Clinical Research

at the

National Institute for Neurological Diseases and Stroke

Analysis and Recommendations

Advisory Panel for Clinical Research

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Clinical Research Report

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CHAPTER 1

Executive Summary

Addressing the Needs of Society. There has never been a more promising and exciting time for the NINDS to reap the benefits of almost 60 years of investment in advancing the understanding of the biological basis of neurological disease. Now, more than ever, NINDS is poised to translate those advances into therapies and interventions that can improve the health of society. The progress and discoveries in basic neuroscience, in particular, have been staggering, and over the past few decades there have been tremendous breakthroughs in applying this knowledge of fundamental mechanisms toward an understanding of disease processes and, in some cases, new and effective therapies. Nonetheless, the public, which through the legislature has supported the ongoing investment in NINDS, wants and expects much more. As exciting as the advances in neuroscience may be, the bottom line for the public is to see dividends of their investment in the form of a lessening in the burden of neurological disease. Indeed, the NIH-NINDS website states: "The mission of NIH-NINDS is to reduce the burden of neurological disease - a burden borne by every age group, by every segment of society, by people all over the world." The mission of the Institute is thus an intrinsically clinical mission and suggests that direct clinical and translational science research should be prioritized highly, along with basic science research that will lay the foundation for future clinical advances.

The Work of the Advisory Panel for Clinical Research. The NINDS Advisory Panel for Clinical Research was appointed in January, 2008 by Dr. Story Landis, NINDS Director. The Advisory Panel was asked to assess the full scope and direction of clinical research activities sponsored by NINDS, and to make recommendations as to what changes should be considered to enable the Institute to launch new, high impact clinical research activities in the most cost effective manner possible. The members of the panel represent a fairly broad range of disciplines and backgrounds in clinical science, including those with experience in clinical trial design and methodology, epidemiological studies, cost-effectiveness research, and clinical research in multiple neurological diseases, both common and rare. Over the course of a year, the Advisory Panel had two face-to-face meetings and numerous teleconferences, and it reviewed a large volume of background material that was circulated electronically. Early on in the process, the Advisory Panel decided there were two, key "mega-issues" that should be the focus of its deliberations, each of which would be handled by a subcommittee. The first mega-issue related to the perception that the NINDS research portfolio has been

relatively imbalanced in favor of basic and translational science over clinical science, and there has been a relative lack of proactive efforts by NINDS to prioritize the development and funding of clinical research that will address the needs of society most effectively. One subcommittee was therefore charged to analyze how the NINDS should set priorities for clinical research in the neurosciences. The second mega-issue related to the manner in which the NINDS is able to work both internally and in collaboration with outside investigators to plan and implement clinical research in the most efficient way possible. The second subcommittee was therefore asked to develop ideas and recommendations that would lead to improvements in the implementation of clinical research. The work of each of these two subcommittees is the basis of the main chapters of this report.

Of note, the Advisory Panel considered studying the issue of the clinical research workforce, including means for attracting young people into the pipeline and programs for the training of clinical investigators. However, after some discussion, and with the approval of Drs. Landis and Koroshetz, it was decided that the topic deserved an extensive review by a separate group. Only brief mention of training is therefore included in this report.

Main Findings and Recommendations Related to Setting Priorities for Clinical Research in the Neurosciences.

Main Findings:

- The return on investment in NINDS-sponsored clinical trials has been very high, with substantial cost-effective, population improvements in health produced by several randomized trials more than justifying the trial budget. Nonetheless, compared to seven other Institutes (including those with a disease focus that partially overlaps with NINDS), NINDS ranks last in the proportion of the total Institute budget devoted to clinical research.

- For the most part, the NINDS has not funded so-called “T2” research, which aims to understand the reasons for a lack of implementation of the findings of clinical research into actual clinical practice and health policy.

- The current processes for defining the portfolio of clinical trials are flawed and fail to acknowledge the importance of these large investments and their potential to impact public health and costs.

- The value of “planning grants” for advancing the conceptual development and timeline of a clinical trial is unclear.

- The existing system of relying on the Clinical Trials Subcommittee (CTS) to help the National Advisory Neurological Disorders and Stroke (NANDS) Council set funding priorities is not optimal. In particular, the CTS do not have sufficient breadth of expertise or information to evaluate all clinical research proposals in terms of their match with Institute priorities.

- The Institute should also be alert and open to opportunities to leverage NINDS support for a clinical strategy by collaboration with other Institutes, other federal resources, industry sources, and philanthropy.

Main Recommendations:

- NINDS should perform a high level strategic review of its current balancing of clinical versus basic science priorities.

- NINDS should begin funding implementation (T2 translational) research in the neurosciences through a specific program announcement with set aside funding.

- Several mechanisms should be used to rebalance the NINDS portfolio of clinical and basic science studies, including reapportionment of RFAs and PAs with a clinical emphasis, increased use of clinical research networks, and separately pooling and funding clinical versus basic science applications.

- NINDS should develop an entirely new granting mechanism for clinical research that includes: 1) acceptance of brief proposals that have an initial focus on need, potential impact of results, and feasibility rather than details of design; 2) a defined process relying on expert panel and NANDS review for assessing potential impact on disease and Institute priority; and 3) collaborative development of a full research protocol that relies primarily on the investigators proposing the study or with major input from a specially-appointed Steering Committee and NINDS staff.

Main Findings and Recommendations Related to Improving the Implementation of Clinical Research

Main Findings:

- NINDS does not currently have in place sufficiently rigorous methods to track metrics for NINDS funded clinical research projects. Also, there is not a uniform requirement or defined standards for response action plans associated with study metrics.

- Clinical research continues to be plagued by regulatory issues, institutional bureaucracy, and a variety of barriers to recruitment of subjects. Although well-

aware of these challenges, NINDS has had a relatively limited role in tackling these problems.

- Developing a rich collaborative network within NINDS, NIH and the extramural community is an opportunity awaiting development at NINDS, but there are relatively few collaborative efforts at present. Growth of this area could be a particularly effective way to capitalize on shared interests, and to leverage limited resources and avoid redundancy.

- There are a number of advantages to developing standardized outcome tools for clinical research, including both observational studies and clinical trials. The NINDS Clinical Trials Group has suggested adding a handful of outcome measures to clinical trials, regardless of the disease being studied. This effort would ideally permit the generation of data on common scales across disease entities, but the relevance and utility of such outcome measures in a diverse number of disease states are uncertain.

- Public and private sector supported clinical research is hampered by the problem of a plethora of database management systems and variable naming conventions. The identification of standardized outcome measures along with standardized database formats would greatly facilitate the ability to combine datasets and do data mining among datasets. However, the challenge is to pre-specify outcome instruments and database formats that do not impede appropriate data collection and are compatible with commonly used database management systems.

- An important rate-limiting factor in conducting both NIH and industry funded clinical research is the supply of adequately trained investigators. There is similarly a dearth of individuals trained and prepared to be the leaders of multicenter clinical research.

Main Recommendations:

- Feasibility plans, methods to collect metrics, and response action plans should be required for all NINDS funded clinical research studies, and the NINDS Clinical Trials Group should actively oversee their implementation. The data on metrics and feasibility should be collected and organized in a way that it can be used to inform the design, metrics, and response action plans for future studies.

- NIH should sponsor a high-level meeting to explore ways of increasing the efficiency of completing the regulatory requirements for both U.S.-based and international studies

- NINDS should join other Institutes in leading a movement to facilitate the use of centralized Institutional Review Boards.
- New methods and protocols need to be developed for improving the efficiency of the contractual process. One approach would be to create a standard workscope and contract for *all* sites involved in a given study.
- All clinical research studies should be required to have a specified planning period in which regulatory and contractual requirements are completed, study infrastructure is put in place, and study methods are tested and found to be ready for full-scale implementation.
- The NINDS should take a leadership role in collaborative clinical research efforts within NINDS and with other Institutes, Centers, the extramural community (including the CTSA network), foundations and industry.
- NINDS should take advantage of research initiatives supported by other organizations to further mission-specific projects.
- NINDS should minimize the impact of scarce resources by developing shared infrastructure resources for clinical research. These core facilities could be shared within NINDS intramural and extramural divisions, as well as with other Institutes whose missions include the neurosciences.
- NINDS should take a leadership role in identification of standardized outcome measurements.
- NINDS should develop an intramural program that is sophisticated in the construction and management of clinical research databases.
- NINDS should continue to expand existing programs and devise new programs aimed at the development and training of experienced clinical researchers.
- The new leader of the NINDS Office of Clinical Trials should consider establishing DSMBs with experienced members that monitor a larger portfolio of studies.

CHAPTER 2

Setting Priorities for Clinical Research in the Neurosciences

I. Prioritizing clinical vs. basic and translational research

Both clinical and basic science research must be high priorities for NIH-NINDS, and defining and achieving the optimal balance among these priorities is challenging. Useful inputs into strategic decision-making include the guidance afforded by the mission statement of the Institute, the richness of the scientific opportunities available at any given time in both the clinical and basic science domains, and lessons on the balancing of these priorities available from other Institutes.

The NIH-NINDS website states: “The mission of NIH-NINDS is to reduce the burden of neurological disease - a burden borne by every age group, by every segment of society, by people all over the world.” The mission of the Institute is thus an intrinsically clinical mission and suggests that direct clinical and translational science research should be prioritized highly, along with basic science research that will lay the foundation for future clinical advances. Past, ongoing, and future support by the public and legislators for the Institute’s work is founded on the premise that NINDS will fund research that reduces the burden of neurological disease.

Neurological disease affects a large proportion of the US population. An estimated 780,000 Americans experience a new stroke each year, 5 million have Alzheimer’s disease, 500,000 have Parkinson’s disease, and another 24 million have one of approximately 5000 other neurological disorders. Importantly, neurologic disease includes many more rare diseases than any other organ-specific category - over 80% of the nearly 7000 rare diseases are neurological. An optimal portfolio will acknowledge the importance of studying rare diseases as well as those with major public health impact. These data highlight the fact that the burden of neurological disease is tremendous, and this burden will not change without additional clinical research that helps define effective therapies and cures.

At the level of intrinsic prolificacy of scientific opportunity, the Institute has an embarrassment of riches. Tremendous opportunities currently exist at both the basic neuroscience and clinical neuroscience levels of inquiry. At the basic neuroscience level, new genetic, imaging, and electrophysiologic tools and approaches are yielding greater understanding of all aspects of nervous system function, from the level of the individual synapse to that of large-scale neurocognitive networks. At the clinical

neuroscience level, the tremendous advances achieved in basic neuroscience over the past 25 years, including the decade of the brain, now lie ready for translation into novel and effective diagnostic and therapeutic interventions. Fundamental advances in developmental neurobiology, neurogenetics, functional brain imaging, neuroplasticity and neurorepair, and cognitive neuroscience are prime areas for clinical study and therapeutic interventions.

The return on investment in NINDS-sponsored clinical trials has been very high, with substantial cost-effective, population improvements in health produced by several randomized trials more than justifying the trial budget. Additional funding for clinical trials would be worthwhile even if the "hit rate" was one-tenth its historical level, and an accelerated rate of basic and translational discoveries should only increase the opportunities. The high-profile health advances produced in clinical trials are obvious rallying cries to increase funding for the entire Institute.

To compare NIH-NINDS' investment in clinical and basic science studies with those of other institutes, our workgroup obtained data on seven other NIH institutes, shown in Table 1.

Table 1 – Data on Clinical Research Dollars Spent by Various NIH Institutes ($ in 000's)

Institute	Total budget FY 2007	Budget rank (on list)	Clinical research $$ FY 2007 Extra & intramural	% of total budget	Clinical research rank (on list)	Clinical trials $$ FY 2007 Extra & intramural	% of total budget	Clinical trials rank (on list)
NCI	$4,797,639	1	$1,677,793	35%	4	$843,748	18%	1&2 (tie)
NIAID	4,417,208	2	1,177,327	27%	5	658,307	15%	3
NHLBI	2,922,929	3	753,235	26%	6 &7 (tie)	214,626	7%	5&6&7 (tie)
NINDS	***1,535,545***	***4***	***342,073***	***22%***	***8***	***115,138***	***7%***	***5&6&7 (tie)***
NIMH	1,404,494	5	861,297	61%	1	149,102	11%	4
NICHD	1,254,707	6	602,162	48%	2	227,103	18%	1&2 (tie)
NIA	1,047,260	7	476,608	46%	3	77,940	7%	5&6&7 (tie)
NIAMS	508,240	8	130,478	26%	6 &7 (tie)	29,338	6%	8

Among the eight institutes, NIH-NINDS ranked last in the proportion of the total institute budget devoted to clinical research. Among the seven other institutes, the proportion of funding devoted to clinical research studies ranged from 26%-61%, with a median of 35%. In contrast, NINDS devoted just 22% of its budget to clinical research.

Thus, there is *prima facie* evidence that NINDS is substantially underfunding clinical neuroscience research. This has occurred despite the fact that the Institute is fundamentally clinical, and tremendous opportunities and the need for clinical neuroscience advances exist. Explanations for this disparity can perhaps be explained by the possibility that clinical neuroscience research is receiving complementary funding from other institutes such as NIA, NICHD, and NIMH, or that NINDS has just not received clinical neuroscience study applications as compelling as its basic neuroscience applications. However, these explanations are unlikely to justify fully, if at all, the current disparity. Moreover, they do not lessen the perception that NINDS has neglected its stated mission.

For new clinical discoveries to reach their full potential impact on health, the actual implementation of these advances needs to find their way directly into the provision of care to members of society. Many proven interventions in the neurosciences, including those introduced into practice through NINDS-sponsored trials, are underutilized. Although disease foundations, public health, and quality-improvement efforts all contribute to improving utilization, none addresses the research needs in implementation, also termed T2 translational research. For the most part, the NINDS has not funded this type of research in the past, unlike many of its peer Institutes. This deficiency is not justified given the primary mission of the NINDS to improve health, and the pivotal role of implementation research in reaping the full benefits of our investment in both basic and clinical neuroscience.

Proposal

1. NINDS should perform a high level strategic review of its current balancing of clinical versus basic science priorities. This review should be conducted by leading intramural and extramural clinical and basic science researchers, and guided by the expectation that the balance of clinical and basic science research funding at NINDS should match those of other Institutes, unless specific and compelling reasons are identified that justify NINDS departing from the practice of other Institutes. A modified Delphi process may be the most expeditious and reliable method for performing this review. In the review, a target level of funding for clinical research should be set and variance from funding by other Institutes should be addressed

explicitly and convincingly, and the panel should address whether an "affirmative action" approach to clinical research is required to regain balance.

2. NINDS should begin funding implementation (T2 translational) research in the neurosciences through a specific program announcement with set aside funding.

3. Several mechanisms should be used to rebalance the NINDS portfolio of clinical and basic science studies. These include: 1) increasing the proportion of RFAs and PAs devoted to clinical neuroscience, thereby opening more opportunities to the research community in these areas; 2) increasing the adoption and support of clinical research networks, as have other Institutes; 3) separately pooling and funding clinical versus basic science applications, ensuring that appropriate proportions of meritorious clinical and basic neuroscience applications are funded each cycle; 4) increasing the efficiency of clinical research so that more studies could be performed within a fixed budget.

II. Prioritizing among potential clinical projects

The vast majority of NINDS-funded trials are investigator initiated, so the portfolio of NIH and NINDS trials depends largely on the interests of clinical scientists throughout the country. This investigator pool is relatively small because there are few individuals with adequate training, leadership skills, and perseverance to propose such randomized trials.[1] The National Advisory Neurological Disorders and Stroke (NANDS) Council must approve submission of large-scale proposals, and burden of disease, overall portfolio of trials, and potential impact of the trial results may influence the initial decision by Council. However, the majority of proposals are approved for submission (55 of 67 proposals were approved between 2001 and 2008), so relatively little control has been exerted over the proposals prior to peer review. Contact with the NINDS Clinical Trials Group can also help shape a proposal or discourage submission of grants for trials that are unlikely to have impact, but the advice given is informal and may be ignored. Among the proposals received, favorable peer review may depend more on the qualifications of the principal investigator and details of the trial design than on the significance of the research question or the potential of the trial to impact health or scientific knowledge. While ultimately the quality of the trial is critical, many of the issues are readily addressed and by having priorities identified with oversight on distribution by disease or public health impact, disparities between disease burden and research spending might be reduced. In sum, the current processes for defining the portfolio of clinical trials (informal advice and study section review of importance) are flawed and fail to acknowledge the importance of these large investments and their potential to impact public health and costs.

Some NIH Institutes set aside a substantial proportion of their clinical trial budgets for trials that they develop internally. A system for estimating the impact of clinical trials, such as that piloted in the NINDS Immediate Practice-Altering Clinical Trials (ImPACT) program, could be used to define this internal agenda by identifying the key disease areas and questions ripe for study. However, such an approach is risky. First, it is impossible to consider and evaluate every possible clinical trial that could be performed. Second, more common and devastating diseases could be ranked as priorities repeatedly, ignoring less common but important diseases and reducing the balance in the program. Third, such an approach would turn the focus of the public and disease-based organizations on the NIH, and dissatisfaction with the current agenda (whatever it is) and lobbying for further funding would only increase. The peer-review system allows the NIH to point the finger elsewhere: to the independent reviewers and to those proposing trials. Thus, we do not recommend that the NINDS establish balance in the portfolio by internally selecting the trials it will develop and fund, although we acknowledge that some high priority areas may need to be met using this mechanism.

Metrics estimating the impact of planned trials might be better used as tools in a more comprehensive evaluation of priorities. For example, if the NINDS evaluated brief proposals for clinical trials that outline the key issues around the interventions, target population, sample size, potential outcomes, and costs, some protection with "investigator initiated" ideas is gleaned and this tradition is largely maintained. At the same time, a larger number of proposals could be expected because they would be much simpler to produce and because the final investigative team might be developed in greater collaboration with the NINDS and some of its key supportive programs, such as the Clinical Research Collaboration (CRC), the Neurological Emergencies Treatment Trials (NETT) network, and the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) program. This would increase the potential pool of proposers, who would not necessarily be purporting expertise in all aspects of trials and in management and leadership skills. Then, metrics could be used to assist a review panel in deciding which proposals should be invited for further development, with some consideration of disease burden and balance in the overall portfolio. In essence, the review process would hinge upon stringent early decisions about potential trials that would allow a greater focus on public health impact and portfolio balance.

The NINDS currently supports planning grants for clinical trials, and this mechanism may be helpful but does not solve the problem. Planning grants are generally as difficult to produce as a proposal for the trial itself. Funding of a planning grant does not guarantee that the subsequent trial will be funded, and the lag time that ensues can change the equipoise, the recruitment potential, and the value of the trial.

Furthermore, it does not allow management of prioritization or a review based more squarely on potential impact.

Proposal

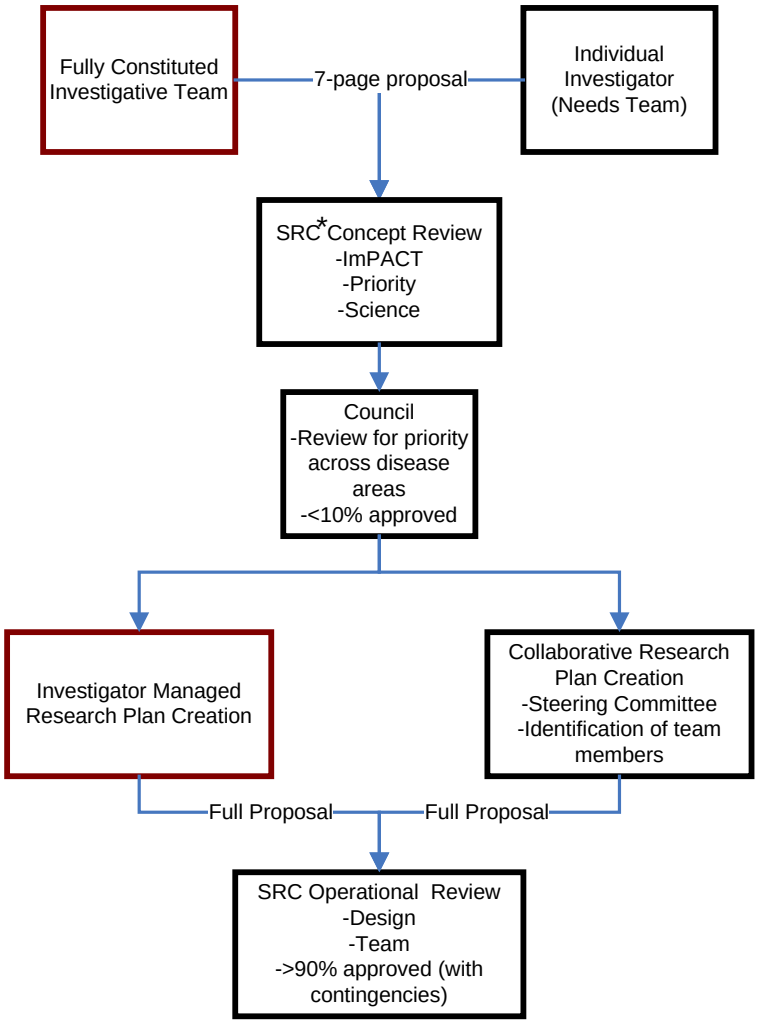
We propose development of a new granting mechanism for clinical research that would normally be reviewed by NINDS committees, in addition to the existing traditional mechanism (to be managed in parallel initially). Key components of this mechanism, as illustrated below, would include:

1. Request for short (up to 7 page) proposals for clinical studies that include discussion of the interventions, target population, sample size, potential outcomes, and costs. (A current model for components is in use by the Clinical Trials Group, but it could be applied to observational, intervention or translational studies as well as trials)
    a. Encourage an initial focus on need, potential impact of results, and feasibility rather than details of design.
    b. Acknowledge that proposers need not and should not expect to lead the trial or large clinical study but will have a major role in its development if the proposal is selected.
    c. Encourage proposals from a wide array of potential sources (and not necessarily just proven clinical trialists and researchers).
    d. Avoid Council pre-approval for expensive projects submitted through this mechanism.
2. A formal assessment of the potential public health impact, as is being piloted by the ImPACT program. For projects other than trials, this step may be unnecessary.
3. Expert panel review, preferably through questionnaires or a modified Delphi approach to:
    a. Provide key review and model inputs, especially the likelihood that the trial will be informative.
    b. Estimate the scientific impact of the study in establishing new methods or clarifying fundamental principles.

    This expert panel should be constituted of physicians and scientists with expertise in the disease under study, with a health economist and biostatistician potentially assisting. A modified Delphi approach would allow multiple experts to contribute from afar by pooling opinions in a non-biased, survey-based methodology until consensus is achieved or dissent is documented.
4. Disease specific expert review to rank proposals within a disease category and compare to prior standards, using the inputs from the review process above.

This review could be distributed to experts within existing or new NINDS networks (such as NETT or CRC leaders), as well as to more traditional NIH reviewers.

5. Council review of highest ranked proposals within each disease area to determine the desirability of funding specific projects, with recognition of the importance of aligning funding decisions with disease burden and potential impact, but also recognizing the importance of including the study of rare diseases. In the initial phase, provide rejected proposals to show selection and validate process.
6. For proposals selected to move forward, collaborative development of a full research protocol. Investigators could fully assemble a team and all components of a project independently or could work with a Steering Committee or Network and NINDS staff to design the full proposal.
    a. Selection of a Steering Committee, in conjunction with the proposer.
    b. Identification of key collaborators, either from funded NINDS programs (e.g., NETT, CRC) or from other institutions (academic institutions or CROs).
    c. Serial development of the best possible protocol and management plan.
    d. Final approval of the study plan by an External Advisory Group with disease expertise – this could potentially be the Steering Committee or the DSMB.



*SRC – Scientific Review Committee

III. Setting target levels for funding within disease categories

The NANDS Council, and specifically the Clinical Trial Subcommittee (CTS) of Council, has been charged with two major tasks that both inform the clinical research plan at the Institute and significantly impact its budget. These tasks include “concept clearance” for clinical research proposals and approval for those clinical trials that have been positively reviewed by study section and moved forward for Council review. Both activities have far-reaching implications for the Institute.

The current strategy for submission of clinical research proposals with annual budgets in excess of $1,000,000 is multi-tiered. Investigators are encouraged to speak first with members of the Clinical Trials Group and subsequently to submit their new proposals for CTS concept clearance. Investigators are requested to include not only the scientific rationale but also to describe both the incidence of the disorder they will study and the societal and personal burden of the disease. Clinical Trials Group staff organizes these documents and sends them to the members of the CTS in a timely fashion for their review. In addition, Clinical Trials Group staff sends the committee members an updated list of all clinical studies that the Institute currently supports; this list is separated by disease categories for ease of review. The chair of the CTS then assigns these concept proposals to the appropriate CTS members for both primary and secondary review and presentation at the closed session of the committee on the first day of each Council meeting. Literature review and discussion among the CTS members are generally used to provide the necessary expertise. In addition, CTS members submit their queries to Clinical Trials Group staff for investigator response. During the CTS meeting, the members review the proposals for concept clearance, discuss how they might fit into the Institute's portfolio and also ask staff of the Institute for their considerations on the proposal. A vote is taken on all concept proposals.

The second major responsibility of the Council is approving funding for randomized clinical trials with annual budgets in excess of $1,000,000. These proposals have been reviewed by Study Section on at least one (and frequently 2 or 3) occasions, and the investigator proposals, Study Section review(s) and investigator correspondence are provided to the CTS members. In addition, the project officer from the Institute composes and submits a one-page review describing the importance of the problem, the innovative therapy, the track record of the investigators and the Institute's enthusiasm for the proposal. Once again, the chair of the CTS requests primary and secondary reviews from committee members with the appropriate expertise, the proposal is discussed with input from NINDS staff and a vote is taken.

Proposal

Both missions of the CTS and thus Council might be improved by implementation of the following steps:

1. Definition of standardized disease categories. With standardized disease categories, review panels and experts providing information concerning potential public health impact would speak a uniform language for both risk assessment and potential impact of the proposed program. Furthermore, with standardized definitions of disease categories, Institute staff, reviewers and Council members could review the

allocation of existing funds and consider targets of opportunity in a more reliable and valid manner.

2. Implementation of a formal, standardized assessment of public health impact and review of available data sets. As described in the Statement of Work for the ImPACT program, reviewers, Council members and Program staff alike all need verifiable data concerning disease prevalence/incidence, burden of disease, therapeutic effect, changes in quality of life measurements, health care costs and utilization rates. With such a program, NINDS might better identify those research programs that have the highest likelihood of lessening the burden of neurological disease. In addition to data from the ImPACT formulae, Council members should also have ready access to other data sets that specifically address those neurologic illnesses which are relatively rare in the population but have significant quality of life effects and high health care utilization rates. These datasets include monitoring data from the CDC, such as vitality records, NHANES, and standardized hospital surveys. Additional standardized data on disability are available through the WHO Global Burden of Disease project. Proposals related to these rarer diseases might have a relatively low ImPACT score but potentially very high impact for those affected by the disease. With this information in hand, NINDS will be better able to facilitate practice-altering research in an expeditious fashion. Finally, as the members of Council routinely review funding decisions with regard the existing NINDS portfolio, they should also examine on a regular basis the influence of the ImPACT program both on funding decisions and on changes in the overall mission of the Institute.

3. Provision of *ad hoc* expert reviewers for both concept clearance and final approval reviews. As described by numerous members of the CTS available for this review, the CTS cannot – by virtue of its small number of members – provide adequate evaluation for every clinical trial/research proposal. During the years 2001 – 2003, outside expert reviewers were occasionally provided to the CTS for consultation during their deliberations. The Institute may benefit by re-configuring such a plan to include a flexible panel of reviewers who can be called upon to provide their expertise in a timely fashion with a particular focus on Institute and overall NIH balance, industry activity and non-NIH research. This group might also be asked to review the ongoing importance of the proposal and to identify targets of opportunity for co-funding with foundation or industry support. These CTS expansion members should have the priorities of the entire Institute in mind and should not advocate for a specific disease or area of research. Furthermore, it is important that if such reviewers are retained there be some reimbursement for their work, such as the rolling submission deadlines for standing study section members.

IV. Achieving a balanced portfolio with respect to clinical research spending and disease-specific spending

It is expected that setting distinct funding lines for clinical research and for specific diseases, and also assessing potential impact of proposals with disease burden in mind, will help to recalibrate NINDS funding appropriately. In addition, RFAs and PAs may also be required, particularly in early years as the broader field adjusts to new priorities and processes for funding.

Proposal

The NINDS should establish priority areas of clinical research based on factors that argue for success of clinical studies within a field. Success can be defined broadly as:

1. Clinical benefit to patients
2. Positioning the field to better bring treatment to patients
3. Gaining crucial perspectives on pathological mechanisms of disease that will inform future studies of treatment
4. Establishing whether treatment benefit is cost effective or can be made cost effective

Success also includes two related dimensions: will a treatment be approved/available for use from a regulatory perspective and will there be an industry or other entity committed to the long term?

The Institute should also be alert and open to opportunities to leverage NINDS support for a clinical strategy by collaboration with other Institutes, other federal resources, industry sources, and philanthropy. This inherently attractive way of “getting more bang for the buck” has a major downside. A large investment of one agency calls for an equally large investment from another and risks placing scientific considerations at a lower priority than monetary ones. It would be essential for the peer review process to consider such decisions.

CHAPTER 3

Implementation of Clinical Research

I. Study Metrics

The goal of NINDS funded clinical research is to answer fundamental questions that result in an improvement in the quality of life of patients in the US and around the world. This goal can only be realized by the timely completion, at reasonable cost, of high quality studies that deliver definitive answers.

A minority of clinical studies achieve their projected recruitment timelines, resulting in delayed study completion and budgetary revisions. This failure to adhere to a projected timeline may arise from unrealistic planning but, nevertheless, results in significant resource consumption. While it is known that delays and extensions occur for NINDS funded clinical studies, exact numbers and reasons are not known.

Study metrics should be used to identify operational and scientific difficulties that compromise data quality and the timely execution of the clinical study. Metric data that are collected must lead to proactive and timely responses that remedy quality and execution problems and provide information on the causes of these difficulties. In addition, metrics of all studies can be used to support planning for later studies and to measure the impact of changes in study processes.

For success, it is important that there is a clear definition of roles and responsibilities for the supervision and conduct of clinical studies. The NINDS does not currently have in place rigorous methods to track metrics for NINDS funded clinical research projects. The NINDS has an existing contract with KAI to track ongoing clinical studies. The advisory committee requested to review the data from KAI on metrics for NINDS funded clinical trials. However, the type of data collected, which clinical studies are tracked, how readily the data are available and how they are shared with NINDS Clinical Trials Group staff and investigators is not easily apparent.

Study Metrics

Study metrics can be defined as measurements of subject enrollment and retention rates, and data quality.

Metrics should be captured and used proactively both in planning a study and in supervising its execution. These data need to be regularly reviewed to allow rapid operational and protocol responses. Individuals or teams need to have responsibility for reviewing these data and be held accountable for responding to these data.

Metrics should be used throughout the lifetime of a study from concept initiation and planning to final completion and analysis of a study. The process should start with adequate and rigorous feasibility analyses to allow for realistic planning, budgeting and expectation setting.

Pre-study initiation metrics

- Study feasibility: A well-executed study feasibility plan is critical to the setting of timelines and budget, to the selection of sites and to the adjustment of the protocol to enable success.
    - A feasibility study must:
        - use “final” protocol concept including detailed description of study population, intervention (if an interventional trial) and patient assessments
        - elicit feedback on study design from the site PIs
        - be performed on all potential study sites
        - include reviews of past site performance
        - include details of IRB turnaround and performance: central or local; average review times, assessment of changes requested, etc.
        - include details of the subcontracting process with times to complete subcontracts.
- Timeline projections are required before study initiation to set the budget, assign resources and create benchmarks for measurement of actual success/ failure using post initiation metrics: Realistic planning is essential, even if a five year time line will be exceeded since it will be harder to stop an ongoing trial than it is not to start after the feasibility phase.
    - Timeline Projections should include:
        - pre-screening, screening and enrollment times
        - regulatory approvals, IRB reviews, Conflict of Interest Boards, Federal Wide Assurance (FWA), State Department clearances, etc.
        - contract negotiations, tracked and compared to feasibility phase as noted above
        - drug/device supply (where relevant)
        - site activation
        - assumptions for projections

Post-study initiation metrics

During the conduct of any study, it is important to measure the operation of the study and to ensure that the data quality is adequate. This will ensure the timely response to any problems and facilitate successful execution of the study.

- Study operational performance data (for both study and individual sites) should be reviewed on a regular basis by the group charged with study supervision (clinical program manager/ lead) and include data on:
    - site activation rates (with granular details as above)
    - prescreening numbers
    - screening and screen failure rates including reasons. This will provide reliable information on possible interventions, including protocol amendment if clear patterns are identified, and potentially inform information on translation of results. It is recognized that in some instances IRB approvals impact what can be collected with respect to screening, but as these metrics become more standard, it might be easier to collect such information without additional costly processes. If not, then the NINDS must be prepared to pay for the added consent process to collect screening data, etc.
    - enrollment rates
    - dropout rates
    - final completion rates for analyses

- Study quality data: Ongoing data monitoring plans should provide for the regular review of blinded study data and predefine minimum standards which, if not met, will trigger site or protocol intervention. The plans (for both study and individual sites) should review quality of study performance that directly influence the primary outcome measures, and therefore focus on:
    - meeting of inclusion and exclusion criteria
    - timely collection of patient assessments
    - adequate follow-up rates
    - collection and tracking of critical lab samples
    - tracking of completion of a minimum percentage of assessments critical to the predefined study endpoints

Response Action Plans

All metrics should be associated with a response action plan. While it is reasonable to seek the advice of the Data Safety and Monitoring Board (DSMB) on how to deal with identified issues, the responsibility for study supervision and conduct should lie with the clinical study lead and their supporting study manager, who should be accountable for the study conduct and for the achievement of predefined operational and quality goals. At least one of these responsible individuals should be inside the funding/ sponsoring agency (NINDS).

What should be done with unexpected or unanticipated problems – for example, new mandates that cause studies to stop in their tracks? At the overall study level, it may be necessary to amend the protocol (population description; testing changes, drug formulation changes, follow-up evaluations; re-prioritization of endpoints etc). Many variables (including luck) cannot be foreseen and so re-projection should be allowed to permit realistic and data driven budget re-forecasting. Nevertheless, study termination, re-budgeting, or site closure events should be specified-up-front; e.g. ”If enrollment is less than X% 18 months into the project, the study will be terminated completely”. This should be emphasized early because later threats can precipitate loose enrollment standards and damage the overall trial.

At the site level, it may be necessary to carry out site interventions that include site motivational visits, the provision of additional coordinator support and, if necessary, placing a site on probation or dismissal. This creates financial challenges, but it has been demonstrated repeatedly that close and personal interactions with study sites and investigators are key to successful recruitment and execution of clinical studies.

In addition to being used throughout the performance of individual studies, metrics and performance data should be shared across studies at the feasibility planning phase. A bank of performance metrics might lead to more realistic planning by understanding the experiences of others, including site performance relative to original feasibility projections. This is particularly important when there are budget constraints to understand what worked and what failed and to select those metrics and interventions that give highest value.

Proposal

Measurement of clinical study performance is feasible and extremely useful at all stages of study execution but requires responsiveness, flexibility and accountability of individuals to have a successful impact on timely and high quality study completion. It is done now, but in a non-standardized manner. To accomplish these goals, we propose the following:

1. Feasibility plans, methods to collect metrics, and response action plans should be required for all NINDS funded clinical research studies.

2. The data on metrics and feasibility on all NINDS funded clinical research studies should be collected and organized in a way that it can be used to inform the design, metrics, and response action plans for future studies. The data should be made public after completion of a study in an accessible form.

3. The NINDS Clinical Trials Group staff should play an important role in ensuring implementation of metric collection and response action plans.

4. For response action plans to work, there will be a need for substantial changes in the way NINDS oversees the implementation of clinical studies. Flexibility and speed of response will be important and should include rapid budget and funding decisions that allow timely interventions when problems are identified.

II. Expediting Initiation of Clinical Research Studies

The process of enhancing the implementation of trials involves everything from initial conceptualization of the trial to the final closeout of the trial. Ideas for expediting the process of trial conceptualization to approval of funding are spelled out in detail in Chapter 3 of this document.

Regulatory Issues

The process of obtaining the necessary regulatory approvals is challenging and often time consuming. The challenges are substantial enough when the trials are conducted solely within the United States. International trials require added layers of approvals that include State Department clearance, which require actions by NINDS staff for which the investigators have only tangential input or control.

Some materials that might be collected and provided to potential investigators include a list of required regulatory approvals from NIH/NINDS and average times for completion, such as Federal Wide Assurance (FWA), State Dept Clearance and IRB approval. It would also be helpful to know what they imply and who should obtain the approval. For example, State Department clearance goes through NIH while FWA goes through the center institution.

While it may be that the NINDS is not in a position to change the regulatory morass that has evolved in research today, some opportunities exist to keep from making it worse and possibly improve it. This includes more careful monitoring of FWA

as this process not only impacts the funding of the original grantee, but downloads the requirement to the recipient to ensure that every subcontractor has a valid FWA in order to issue a subcontract. This may be an important requirement to receive federal funding, but is one additional step in the slow process of negotiating contracts with clinical sites and ancillary centers in a multinational clinical trial. International trials face an additional burden in that our system does not recognize established regulatory systems in other countries, and those institutions in other countries need to adhere to the rules and regulations of the U.S. FWA requirements.

The Institute should investigate the possibility of using a “centralized IRB”. While the NIH or FDA does not mandate that an institution use its own IRB, the consequences of mistakes potentially shutting down all funding pushes a university to maintain control over this vital link to funding. The current system of using individual IRBs can result in the vetting of multicenter projects by hundreds of IRB members. The process often requires local as well as centralized responses to questions that have typically been addressed numerous times, and certainly causes delays of significant magnitude. A centralized IRB with national representation is likely to be adequate for trial approval, since IRBs almost universally defer their monitoring responsibilities to independent data safety and monitoring boards (DSMBs). Additional advantages of a centralized IRB include major reductions in cost and the requirement for single annual updates.

A newly evolving area with no clearly understood process is the conflict of interest review. These reviews now take many forms and at the lead or coordinating center level have in some instances been deemed the responsibility of the center to insure compliance of all subcontracts, which often means providing assurances of lack of conflicts at the investigator as well as Institution level. While the process of being conflict of interest free is recognized, the increasing burden of the documentation should be considered.

Contract Approval Process

As workloads on IRBs increase, many universities now require a contract to be in place before IRB review can begin. At the same time, many universities refuse to execute a contract without IRB approval. While this circular logic typically gets resolved, there are unnecessary delays caused by these reasoned positions. There are several major changes that could simplify the process and greatly speed the startup of multicenter research.

1. Prepare a standard workscope and contract for all sites involved in a clinical trial. A site could either accept or reject the contract, which would be simply written and save numerous months of negotiation. Care must be taken as to include what is

ultimately local, although variation for some local issues could indeed be accepted. These would be instituted and signed off by the universities or clinic centers involved before the main trial is initiated.

a. One common issue that delays contract execution is the negotiation over the venue for litigation. Some standard manner to simplify this back and forth is warranted.

b. It has become common and cost effective to pay for trials using a cost per patient charge structure. While this is warranted and rewards performance rather than participation (so-called "pay for play"), it also becomes a serious point of negotiation. Facilities and Administrative Costs (F&A or indirect costs) are an important form of revenue for universities. However, they are also a source of discontent and frustration by investigators who are caught between what the institutions demand as policy and the resource allocation at these same institutions that may not reflect the individual project use of the dollars collected. The institution argues that since personnel are involved, they should be supported with their normal IDC fees; the U01 or Grant often stipulates that no IDC is collected on patient care costs. Clearly, these costs drive up the cost of research. Nevertheless, both sides (the awardee trying to get his or her institution to negotiate a subcontract without IDC and the recipient institution arguing they deserve IDC) are on solid ground for their respective positions. NINDS could make a decision that simply sets policy on this, which would be terms of the contract to be accepted or rejected before a trial starts.

c. The paperwork burden to "assure" is repeated too many times. Certain levels of approval could be housed at a national level and involve medium to long term approvals where checking would only be required of a central source. At present, these checks occur at multiple levels annually by at least two or three sources.

2. <u>Advance the use of formal planning periods as part of study management</u>. Experienced investigators learn that the completion of all regulatory requirements, let alone the many other start-up components of a study, are almost never achieved within the pre-specified, "ideal" timeframe. Because of this, the timeline of most, if not all, clinical trials should include a formal, funded planning period in which resources are efficiently used to prepare for and complete the regulatory requirements, contractual agreements, and infrastructure (management, informatics, etc.) for the study. Also, where appropriate, the planning period should include testing of study methodology at pilot sites.

3. Involve the DSMB early in the formal planning process. Since protocols cannot go to IRBs until finalized, greater integration of the DSMB needs to occur earlier in the process, since delays after the start of funding wastes resources.

Recruitment

Recruitment of subjects into clinical studies is almost always difficult, and incentives to recruit are complex. They involve motivation, population, hurdles and rewards. The populations available for any trial are difficult to assess and estimate, but are often optimistically estimated without careful attention to exclusion criteria, competing opportunities, etc. A potential rate limiting step is the limit of 5 years for a grant proposal. This can lead to unrealistic estimates of recruitment coupled with unanticipated and increasingly lengthy delays due to the regulatory and contracted processes noted above. Incorporation of a one to two year startup process might go a long way to help recruitment match the planned curves. Incentives need to be realistic. Institutions do not remunerate for the mission of research independently of the monies obtained by the researcher. Researchers at the clinical sites have fewer incentives to meet goals. The “pay for play” is a wise idea that saves money paying researchers who don’t actively participate, but its down side is that studies with difficult recruitment do not bring in sufficient dollars to warrant increased efforts in recruitment.

Proposal

1. NIH should sponsor a high-level meeting to explore ways of increasing the efficiency of completing the regulatory requirements for both U.S.-based and international studies. One of the goals of the meeting would be to identify the critical, high-priority roadblocks that, despite institutional or bureaucratic inertia, need to be modified.

2. NINDS should join other Institutes in leading a movement to facilitate the use of centralized IRBs.

3. New methods and protocols need to be developed for improving the efficiency of the contracting process. One approach would be to create a standard workscope and contract for *all* sites involved in a given study.

4. All clinical research studies should be required to have a specified planning period in which regulatory and contractual requirements are completed, study infrastructure is put in place, and study methods are tested and found to be ready for full-scale implementation. The study DSMB should be engaged in this process.

III. NINDS collaborations

Developing a rich collaborative network within NINDS, NIH and the extramural community is an opportunity awaiting development at NINDS. Based on the information provided to the committee, there are relatively few collaborative efforts at present. Growth of this area could be a particularly effective way to capitalize on shared interests, and to leverage limited resources and avoid redundancy.

Intramural and extramural investigators

There are currently few intramural and extramural collaborations funded or otherwise supported by NINDS. The only collaborations are: 1) two ongoing extramural Phase III trials that include biomarker sub-studies supported through separate intramural contracts; and 2) inclusion of the intramural acute stroke program in SPOTRIAS.

Additional collaborations would be of benefit to both intramural and extramural programs. The intramural program would benefit from the broad patient base, especially when dealing with rare diseases. The extramural programs would benefit from specific expertise, and perhaps reduced costs for services. The greatest obstacles are lack of knowledge among extramural scientists of specific expertise in the intramural program, and how shared grant funding can be operationalized.

A good example of what has worked is the NINDS Human Genetics DNA and Cell Line Repository. This repository will ultimately allow investigators to obtain DNA samples and associated clinical information from patients with various neurological diseases, e.g. epilepsy, stroke, PD, and ALS, at a reasonable cost. The fact that DNA extraction and creation of cell lines occurs at no cost to the investigators is of tremendous benefit. This type of shared resource should be encouraged. Another example is the PD Data Organizing Center (PD DOC), which allows investigators access to de-identified datasets for hypothesis testing and generation of preliminary data.

NINDS and other NIH Institutes/Centers (I/Cs)

NINDS has collaborated with several NIH institutes including NIMH, NHLBI, and NICHD on a number of large clinical trials and epidemiology studies as well as workshops and contracts for the development of a specific clinical tool. NINDS was a

secondary source of funding on 7 NIMH studies, 5 NICHD studies and 5 NHLBI studies over the past 5 years. NINDS has taken the lead in at least four studies, including:

	Other Institutes
Locomotor Experience Applied Post-Stroke (LEAPS)	NICHD, NCMRR
Wellstone Muscular Dystrophy Centers	NIAMS, NICHD, NHLBI, Muscular Dystrophy Association
Deep Brain Stimulation vs. Best Medical Therapy for Parkinson's Disease	Dept of Veterans Affairs, Medtronics Neuromodulation
Neurological Emergencies Treatment Trials Network-RAMPART TRIAL	Biomedical Advance Research and Development Authority (BARDA), NIH CounterACT

NINDS and Advocacy Groups

While this committee is not recommending the use of advocacy groups in setting the scientific agenda, it nevertheless recognizes they are a collective force with valuable perspectives on the quality of life issues imbedded in the NINDS Mission.

There appear to be two successful models for collaborations among Institutes and advocacy organizations. The first is a top down model that emanates from a congressional mandate. As an example, The Wellstone Muscular Dystrophy Centers arose from a Congressional mandate that was fostered by advocacy groups. The NINDS now serves as a central coordinating center for these activities, which include distribution of unsolicited research grant applications among Institutes and centers the funding and management of Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, the NIH Translational Research Program in the Muscular Dystrophies, an NIH Translational Research Workshop in the Muscular Dystrophies, cooperation across I/Cs and advocacy groups to foster research in understudied muscular dystrophies, cooperation between NIH and advocacy groups in muscular dystrophy research planning and funding, and a new NINDS internal working group focused on neuromuscular diseases. Clearly it is of benefit if NINDS can serve as a coordinating center for the broad range of individuals interested in muscular dystrophy, including advocacy groups, industry, academia, private philanthropy and

intramural programs. It would be helpful to understand more about the genesis of the Muscular Dystrophy Coordinating Committee (MDCC) and the development of the MDCC Action Plan for the Muscular Dystrophies. This might serve as a model for future collaborations.

A second model for collaboration has involved the efforts of advocacy groups which provide an initial impetus for either workshops and or small grants that may be matched by the NINDS for some portion of funding or expertise (e.g. in Tourette's syndrome, Rett syndrome, lysosomal storage disease, and dystonia). This seems to be an excellent model for less common diseases that have active advocacy groups. The advocacy groups can provide the infrastructure for patient recruitment and education, and the NINDS can provide the central coordination and expertise to form consortia to study these diseases.

NINDS has also been responsive to requests for shared sponsorship of workshops and clinical research projects with other ICs, such as the collaborative workshop with NIMH on Parkinson's disease and depression. The NINDS has also successfully partnered with other governmental agencies such as the VA in their deep-brain stimulation trials (providing non-VA academic sites), and with the FDA. The five-year MOU agreement signed in 2002 with the FDA identifies the following six areas for interagency interaction: (A) Information Exchange; (B) Education; (C) Resource Leveraging and Staff Collaborations; (D) Policy Development; (E) Promotion of Interagency Joint Reviews, and (F) Joint Sponsorship of State-of-Science Workshops/ Conferences.

NINDS and Industry

Compared to the other NIH institutes which have launched large programs with the help of the NIH Foundation, the NINDS has no large scale industry partnerships and has not partnered with the NIH Foundation. Industry participation appears to be in the donation of drugs (i.e. CombiRX) or devices (i.e. CREST) for use in trials, but little in the way of general investment for research. In the 2007 annual report, the only neuroscience-related lay organization, exclusive of Alzheimer's disease associations, that provided funding to the foundation was the Michael J. Fox Foundation for Parkinson's Research. The foundation biomarkers group has not yet focused on a neuroscience initiative, and none of the 6 common diseases in the GAIN (Genetic Association Information Network) has a neurological focus.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) study is an excellent example of how partnerships between industry, private foundations, academia and NIH have led to a large scale project that could not have been done at one center or without collaboration among these partners. Despite reaching the end of the grant, additional

funding was obtained in 2007 to perform genome-wide association studies, Pittsburgh Compound-B (PIB) imaging, and CSF analyses. Another successful collaboration for Breast Cancer research has involved the Avon Foundation and NCI and has funded 59 grants spanning basic science to patient initiatives.

Thus, the NIH Foundation is an underutilized resource for fostering clinical translational research for neurological diseases.

Another area for potential collaboration is the network of institutions that has been created over the past two years through implementation of the Clinical and Translation Science Awards by the National Center for Research Resources (NCRR). There is great interest in developing new consortia among CTSA institutions that might improve efficiency, especially for rare diseases. There is also interest in incorporating the NIH Clinical Center into these activities.

Given the difficulties in creating a comprehensive list of collaborations in which the NINDS is engaged, it is not possible to comment on whether the current number of these collaborations is adequate. It is also not clear if NINDS is playing a lead role in determining Institute priorities, or if it is waiting for advocacy and industry groups to either mandate priorities through congressional acts, or come to the NINDS with ideas. The NINDS could significantly broaden connections with other clinical research efforts taking place at other Institutes, other academic institutions, private foundations and industry.

Proposal

1. The NINDS should take a leadership role in collaborative clinical research efforts within NINDS, with other I/Cs, with the extramural community, foundations and industry. NINDS should be aware of ongoing and developing clinical research efforts with potential relevance to the NINDS mission, and actively explore opportunities to collaborate in order to maximize the scientific yield.

2. The NINDS should make more efforts to inform advocacy groups about the benefits of working together with NINDS, which include, among other things, expertise, indirect cost sharing and banking of DNA samples.

3. Industry, advocacy groups, and related organizations should meet with representatives from NIH and academia to determine priorities for research. It would be helpful to learn more about the origins, successes and failures of ADNI and the Muscular Dystrophy Cooperative Research Centers. The NIH Foundation has not been used by the neuroscience community to its full potential.

4. NINDS should take advantage of research initiatives supported by other organizations to further mission-specific projects. A positive example is the proposed NINDS collaboration with NHLBI to study vascular dementia in the ARIC (Atherosclerosis Risk in Communities) population. A proactive approach by NINDS, initiating conversations with other I/Cs, the VA system, DARPA, foundations and industry, could potentially identify many such opportunities. Sharing the costs of these large efforts will increase the opportunities for clinical research in neuroscience.

5. Continued exploration of interactions with the CTSA network should be encouraged.

6. Applicants for NIH grants should continue to be encouraged to use shared resources such as the NINDS Human Genetics DNA and Cell Line Repository and other data resources for small grants/pilot data.

7. NINDS should minimize the impact of scarce resources by developing shared infrastructure resources for clinical research. These core facilities could be shared within NINDS intramural and extramural divisions, as well as with other Institutes whose missions include the neurosciences. One such example might be the development of an across-institute biostatistical core.

IV. Research Infrastructure

Developing standardized measurement tools (outcome measures) for clinical research

There is a theoretical advantage to developing standardized outcome tools for clinical research, including both observational studies and clinical trials. The use of standardized outcome measures will allow the comparison of the magnitude of treatment effects across individual studies and among different disease entities. Some standardized outcome measures can also be converted to utilities, which facilitate cost effectiveness analyses. The use of standardized outcome measures can also facilitate the identification of a “minimal clinical significant change,” which can be useful for power analysis and sample size estimation. On the other hand, standardized outcome measures present some difficulties. They may not be specific enough to a disease state to detect clinically relevant change. In general, the instruments tend to be relatively insensitive to change, which may lead to an increase in necessary sample size. Lastly, the measures may be so generalized as to not have clear relevance to the disease or condition being studied. Overall, the benefits of the use of standardized outcome measures probably outweigh their problems, but they should be used judiciously.

While there are generic health status outcome measures, such as the medical outcomes study short form 36 (MOS-Sf36), the EQ-5D, and the Sickness Impact Profile, there is a relative paucity of neurologically-oriented standardized measurement tools. In an effort to address this deficiency, the NINDS developed a contract with Northwestern University, dubbed NeuroQOL, to look at the experience with outcome measures in NINDS sponsored clinical trials and observational studies, and to develop recommendations on suitable outcome measures. The results of this activity are still pending. In the interim, the NINDS Clinical Trials Group staff have suggested adding a handful of outcome measures to clinical trials, regardless of the disease being studied. Examples of this are the symbol digit modalities test (SDMT) and the Modified Rankin Outcome Scale. This effort would ideally permit the generation of data on common scales across disease entities, but again the relevance and utility of such outcome measures in a diverse number of disease states are uncertain.

Complementing the NINDS effort, there is a broader NIH initiative to develop outcome measures that are completed by research participants themselves, or in collaboration with their caregivers. The “Patient-Reported Outcomes Measurement Information System (PROMIS)” initiative is an effort to not only generate standardized outcome measures, but to rely on the observations and impressions of the research participant him or herself. One advantage of participant-reported outcomes is that the participant is often the individual most likely to be able to assess the relative impact of an intervention on their health state. On the other hand, such instruments may be influenced by other health states, such as depression or cognitive impairment, and could possibly be perceived by researchers and regulators as excessively “subjective.” Again on the whole, the development of participant reported outcomes is probably a net benefit and may provide cost effective alternative to large scale trials requiring clinic visits.

There may be other efforts to identify standardized outcome measures that are broadly applicable across health states, but the Advisory Panel is not aware of these. There is an opportunity for the NINDS to take a leadership role in this effort. Participation in the NeuroQOL and PROMIS activities are a starting point. Integration of efforts with NIA, NIMH, and NIDA, which share diseases of common interest, would likely have a benefit as instruments could broadly assess the health impacts of diseases of the nervous system. Furthermore, it should be a goal to hire into the NINDS staff an individual with knowledge and experience in outcome measurement tool assessment and development. This would add significant expertise to the Institute, provide for the opportunity of leadership in this area among Institutes and Centers, and be of direct benefit to investigators as they seek to improve the outcome measures used in their observational and interventional studies.

Standardized Data Management Formats

Public and private sector supported clinical research is plagued by the problem of a plethora of database management systems and variable naming conventions. This leads to a situation where each study tends to have a unique database, containing unique outcome measures, which are named and stored in the database in a unique way. This essentially thwarts any attempt to combine data across databases or to analyze differences among data in different databases. To a certain extent this problem has been overcome in private sector drug development within a company when the intention is to combine data across several studies and data management plans are constructed with that use in mind. However, for the NINDS, most studies are unique in their data management structure and outcome measure choice (see above) and there is little or no ability to meaningfully combine datasets without added conversion and mapping of datasets. This also inhibits any attempt to do electronic or machine based data mining without extensive conversion of databases. This problem has been widely acknowledged both in the public and private sector interested in clinical research. There have been voluntary public efforts to identify rules for developing standardized means for database construction and variable naming (e.g. the Clinical Data Interchange Standards Consortium, or C-DISC) but these are not finalized or universally agreed upon. The NINDS has a contract with KAI for a “common data elements (CDE)” project, which is in process. Draft documents from this project suggest the effort is oriented towards the development of specific data forms, specification of the naming and formatting of common variables (e.g., age, gender, education), and mapping of local databases into a common set of data elements. The identification of standardized outcome measures along with standardized database formats would greatly facilitate the ability to combine datasets and do data mining among datasets. However, this ability would come at a price. Pre-specifying outcome instruments and database formats may impede appropriate data collection and be incompatible with certain database management systems, and may deter development of better systems or approaches. A potential implication for the Institute would be that it may need to provide funding to enable an investigator to acquire data management systems that would be compatible with the proposed data architecture.

Another potential solution to the problem of multiple, unique databases is to identify the format and structure that the Institute expects to receive from grantees and contractors for public database deposition. This would allow investigators and contractors to create and generate databases in whatever format they choose in keeping with their relevant data management infrastructure. However, by setting these guidelines the investigators would then know that they would have to “map” their unique data architecture to the format that is specified by NINDS for public disclosure. A highly standardized format (such as SAS transport files) and the identification of anticipated

variables (e.g., age, gender, education) could be specified in advance along with desired standardized outcome measures in addition to whatever disease specific outcome measures the investigators could choose. For the latter there may be more flexibility on structure of variables. However, the Institute could recommend variable structures to the extent such variables are used widely across disease states. Again, the Institute is relatively weak on data management, having no intrinsic ability to house and manage clinical research data. Given the increasingly important nature of database management in the conduct of clinical research, it would be of value for the Institute to have at least one individual with expertise and experience in this area of clinical research. This individual could assist with the specifications for NINDS datasets required for public disclosure as well as assist investigators with the creation of their project specific databases. It may be possible to identify an individual who has experience both with outcome measure development and database construction, although this seems somewhat unlikely. On the other hand, since database development is a very active field, an alternative would be to identify a contractor to provide consultation and assistance to the Institute in this area. Also, as an electronic medical record and/or national standards evolve, NINDS should be not only aware, but looking for the potential of such data to inform policy and priorities.

The Advisory Panel sees this as an excellent opportunity for leadership on the part of NINDS. Few Institutes have developed outcome measure, database management, or biostatistical expertise among their staff. In addition to taking a leadership role amongst I/Cs, this is also an area that could span intramural and extramural research. Extramural investigators would benefit from the opportunity to visit and emulate an intramural program that is highly sophisticated in the construction and management of clinical research databases and in biostatical methodology. This could likely be an important area of collaboration between the new Directors of the Offices of Extramural and Intramural Clinical Research. It would also enhance the ability of the intramural program to be an investigative site in multi-center studies.

Training in Clinical Research Methods

One of the rate-limiting factors in conducting both NIH and industry funded clinical research is the supply of adequately trained investigators. This is true both for investigators serving at the site level and for principal investigators of multicenter investigations. The limited supply of investigators is partly due to a traditional bias in academia that clinical research is inferior or otherwise not as valuable as basic research. NINDS has made significant efforts in reversing this impression and in increasing the supply of clinical researchers. These efforts include the K23 mentored clinical research award program and T32 fellowship training programs, including the

Experimental Therapeutics Program at the University of Rochester, and T32 programs in biostatistics at UAB, UMC and HSPH. In addition, the recently initiated Clinical Trials course through contract with the University of Rochester provides young investigators with the opportunity to receive rigorous didactic instruction in clinical research methods over a relatively short timeframe. While these efforts are significant and effective, they are insufficient in the face of the great need for more and better-trained investigators.

The Clinical Research Collaboration (CRC) effort has been an attempt to engage community-based and practice-based individuals in clinical research. This is a laudable goal. But whether practice- or university-based, many investigators participating in studies need additional formal and ongoing training in the approaches for running an effective clinical research site, which is often housed in the setting of an busy clinical practice site. While many of the activities and skills are similar between practice and research, there are also extensive differences. Acknowledgement of and training in these differences would greatly augment the body of available clinical researchers. The Advisory Panel learned that there are a number of family practice networks that have been fairly successful at balancing the limitations placed by the office practice ecology and rigors of research, and NINDS could learn a lot from these experiences in developing its own initiatives. Again, the NINDS could have a leadership position in identifying effective adult learning techniques for educating individuals who are expert in one area (clinical practice) but may be relatively novice in another area (clinical research). This could be broadly applicable across Institutes with interest in disorders of the nervous system.

There is similarly a dearth of individuals trained and prepared to be the leaders of multicenter clinical research, whether observational or interventional. There is currently a relatively small number of individuals who receive the vast majority of NINDS funding for large multicenter trials. While this in and of itself is not necessarily problematic, as it likely leads to efficiencies of scale and takes advantage of experience, it does have the effect of limiting the capacity of the system. This situation also increases the possibility of “established” ideas becoming “entrenched” ideas. Hence, there is an imperative for the development of a core of new leaders of multicenter research. The skill set required for this activity is quite different from what is required to be an individual site investigator, as well as an individual bench-based researcher (although there are clearly areas of overlap). The NINDS could take a leadership role in this perhaps in conjunction with other organizations interested in this area. For example, the NINDS Clinical Trials course has tried to forge a relationship with the American Society of Experimental Neurotherapeutics. This is an area of need for both the public and private sector and the chance for a public/private partnership in developing leadership training and creating opportunities for individuals who are interested in a clinical research

career. Internships, training grants and career development awards should be encouraged and might include one or two year on site stints at NINDS.

Proposal

1. The NINDS should take a leadership role in identification of standardized outcome measurements. This would require the creation of a staff position with expertise and knowledge in outcome measurement assessment and development.
2. The NINDS should develop an intramural program that is sophisticated in the construction and management of clinical research databases. This would require the creation of a number of additional positions with expertise in bioinformatics, data management and data analysis.
3. The NINDS should continue to expand existing programs and devise new programs aimed at the development and training of experienced clinical researchers.
4. Developing expertise in regulatory processes (not just requirements) at NINDS would be helpful to intramural and extramural investigators. These staff members could develop expertise and knowledge of evolving and innovative trial designs.
5. The new leader of the NINDS Office of Clinical Trials should have experience in the conduct of multicenter clinical research studies and a strong interest in mentorship and establishing cross institution programs.
6. The new leader of the NINDS Office of Clinical Trials should consider establishing DSMBs with experienced members that monitor a larger portfolio of studies.