Final Report
National Heart, Lung, and Blood Institute
Level 1 Strategic Planning Working Group
August 17-18, 2006

Cardiovascular Program – Theme # 12: Clinical Trials Methodology

Introduction:

The pace of scientific discovery is far exceeding the capability of our clinical research system to evaluate preventive, diagnostic, and therapeutic strategies. As society appropriately demands evidence to justify use of new strategies to prevent and treat disease, the infrastructure for the design and conduct of clinical trials in cardiovascular disease (CVD) needs urgent reform. The following recommendations are intended to lead to a significant improvement in our national capability to develop evidence that, when applied, will reduce CVD death and disability.

Recommendations:

1. NHLBI should convene an open iterative process to develop a "national problem list for CVD" to determine priorities for new, large clinical trials. The process would include:

a. Pre-identified evaluation criteria such as: potential for improving the public's health (evidence-based, using modeling where appropriate), feasibility and timeliness of conducting a clinical trial on the topic, relevance of the research question to providers and public, assessment of likely source of funding for trials to address the problem, and topic area (e.g., prevention, risk factors, CAD, heart rhythm disturbances, heart failure, imaging, valvular disease, congenital heart disease)
b. Broad participation by relevant groups: clinical trial investigators, NIH experts, professional and volunteer societies, healthcare providers, other Federal agencies (FDA, CMS, AHRQ, CDC, VA, DoD), industry (medical products/drugs; food), payers and health systems, research networks, academic medical centers, patients, the public
c. Review of clinical practice guidelines, clinical performance measures, and national data to identify gaps in knowledge for prevention and treatment
d. Publication of the priority list and annual updates as a "living document" with feedback regarding results and progress.

2. NHLBI should proactively collaborate with other Federal and non-Federal entities to prioritize, design, fully fund and conduct clinical trials relevant to delivery of cost-effective healthcare. This approach would enhance public trust, promote a more effective infrastructure, ensure adequate funding, enable inclusion of mechanistic ancillary studies, improve translation into practice, and improve the degree to which trials predominately funded by industry address public health and clinical concerns. NHLBI should:

a. Pursue specific measures to enhance collaboration and co-sponsorship with other entities (other NIH institutes and Offices, AHRQ, FDA, VA, healthcare systems, CMS, health insurance companies, the pharmaceutical/device industry, professional societies, the food industry, and academic health centers).
b. Develop standards to increase public confidence in the integrity of clinical trials, e.g., a "seal of approval." Criteria should include whether the trial hypothesis addresses an important problem, the appropriateness of the study design, whether the trial meets best practices regarding conflicts of interest, decision-making processes, informed consent, data and safety monitoring, data quality, completeness of follow-

up, approach to publication of results, accessibility of trial databases, and intellectual property. NHLBI funded institutions should track their participation in trials receiving this "seal of approval", and their participation should be made public.

c. Work with the media and organizations, both public and private, to enhance the understanding and acceptance of, and participation in, clinical research in the U.S.

3. NHLBI should improve efficiency of clinical trials by providing proactive central support, expertise, tools, and resources. The following actions are recommended:

a. Have the newly established Office of Clinical Research facilitate clinical trial implementation and conduct in conjunction with the project officers. This office should not add impediments and should be adequately staffed. Issues include: regulatory requirements including HIPAA, standardized operating procedures and monitoring approaches, establishment of a central NHLBI IRB, facilitation of tissue repositories, facilitation of drug distribution centers, template subcontracts, a database of investigators and coordinators certified in Human Subjects Training, review and oversight of informed consent documents, sharing of "Best Practices".
b. Facilitate use of international sites at the outset of a trial, when appropriate.
c. Encourage the use of clinical networks (national and international), and support creation of electronic "virtual networks" to share resources, templates, and practices.
d. Establish a system to expedite evaluation and funding of mechanistic ancillary studies.
e. At trial inception, consent participants for centralized ascertainment of long-term follow up and storage and use of biological samples.
f. Develop a standardized site payment structure, to include fixed and per-patient costs.
g. Facilitate use of statistical sampling methods for quality control and site monitoring.

4. NHLBI should lead efforts to standardize methods and measures to improve efficiency and scientific yield of clinical trials. The following actions are recommended:

a. Develop standard terminology, definitions, and data collection approaches (including recommended Case Report Forms) for demographic variables, risk factors, efficacy and safety outcomes, quality of life, and for health care utilization to assess cost-effectiveness. Develop efficient models for events adjudication.
b. Coordinate standardization with other agencies (e.g. FDA) and encourage collaboration with industry, and collaborate with standards development processes.
c. Develop a prioritized system for supporting collection, storage, and analysis of biologic samples with appropriate broad-based consent for their analyses in conjunction with the trial databases, first by study investigators and then by the broader research community.

5. With regard to clinical trial monitoring, NHLBI should:

a. Continue to use DSMBs to assure participant safety by reviewing interim data and monitoring trial results in relation to pre-specified stopping guidelines.
b. Convene a meeting to establish best practices for operations of DSMBs (such as who would be privy to interim outcome data, use of a template-based charter).
c. For multi-center studies with DSMBs, inform study sites about the role of the DSMB so that individual adverse events need not be reported to the IRB.
d. Work with OHRP and FDA to assure that only significant and relevant events are reported as SAEs.
e. Assure that DSMB members are indemnified.

6. NHLBI should increase attention to design and analysis approaches to improve efficiency, scientific quality, and inferences from clinical trials. The following actions are recommended:

a. Investigate study methodologies for assessing safety, efficacy, and generalizability, including: various study designs (large simple trials, multiple randomized groups, factorial designs, studies of therapy combinations, group randomized trials, event-driven designs); types of outcomes (composite and intermediate outcomes, patient-centered outcomes like quality of life), modeling generalizability, subgroup analyses, use of intermediate measures (biomarkers, imaging), longitudinal data analysis, adaptive designs, Bayesian approaches, data pooling, cost-effectiveness analyses, and methods for evaluating the use of "-omic" discoveries to target therapy.
b. Support embedding statistical, study design, and trial conduct questions into clinical trials.
c. Support the use of existing clinical trial databases to study methodological questions.
d. Develop and fund an extramural research program in statistical and study design methodology for clinical trials.
e. Develop and fund training programs: (1) to educate clinical researchers in clinical trials methodology, and (2) to increase the number of well-trained biostatisticians and clinical trialists working on methodology issues.

09/29/06

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Recommendations:

Results of "voting" on the pre-written recommendations:

	High	Medium	Low
1. streamlined procedures for renewing grants	0	4	14
2. funding and award mechanisms for new investigators	12	5	1
3. incentives/mechanisms for cross-Institute/interagency funding	15	3	1
4. review NHLBI pre-approval process	7	12	0
5. infrastructure support for large studies to facilitate ancillary studies	12	5	2
6. issues related to CSR and study sections	6	13	0
7. dissemination/communication of advances/discoveries/resources	7	7	5

Comments on Business Operations Areas and Recommendations Above

Comments about #1:

- I like the proposal in the 2nd paragraph.
- As written above, #1 only includes the first half of the recommendation – The second part, Procedures of Grants within 3 – 5 points of payline, I believe should be supported with high enthusiasm.
- Review of established investigator grant awards should be based on productivity. Review of young investigator grant applications should be based on merit of grant with larger point advantage, i.e. > 10 pts.
- #1 Concerned about how #1 sends a negative message to younger/junior investigations, but streamlining for all applications is worth considering.
- I would favor the 2nd paragraph in #1 – streamlining & expediting re-review of applications scoring close to payline.
- #1A [first paragraph] is a terrible idea
- I am supportive of 2nd part of #1, allowing a streamlined response for near-miss proposals. I'm also in favor of increasing the $500k trigger point to reflect inflation (a part of #4).
- For #1, High priority for payline.
- #1, paragraph A-Low /paragraph B-high.

Comments about #5:

- #5 is a good idea, but investigators should retain exclusive access to data for a period of time after the study, before releasing the data.
- ok for randomized trials and observational studies.
- should cover all kinds of studies, observational and controlled.
- Strongly support for randomized clinical trials; moderate support for prospective epi studies; delete "observational"-does this refer to long-term follow-up?
- Paragraph #2 low-support – investigators should have 1st dibs-should not give up access immediately.

Comment about #6:

- Who can object to improvement?

Comments about #7:

- Too many pieces to vote higher [than low], of course, it's good to have careful dissemination of results, but some of these specifics are not good.
- With regard to communications I'm in favor of better, more coordinated dissemination of scientific advances but the plan outlined here seems too uncoordinated and geared more toward self-promotion as opposed to real education.

Comment about #8:

- Need to create mechanisms for "protecting" access to the data by the primary investigators.

Additional Business Operations Areas and Recommendations

a. Don't like the idea of establishing the cardiovascular centers of excellence.
b. Collaborate with AHA, ACC and subspecialty societies to expand communication networks.
c. Agree with "designated cardiovascular center". US News & World Report should <u>not</u> be the "accrediting entity" for CV center.
d. Need to consider ways of competing with industry marketing in order to "get message out"
e. Include interagency creation of large new projects, e.g., Cancer & Heart disease, Diabetes & Cognition, Nutrition & infection.
f. Centralized IRBs

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