate how they are conducted. More than 50 members of the renal community attended the meeting and contributed their experience and ideas to developing a framework for a kidney disease clinical trials collaborative network.

Dr. Eric Neilson, Morgan Professor and Chair of the Department of Medicine at Vanderbilt University Medical Center, called the meeting to order and introduced **Dr. Allen Spiegel,** Director, NIDDK. Dr. Spiegel welcomed participants and thanked them for coming to this important activity. He expressed his certainty that all present shared the same goal—to amass knowledge that would help people with kidney disease, that would prevent kidney disease, and that would do so cost-effectively within available resources.

Dr. Neilson stressed that those present were looking forward, not backward. The constituencies represented at the meeting already had done much preliminary work about how to improve the quality of clinical trials offered by the National Institutes of Health (NIH) and by the various members of the Council of American Kidney Societies (CAKS). He affirmed that they are deeply interested in seeing this program enlarge or perhaps take on a new dimension. The participants gathered for this meeting, he said, should think creatively about how to do this, put their various ideas on the table, and propose a trial collaborative that would be feasible and would work for a very positive triangle—the nephrology community, NIH, and industry.

Perspectives and Aspects of Developing a Collaborative

The meeting's agenda included presentations and panels on the various perspectives and aspects of developing and implementing a kidney disease collaborative. (In-depth précis of presentations are at the end of this meeting summary.) **Dr. Roland Blantz**, ASN President and Head of the Division of Nephrology, University of California, San Diego, presented an overview of the events leading up to this meeting. Guidelines were developed at Renal Research Retreats in December 1998 and February 1999, sponsored by NIDDK, ASN, and the Council of American Kidney Societies (CAKS). The retreat work groups recommended establishment and maintenance of a permanent, cooperative, multicenter collaborative for renal disease clinical trials. The collaborative network's goal would be to provide scientific evidence to have a significant impact on diagnosis, delivery of care, treatment, and outcome for patients with kidney disease and related disorders. Dr. Blantz also described a model collaborative developed by ASN's Government Relations Committee.

Dr. Josephine Briggs, Director, Division of Kidney, Urologic, and Hematologic Diseases (DKUHD), NIDDK, traced the growth of NIH's clinical trials and studies in kidney disease from 1997 to what is

projected for 2003. She encouraged the group to focus on what the goals of a cooperative should be, such as improving the identification of research objectives, cost-effectiveness, utilization of resources, and training and career support for clinical investigation.

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). These presentations looked at the common elements and ideas in these areas that are relevant to the structure of a clinical trial collaborative. In discussing clinical trials in adult kidney disease, **Dr. Daniel Cattran**, Professor of Medicine, University of Toronto, described the regional data collection system for the Toronto Glomerulonephritis (GN) Registry. The registry is used to develop clinical trials, studies of the natural history of diseases, and basic investigational research. Dr. Cattran stressed that feedback to the patients and physicians and establishment of a community connection were critical to recruit the needed participation in these trials.

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 the importance of open competition along with group cohesiveness, leveraging of ASN/NIDDK's reputations as endorsement, and empowerment of persons with demonstrated competence, commitment, and excellence.

Dr. William Owen, Chief Scientist, Baxter Healthcare, and Adjunct Professor, Duke University School of Medicine, noted that collaborations have both opportunities and challenges, such as those that he had encountered in ESRD clinical trials. Dr. Owen presented some of the "lessons learned" from his current role in industry. These lessons, he said, are crucial to partnering with NIH, and they include protection of intellectual property, timeliness in trial execution, selection of investigators experienced in clinical trials, and provision for marketing the outcomes. He also spoke of the advantages for industry in doing trials with NIH, such as enhanced credibility and scientific rigor.

Three other aspects important to clinical trials—implementation in a clinical center, administration and structure, and determinants of cost—were described next.

Dr. Lawrence Appel, Associate Director, Johns Hopkins University, presented the perspective of the clinical center at an academic institution conducting NIH-sponsored multicenter and observational studies. He described four aspects he considered critical in forming a collaborative: (1) the principal investigator's time to administer a grant; (2) the cost, time, and patience needed to recruit; (3) the failure of most grants to cover the trial's costs; and (4) the inefficiency in oversight of multicenter trials.

Dr. John Kusek, Clinical Trials Program Director, DKUHD, NIDDK, provided an overview of the clinical trial organizations and funding mechanisms that NIDDK currently has in place. Funding mechanisms include R01s and cooperative agreements, with the latter being the most common for large clinical trials. Among the organizational structures used, the predominant model is independently funded clinical centers. Another current model is a regional network for a well-defined initiative and target population. Both types are supported by a data-coordinating center and usually by a central facility. Start-up funds, capitation for recruitment, and sometimes subcontracts within the grant are the general funding mechanisms. Dr. Kusek stated that of particular importance to the collaborative is the current existence of a substantial network or group of investigators experienced in pairing up clinical trials and epidemiological studies.

Dr. Paul Eggers, Program Director for Kidney and Urology Epidemiology, DKUHD, NIDDK, presented the determinants of costs that affect clinical trials. These determinants include complexity of the trial, number of patients to be recruited, number of participating centers, trial length, protocol costs, intervention costs, and miscellaneous items such as patient payments and acquiring IRB approval. He stressed that interventions—not just a drug itself but the counseling and other support needed—greatly increase trial costs. Costs per person varied from $75,000 in the MDRD to less than $6,000 for FIND. Dr. Eggers explained that startup costs are always higher than other annual costs.

Three panels provided additional insights. **Dr. Gerald Beck**, Cleveland Clinic Foundation, **Dr. Donald Stablein**, the EMMES Corporation, and **Dr. Vern Chinchilli**, Pennsylvania State College of Medicine, described the roles and costs of data-coordinating centers. **Dr. Linda Wright**, National Institute of Child Health and Human Development, **Dr. Gordon Bernard**, Vanderbilt University Medical Center, and **Dr. Richard Kaplan**, National Cancer Institute, described current NIH trials networks. **Dr. Edmund Lewis**, Rush Medical College, spoke on academic collaborative study groups in nephropathy jointly funded by NIDDK and industry, and **Dr. Bradley Maroni**, AMGEN, Inc., **Dr. William Keane**, Merck & Co., Inc., and **Dr. Melissa Cooper**, Bristol Myers Squibb, presented the pharmaceutical industry's viewpoint on which trials are best left to industry and which would be areas for collaboration. Summaries of those panels are as follows:

Roles and Costs of Data-Coordinating Centers (DCCs). All three of the DCC panelists stressed the importance of a strong working relationship between the DCC and the clinical centers, especially with the investigator at the lead clinical center. Advantages of one or more DCCs supporting a single network included the ability to conduct multiple trials simultaneously; the standardization of procedures and data forms; the savings in equipment, labor, and training; and the ongoing collaborative expertise of the scientific team. Each panelist pointed out that compliance with regulatory requirements is becoming more complex, time-consuming, and costly for the DCC and the investigator, especially if the trial requires interfacing with the Food and Drug Administration (FDA). It was thought that one DCC could handle multiple studies, depending on the size, complexity, protocols, and number of trials being coordinated. Panelists estimated that the DCC for a renal clinical trials collaborative network would require approximately eight FTEs and supplies, travel costs, and miscellaneous expenses for a total annual budget of approximately $140,000 to $150,000.

Some Current NIH Trials Networks. National Institute of Child Health and Human Development's Neonatal Research Network, the National Heart, Lung, and Blood Institute's ARDSnet, and the National Cancer Institute's Cancer Cooperative Groups all have similar organizational structures. A steering committee has oversight and is responsible for setting policy and procedures. Subcommittees review protocols, ensure patient and data safety and monitoring, and review center performance. Centers are supported by a central data-coordinating center and sometimes by a clinical coordinating center. Most funding is through cooperative agreements, even though studies are investigator-initiated. Cooperative agreements have facilitated industry's participation. "Lessons learned" have included the need for care in selecting principal investigators, for a reasonable start-up time and length of trial, for appreciation of equipoise, and for recognition of the value of databases. Advantages of the networks have been efficiencies such as the standardization across trials and the increased ability to work with industry and the FDA. Panelists also cited the increased ease of obtaining institutional review board (IRB) approval and even some of the lessening of data collection requirements negotiated with FDA. A challenge has been the cost of translating results if the trial is not industry-supported. A change that has helped in translation has been the move away from academic institutions to inclusion of more non-academic

institutions and local physicians to show the new clinical practice is "do-able" in the community.

Current Academic and Pharmaceutical Approaches. The cost of bringing a drug to market is approximately $800 million and requires about 10 years from bench to FDA approval. 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 usually makes it difficult to collaborate with NIH. Panelists agreed that the best areas for collaboration with industry involve post-drug approval studies of the mechanisms of action, additional uses for the drug, and identification of surrogate markers and outcomes. Partnership benefits include identifying needed interventions, studying orphan drugs and drug combinations, and sharing of patients, especially in renal disease, where recruitment is a difficult issue, particularly for chronic renal disease.

The same type of structure as described in the other networks would be applicable to these partnerships, but there might be a need for rethinking of current NIH approaches. For example, most corporations in the pharmaceutical industry are multinational, need to enroll patients quickly, and need a lot of clinics to do that. NIH has been reluctant to fund foreign centers. Data control, intellectual property ownership, and the timeliness of decision making are important issues to industry. It costs the industry nearly twice as much to conduct a study today because of all the quality assurance needed for patient safety and data integrity. Working with the FDA and other regulatory agencies to obtain acceptable clinical proof that a drug is effective or to study drug interactions would be areas for clinical trial collaboration. The DCC's capability was also thought to have potential for synergy of effort with a collaborative group in terms of developing and sharing uniform data sets, auditing the data, querying, and conducting additional analyses. Trials driven by a company's commercial needs would generally not be relevant for NIH or academia, whereas, with a few exceptions, epidemiological studies and basic research in disease mechanisms and the natural history of diseases would be of less interest to industry. However, NIH-industry-academia collaborations can benefit the triad, given today's substantial pressure on all to perform trials in a more efficient and effective manner. In addition, collaborative networks tend to improve study design and protocol development.

The presentations and the discussions provided the four breakout groups with important information on what was needed to structure, implement, and fund a collaborative. To open the breakout groups' deliberations, Dr. Neilson listed the following four questions for groups to consider in evaluating their options:

- What are the types of issues the group wants to study? These issues 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 two categories of issues are very different methodologies; some people may recommend that two kinds of collaborative 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 collaborative groups is that, once established, other kinds of monies become available.

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

Recommendations from Breakout Groups

The following recommendations emerged from the discussion of the breakout groups' presentations on March 8, 2002. They are intended to represent a framework from which there can be further dialogue and evaluation of scope. Consensus suggests the program etched in Figure 1 would increase, improve, and diversify our clinical knowledge of kidney and urologic diseases.

The principal, unanimous recommendation was to support the development of a *DKUHD Cooperative Study Group,* comprising in its mature form several steering committees and multiple clinical patient centers. The steering and protocol evaluation committees (acute renal failure [ARF]; end-stage renal disease [ESRD]; chronic, pre-end stage kidney disease [preventive trials]; pediatrics [Peds], and perhaps urology) (Figure 1) would serve both DKUHD and clinical patient centers.

The group's intention was to recommend a cautious, gradual start-up and an incremental addition of trial portfolio, and not try to take on too much at once. For example, the initial steering committee could be constructed to start one to three trials in several areas, and as traction was achieved, subdivide based on focus and extent. Furthermore, funding for infrastructure committees and cores could be modular and increased with performance benchmarks.

KUH Cooperative Study Group. The group suggested that the *DKUHD Cooperative Study Group* have the following components:

- *Steering Committees*: These committees would comprise several groups of rotating investigators—a mixture from some of the clinical patient centers and other non-center investigators appointed by the DKUHD. The chair of each committee, or the inaugural single committee, will have a tremendous impact on the success of this endeavor and needs to be chosen carefully. This person needs to have a persona of enthusiastic leadership and a reporting relationship to the DKUHD program director. DKUHD could request further external review of any protocol under consideration by a steering committee. Special duties of the steering committees are as follows:
    - Evaluate and facilitate submission of well-designed research protocols and career or training grants, employing the resources of the Biostatistical Center for Design Analysis.
    - Execute and be responsible for trials initiated under the steering committees' purview.
    - Evaluate available data and samples for ancillary studies.
    - Enlist additional centers for recruitment of services for trials in need of more subjects.
    - Charge a subgroup to form a primary writing committee for trial data.
- *Clinical Patient Centers*: As many as 15 to 20 centers would be needed. The PIs of the centers

would receive a small amount of start-up, a stipend, or perhaps a K-award and would be responsible for all local trial activity.

- Clinical patient centers would be expected to enroll patients into multiple protocols.
- Centers would receive a capitation payment for each enrolled patient.
- R-type awards accepted for trial would make the application PI a new clinical patient center.
- Centers could collapse or grow based on patient enrollment and overall participation.

- *Clinical Coordinating Center*: This center would be bid as a modular contract and would be responsible for data collection for all trials. It would periodically update the steering committees on trial progress. Ideally, data entry would be web-based from each clinical patient center. The funding to the center would be based in part on the numbers of applications and trials supported.

- *Protocol Entry or Development*: Protocols could come to the KUH Cooperative Study Group from several directions. They could be conceived by a group of investigators from the clinical patient centers, by a steering committee, by industry, or by an independent investigator who submits an R- or K-type grant.

- *Sample Core*: This core would be bid as a modular contract and established as a KUH repository for trial or registry biosamples and genetic material.

- *Quality Committee*: This group would independently evaluate protocol progress or breech, and with consultation from the biostatistical center, assume responsibility for monitoring or early closing of a trial at the request of a steering committee. The steering committees would work in close consultation with the quality core.

- *Biostatistics Center*: This could be "stand-alone" or part of the clinical coordinating center. It would be bid as a modular contract and responsible for all data analyses requested by steering committee trials.

- *Registry*: Registries should be developed in thematic areas such as chronic kidney disease, diabetes, or a particular developmental or glomerular disease. Industry and one or more professional societies could consider supporting such activity. The registry would be web-based and fee-paid for patient entry and maintenance. The registry would identify new sources of patients for orphan trials.

- *Role of Industry*: The DKUHD Cooperative Study Group will encourage and invite collaboration with industry for appropriate studies. Industry would cover patient costs for drug, biologic, or special-device trials. The Cooperative Study Group would conduct the trial in a cooperative and interactive arrangement through the steering committee accepting the trial.

- *Financing*: DKUHD would fund the steering committee(s), data-coordinating center/biostatistics

center, sample core, and quality committee as modular units with the intent of migrating all future trials into this mechanism. The modular design of the program will better tailor costs to performance. Trials could be funded by independent R-type awards; limited to $500,000 direct costs unless pre-approved for a greater request, by industry or foundation partnerships, or by contract through DKUHD.

Figure 1

Organizational Structure and Flow of Recommendation Components