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EPILEPSY RESEARCH BENCHMARKS
IMPLEMENTATION PLAN

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Epilepsy Research Benchmarks Implementation Plan

Executive Summary

In Senate Report 107-84, the Senate Committee on Appropriations requested that the National Institute of Neurological Disorders and Stroke (NINDS) develop a plan to implement the Epilepsy Research Benchmarks. (p. 139) The following is submitted in response to the request.

In March 2000, the NINDS, together with several patient and professional groups, jointly sponsored a White House-initiated scientific conference entitled “Curing Epilepsy: Focus on the Future.” A major outcome of the conference was the creation of an epilepsy planning group that developed a set of seventeen specific research “benchmarks” for the epilepsy research community to use as milestones to measure their progress towards finding a cure for epilepsy. A unique feature of the Benchmarks is that their implementation is the shared responsibility of the entire epilepsy community. Rather than establishing a formal Interagency Epilepsy Coordinating Committee, NINDS will work collaboratively with other NIH Institutes, the epilepsy research community, and patient advocates to coordinate efforts to implement the Benchmarks.

To emphasize this point, the planning group developed the concept of “stewardship,” which refers to active involvement by senior well-established individuals in the epilepsy community in the status of existing and planned research that advances the goals of the specific benchmark. Other elements of the implementation plan include the creation of a non-technical lay version of the Benchmarks, the creation of an Epilepsy Benchmarks website, and a periodic analysis of the NIH epilepsy grant portfolio and epilepsy research literature.

NINDS, together with the rest of the epilepsy community, has already made significant progress on the Benchmarks implementation plan, including confirming the initial list of Benchmarks stewards and working with several advocacy representatives to produce a lay summary of the Benchmarks. In addition, significant progress has already been made on several of the Benchmarks, including a number of workshops and several program initiatives.

NINDS is committed to building on its ongoing significant efforts in epilepsy, and, through the concept of stewardship, to working closely with the research and

advocacy communities to achieve the Epilepsy Benchmarks and move the field closer to the ultimate goal of curing epilepsy.

Introduction

In its report on the Fiscal Year 2002 budget for the Department of Health and Human Services, the Senate Committee on Appropriations stated:

“The Committee believes that NIH should make finding a cure and effective treatments for epilepsy a priority. The Committee is encouraged by the establishment of 13 epilepsy research benchmarks resulting from the NINDS March 2000 conference “Curing Epilepsy: Focus on the Future.” The Committee encourages NIH to develop a plan to implement the research benchmarks, as the Director deems appropriate, including the funding projections needed to carry out the plan. The Committee directs that the plan be submitted to Congress by **April 1, 2002**. Further, the Committee encourages the establishment of an Interagency Epilepsy Coordinating Committee comprised of agency scientists, industry, and patient representatives.” (Senate Report No. 107-84, page 139)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

Background

Epilepsy is a chronic brain disorder characterized by spontaneous, recurrent seizures. These seizures are caused by the uncontrolled electrical activity of nerve cells in the brain. Epilepsy can result from head injuries, brain tumors, cerebrovascular events (e.g., strokes), lead poisoning, neurodevelopmental problems, certain genetic conditions, and infectious illnesses. However, in over half of all cases, no cause is ever found. Epileptic seizures can have varied manifestations, ranging from brief lapses of attention (absence seizures) to limited motor, sensory, or psychological changes (partial seizures) to prolonged losses of consciousness with convulsions (tonic-clonic seizures). The consequences of seizures, especially in children, can be serious or even fatal.

Epilepsy is estimated to affect 2.5 million Americans of all ages and ethnic groups. According to the 1990 NIH Cost of Illness report, epilepsy costs the

nation more than \$3 billion per year in direct medical costs. More recent estimates put the total annual cost at close to \$12.5 billion, including indirect costs such as loss of employment. For about 80 percent of those diagnosed with epilepsy, seizures can be controlled with medicines and/or surgical techniques. Most of these medicines, though, have significant side effects, which are especially of concern for women and children. About 20 percent of people with epilepsy will continue to experience seizures even with the best available treatment.

In March 2000, the National Institute of Neurological Disorders and Stroke (NINDS), together with the Epilepsy Foundation, the American Epilepsy Society, Citizens United for Research in Epilepsy (CURE), and the National Association of Epilepsy Centers, jointly sponsored a two-day international scientific conference entitled “Curing Epilepsy: Focus on the Future.” The conference, initiated by the White House, galvanized the epilepsy research community to begin focusing on curing epilepsy - defined as “preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder” - rather than just treating the symptoms. The proceedings of the conference were published in the journal *Neurology* in October 2001.

A major outcome of the Cure Conference was the creation of an epilepsy planning group to develop a research plan for the next 5-10 years. Comprised of researchers, clinicians, representatives of the advocacy community, and NINDS professional staff, this group met several times during the summer and fall of 2000 to identify scientific questions and promising research opportunities. From these discussions, the planning group developed seventeen specific research “benchmarks” for the epilepsy research community to use to measure their progress towards finding a cure for epilepsy. The benchmarks were published on the NINDS website in January 2001.

Epilepsy Research Benchmarks

The overall purpose of the Epilepsy Research Benchmarks is to help epilepsy investigators maximize the translation of basic science findings into improved clinical therapies. They are not meant to encompass all areas of epilepsy research, but rather represent research milestones whose attainment will result in significant progress towards finding a cure for epilepsy. While some are attainable in the short term, others will require a basic understanding of the causes of epilepsy, advances in technology, or increased long-term collaboration among scientists, industry, and patient groups.

Due to the technical nature of the Benchmarks, this report will only broadly summarize the main points. The complete set of Benchmarks can be found on the NINDS website at http://www.ninds.nih.gov/about_ninds/epilepsybenchmarks.htm. A collaborative group of NINDS professional staff and representatives of several patient advocacy groups are developing on a summary of the Benchmarks in non-scientific language, which will also be posted on the NINDS website.

The Benchmarks are divided into three broad categories. The first of these categories involves understanding the underlying mechanisms by which epilepsy develops. This category, which encompasses eight specific benchmarks, includes increased knowledge of the molecular, physiological, and anatomical bases for epilepsy, continued identification of genes that predispose individuals to epilepsy, and the development and use of better model biological systems for testing novel therapies.

The second broad category focuses on the creation and implementation of new therapies aimed at preventing epilepsy in individuals at risk. This category, which encompasses two of the specific benchmarks, includes identification of susceptible brain regions in which a preventive therapy might work, and completion of at least two clinical trials to test the effectiveness of potential preventive therapies in individuals at the highest risk of developing epilepsy.

The third broad category seeks to create and implement new therapies for patients with epilepsy that will prevent seizures without producing side effects. This category, which encompasses seven specific benchmarks, includes development of a genetic diagnostic test to help identify patients who will best respond to a given therapy, discovery of a biosensor device that could be implanted in a patient's brain to either anticipate or detect seizures as they occur and deliver a specific treatment that would stop the seizures, and development of new therapeutic approaches (e.g., gene therapy, cell transplantation, vaccination) that would significantly reduce the frequency of seizures.

Implementation Plan for the Epilepsy Research Benchmarks

The Epilepsy Benchmarks planning group has been addressing the best strategies to implement the Benchmarks via electronic correspondence during the spring and summer of 2001 and at another formal meeting of the group in December of

2001.

Central to the concept of the Benchmarks is the belief that they are milestones for the entire epilepsy community. Thus, implementing the Benchmarks will require not only the active participation and involvement of the NIH, but also the research community (both basic scientists and clinicians), the epilepsy professional organizations, and the epilepsy patient community. All of these communities must work collaboratively if the goals are to be reached.

Although NINDS is the lead NIH Institute for epilepsy research, several other NIH Institutes also fund epilepsy related projects, including the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), and the National Human Genome Research Institute (NHGRI). NINDS has discussed with patient advocates what the objective would be of establishing an Interagency Epilepsy Coordinating Committee, as well as the advantages and disadvantages associated with formally establishing such a committee. The main objective would be coordination and information sharing to facilitate achievement of the research benchmarks, and it was agreed that this could be achieved effectively, but more efficiently, through other approaches. Accordingly, NINDS will work with the other NIH institutes to coordinate epilepsy research efforts, including their involvement, as appropriate, in the implementation of the research benchmarks. This might include joint sponsorship of workshops and conferences, joint funding of initiatives, and periodic meetings to identify and discuss areas of common interest and opportunities for collaboration. NINDS has already initiated such efforts, with NHGRI being invited to participate in a recent workshop on molecular analysis of complex genetic epilepsies.

Stewardship of the Epilepsy Benchmarks

In order to emphasize this collaborative relationship, the Epilepsy Benchmarks planning group has developed the concept of “stewardship,” which refers to active involvement in the status of existing and planned research that advances the goals of the specific benchmark. The idea is for senior well established individuals in the epilepsy community to accept primary responsibility for a given benchmark for approximately 3 years in conjunction with the NINDS. Stewards’ responsibilities include monitoring relevant research efforts, making the research community aware of the benchmark and related funding programs or

opportunities, acting as a catalyst for new initiatives, and providing regular progress reports to the NINDS. Specific activities might include writing updates or reviews for journals and newsletters, discussing benchmarks at seminars, symposia, or other forums, establishing electronic LISTSERVs that link researchers sharing common, benchmark-related interests, organizing workshops and conferences, and acting in an advisory capacity to NINDS and other organizations.

The stewards will meet with each other and with members of the Epilepsy Benchmarks planning group and NIH staff approximately twice each year to review progress on each of the benchmarks. It is anticipated that one of these meetings will take place at the annual meeting of the American Epilepsy Society, and the other at the NIH, possibly in conjunction with the annual Judith Hoyer Epilepsy Lectureship. This lectureship was recently created by NINDS to honor the memory of Mrs. Hoyer and pay tribute to her efforts to assist families dealing with epilepsy and to promote research into a cure.

Other Elements of the Implementation Plan

In addition to the concept of stewards, other elements of the implementation plan for the Epilepsy Benchmarks include the following:

- The creation of a non-technical version of the Benchmarks. Since the Epilepsy Benchmarks are geared towards the entire epilepsy community, the Epilepsy Benchmarks planning group felt it important that the Benchmarks be understandable to the patient community. NINDS will work with representatives of the epilepsy advocacy community to develop the non-technical version of the Benchmarks.
- The creation of an Epilepsy Benchmarks website. This website, to be hosted by NINDS and linked to other epilepsy organizations, will serve as a central clearinghouse for information on the Benchmarks and the progress towards achieving them. Elements of the website will include the original and lay versions of the Benchmarks, the annual reports of the Benchmark stewards, and announcements of related research initiatives, workshops, and conferences.
- An analysis of the NIH epilepsy grant portfolio/epilepsy research literature. In order to assist the Benchmark stewards in understanding the types of research projects currently being funded, and the results of that research, NINDS program staff will provide stewards with periodic analyses of the NINDS epilepsy grant

portfolio, together with those of relevant NIH Institutes and Centers. Currently, the NINDS portfolio comprises approximately 225 epilepsy-related grants, including 8 clinical trials and one large multicenter clinical study. The analyses will also include detailed searches of the research literature that should help the stewards identify gaps in the field and research priority areas for their assigned benchmarks.

Epilepsy Benchmark Implementation Plan - Current Status

NINDS, together with the epilepsy community, has already made significant progress on the implementation plan. After wide dissemination of the Epilepsy Benchmarks to the epilepsy community, and discussion of them at a number of professional meetings, the initial list of stewards for the Benchmarks was confirmed at the December 2001 meeting of the Epilepsy Benchmarks planning group. At this meeting, NINDS program staff reported on the results of a preliminary analysis of the NINDS epilepsy grant portfolio, along with the results of a search of the epilepsy research literature from the time of the Cure Conference to the present. Stewards were asked to submit an initial report on the current status of their assigned benchmarks by the end of January 2002, and NINDS is currently compiling these reports.

As mentioned previously, NINDS program staff are working with representatives of several patient advocacy groups to produce a lay summary of the Benchmarks. This summary should be completed later this spring.

Progress in Implementing the Benchmarks

In addition to the implementation plan, NINDS, working with the rest of the epilepsy community, has begun to make progress on several of the Benchmarks.

As part of the Cure Conference, NINDS announced a Request of Applications (RFA) on "Innovations in Translational Epilepsy Research for Junior Investigators." The purpose of the RFA was to promote cross-disciplinary collaborative projects among junior investigators in the fields of patient-oriented research, developmental neurobiology, genetics, advanced technology, imaging, pharmacotherapeutics, or other research areas that would be likely to lead to a cure for epilepsy. Seven proposals were funded from this RFA, for a total of approximately \$1.2 million, and the initiative was so well received that NINDS has re-released it as an ongoing Program Announcement (PA).

On March 1-2, 2001, NINDS hosted the first of a series of workshops on “Models for Epilepsy and Epileptogenesis.” The workshop was designed to address an Epilepsy Benchmark on the development and use of better model biological systems for testing novel therapies, and included representatives from government, academics, industry, and the advocacy community. A manuscript of the workshop proceeding has been submitted for publication.

On March 8-9, 2001, NINDS, together with the American Epilepsy Society, the Epilepsy Foundation, and Citizens United for Research in Epilepsy, held a workshop on “Antiepileptic Drug (AED) Monotherapy Indications.” The purpose of this workshop was to discuss what would be the ideal clinical trial design that will protect patients and satisfy FDA approval criteria for the approval of AEDs for monotherapy treatment of epilepsy. This workshop was of direct relevance to the set of Benchmarks dealing with improved therapies for patients already affected by epilepsy. More than 125 individuals attended, including representatives from academia, government, pharmaceutical companies and contract research organizations. An article summarizing the workshop is in preparation for publication in a supplement to the journal *Epilepsia*.

Also in March of 2001, NINDS, together with NIA and NIMH, released a Request for Applications (RFA) entitled “Gene Discovery for Neurological and Neurobehavioral Disorders.” The purpose of this RFA was to promote the identification of genes that cause or contribute to human neurological and neurobehavioral diseases, including epilepsy. This RFA was directly relevant to the Epilepsy Benchmark that calls for continued discovery of genes that predispose individuals to epilepsy.

Several of the major presentations at the December 2001 Annual American Epilepsy Society Meeting highlighted topics directly related to the Epilepsy Benchmarks, including a plenary session on “What Animal Models Tell Us About Human Epilepsy,” a featured lecture on animal models of early onset seizures, and a Presidential Symposium on seizure prediction using quantitative EEG data.

On January 31- February 1, 2002, NINDS, together with the American Epilepsy Society and the International League against Epilepsy, sponsored a workshop on “Molecular Analysis of Complex Genetic Epilepsies.” The purpose of this workshop - which was directly relevant to several Epilepsy Benchmarks related to understanding the genetic influences on epilepsy - was to establish a scientific basis for the next steps in genetic analysis of the complex genetic epilepsies by

the use of molecular methods.

The NINDS is currently planning a workshop for summer 2002 tentatively entitled "Imaging and the Neurobiology of Epilepsy: Clinical Implications." The workshop is designed to address an Epilepsy Benchmark on the use of imaging technology to improve our understanding of the underlying mechanisms of epilepsy and its causes.

Epilepsy Benchmarks and Funding Projections

As discussed previously, the Epilepsy Benchmarks are a set of research milestones whose attainment will result in significant progress towards finding a cure for epilepsy. While some are attainable in the short term, others will require an understanding of what causes epilepsy, advances in technology, and increased long-term collaboration between epilepsy researchers. For this reason, the Epilepsy Benchmarks planning group identified a 5-10 year time frame as appropriate for achieving them. The Benchmarks were created by and for the entire epilepsy community (including basic scientists, clinicians, professional societies, patient groups, and the NINDS) and serve as a way to measure progress towards the goal of a cure. The whole community must be involved if the Benchmarks are to be achieved, and we anticipate this will happen.

Success in reaching the benchmarks depends on progress being made in broad areas of basic neuroscience that have application to epilepsy, such as brain development and brain plasticity, and in further development of techniques at the frontiers of medicine, such as gene therapy and cell transplantation therapy, that have great therapeutic potential.

Because the Epilepsy Benchmarks require the commitment of financial and scientific resources and manpower by the professional and advocacy organizations, the epilepsy research community, and the NINDS, it is not possible to generate a central set of useful funding projections. In addition, the long-term framework of the Benchmarks makes it difficult to anticipate funding availability, given that NINDS does not know either what its level of appropriation will be in future years, or the type or number of competing research priorities that then will be part of its mission. However, NINDS estimates that its FY 2002 funding for epilepsy research will be \$81.935 M, rising to \$88.914 M in FY2003.

NINDS is committed to working closely with the Benchmark stewards to monitor progress and identify the types of research projects NINDS and the other NIH

Institutes and Centers are funding, identify where gaps exist, and determine the best ways of addressing these gaps.

Conclusions

The March 2000 “Curing Epilepsy: Focus on the Future” conference was a landmark event for the epilepsy field, in that for the first time scientists, clinicians, and patients began to focus on curing epilepsy, rather than on treating its symptoms. Out of the conference emerged an ongoing planning process based upon the Epilepsy Research Benchmarks that can be used to measure progress towards a cure.

NINDS, working closely with the epilepsy research and advocacy communities, has developed a plan to implement the benchmarks, the main component of which is the concept of stewardship. Benchmark stewards are prominent members of the epilepsy community who will take an active and sustained role in the status of research, both existing and planned, that will advance the goals of the specific benchmark

Stewards for each of the Benchmarks have been chosen, and have begun to prepare initial reports on the status of their assigned benchmark. In addition, a number of workshops and meetings have already been held or are planned that address several benchmarks.

The Epilepsy Benchmarks represent research milestones, but are not meant to encompass all important areas of epilepsy research. NINDS is committed to building on its ongoing significant efforts in all areas of epilepsy, and to working closely with the research and advocacy community to achieve the Epilepsy Benchmarks and move the field closer to the ultimate goal of curing epilepsy.