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Clinical Trials in the Neurosciences

Editors
K.M. Woodbury-Harris
B.M. Coull

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K.M. Woodbury-Harris Redmond, Oreg.
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11 figures and 15 tables, 2009

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John Marler who made it happen

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Introduction

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Advances in the diagnosis, prevention, treatment and cure of neurological diseases are based upon scientific discovery. The journey from discovery to treatment is often arduous and involves both basic and clinical science. Over the ages, multiple intertwined paths of discovery connect the recognition of distinct diseases of the nervous system to exquisite diagnostic descriptions, which, when coupled with the scientific understanding of the disease, have allowed the development of effective treatments and interventions. This course spans recorded history for virtually all classical neurological afflictions such as epilepsy, stroke and Parkinson's disease. For many diseases of the nervous system, the earliest clinical descriptions are found in the earliest writings of recorded history, but pathophysiological enlightenment and effective treatments that follow have happened in only the last century. Despite recent treatments for many neurological diseases that have in the past been highly refractory to treatment, such as multiple sclerosis and Parkinson's disease, to date very few cures have been discovered. To find more effective ways to prevent, treat or cure neurological illness remains among the greatest challenges for modern medicine. Fueled in part by completion of the human genome project, the pace of scientific discovery along with the advancement of drug development from bench to bedside is increasing. Whether based upon animal studies, clinical case reports or pilot trial observations, no matter how elegant the science or promising a given drug or intervention is for treatment of any neurological disease, the ultimate proof of such benefit is dependent upon evidence derived from a well-designed and well-executed phase III clinical trial.

A properly designed and executed clinical trial that addresses an important question and delivers a definitive result can change the practice of medicine worldwide. Consider, for example, the effect that the Canadian Aspirin Trial headed by Henry Barnett had on aspirin use for the secondary prevention of stroke. Furthermore, a well-designed and well-conducted clinical trial need not be positive to have such an enormous clinical effect and consequence. One such example is given by the EC/IC bypass trial, again directed by Dr. Barnett, which virtually halted the use of cerebral

bypass surgery for treatment of carotid occlusive disease. To have such an impact, the trial should address and be designed to definitively answer an important clinical question. This is a key point, since not every problem or question in clinical medicines needs to be addressed by conducting a large-scale multicenter clinical trial. Some clinical questions are trivial and other questions, even if important, may not be adaptable to large-scale trial design for a variety of practical reasons. There are not enough patients and too little money to address all questions in clinical neurology with a phase III trial, especially in the case of rare disorders. However, large-scale clinical trials are needed when the stakes are high, as when new and potentially dangerous treatments are proposed, or when the community of physicians collectively have divergent or opposing, but often strongly held, opinions about a given treatment such as a drug therapy or surgical procedure for any of the spectrum of neurological illnesses. Unfortunately, in neurology and neurosurgery, evidence has too often been driven by expert opinion rather than data derived from high-quality clinical trials. Equipoise does not mean that an individual physician believes that a treatment does or does not work, it means that the community of providers as a whole has not agreed on the appropriate treatment. Often, additional clinical trials are needed to help confirm the outcome of a previous trial or settle conflicting results from multiple trials. Ultimately, the clinical trial should lead to the betterment of human health and well-being.

Designing and conducting a clinical trial that will provide a definitive answer to an important clinical question is not a simple matter. Well-designed trials require a team approach and the inclusion of investigators with differing disciplines and backgrounds. Phase III clinical trials in neurological disorders will often require multiple geographically dispersed sites with an increasing trend to international representation. The logistics of such trials can be extremely complicated, and in addition to scientific and clinical issues, cultural, ethnic and political considerations enter into the trail design and execution. To effectively conduct a trial, the team of investigators must be cohesive and highly collaborative. Besides the requisite clinical expertise in the area of investigation, the ideal team for most large-scale clinical trials will include individuals with expertise in biostatistics, informatics and data management, among others. It is important to have such expertise on board from the very conception of the study. The importance of trials done correctly cannot be emphasized enough; when it comes to clinical research, human beings are a precious resource and it is unethical to involve them in clinical trials not done properly or well designed. In neurology, there are special considerations, such as low prevalence of rare diseases. Because one is dealing with the brain, involving the very essence of what we are, the sense of self, particular care is required. Furthermore, there are the issues of special populations, cultural differences, patients who have limited consent ability as well as non-English speakers.

This book is intended to give a comprehensive and practical overview to the clinician researcher who wants to design and conduct clinical trials in neurology and

neurosurgery. Our perspective for the book is that of an experienced grant reviewer who carefully examines an application with respect to the key components and facets that are involved in designing and executing phase I/II/III clinical trials. The wellspring of most clinical trails begins with basic science. While it is not our intent to provide an in-depth background of the preclinical sciences from which subsequent clinical trials are formulated, we do provide an overview for the clinical trialist as to what constitutes solid preclinical data from which to formulate a clinical investigation. We do not intend for this to be a textbook of epidemiology, biostatistics or clinical pharmacology, but we have attempted to give sufficient coverage of the basic science and translational approaches so as to assure that all these components are incorporated in developing good clinical trial design. In our experience of participating in or reviewing numerous clinical trials, many applications are lacking in scientific sophistication in one or more aspect or area that needs to be addressed so as to increase the likelihood that the trial can be successfully accomplished. We hope that this is an instructive book for both neophyte and experienced trialists and that these efforts will improve the quality of clinical trail design and execution, and ultimately will help our patients with neurological illnesses.

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Evolution of Clinical Trials in Neurology

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Clinical and health policy decision making is ideally based on high-quality evidence from controlled clinical trials or population-based longitudinal studies. Population-based epidemiological research is the preferable approach to describe the population burden of a given condition, its natural history risk as well as longitudinal effects of its potential risk factors and of predefined health policy interventions. By comparison, controlled clinical trials usually test the effect of a specific intervention in a selected patient subgroup at risk.

While epidemiological protocols appear to remain relatively stable over several decades, the way clinical trials are designed and organized is subject to change depending on available resources, infrastructure, type of intervention and endpoint evaluation. The main elements impacting on future evolution of clinical trials are based on both pragmatic adjustment to changing practice pattern and conceptual innovation of trial aims and methods.

Pragmatic Adjustment to Changing Practice Pattern

Any evaluation tools used for clinical quality assessment have to adjust to constantly changing clinical practice patterns. This is particularly true for the scientific evaluation of patient management strategies and therapeutic interventions. In his context, the design of so-called practical clinical trials responds to the increasing need of pragmatic answers to unsolved clinical decision problems.

Comparing the overall aim of different trial designs, 2 general approaches may be distinguished in principle.

Explanatory clinical trials aim at better understanding how and why an intervention works. They are designed to maximize the chance that a study will reveal some biological effect related to a new treatment. Many phase III drug or device trials fall into this category. Funding is usually available and driven in part by the prospect of eventual marketing of a promising new drug or device. By comparison, so-called pragmatic or practical clinical trials are defined as trials for which the hypothesis and study design

are formulated based on information needed to make a decision. Practical clinical trials compare clinically relevant intervention strategies and address practical questions about the risk, benefit and cost of therapeutic interventions as they would occur in clinical practice. The study design usually tests the principle of one versus another treatment algorithm or intervention (for example, carotid surgery versus stenting in patients with high-grade stenosis) rather than a specific drug or device [1].

Clinical research projects with the aim of improving evidence-based decision making tend to be underfunded as no secondary financial gain can be expected for the sponsor. This, of course, is in strong contrast to the increasing demand by clinical and health policy decision makers for reliable answers to pressing practical questions [2].

Conceptual Innovation of Clinical Trials

Recent conceptual innovation has been mainly inspired by the idea of translational research algorithms. These concepts are usually based on both, vertical (from bench to bedside and from bedside to bench) and horizontal translation (such as from single center to multicenter studies, from single discipline to multidisciplinary trials and from research hospitals to the community) and have shaped an increasing number of recent trial protocols.

Vertical Translation

The term translational research has been widely used in recent years, mostly in reference to studies designed to develop so-called basic science results into clinical research protocols involving actual patients and specific disease conditions. This vertical bench-to-bedside approach harnesses knowledge from basic science to produce new drugs, devices and treatment options for patients (fig. 1, part A). In the context of neurological disorders, clinical pharmacology has been one of the driving forces promoting research translation from lab results into clinical use via the various steps of phase I through phase III clinical trials.

In some circumstances, the translational process between bench and bedside may be reversed, as for example in studies on the clinical phenotype of familiar diseases that will finally translate back (that is, from bedside to bench) to the molecular identification of the underlying genetic disorder (fig. 1, part B). Also, for many neurological diseases (such as multiple sclerosis, Parkinson's disease, stroke and many genetic disorders), the clinical characteristics have been successfully translated into animal models allowing further experimental studies on molecular and other mechanisms of disease progression and possible treatment interventions. Any results may eventually translate back from bench to bedside via phase I to III clinical trials (fig. 1, part C).

These vertical translations between bedside and bench have proven very successful in many areas of neurology given recent advances in the treatment of multiple sclerosis, epilepsy and Parkinson's disease. However, stimulating and challenging vertical translation may be as a research algorithm, its application alone may not necessarily

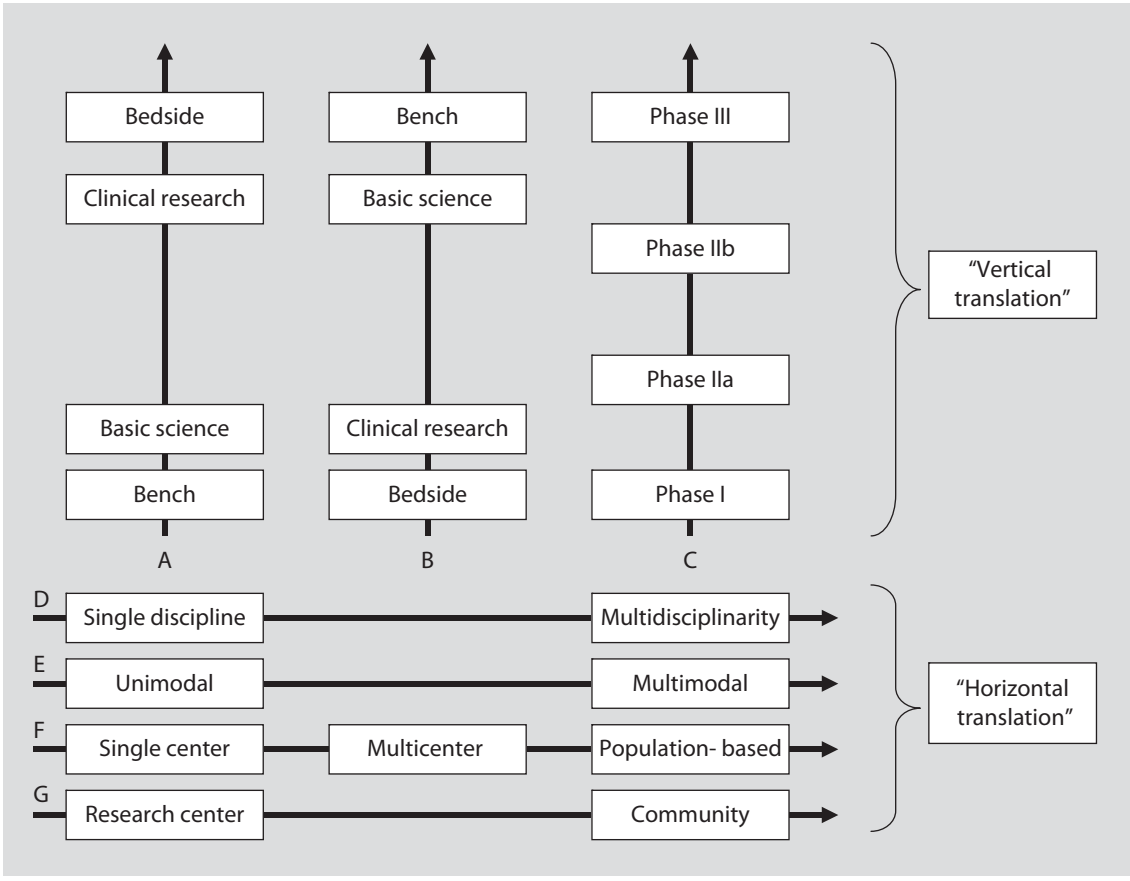

Fig. 1. Bidimensional model of translational research.

constitute an a priori guarantee for scientific success. An illustrative, though disappointing, example may be that in neurovascular research many neuroprotectants that have been found to be effective in animal stroke models have not shown an evident clinical benefit in clinical practice. The repeated failure has been casting doubt about the appropriate translation from the actual bedside situation into the bench model and vice versa [3]. In this context, recent developments in the formulation of guidelines for design and interpretation of animal experimentation may improve the selection of potential candidate drugs for clinical trial [4].

Horizontal Translation

Many recent trial designs apply models of horizontal translation, the most important of which is the ongoing trend moving from single specialty to multidisciplinary research protocols (fig. 1, part D). Naturally, multidisciplinary study concepts are facilitated by the clinical interplay between various subspecialties of neurology and

their neighboring disciplines, such as neuroradiology, neurosurgery, vascular surgery and pharmacology, to name but a few. Taking neurovascular clinical research as an example, much in this context can be learnt from the history of internal carotid artery disease management. It constitutes one of the most encouraging examples on how multidisciplinary clinical research succeeded in implementing neurological and morphological decision criteria for treatment of both symptomatic and asymptomatic lesions. The carotid surgery trials not only established proven clinical benefit of interventional treatment in defined subgroups at risk, but also helped to foster the idea that multidisciplinary decision making is the gold standard of neurovascular patient management [for more details, see chapter by Stapf, this vol., pp. 106–113].

The advantage of sharing research interests, trial logistics and funding sources have been the major advantages motivating investigators to consider horizontal translation of a single trial concept into a modular trial design (fig. 1, part E). One of the most frequently encountered constellations is a complementary genetic or imaging study as a piggyback protocol to a larger parent study, as has been the case in neurological clinical trials on stroke and dementia, among others. One of the recent landmark studies in stroke prevention, the Warfarin Aspirin Recurrent Stroke Study [5], has served as a platform for 4 additional stand-alone protocols [6], including the Antiphospholipid Antibodies in Stroke Study [7], the Patent Foramen Ovale in Cryptogenic Stroke Study [8], the Hemostatic System Activation Study [9] and the Genes in Stroke Study. This arrangement has proved useful not only to share structural resources (in the case of the Warfarin Aspirin Recurrent Stroke Study, an automated mechanism for double-blinded anticoagulant therapy) but also to support patient recruitment in the parent trial, and to allow independent conduct and publication of eventual trial results for each supplement study.

Some research protocols have developed from single-center to multicenter studies, and finally to population-based registries. Independent epidemiological samples may also serve as parallel quality control for randomized clinical trials, allowing to test for potential recruitment bias or skewed preselection of patients enrolled in the trial (fig. 1, part F). This may allow to address the important issue whether or not the actual trial results may be easily applied to affected patients seen in daily routine [10]. Horizontal translation from clinical research to community practice and health decision making may therefore be subject to dedicated research protocols (fig. 1, part G) [11].

Practical Issues for Future Protocols

Whatever the source of innovation in the design and conduct of future clinical trials in the field of neurology, the research community still struggles to complete trials in a reasonable amount of time and at a reasonable cost. This difficulty may increase in the future, as trials tend to include larger numbers of patients in order to test clinically relevant hypotheses with high enough statistical power. Also, trials that compare one

treatment to an existing effective therapy require larger numbers of participants than placebo-controlled trials introducing a new treatment option or tool.

One of the main factors defining the overall length of a clinical trial is the dynamics of patient enrollment. Trials with less restrictive selection criteria will recruit more easily eligible cases and may eventually be more likely to change practice. Higher recruitment rates are usually encountered in more extensive networks, as they will provide a larger number of recruiting sites. In the future, the increasingly international participation in neurological clinical trial protocols is desirable to speed trial completion and increase the patient population to which the results will eventually apply [12].

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Preclinical Trials

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Role of Animal Studies in the Design of Clinical Trials

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The goal of this chapter is to discuss the importance of preclinical evaluation of potential therapies for neurological disorders in animal models that mimic the target human disorder as a prelude to the translation of these into clinical trials. The scope of neurological and/or neurosurgical disorders that could be considered herein includes both acute neurological insults as well as chronic conditions such as epilepsy, neuropathic pain and the neurodegenerative disorders, primarily Alzheimer's disease, Parkinson's disease and the motor neuron diseases, mainly amyotrophic lateral sclerosis. Animal models for all of these conditions have been devised and used to evaluate potential therapies. However, a single chapter cannot possibly do justice to this wide range of disorders and associated models. Thus, in order to keep the subject of neurological animal studies manageable, the focus of this chapter will be on models and basic principles of preclinical evaluation of therapies in the context of acute neurological injuries including stroke, cardiac arrest and cardiopulmonary resuscitation (CA/CPR), traumatic brain injury (TBI) and spinal cord injury (SCI). These acute insults represent 4 of the most catastrophic consequences that human beings can suffer. Furthermore, the discussion of how to test therapies in models of these conditions will be couched primarily in relation to pharmacological therapies. However, many, if not all principles that define a thorough preclinical evaluation of drugs in animal models are in fact equally applicable to gene and cellular transplant therapies.

There are approximately 750,000 strokes per year in the US, most, but certainly not all, affecting the elderly population. About 85% of strokes are ischemic in nature, involving a thromboembolic blockage of a brain artery; up to 15% of strokes are hemorrhagic. There are 2 types of hemorrhagic strokes: intracerebral hemorrhage (ICH) when blood is released into brain parenchyma producing brain damage by triggering brain edema (swelling) and mass effects, resulting in secondary ischemia within the

brain tissue, and subarachnoid hemorrhage (SAH) when blood is released into the subarachnoid space from an aneurysm ballooning out from one of the major arteries, also causing a secondary ischemic insult from induction of delayed cerebral vasospasm peaking at 4–7 days after SAH. There are about 30,000 aneurysmal SAH per year in the US with a 2:1 female:male preponderance.

Cardiac arrest strikes about 600,000 people per year in the USA and leads to high mortality and poor neurological outcome. Many survivors of CA/CPR have moderate to severe neurological deficits many months following the event. Survival rates following CA/CPR have not changed for decades despite improvements in resuscitation techniques. The lack of effective treatment options to ameliorate reperfusion injury in the postresuscitation period likely accounts for the disappointing survival rates. Recently, however, induction of mild hypothermia in unresponsive cardiac arrest survivors showed improved neurological outcome and 6-month survival. This was the first demonstration in humans that development of brain injury after CA/CPR could be positively influenced by a postischemic intervention.

There are an estimated 1.5 million cases per annum of TBI in the US, ranging from mild to severe. Although most TBI cases are mild in severity, about 58,000 are severe (Glasgow Coma Score: 3–8) and 64,000 moderate (Glasgow Coma Score: 9–12) and such individuals often require intensive medical treatment and extended recovery periods. Further, there are about 11,000 new cases of SCI each year in the US with an overall prevalence of approximately 250,000. Although TBI and SCI affect active individuals of any age, most occur in young adults in the second and third decades of life. Moreover, the majority of stroke, TBI and SCI patients now survive their neurological insults due to improvements in emergency, neurological intensive care and surgical treatments. Nevertheless, the need for intensive rehabilitation and the reality of prolonged disability exacts a significant toll on the individual, his or her family and society. Effective ways of maintaining or recovering function could markedly improve the outlook for persons with these insults by enabling higher levels of independence and productivity.

Goals of Drug Therapies for Acute Neurological Disorders

Neuroprotection

The focus for pharmacological intervention to preserve neurological function after these acute central nervous system (CNS) injuries is based on the idea that most vascular and/or neurodegeneration that follows these injuries is not due to the primary ischemic, hemorrhagic or mechanical (that is, shearing of blood vessels and nerve cells) insults, but to secondary injury events set in motion by the primary injury. For example, most SCI cases do not involve actual physical transection of the cord, but the spinal cord is damaged as a result of a contusive, compressive or stretch injury. Thereby, usually some portions of the ascending sensory and descending motor

tracts remain intact allowing for the possibility of neurological recovery. During the first minutes and hours following injury, a secondary degenerative process is initiated by the primary mechanical injury proportional to the magnitude of the initial insult. Nevertheless, the initial anatomical continuity of the injured spinal cord and our present knowledge of many factors involved in the secondary injury process have led to the hypothesis that pharmacological treatments which interrupt the secondary cascade, if applied early, could improve CNS tissue survival, and preserve the necessary anatomic substrates for functional recovery to take place. The goal of ameliorating the secondary injury is referred to as neuroprotection. Several reviews of poststroke, TBI or SCI secondary injury have been published [1–5].

In SCI, the secondary events occur initially in central gray matter and then spread to the surrounding white matter. The key issue in predicting recovery of function is the degree of preservation of the ascending and descending white matter tracts. However, many of the surviving white matter tracts do not conduct impulses due to posttraumatic demyelination or incomplete remyelination (that is, dysmyelination). Therefore, the goal of neuroprotective pharmacotherapy in SCI is to preserve as many of the white matter axons and as much of their investing myelin as possible. In TBI, a key determinant in neurological recovery is also the loss of axons. Based upon the often widespread loss of axons in injured brain, this phenomenon is referred to as diffuse axonal injury. However, it should be realized that a significant factor in influencing extent of neural injury both in TBI and SCI is a decrease in brain or spinal cord microvascular perfusion (that is, secondary ischemia). When this occurs, the result is an exacerbation of the injury process due to superimposed tissue ischemic hypoxia. Moreover, deficiencies in CNS hypoperfusion can be aggravated by systemic hypotension and/or hypoxia. Thus, it is important to note that secondary injury involves both parenchymal and microvascular events.

For focal ischemic stroke, the goal is to limit the extent of the infarction by preventing secondary injury in the partially perfused penumbral region surrounding the core of the infarct. For CA/CPR, which involves a transient global ischemic insult, the aim is to prevent the secondary degeneration of selectively vulnerable neuronal populations (for example, CA1 region of the hippocampus, layers 3, 5 and 6 of the cortex and intrinsic neurons of the caudate) that are caused by a combination of the ischemic episode plus the reperfusion of the brain after successful resuscitation (that is, reperfusion injury). In SAH, the main focus of attention has been on finding pharmacological ways to prevent the delayed vasospasm phenomenon that leads to secondary ischemic brain damage that might be focal or global in its extent. For ICH, the goal is to limit the deleterious effects of the hematoma on the surrounding tissue by preventing edema and ischemic damage.

Neurorestoration

Another approach to the treatment of acute neurological injuries involves the attempt to restore lost neurological function once the extent of the acute injury to the brain

or spinal cord and associated neurological deficits has stabilized. Until a decade ago, it was firmly believed that once the brain or spinal cord was damaged by the secondary injury process, there was little, if any, capability for regeneration of axons and formation of new synapses to take place. However, over the last several years, it has been discovered that the CNS is indeed capable of significant structural and functional repair, plasticity and regeneration that might be pharmacologically or otherwise enhanced. Approaches for accomplishing this include reawakening the growth potential of the surviving neurons or antagonizing the multiple inhibitory factors that interfere with axonal growth and synaptogenesis. Alternatively, cellular replacement may be achievable in certain brain regions which possess nascent neural stem cells. It is increasingly apparent that these endogenous stem cell populations in brain and spinal cord might be pharmacologically stimulated to divide and differentiate into neuronal or oligodendroglial precursor cell types and ultimately neurons and remyelinating oligodendroglia, respectively. Indeed, the molecular mechanisms that control neurogenesis and gliogenesis can be targets for pharmacological intervention. Several pharmacological mechanisms can be targeted to enhance the function and/or structural plasticity of neuronal pathways that survive the ravages of postischemic or posttraumatic secondary injury [6–9].

Acute Neurological Injury Models

A listing of the in vivo models of acute neurological injury (that is, ischemia, hemorrhage, TBI and SCI) that have been or are currently being utilized for preclinical evaluation of neuroprotective or neurorestorative agents are provided in table 1.

Focal Ischemic Stroke Models

Various stroke models have been developed during the past 20 years [10]. However, the main ones in use today are the unilateral middle cerebral artery occlusion (MCAO) models used in rats and mice. Since these models were first developed in the 1980s, the MCAO has been variably induced by surgical ligation or cauterization via a small craniotomy over the middle cerebral artery (MCA), passage of an intraluminal nylon suture up into the ipsilateral cerebral circulation via the external carotid in the neck or via injection of a small autologous thrombus into the common carotid artery. The latter 2 are the most commonly employed today, and the thromboembolic paradigm is the most clinically relevant since the majority of human focal ischemic strokes involve a thromboembolic occlusion of the MCA. The MCAO models come in 2 varieties, temporary and permanent. The temporary MCAO involves removal of the vascular occlusion at varying times (30, 60, 90, 120 and 180 min) after the onset in order to allow reperfusion of ischemic tissue to take place. This is accomplished by surgical removal of the extraluminal or intraluminal occlusion device, and mimics either the instance where spontaneous thrombus dissolution may take place during

Table 1. In vivo models employed for discovery of neuroprotective and neurorestorative agents

Stroke (focal ischemia)
Rat, mouse, cat or monkey temporary MCAO-microclip or intraluminal suture for 30 min to 2 h
Rat or mouse permanent MCAO-electrocoagulation or intraluminal suture
Cardiac arrest/resuscitation (transient global ischemia)
Rat 2-vessel (bilateral carotid) occlusion plus hypotension for 5–30 min
Rat 4-vessel occlusion for 5–30 min (permanent bilateral vertebral artery electocoagulation followed 24 h later with transient bilateral carotid occlusion)
Gerbil bilateral carotid occlusion for 5–15 min
Swine or canine cardiac arrest/resuscitation model with varying duration of arrest
Hemorrhagic stroke models (SAH or ICH)
Rabbit, cat or dog intra-cisterna magna injection of autologous blood
Rat intracranial injection of autologous blood via dorsolateral cranial burr hole
Monkey SAH via surgical placement of autologous blood clot around base of MCA
Rat striatal ICH
TBI
Diffuse
Rat or mouse fluid percussion – can be combined with hypotension or hypoxia
Rat impact acceleration – can be combined with hypotension or hypoxia
Mouse weight drop
Pig or primate rotational acceleration (nonimpact)
Focal
Rat or mouse controlled cortical impact
Axonal
Mouse optic nerve stretch
Subdural hematoma
Rat intracranial injection of autologous blood via dorsolateral cranial burr hole (same as SAH model)
SCI
Weight drop contusion
Wrathall device and model
Rat New York University (MASCIS) device and model
Rat Ohio State University (ESCID) device and model
Rat or mouse University of Kentucky (Infinite Horizons) device and model
Compression
Rat aneurysm clip compression (Fehlings and Tator model)
Cat weight compression (Anderson model)
Combination contusion and compression
Rat contusion followed by placement of Teflon wedges underneath vertebrae
Ischemic injury
Rabbit balloon in descending aorta inflated transiently above level of lumbar spinal arteries
Rat laser photoablation (Rose Bengal dye intravenously)
Excitotoxic injury
Kainic, quisqualic or ibotinic acid or dynorphin spinal cord microinjection
Regeneration models
Spinal cord transection, resection or hemisection
Dorsal rhizotomy

the first 3 h after the beginning of the stroke due to activation of endogenous thrombolytic processes (believed to be a fairly rare occurrence), or the situation in which tissue plasminogen activator (tPA) is used for the purpose of dissolving the clot and restoring recirculation. Although removal of the vascular occlusion and reestablishment of the normal cerebral circulation is an obviously desirable therapeutic goal, it is well known that it can lead to reperfusion injury, caused by a burst of reactive oxygen species in the previously ischemic brain tissue. Thus, there is a need for neuroprotective agents to reduce the pathophysiological events from the initial ischemic insult and the subsequent deleterious side effects of recirculation. Accordingly, the temporary MCAO models are most useful for evaluating neuroprotective strategies that are used in conjunction with tPA and other treatments to reestablish blood flow. The effectiveness of pharmacologic thrombolysis decreases rapidly within 5 h of the onset of ischemia. Because of the narrow therapeutic window, currently only a small fraction of ischemic stroke patients receive treatment. Furthermore, MCAO animal studies have shown that reperfusion beyond the first 3 h does not lessen the extent of ischemic damage. Thus, the temporary MCAO models, although widely used in stroke research, actually have limited relevance to the majority of MCA territory strokes.

Another variety of focal ischemic stroke model, the permanent MCAO, where the occlusion is permanently left in place, may be a better model of the vast majority of strokes where recirculation has not been reestablished either spontaneously or pharmacologically during the critical first few hours after stroke onset. In this instance, the therapeutic goal is to reduce the expansion of the ischemic damage from the severely ischemic core area into the surrounding penumbral area. The ischemic penumbra is potentially salvageable for several hours due to its partial circulation from collateral blood vessels. While the permanent MCAO version may be the best option for preclinical evaluation of potential neuroprotective agents, testing of compounds in the temporary MCAO paradigm is also recommended. In either model, historically, investigators have used reductions in infarct size after short periods of observation (that is, 7 days) as the primary endpoint. This is not an ideal outcome measure since infarct size correlates poorly with functional outcome.

Most current stroke research with either the temporary or permanent MCAO models is carried out in mice or rats. The primary endpoints are generally behavioral and in motor or neurological function typically determined between 24 and 72 h after stroke onset, and sometimes after longer periods of time. However, MCAO models have been developed and are occasionally used in higher species including the cat, monkey and baboon; the use of these animal models for neuroprotective drug evaluation carries considerable expense. Some investigators believe that it is important to replicate pharmacological neuroprotective actions in these gyrencephalic species prior to movement of the compound into human clinical trials. In actuality, there is no solid comparative evidence that supports the notion that neuroprotective effects seen in rodent stroke models are not predictive of human efficacy. Furthermore, there

are presently no firm data which support the commonly held idea that the therapeutic time window for a particular neuroprotective mechanism in a rat stroke model (for example 1 h) may be longer in nonhuman primates or humans (for example 6 h). On the contrary, the fact that various neuroprotective compounds which demonstrated a rather limited (1–2 h) therapeutic window for reduction of infarct size in rat MCAO models subsequently failed to improve outcome of stroke patients in clinical trials where the treatment initiation time varied from 6 to 24 h is consistent with the concept that the therapeutic window for neuroprotective effects may not be all that different between rodents and primates. At least no difference has been firmly demonstrated.

Cardiac Arrest/Resuscitation (Transient Global Ischemia) Models

Cardiac arrest produces immediate total body ischemia. Upon successful resuscitation, the previously ischemic organs, including the globally ischemic brain, are reperfused with blood and in the process suddenly flooded with oxygen. As noted before, this reperfusion/reoxygenation, while essential for maintenance of life, can nevertheless result in reperfusion injury. The combination of the ischemic insult plus the subsequent reperfusion injury phenomenon can damage selectively vulnerable neurons in proportion to the duration of blood flow interruption. The therapeutic goal is to mitigate this secondary neuronal injury which does not become fully manifest until between 24 and 48 h and perhaps a month after the insult. The most straightforward animal models involve the induction of a human-like cardiac arrest and resuscitation within the next several minutes. Most such studies have been performed in dogs, but rat, mouse and swine models are also utilized.

The vast majority of cardiac arrest/resuscitation neurologically focused studies utilize rodent models of transient global cerebral ischemia without stopping and restarting the heart. This general approach allows for cerebral ischemia like that occurring in cardiac arrest in humans to be studied in isolation. Of the 3 commonly used transient global cerebral ischemia models, the oldest is the gerbil bilateral carotid occlusion model. The gerbil brain has a high incidence of an incomplete Circle of Willis due to lack of the posterior communicating arteries that in other mammals connect the basilar to the carotid circulation. Therefore, 5 min of forebrain ischemia followed by reperfusion in the gerbil leads to a selective loss of hippocampal CA1 neurons that is apparent by 48 h; 10–15 min results in broader hippocampal damage as well as loss of cortical, striatal and nigrostriatal neurons [11, 12]. The gerbil model has fallen out of favor due to a high degree of interanimal variability based upon the fact that the circulatory anomaly is inconsistent with some gerbils having one or both posterior communicating arteries. Two other commonly used rat transient forebrain ischemia models are the 2-vessel occlusion plus hypotension paradigm developed by Siesjo and colleagues nearly 25 years ago [13, 14] and the 4-vessel occlusion model which involves prior surgical cauterization of the vertebral arteries followed by transient occlusion of both carotid arteries for 5–20 min [15, 16]. Brief episodes of forebrain

ischemia (5–10 min) in either model produce selective hippocampal CA1 damage with longer episodes (10–20 min) producing additional damage in the cortex and striatum. Efficacy of neuroprotective compounds in the transient forebrain ischemia models suggests that these might be useful in cardiac arrest and resuscitation. However, confirmation of efficacy should be obtained in an actual cardiac arrest resuscitation model with improved survival, neurological recovery and a reduction in neuronal damage.

Hemorrhagic Stroke Models

As noted earlier, the 2 basic types of hemorrhagic strokes are ICH and SAH. For the former, the approach is simply to inject a volume of the animal's own blood directly into brain parenchyma followed by an analysis of the volume of damage to the surrounding brain tissue. In the latter, most models involve injection of a volume of autologous blood, withdrawn immediately prior to SAH induction from the systemic circulation of the animal (for example, pig, rat, cat, rabbit and dog), into the subarachnoid space via injection into the cisterna magna or over one of the cerebral hemispheres via a small burr hole and puncture of the dura mater covering the brain. Common endpoints for drug evaluation include measurement of blood-brain barrier compromise or decreases in cerebral blood flow during the first several post-SAH hours or the assessment of cerebral vasospasm by histological or arteriographic methods between 2 and 7 days. A sophisticated SAH model involves the neurosurgical placement of an autologous blood clot around the base of the MCA in monkeys followed by arteriographic and histological ischemic damage measurements at 7 days. However, the cost of evaluating a single-dose level of a drug for its ability to inhibit delayed cerebral vasospasm in that model runs into the hundreds of thousands of dollars.

Subdural Hematoma Model

The rat lacks an arachnoid membrane, and thus the rat version of the SAH model involving injection of blood through the dura mater can also be thought of, and employed, as a subdural hematoma model. When autologous, nonheparinized blood is injected through the dorsal burr hole through the dura mater, it typically forms a clot over the dorsal surface of the brain mimicking a posttraumatic subdural hematoma, similar to the management of human subdural hematomas, the experimental protocol involves surgical removal of the clot at a specified time followed by histological measurement of ischemic damage caused by the hematoma [17].

TBI Models

In vivo TBI models include 3 basic types: diffuse, focal and axonal injury (table 1) [18]. Of the 3 diffuse injury models, the first is the rat fluid percussion TBI paradigm in which a transient hydraulic pressure pulse is applied to the exposed dura mater either over the midline of the brain or laterally over one of the hemispheres.

The second is the rat impact-acceleration injury model in which a 0.5 or 1.0 kg weight is dropped onto a steel helmet cemented onto the exposed skull, and the third is the mouse weight-drop concussion paradigm. The pig or primate rotational acceleration models are useful for studying the phenomenon of diffuse axonal injury.

For the induction of focal TBIs, a controlled cortical impact model is widely used in either rats or mice and involves the infliction of a contusion injury through a small craniotomy. The magnitude of the injury is generally varied by the depth of the cortical indentation (usually 0.5–1.0 mm in mice and 1.0–2.0 mm in rats). The controlled cortical impact model mimics TBI-induced brain contusions, although a recent study has shown that the subsequent neurodegeneration is not as focal as generally thought [19]. A relatively new in vivo model utilizing a controlled stretch of the optic nerve in mice has been developed to examine the effects of stretch injury on axons.

SCI Models

Many SCI paradigms have been developed over the past 100 years. As shown in table 1, for evaluation of neuroprotective agents, the current rodent models use contusion, compression, ischemic and excitotoxic injury mechanisms. By far, the contusion models predominate in the experimental acute SCI field, and in particular the New York University [20] and University of Kentucky [21] controlled contusion devices dominate acute SCI research. For investigations of axonal regeneration in the injured spinal cord, either complete transaction or hemisection of the spinal cord or dorsal roots (rhizotomy) followed by histological assessments of axonal growth across the lesion site is used. Assessment of neurological recovery in rat SCI models most commonly employs the Basso/Beattie/Bresnahan locomotor recovery assessment tool (BBB Score) [22]. However, a variety of other motor recovery assessment tools are also often employed along with the BBB scoring system.

Pediatric Stroke and TBI Models

Ischemic brain injury and TBI occur in children and adults, and there is an alarming incidence of neonatal and pediatric stroke and TBI [23, 24]. Over the past several years, there has been an increasing realization that the response of the brain to ischemic brain injury or TBI in infants and children differs from the adult brain in regards to pathophysiology, secondary injury processes, cell death mechanisms (for example, necrotic vs. apoptotic), susceptibility of different brain regions and the capacity for plasticity and recovery [23–26]. This has prompted the development of stroke and TBI models in immature animals that are either uniquely designed for younger animals or are scaled-down versions of adult stroke or TBI models in either rodents or larger animals [23, 25–29]. Clearly, the development of therapies for acute neurological insults in the pediatric population should be preceded by studies of these in models employing immature animals.

What Have Previous Clinical Trials of Neuroprotective Agents Taught Us about the Needs for Preclinical Drug Evaluation in Animal Models?

In the early 1980s, pharmaceutical companies began developing neuroprotective drugs for the acute treatment of stroke and CNS injury. Eventually, many compounds made their way into large double-blind multicenter phase III clinical trials for stroke (ischemic and SAH), TBI and/or SCI. These efforts, which dominated neuroprotective clinical trials in the late 1980s and 1990s, were primarily directed at 3 general pharmacological mechanistic strategies to interrupt secondary injury processes: (1) inhibition of glutamate-mediated excitotoxicity [glutamate receptor antagonists and γ-amino-butyric acid (GABA) agonists], (2) reduction of intracellular calcium overload (L-type calcium channel blockers) and (3) interruption of reactive oxygen-mediated damage (free radical scavengers/antioxidants). Unfortunately, despite the multiple trials and literally hundreds of thousands of patients studied, little clinical benefit has resulted from these efforts as briefly reviewed below.

Glutamate Receptor Antagonists

Multiple glutamate receptor antagonists were taken into phase II and III trials, including the competitive NMDA receptor antagonists selfotel (CGS 19755) and aptiganel (CNS 1102) which block the binding of glutamate to its receptor complex recognition site, eliprodil which blocks the polyamine site and CP-101606 which blocks the NR2B subunit on the NMDA receptor complex. None of these produced a statistically significant improvement in neurological recovery in TBI or ischemic stroke trials [30, 31].

GABA Receptor Agonists

Another mechanism for countering glutamate excitotoxicity is to increase GABA-mediated inhibitory transmission with the administration of GABA receptor agonists. This approach resulted in the clinical evaluation of the GABA partial agonist compound chlomethiazole in a phase III stroke trial. However, no significant beneficial effect was demonstrated [30, 31].

Calcium Channel Blockers

Accumulation of intracellular calcium plays a major role in secondary injury after CNS injury or stroke. One mechanism for postinsult calcium overload involves depolarization-induced entry via voltage-dependent L-type channels. Accordingly, the first neuroprotective approach to be tested in phase III clinical trials in TBI or stroke was the competitive L-type calcium channel blocker, nimodipine, which was entered into the clinical trials in the late 1970s. In 2 different phase III multicenter TBI (moderate and severe) trials [32] and a single-stroke trial [31], no overall benefit was revealed with nimodipine treatment. However, retrospective analysis of the TBI trials has revealed that nimodipine may improve outcome in

patients with traumatic SAH (tSAH) [32]. This is not an insignificant finding since about half of all patients with severe TBI, have tSAH as part of the pathophysiology. Furthermore, nimodipine has been shown to produce a slight, but significant increase in survival in aneurysmal SAH patients and have been approved in most countries for the treatment of that condition. Indeed, nimodipine represents the first agent to be approved for neuroprotective use even though much of its effect is probably mediated via protection of the microvasculature and vasodilation-mediated improvements in cerebral blood flow. Due to a manifestation of its microvascular vasodilation, the compound must be used with care, since it can lower arterial and cerebral perfusion pressures which can exacerbate posttraumatic, postischemic or post-SAH secondary brain injury.

Free Radical Scavengers

In order to interrupt reactive oxygen damage, the polyethylene conjugated form of the superoxide radical scavenger Cu/Zn superoxide dismutase (PEG-SOD) was evaluated in trials conducted in moderate and severe TBI patients. Although a positive trend was found in an initial small phase II trial [33], subsequent phase III trials failed to show any enhancement of neurological recovery [34].

A bigger development program was undertaken with the 21-aminosteroid lipid peroxidation inhibitor tirilazad. Tirilazad was extensively evaluated in animal models of SCI, TBI, ischemic stroke and SAH, and shown to exert a variety of neuroprotective and vasoprotective effects [35, 36]. Based upon these preclinical studies, clinical trials of tirilazad were conducted in TBI [34, 37], SAH [38], ischemic stroke [30, 31] and SCI [39]. In TBI, an initial North American trial of 1,100 patients comparing tirilazad treatment with placebo for 5 days, either initiated 4 h after injury, ended with such a confounding randomization imbalance that no meaningful efficacy analysis could be extracted. In contrast, a successfully completed European phase III trial failed to show an overall effect in moderately and severely injured patients. However, post hoc analysis revealed that the compound significantly improved survival in both moderately and severely injured male patients with tSAH [37]. This beneficial effect in the tSAH subgroup, which represents about half of severe TBIs, was not surprising, since the drug had previously been shown to improve recovery and survival in a phase III trial in aneurysmal SAH patients [38]. Interestingly, this effect in tSAH and aneurysmal SAH was mainly apparent in male patients. This gender difference was found to be partially due to a faster rate of metabolism of the drug in females. Nevertheless, subsequent female-only trials with higher tirilazad doses that were calculated to duplicate the exposure levels in males did not reveal the same level of efficacy as seen in male patients, although beneficial effects were apparent in the more severe SAH females [40, 41]. The issue of gender differences in neuroprotective drug responsiveness clouds the interpretation of tirilazad's as well as other drugs' neuroprotective efficacy.

Tirilazad was also extensively evaluated in 4 different phase III stroke trials [30, 31]. The first 2 (TESS I in Europe and RANTTAS I in the US) evaluated the effects of 6 mg/kg intravenously per day for 3 days with treatment beginning within 6 h after onset of the stroke. No effect was seen on 3- or 6-month outcome. Two subsequent higher dose trials (10 mg/kg per day in males; 15 mg/kg per day in females) were conducted. The first of these, the European TESS II which included patients enrolled within the first 6 h of the stroke, was stopped prematurely due to a significant increase in morbidity and mortality in the high-dose tirilazad group. Prudence dictated the simultaneous cessation of the parallel US high-dose RANTTAS II trial. However, subsequent analysis of the 3-month recovery scores of the approximately 100 patients who had already been enrolled in RANTTAS II revealed a nearly significant improvement in neurological recovery. The only difference between the 2 trials was that in TESS II, the enrollment window was 6 h, whereas in RANTTAS II, treatment began within 4 h. The contrasting results of TESS II and RANTTAS II indicate that tirilazad may be effective in stroke patients if given in the first 4 h, but may in fact be harmful if delayed until 6 h. Another issue besides the therapeutic window is the issue of how long to maintain treatment. The decision to treat stroke patients in all tirilazad trials for 72 h was based on the limits of safety rather than on a demonstration of the benefits of such lengthy treatment in preclinical stroke models [35]. The toxicity of the drug in TESS II indicates that it is possible to overtreat with the drug. Thus, the possibility exists that a shorter treatment duration may have yielded more positive results. The fact that neither the optimum therapeutic window nor the optimal treatment duration were ever determined for tirilazad or any other neuroprotective drug prior to their being advanced into clinical trials for TBI or stroke may have played a role in the failures of NMDA antagonists, the calcium channel blocker nimodipine and the antioxidants PEG-SOD and tirilazad in achieving an overall beneficial effect.

Most recently, the nitrone-based free radical scavenger NXY-059, which had been more thoroughly tested in stroke models than any previous stroke-directed neuroprotective compound [42], was evaluated in phase III trials in ischemic stroke. Although an initial trial showed an apparent benefit [43], a subsequent larger trial failed to confirm the efficacy of the drug [44].

This brief history of neuroprotective drug discovery and development over the past 20–25 years could be fairly characterized as a series of often high profile and expensive failures. Although these have largely dampened the enthusiasm of the pharmaceutical industry for this therapeutic area, much has been learned from them that could, and should, serve as a roadmap for future efforts aimed at pharmacological neuroprotection and improved neurological recovery after stroke, TBI and SCI. Postmortem analyses of mistakes made in stroke [30, 31] and TBI [32] drug development have been published and a careful reading of them reveals a host of shortcomings in past preclinical testing of candidate neuroprotective agents and in clinical trial design and conduct that need to be addressed in the future. A summary is provided in table 2.

Table 2. Reasons for past failures in neuroprotective drug discovery and development

Inadequate understanding of secondary injury mechanisms
Lack of definition of time course of glutamate receptor functional changes
Lack of definition of the sources and spatial and temporal characteristics of reactive oxygen generation → inability to rationally determine therapeutic window and optimum treatment duration
Lack of understanding of the interrelationship of secondary injury mechanisms
Focus on secondary injury mechanisms with short therapeutic windows → need to identify and target injury mechanisms with longer therapeutic windows
Lack of understanding of the relative therapeutic windows in animal models and humans; is the time course of secondary injury in mice, rats and men similar?
Inadequate preclinical testing
Lack of testing in multiple models
Failure to compare efficacy in male and female animals
Incomplete dose response and definition of therapeutic plasma levels
Incomplete definition of therapeutic window
Lack of definition of pharmacokinetics, timing of needed maintenance dosing and optimum treatment duration
Poor clinical trial design
Gross mismatch between preclinical and clinical testing
Imprecise outcome scales (Glasgow Coma Scale; Glasgow Outcome Scale; ASIA scale, NIH stroke scale)
Lumping of all kinds of ischemic strokes or moderate and severe TBIs
Lack of identification and a priori plan to analyze subgroups (tSAH; MCA territory strokes)
Lack of biomarker to follow the progression of the pathophysiology and monitor mechanistic drug effects
Lack of standardization of neurorehabilitation protocols

First of all, the discovery of the first generation of neuroprotective agents including glutamate receptor antagonists, calcium channel blockers and antioxidants occurred prior to the elucidation of an adequate understanding of the intricacies of the targeted secondary injury mechanisms. In each case, there was an inadequate knowledge of the time course and interrelationships of these events, their therapeutic windows for effective treatment intervention and how these were either similar or different between species, injury models, genders as well as between animals and humans. In the case of reactive oxygen mechanisms, our knowledge of the key reactive oxygen species as well as their sources and cellular targets was inadequate to guide the design of optimum antioxidant neuroprotective compounds. Secondly, the preclinical efficacy testing of compounds was often woefully inadequate and even naïve. From this experience, we can derive several lessons that need to be considered in preclinical evaluations of neuroprotective agents so that the chance of translational success in clinical trials is maximized.

Issues that Need to Be Addressed in Preclinical Neuroprotective or Neurorestorative Drug Evaluation

Neuroprotective Drug Evaluation

The following issues/questions need to be addressed in preclinical evaluation of drugs for acute neuroprotection.

1 A thorough demonstration of the time course of the target pathophysiological mechanism in relevant animal models is necessary to determine when treatment needs to begin and how long it must be maintained. This must be done in both male and female animals based upon several studies showing that the magnitude and duration of post-ischemic and posttraumatic pathophysiology may differ greatly between genders in certain models [45–50].
2 A rigorous dose-response analysis in regards to effects on the target mechanism, ability to reduce posttraumatic neurodegeneration and improve behavioral and neurological recovery is necessary.
3 A correlation of neuroprotective action with plasma and CNS tissue pharmacokinetics; that is, a definition of the effective neuroprotective concentration and a dosing protocol that is adequate to maintain the therapeutic concentration for as long as the target secondary injury mechanism is active is needed.
4 A comparison of single- versus multiple-dose regimens in order to establish optimum treatment regimen (intravenous bolus plus infusion make the most sense) should be undertaken.
5 A determination of the therapeutic window in order to know how early treatment must begin is necessary. It has been argued that even if a particular agent only has a 1-hour window in a rat stroke, TBI or SCI model, the window in humans with the corresponding condition is likely to be much longer. However, there is little evidence to support this assumption. Consequently, clinical trial design should take the preclinical therapeutic window definition for a particular agent seriously in regards to how soon the compound may need to be given to patients. With this in mind, a failure to demonstrate a clinically practical therapeutic window for a particular agent in an animal model may mean that this agent and its corresponding secondary injury mechanism may be too short to be effectively addressed in real world therapeutics.
6 The above-mentioned parameters dose response, optimum treatment duration and therapeutic window are most likely to vary between TBI, ischemic stroke, cardiac arrest/resuscitation, SAH and SCI models.
7 A comparison of the neuroprotective pharmacology (dose response, optimum treatment duration and therapeutic window) in multiple injury models (focal versus diffuse TBI) in order to determine whether the agent in question only works in certain types of injuries is needed.
8 A comparison of the neuroprotective pharmacology in male versus female animals is necessary.
9 A determination of pharmacodynamic and pharmacokinetic interactions with other commonly used ancillary treatments (anticonvulsants, minor and major tranquilizers) should be undertaken.

10 Health characteristics of animals must be taken into consideration. While much has been learned from preclinical ischemia studies concerning mechanisms of injury and neuroprotection, it must be considered that the animal models of ischemia do not closely mimic the human disease. In most cases, animals that are studied are usually young, normal, healthy animals, whereas humans suffering the diseases/disorders mentioned often have other existing morbidities, such as age, hypertension, diabetes, myocardial infarction, arrhythmias or other ongoing disease processes. These ongoing disease processes likely alter how and when therapies may be effective.

For a further discussion of the ideal characterization of an acute neuroprotective agent, the reader is referred to the chapter by del Zoppo et al. [this vol., pp. 34–38] which discusses the STAIR criteria for preclinical evaluation of therapies for acute stroke.

Neurorestorative Drug Evaluation

The issues/questions discussed above for testing of neuroprotective drugs are equally relevant to neurorestorative drug evaluation:

1 A definition of the time course of endogenous repair mechanisms (trophic and growth factor expression, growth-associated protein expression) is necessary.
2 A rigorous dose-response analysis in regards to effects on the target mechanism and ability to improve behavioral and neurological recovery is required.
3 A correlation of neurorestorative action with plasma and CNS tissue pharmacokinetics is needed; that is, a definition of the effective neurorestorative concentration, be it cellular or pharmacologic, and a dosing protocol that is adequate to maintain the therapeutic concentration for as long as it is needed to maximize the behavioral recovery improvement.
4 Optimum treatment regimen should be established (Is chronic short-term treatment all that is required?).
5 A determination of the therapeutic window is necessary in order to know how early treatment must begin.
6 A comparison of the neurorestorative pharmacology and cellular therapy (dose-response, optimum treatment duration and therapeutic window) in multiple injury models (focal vs. diffuse TBI) is required in order to determine whether the agent in question only works in certain types of injuries.
7 A comparison of the neurorestorative approach in male versus female animals is needed.
8 A determination of pharmacodynamic and pharmacokinetic interactions with other commonly used ancillary treatments (anticonvulsants, minor and major tranquilizers) should be undertaken.

Gene and Cellular Therapies

The principles and needed therapeutic definitions outlined above for neuroprotective or neurorestorative drugs are equally applicable to the preclinical evaluation of gene

or cellular therapies for either acute neurological injuries or chronic neurodegenerative conditions. What is the ideal number of gene copies or cells needed to achieve the best effect (that is, dose)? What is the ideal timing for gene vector administration or cellular transplant (that is, therapeutic window)? Is a single administration all that is required or is repeated administration or transplant needed in order to maximize efficacy (that is, optimum duration of treatment)? Do gender-based hormonal differences or ancillary drug treatments make a difference in the response to gene administration or transplant survival and proliferation?

Utility of Transgenic and Gene Knockout Models for Preclinical Therapeutic Evaluation

The development of transgenic and genetic knockout (KO) technologies in mice (and to some extent in rats) has provided important tools that have helped to identify and validate the importance of certain secondary injury mechanisms as well as genes that control neuronal repair, plasticity and axonal regeneration. These have been employed extensively over the past decade in neurological research. For example, the importance of oxidative damage mechanisms in acute neurological injury models has been confirmed by the demonstration that if one increases the expression of certain antioxidant genes (such as Cu,Zn superoxide dismutase) by incorporation of multiple copies of that gene into the mouse genome, this results in a decreased sensitivity to ischemic or traumatic insults [51]. Alternatively, genetic knockout of the same antioxidant gene increased vulnerability of the CNS to the same injuries [51]. However, certain caveats are often cited in regards to the use and interpretation of genetically modified mice. One of the main ones is that the overexpression or KO of a gene does not necessarily occur in isolation. Changes in one gene may lead to upstream or downstream changes in the expression of other genes which play a role in the phenotype of the model.

An increasingly employed contemporary strategy for controlling genetic overexpression or KO is through the use of gene constructs that include a switch for regulation of the temporal expression of the gene in question via activation or inhibition of the promoter region of the gene. This strategy, referred to as conditional overexpression or more commonly conditional KO, typically involves a genetic response element (switch) that can be triggered to turn off gene expression upon administration of a drug. The most common one is the TET-OFF switch which shuts off the expression of the target gene upon administration of the tetracycline compound doxycycline via the drinking water. Cessation of doxycycline administration usually allows the gene to come back on. This technology is being increasingly applied in neurological research. For instance, conditional KO mice are being used to explore the role of certain matrix proteins in TBI models [52] and the effects of altered neurofilament expression in neuronal structure and function [53], just to name 2 examples. This approach lessens

the problem seen in nonconditional transgenic and KO mice in which the chronic change in one gene may cause changes in other genes such that the phenotype is not specifically related to the changes in expression of the target gene. Moreover, the conditional on-off approach allows for the manipulation of genes, whereas if they were knocked out permanently in the mouse, the result would be embryonic or early postnatal lethality.

In addition to the control of the temporal expression of a gene, it is now possible to specifically manipulate the expression of a particular gene in specific brain regions. This region-specific KO is accomplished by use of the Cre recombinase (also known as Cre-Lox) technology in which mice are first generated with an inducible tissue-specific promoter for expression of Cre. These mice are crossed with a second mouse line in which the gene of interest can be knocked in by flanked Cre recognition sequences known as Lox-P sites. The target gene in the resulting double transgenic mouse is then induced through administration of a drug [54]. One recent application of this technology involved an examination of the role of vascular endothelial growth factor in regulating brain angiogenesis and neuronal apoptotic cell death [55]. Lastly, it is now possible to develop conditional KO mice in which a gene of interest can be knocked out in a particular cell type such as in astrocytes [56] or endothelial cells [57].

Although there may be some applications of genetically modified mice in drug testing, these technologies are mainly useful for identifying the physiological or pathophysiological role of certain candidate genes and validation of potential neuroprotective or neurorestorative therapeutic targets.

Outcome Measures in Preclinical Models

A multitude of physiological, neurophysiological, neurochemical, histological, imaging and behavioral outcome measures have been employed in animal models of acute neurological injury. The choice of endpoints depends upon the species, the particular acute insult, the main pathophysiological elements, whether the therapeutic approach is neuroprotective or neurorestorative and whether the target mechanism is known and measurable. In general, the preclinical evaluation of potential therapies should include multiple endpoints. Table 3 lists the main endpoints/outcome measures and their timing range that have been employed for therapeutic efficacy evaluation in models of the different types of acute neurological insults.

Restrictions and Ethical Considerations in Animal Studies

Animal modeling in the acute neurological injury arena is associated with a higher degree of relevance for therapeutic evaluation due to the fact that the current stable of models are able to reliably replicate human traumatic, ischemic or hemorrhagic neurological

Table 3. Endpoints and outcome measures commonly employed in in vivo models for discovery of neuroprotective and neurorestorative agents

Indication	Endpoints/outcome measures	Timing
Stroke (focal ischemia)	Metabolic imaging (PET, MRS)	minute→ hours
	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Physiological – CBF, edema	minutes → hours
	Infarct size – histological or by MRI	24 h → 7 days
	Behavioral recovery – multiple scales	24 h → 7 days
Cardiac arrest/resuscitation (transient global ischemia)	Metabolic imaging (PET, MRS)	minutes → hours
	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Physiological – CBF	minutes → hours
	Neurophysiological – evoked potential, EEG	minutes → hours
	Histological assessment of neuronal loss	3 h → 7 days (sometimes longer
	Survival and behavioral recovery	24 h → 7 days (sometimes longer)
Hemorrhagic stroke models (SAH or ICH)	Physiological – CBF, BBB opening, edema	minutes → hours
	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Biochemical measurements in SAH clot	1 → 7 days
	Cerebral vasospasm – angiography	48 h → 7 days
	Histological assessment of ischemic damage	48 h → 7 days
TBI	Metabolic imaging (PET, MRS)	minutes → hours
	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Physiological – CBF, BBB opening, edema	minutes → hours
	Histological assessment of neuronal/ axonal loss	24 h → 7 days
	Behavioral recovery – motor and cognitive scales	48 h → 28 days
Subdural hematoma	Metabolic imaging (PET, MRS)	minutes → hours
	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Physiological – CBF, BBB opening, edema	minutes → hours
	Histological assessment of neuronal/ axonal loss	24 h → 7 days
SCI	Neurochemical or immunohistochemical mechanistic markers	minutes → hours
	Physiological – SCBF	minutes → hours
	Neurophysiological – sensory or motor evoked potentials	minutes → hours → days 42 days
	Histological assessment of neuronal/ axonal loss	42 days
	Locomotor recovery	

injuries. In other words, the animal models are closer to the human condition. This has been achieved largely as a result of our fairly well-established understanding of the pathophysiology and neuropathology of human stroke, TBI and SCI, epilepsy, Alzheimer's disease and Parkinson's disease. Thus, the rationale for the use of animal models in the discovery of therapeutic approaches for these diseases is strong even though there are lingering questions about the similarity in the pathophysiological time courses in mice and rats versus humans. In sharp contrast, animal modeling of many of the psychiatric disorders currently involves guesswork and assumptions. Psychiatric disease models can at best emulate a particular aspect, but not the complete symptom complex seen for example in schizophrenia, depression or anxiety. However, despite the arguably greater validity of acute CNS injury models, because they each involve surgical preparation and inflicting damage to the brain or spinal cord, there is the possibility of pain and distress which must be considered and minimized by appropriate use of analgesics and other veterinary care. As with all types of animal models, approval for the use of CNS injury paradigms requires careful review by veterinary staff and an Institutional Animal Care and Use Committee to insure that the models are being used by competent investigators and that that the methods have been refined to minimize distress, alleviate pain and reduce the number of animals necessary for the conduct of good scientific evaluation. In regards to pain assessment and minimization, table 4 provides a pain assessment scale for use in mouse or rat CNS injury paradigms. Figure 1 shows an algorithm that can be used for pain management, should the pain assessment indicate that analgesic intervention is needed; however, it is exceedingly rare that analgesia is required. Moreover, although neither of the analgesics listed – carprofen, a nonsteroidal anti-inflammatory agent and buprenorphine, a κ-opoid receptor agonist – have been specifically examined in acute neurological injury models, other NSAIDS and κ-agonists have been shown to produce neuroprotective effects. Thus, the use of these analgesic agents might potentially complicate acute neuroprotection studies. However, current National Research Council Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) dictate that pain assessments and pharmacological analgesia be available should particular animals require it. The guidelines also call for the responsible minimization of the number of animals used. Concerning the responsible reduction of the number of mice, rats or other animals used in preclinical evaluation of therapies for acute neurological injuries, all models covered in this chapter have a long record of published use employing a variety of short-term and longer-term endpoints. Consultation of this literature can provide a clear idea of the variability and required sample sizes that are needed in the hands of experienced investigators.

Summary

This chapter on the role of animal studies in preclinical therapeutic evaluation has been set within the context of acute ischemic, hemorrhagic and traumatic injuries.

Table 4. Pain scale for rodents after cranial surgery

Criteria/score	0	1	2	3	Total
Locomotion	Moving normally around cage, not hugging the sides of the cage	Stumbling, falling or hugging the sides of the cage	Writhing, stumbling and/or falling; OR movement only when stimulated	No movement	
Pain on palpation of surgery site	None	Mild (occasional vocalization or pulls head back, or kicks at evaluator)	Moderate (frequent vocalization and pulls head back, or kicks at evaluator)	Severe (vociferous vocalization, withdraws head, bites, struggles)	
Behavior	Normal cage exploration, normal food and water consumption, animal calm in cage; previously social animal still social	Minimal exploration, increased or decreased food and/or water consumption; previously social animal has become withdrawn or aggressive	No cage exploration, hunched posture, anorexic for 24 h	No cage exploration, hunched posture, piloerection, anorexic, increased respiratory rate or labored breathing	
Appearance of incision	Clean, no scratching at incision, no redness, no swelling	Mild scratching at incision, redness, suture intact; mild swelling	Severe scratching, incision open; obvious swelling	Incision infected (redness, swelling, purulent drainage)	

Total pain score: _____
Initials: _____
Date: _____
Time: _____
Analgesic administered based on total pain score and flow chart: _____

Although there has been a long list of translational failures in regards to neuroprotective drugs for ischemic stroke and TBI, this experience has provided us with several valuable lessons in regards to what we did wrong in past efforts and what we need to do better to achieve translational success in the future. Among these lessons is the knowledge that preclinical evaluation of drugs, gene therapies and cellular transplantation in animal models needs to be thorough and define the optimal treatment

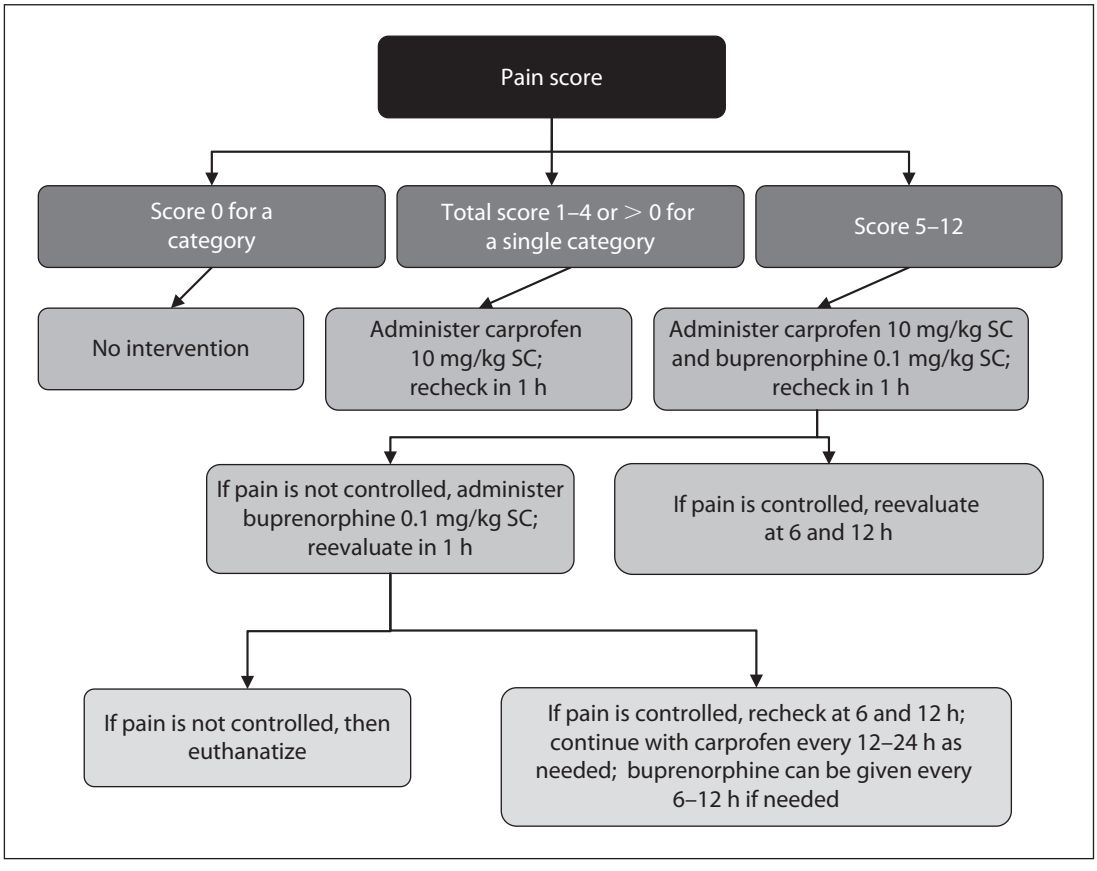

Fig. 1. Analgesic flow chart for rodents after cranial surgery.

parameters, that is, dose, timing, duration, gender differences in responsiveness and how other pharmacological treatments may positively or negatively impact neuroprotective or neurorestorative efficacy. Subsequent to a thorough preclinical evaluation, clinical trial design needs to carefully consider and take full advantage of the therapeutic parameters derived from animal studies. Although preclinical evaluation in animal models needs to be thorough and statistically rigorous, careful consideration of animal welfare and minimization of sample sizes should not be ignored in the process.

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Translating Interventions from Ischemic Stroke Models to Patients: The View in 2009

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Developing effective treatments for neurological diseases often requires animal models that simulate or replicate the fundamental pathophysiology of the disease in humans. This bench to bedside translation forms the foundation of medical therapeutics. The approach, although simple in concept, can be extremely difficult to actualize. The following discussion focuses on one such area, acute treatment of ischemic stroke. The lessons to be learned have a much broader application.

Because successful therapeutic translation from bench to bedside has been achieved in other diseases and in other specialties, there is no apparent reason why this should not also be possible for stroke. Success assumes, of course, that the targets are relevant, the agents protecting neurons and glia penetrate the brain, the time constraints for drug administration are taken into consideration and the patient population is well chosen and well studied. As outlined below, there is cause for uncertainty.

The Stroke Therapy Academic Industry Roundtable (STAIR) was convened in an effort to provide such a roadmap and to codify a uniform set of recommendations for preclinical and clinical drug development. Equally important, the initial conference provided a forum to begin a much-needed dialogue between the stroke community and industry. A summary of the major discussion points and recommendations was published for preclinical studies in the journal *Stroke*. [1]

Modeling Considerations by the STAIR Initiative

Nearly 10 years on, observations that were raised to the level of recommendations now suggest another look. It seems unlikely that drugs will be developed without first testing them in animal models of stroke. Discussions at the first STAIR emphasized the need to choose these models wisely. Most investigators begin testing in rodents

and if successful, progress to more complex species such as cats or nonhuman primates. Models are available for focal and global ischemia, although their natural histories and mechanisms are only overlapping, but not identical. The same drugs do not necessarily reduce injury in both models and the therapeutic targets may not be the same. Focal ischemia can be permanent or reversible. Factors to consider when choosing among these models include the therapeutic target, the in vitro data as well as pharmacokinetic characteristics of the tested agent. For example, mitigating oxygen free radical damage is best achieved in models of reperfusion and requires drug penetration into brain tissue. Hence, outcome is likely to be influenced by whether the drug penetrates the blood-brain barrier. Outcomes may also be influenced by perturbations in physiology caused by anesthesia and by the tested drugs. Temperature, blood pressure, blood gases and tissue pH all impact measures of tissue outcome and these variables must be monitored and controlled.

The importance of complete dose-response studies has been emphasized as has the need to achieve a robust effect in severe injury models replicated by multiple laboratories using multiple models.

Species and the choice of animal strain remain important considerations, especially in rodent studies; outcome measures in the C57BL6 murine strain, for example, may be different than SV129 [2]. These strain differences may impact studies using genetically engineered mice to dissect the importance of a particular protein such as nitric oxide synthase or superoxide dismutase. Strain differences may also prove significant in primate experiments (for example, considering marmosets, rhesus monkeys or the baboon). Although recommendations for a standardized model in nonhuman primates have not been promulgated, work over 40 years has clearly supported the model of focal ischemia in the baboon as pathophysiologically and neurologically most similar to humans [3, 4]. Sex differences have been emphasized and in general the female brain appears more resistant to ischemic insult than the male brain. These differences partly relate to the presence of gonadal hormones or possibly even sex differences in metabolism. Whether such differences relate to susceptibility in human males and females is not known.

The therapeutic window or the time period that drugs could reduce tissue injury after ischemic onset is the source of much discussion. The consensus is that early drug administration has the greatest chance to achieve maximum drug benefit. This conclusion appears sound and prudent based on preclinical and clinical data with plasminogen activators (thrombolytics), and in reperfusion models. However, the therapeutic window for a particular drug may not be the same in animals and humans. Moreover, the time of stroke onset in humans can only be estimated in the majority of cases. There are no well-established criteria to determine the duration of an ischemic injury, and this weakness does impact entry criteria in clinical trials. Such shortcomings notwithstanding, careful preclinical testing to determine whether a test agent does have a clinically appropriate therapeutic window was strongly recommended by STAIR.

The initial STAIR discussions also considered the importance and difficulties when drugs are combined to reduce ischemic injury. Drugs with different mechanisms might act additively or synergistically to protect tissue and both have been documented in animal models. Combinations can also extend the therapeutic window, an advantage when using rt-PA, and may reduce toxicity if lower doses are effective.

Another Look at the Problem of Translating Stroke from Animal Models to Humans

The general problem of effectively managing the consequences of ischemic stroke has been how to bring potential interventions through a series of models in preparation for clinical trials. There has also been concern over what constitutes the most appropriate questions to ask of these models, and how the answers might be applied to patients. The accepted approach has evolved from the premise that small animal models adequately mimic the pathophysiology of human ischemic stroke in mechanism and time course, and that the therapeutic targets are shared by small animals and humans. This approach also assumes that before applying the discoveries to humans, testing drugs in lower- and then higher-order species will reveal inherent weaknesses that will/can be identified, dealt with and possibly overcome. In this way, adjustments with larger more mature and complex animal systems could be made. Presumably, refinements in chemistry, dosing and delivery, timing of delivery as well as definition of the most relevant outcomes could be incorporated into the clinical trial design as noted above. This general approach has been much discussed in the series of STAIR conferences [5, 6]. Unfortunately, few of these considerations have been successfully applied to an agent in the preclinical testing phase. It is unclear how many clinical programs have been altered or terminated based upon negative data in the model arena.

The development of preclinical testing strategies to both facilitate the clinical testing of agents that protect brain or those which improve the microcirculation has presumed that the animal models are appropriate for these tests. They were developed to study pathophysiology and not for the purpose of drug discovery. The notion of a phylogenic ladder beginning with smaller mammals with lissencephalic brains to those larger primates with human-relevant cerebral vascular systems and neuroanatomy is logical. But the ability to translate outcomes (or interchange them) with human patients presenting with focal ischemic lesions has not been formally tested. Limitations regarding the suitability of these test systems have become evident with time. Some of the concerns about the proposed approaches based upon the STAIR criteria include:

1 The types of animal models and their priority were made when the relevance of many model systems to human focal ischemia had not been developed
2 Understanding of the maturation of ischemia-dependent cerebral injury is still incomplete and the fundamental mechanisms of injury evolution are not known

3 Continued lack of understanding of the relationships between ischemia in the central nervous system of small mammals and the adult human central nervous system, reflecting, in part, significant differences in size and complexity
4 Weaknesses in the interpretation of the outcomes in small animal focal ischemia studies (for example, the use of improvement rate as an outcome instead of endpoint in behavior-based trials)
5 Failure to integrate knowledge of the pharmacokinetics, pharmacodynamics, target effect and dose dependency in subhuman species
6 The use of anesthetics in most animal model systems during the ischemic event in contrast to the majority of ischemic strokes which occur in the sentient state, thereby perturbing injury and recovery in unpredictable or yet to be clarified ways
7 The lack of known clear relationships between injury in primates and that in rodents
8 The lack of feedback of negative results in human trials to the designing of preclinical work
9 The minimal input from veterinarians as well as cell biologists, basic physiologists, chemists and those preclinical scientists at the drug discovery level prior to animal testing

These concerns are borne out by the inability of drug testing in rodent models to anticipate outcomes in human stroke patients, as observed with the recent clinical trials of NXY-059 (SAINT I and SAINT II) [7, 8]. Further concerns highlight the absence of clinical trial designs that match the test design in preclinical experiments (such as the tirilazad mesylate studies) [9, 10], the absence of any preclinical work to expose the evident risk of untoward effects in advance of the clinical trial (such as enlimomab) [11, 12] or the pursuit of treatments even in humans in the presence of preclinical data indicating the variability of its success (such as the rNIF studies) [13].

In contrast, examples of successful translation derive from the experience with arterial recanalization. A progressive understanding of the impact of the reinstitution of flow in human patients on brain injury evolution has paralleled work in both small animal models of focal ischemia and work in the nonhuman primate. This has also led to further understanding of the molecular responses of neurons and the microvasculature (the neurovascular unit) to ischemia. However, the absence of an ability to directly translate alterations in hemostasis in rodents and small mammals to humans has hampered preparatory work with many antithrombotics in roles of stroke recovery and injury control.

These considerations suggest a number of refinements in our approaches to the development of agents for stroke intervention. These include (1) further active strong support for fundamental research into the mechanisms of focal cerebral ischemic injury and its various subtypes (2) detailed understanding of the targets of potential interventions across species (3) use of the full collection of models available based upon formal prospectively conducted tests of their suitability, and particularly those models assessing damage in both gray and white matter, and (4) formal testing of the steps of preclinical modeling recommended by the STAIR criteria.

Caution is suggested about the manner in which the outcomes of preclinical studies are interpreted to support clinical interventions in stroke. Obvious weaknesses can be addressed in the preclinical and clinical trial programs (for example inappropriate targets and inadequate pharmacokinetic investigations). These would help to clarify weaknesses in individual models. The positive course observed with plasminogen activators and other reperfusion strategies offers hope that strategies to translate non-vascular interventions in stroke can be successfully developed.

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Scaling Up from Animal to Human Studies

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Finding new treatments for complex pathophysiological diseases such as cerebrovascular and neurodegenerative diseases requires a stepwise approach [1]. It is important to try to understand the mechanisms, pharmacokinetics and pharmacodynamics of therapeutics before being able to test their use in humans. Initial data from cell cultures and animal studies are needed in the planning of human clinical trials. The design of clinical trials is separated into 4 phases. The pivotal phase proving clinical efficacy is phase III. However, well-designed earlier stages are needed to guide in the design plans for much larger and more expensive phase III trials [2].

Preclinical Phase

The goal of the preclinical trial phase is the search for a compound or therapeutic concept, using cell cultures and animal data [3]. During this phase the therapeutic concept, early safety data, side effects and dosing regimens are examined.

Often, new drug discoveries result from random testing of compounds in simplified systems such as cell cultures. Sometimes animal models can aid in new drug discoveries such as seen after the development of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys for Parkinson's disease [4], which led to the development of new chemical compounds through testing strategies not possible without nonhuman models. Frequently, biological or chemical compounds that are similar to existing molecules in nature are synthesized and introduced as therapeutic medications. These sometimes have better side effect profiles and efficacy. Other strategies for the development of new medical treatments are modifications of older drugs or chemicals, which is often done to extend patent protection for existing therapies. On occasion, drugs are developed for one condition, but later found to be active against another, such as the case with amantadine, which was first used against influenza and later found to aid Parkinson's patients [5].

Strategies successfully used in cell culture or animal model cannot simply be directly transferred to human treatment. For example, antibodies may not have the same effects in nonprimate species. Major reasons for failure of clinical trials based on promising preclinical data are critical differences between the preclinical models and human disease.

Most animal research is done in young and previously healthy animals, while human disease often occurs mostly in the elderly with multiple medical comorbidities [6]. A drug with neuropsychiatric side effects, for example, may be used safely in young healthy subjects, but causes severe behavioral changes in the elderly. Drug-dosing schedules used in preclinical trials may not be safely transferred to human studies. To avoid human toxicity, some trials have used a significantly lower dose than that shown efficacious in animals. On the other hand, many animal studies used single bolus infusions, while subsequent clinical trials used prolonged treatments either intravenously or orally.

Another issue of discrepancy between preclinical and clinical trials is the way outcome and functional status are assessed. Animal studies often use histological outcomes. However, regulatory agencies generally require outcome to be assessed by neurological function, quality of life or mortality. Functional assessment in animals is usually limited to simple tasks of limb pacing, beam and grid walking, while many outcome measures in clinical trials assess social function and activities of daily living.

In some conditions, such as cerebrovascular disease, the treatment window is important and many compounds have failed to show efficacy in human trials, because the experimental efficacy was only proven in preclinical trials when used prior to the insult or immediately afterwards. During human studies, the drug cannot be delivered within the time it was proven efficacious in preclinical experiments and thus fails to show benefit in patients. We now know that thrombolytic agents are effective for 3 h after artery occlusion [7, 8]. However, many clinical trials of neuroprotective agents have used far longer treatment windows, as long as 6–48 h [9].

Obtaining good preclinical data is a foundation of most clinical trials, but the data must be considered in light of its applicability for the use in people. It is not helpful to find a compound that reduces stroke size in animal models, but requires prestroke administration or shows highly toxic side effects, which could not be tolerated in human stroke victims. Nor is it helpful finding a compound that increases the L-DOPA secretion by the substantia nigra in patients with Parkinson's disease, but fails to improve patient functional status.

Phase I

This phase is the first involving human subjects and tests safety of the treatment strategy in people. Sometimes multiple phase I trials are needed (such as phase

Ia and Ib) in order to move from single- to multidose regimens and from normal volunteers to affected patients. Initially, healthy volunteers are often used to examine safety, tolerability and pharmacokinetics. When patients are then included in phase I studies, the outcome measures should reflect concerns of safety and not efficacy.

One major hurdle in a phase I study is the determination whether the incidence of certain serious adverse events is above the level expected for a given patient population. In patients with neurological disease, the severity of the underlying condition and comorbidities correlate strongly with outcome and the occurrence of adverse events. For example, in phase I studies involving patients with severe strokes, the rate of intracranial hemorrhage is expected to be higher than the rate in studies enrolling mildly affected stroke patients [10].

The design of phase I studies should not focus on prespecified stopping rules. Comparison with previous studies with similar related design and similar populations can be helpful in planning the projected sample size needed to assess the safety of a given therapy. For some interventions designed to improve the safety profile, the expected rate from previous studies might be unacceptably high and the stopping rule might be based on a lower value. Rigid prespecified stopping rules can unfairly stop therapy development prematurely, so data monitoring and safety boards who are independent from the clinical investigators make these decisions after looking at all data collected up to that time.

Phase II

While phase I is designed to identify safety concerns and establish a range of dosages deemed safe in human studies, phase II comprises clinical studies to obtain preliminary data on the effectiveness of a drug or medical intervention [11]. This phase of testing helps determine common short-term side effects and risks of the treatment. Sometimes, more than one phase II trial is needed before moving to a phase III study. Phase II studies should not be designed as underpowered phase III trials. Rather, like phase I trials, they should further develop safety and dose profiles and, to a lesser extent, efficacy effects. Phase II studies are typically well controlled, closely monitored and conducted in a relatively small number of patients, usually involving less than several hundred people [12]. The primary goal is to develop a protocol that will be successful at phase III.

Trials of a new therapeutic concept often fail when they are rushed from phase I to III. The pivotal phase III can only be correctly planned once the sample size and dosing regimen are carefully evaluated in preliminary phase II trials. Trying to guess the numerous variables that are encountered in patient care without adequate phase II testing does save money in the short run, but often results in poorly designed phase III trials that are destined to fail.

Additionally, phase II trials are used to seek out the optimal study endpoints, which are reproducible, valid, clinically meaningful and resistant to bias. Most endpoints are validated clinical outcome measures, such as mortality in cardiac disease, Expanded Disability Status Scale in Multiple Sclerosis, Unified Parkinson's Disease Rating Scale in Parkinson's disease or modified Rankin Scale in stroke.

Some phase II studies have used nonclinical endpoints, surrogate outcomes that were anticipated to correlate with important clinical results [13]. The use of such surrogate markers may allow finding signals of therapeutic efficacy in smaller sample size or with shorter follow-up time. However, selecting an appropriate surrogate marker requires careful planning and may not be possible without many human studies. For example, lesion size after stroke was used as a surrogate marker in one study of cerebrovascular disease, but lesion size on a 30-day CT did not correlate well with neurological status, because small strokes in the brainstem can cause much more profound deficits than larger cortical ones [14]. Conversely, in multiple sclerosis, the number of MRI lesions has been shown to correlate well with disease course and is widely accepted as a valid surrogate marker [15]. Use of a measure which can serve as a marker of activity of a drug such as drug level, can also be considered.

Phase III

Phase III of a clinical trial is the pivotal step in finding proof of efficacy of the tested medical or interventional procedure. The sample size is calculated based on the expected effect of the intervention [16]. The magnitude of this effect is usually based on historical experience and earlier trial phases. Many phase III trials fail because they are underpowered. For example, a trial with 200 subjects in a placebo-controlled double-blinded study may have statistical power to be able to detect a relative treatment effect of larger than 30%. However, many important therapeutic interventions show a far smaller treatment effect. The most appropriate effect size to choose is that which is clinically meaningful. To demonstrate efficacy of thrombolytics after myocardial infarction, the GUSTO trial enrolled 41,021 subjects [17].

As discussed earlier, proper use of outcome measures contributes greatly to the success of phase III trials. Success in a well-designed clinical trial should not only mean finding a positive answer, but answering the question definitely. Even a negative trial result can give important clinical information, since finding that a therapy does not improve patient outcome can be important information. Furthermore, in order to avoid publication bias, it is equally important to publish negative trial results as it is to publish positive ones.

In addition to clinical outcome markers, surrogate markers can be used in phase III trials. In phase III trials they mainly serve as secondary outcome measures, while primary outcome remains measured by clinical scales [14]. Findings using surrogate markers can mostly be used to create new experimental hypotheses.

In a separate, but equally important matter, the study population should closely represent the general patient population and clinically relevant outcome measures should be studied. Some trials have included a highly selective patient population. Results of these studies could only partially be applied to routine patient care. For example, trials for the prevention of stroke related to atrial fibrillation have excluded patients with cardiac comorbidity or age above 75 [18]. Since atrial fibrillation is most common in the elderly and many patients suffer from cardiac comorbidities, the study results were not applicable for the majority of patients with atrial fibrillation, and subsequent studies had to be completed to include more common patient populations [19].

Statistical Approaches

Statistical analysis and the understanding of its calculation are vital when examining the results of clinical trials. If the data are well balanced, randomization and blinding adhered to, a prespecified statistical test can be used to calculate the likelihood that the results of the trial wrongfully reject this hypothesis.

A more recently used statistical method in clinical stroke trials is the Bayesian approach of continuous learning [20]. In conventional (frequentist) trial design, the information accruing during a trial remains untouched in a sealed database as the trial progresses [21]. This approach assures blinding of treatment effect of all parties involved in a clinical trial until the database seal is broken. In the Bayesian trial design, each treatment group is continuously compared to a historical control group [22]. This can affect trial design such as a dose-finding trial. By continuously comparing the various dosing regimens, a dose tier can be abandoned once futility or safety endpoints are reached so it is not necessary to wait until a prespecified number of patients are accrued. This can result in markedly decreasing the number of subjects needed for a drug development program, especially if it is possible to terminate the trial early. Since possible bias can be introduced by including historical controls, this design is most useful for phase II trials.

Study Logistics

The logistics in conducting clinical trials are as important as planning and design. Even the best-planned research protocol is only as good as its logistical structure. [23] Clinical trials can be planned and sponsored by academic centers or the pharmaceutical industry.

Although the industry can organize a clinical trial without outside assistance, the use of academic centers enables access to qualified clinicians, medical institutions and lends credibility to an industry-sponsored trial. Projects funded through

governmental grants carry the highest credibility. In obtaining these grants, the research plan and its creators are held to a high level of scrutiny. In the US, this is done through the National Institutes of Heath or the Department of Veterans Affairs. This way of research funding was vastly propelled in the late 1970s when the Baye-Dole Act regulated ownership transfer of intellectual property funded through federal research grants to universities and investigators [24].

Many pharmaceutical companies have outsourced the organization of clinical trials to clinical research organizations. They are independent from the sponsor, have medical expertise, know who the best and most productive investigators are and know how to avoid poorly performing research sites. Clinical research organizations are highly flexible and often specialized in one area of medical research. However, using a clinical research organization is more expensive and may carry less credibility than trial organization through academic centers [25].

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FDA Requirements for Preclinical Studies

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Before a new investigational agent can be used in humans in the United States, the FDA requires submission of data demonstrating that the agent is reasonably safe for use in initial clinical studies. These preclinical data are provided to the FDA in an investigational new drug (IND) application (21 CFR 312), submitted either by an industry sponsor or by a physician-investigator. Depending on whether the investigational agent has been studied or marketed previously, there are several options for fulfilling this requirement: (1) provide a summary of existing data from past in vitro laboratory or animal studies on the compound; (2) provide a summary of data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the United States population; (3) perform new preclinical studies designed to provide sufficient evidence to support the safety of administering the investigational agent to humans.

There is no 'one size fits all' approach to the design of preclinical studies. Rather, the preclinical studies must be tailored to the specific investigational agent and the proposed clinical trials. The FDA requires that animal studies be reasonable predictors of the pharmacological activity of the investigational agent. In addition, toxicity studies must be designed such that they are likely to reveal adverse events that could be relevant to humans. While FDA regulations do not prescribe a standard set of tests for all experimental agents, the FDA has issued guidelines for the selection of preclinical studies. IND regulations and current guidance documents are readily available on the FDA website (http://www.fda.gov). Guidance documents can be easily searched, downloaded and printed (http://www.fda.gov/cder/guidance/index.htm). Two guidance documents that are particularly relevant are 'M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutical Products' (1997) (http://www.fda.gov/cder/guidance/1855fnl.pdf) and 'S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals' (1997) (http://www.fda.gov/cder/guidance/1859fnl.pdf).

The FDA requires that all preclinical studies be conducted according to their good laboratory practice (GLP) regulations (21 CFR 58). These regulations were instituted in the late 1970s to set minimum standards for laboratories conducting all nonclinical studies that will be submitted to FDA. GLP regulations are based on the premise that quality control must be built into preclinical testing in order to eliminate careless errors. These regulations, which are quite stringent, include advance standardization of procedures combined with meticulous record keeping.

A number of general principles apply to the preclinical studies that are required to support a phase I clinical trial, as outlined in the guidance documents mentioned above. The studies usually include acute (single-dose) studies and repeat-dose studies, along with a single genetic toxicology study and reproductive toxicology studies if the investigational agent will be used in pregnant women. Acute toxicology studies in 2 mammalian species and repeat-dose studies in 2 species (1 rodent and 1 nonrodent) are often required; however, variations on this requirement are possible depending on the product class and extent of the proposed clinical program. The duration of repeat-dose studies is related to the duration, therapeutic indication and scale of the proposed clinical trial. In principle, the duration should be equal to or exceed the duration of the human clinical trials. Doses of the investigational agent that are administered in the preclinical studies should include the maximum proposed human dose. Higher doses aimed at determining a 'no observed effect level' are suggested in the repeat-dose study, but the number and size of the doses can vary with product class. The route of administration should mimic that which will be utilized in the clinical setting. Toxicology parameters to be evaluated generally include the following: mortality, clinical signs, body weight, clinical chemistry, hematology, food consumption, gross pathology and histopathology.

Consideration must be given to the choice of an appropriate animal model, one that will provide the most accurate prediction of potential toxicity to humans. For a drug, an appropriate animal model could be one in which the metabolism of the drug is similar to that in humans. Consideration must also be given to the importance of absorption, distribution, metabolism and excretion and pharmacokinetics studies, as well as the immunogenicity of the investigational agent. Depending on their origin (for example, human and murine), monoclonal antibodies and other proteins can induce immunogenicity that could significantly complicate interpretation of toxicology results. Pharmacokinetics studies are important for drugs, while distribution studies are important for agents such as gene therapy products. Each product class has a specific set of safety concerns that must be considered in planning the initial preclinical studies. To complicate things even further, each individual agent within a given class may have additional safety concerns based on the specific properties of that agent.

The purpose of preclinical studies is to characterize the toxic effects of an investigational agent with respect to target organs, dose dependence, relationship to exposure and potential reversibility. The results of these studies are used to determine an

initial safe starting dose for clinical trials and also to identify parameters for clinical monitoring for potential adverse events. Existing FDA regulations permit some flexibility in the amount of preclinical data that must be submitted in an IND application. Depending on the goals and specifics of the proposed clinical investigations and the expected risks, 2 IND approaches are available. The preclinical data required for a traditional phase I IND are outlined above and in the referenced FDA guidance documents.

An alternate approach is that of an exploratory IND, which may be used for clinical trials that are (1) conducted early in phase I, (2) involve very limited human exposure and (3) have no therapeutic or diagnostic intent. Exploratory IND studies involve administration of either subpharmacologic doses of an experimental product or doses expected to produce a pharmacologic, but not a toxic, effect. The exposure of human subjects is to be limited to 7 days or less. The potential risk to humans is expected to be less than for a traditional phase I study. Therefore, exploratory IND studies in humans can be initiated with less preclinical data than are required for traditional IND studies. The specific preclinical studies required for an exploratory IND depend on the nature of the investigational agent and the proposed study design. All studies must be performed under GLP conditions, as with those for a traditional IND. One example of a clinical study that could be carried out under an exploratory IND is the use of single administrations of microdoses of new agents. A microdose is defined as less than one hundredth of the dose of a test substance calculated based on animal data to yield a pharmacologic effect (with a maximum dose of 100 μg for a small molecule or 30 nmol for a protein). Many imaging agents fall into this category. Human studies using microdoses can be supported with single-dose toxicity studies in a single mammalian species. The results of these studies must demonstrate that a 100-fold multiple of the proposed human dose (based on body surface area) produces no adverse effects in the experimental animals. FDA's current thinking on the exploratory IND approach, including discussion of preclinical data requirements for specific types of clinical trials, is summarized in a guidance document, 'Exploratory IND Studies' (2006) (http://www.fda.gov/CDER/guidance/7086fnl.pdf).

Prior to initiation of preclinical studies to support an IND submission, it is prudent to consider discussion of the proposed studies with the FDA. This consultation with the FDA can occur during a pre-IND meeting, at which time other aspects of the proposed clinical trial are also addressed. Such a meeting must be requested in writing to the appropriate FDA reviewing division. The meeting request must include background information, meeting objectives, a proposed agenda, attendees and the approximate date on which supporting documentation will be sent to the reviewing division. The FDA must receive a full information package at least 4 weeks prior to a formal pre-IND meeting. Details regarding the procedure for requesting a pre-IND meeting and the requirements for the information package are summarized in a guidance document 'Formal Meetings with Sponsors and Applicants for PDUFA Products' (2000) (http://www.fda.gov/CDER/guidance/7086fnl.pdf). It is wise to take

detailed notes during a meeting with the FDA, and to prepare draft minutes of the meeting. Submission of these draft minutes to the assigned project manager at the FDA promptly after the meeting is a useful way to assure that there is agreement on the outcomes of the meeting.

Demonstration that it is safe to administer an investigational agent to humans for the first time is an important step in the overall development process for a new investigational agent. In carrying out this task, consideration must be given to the FDA regulatory process, appropriate FDA guidance documents, specific safety considerations related to the class of the investigational agent and an analysis of any risk-benefit issues associated with the agent. This is a time-consuming process that requires careful planning and evaluation. It is recommended that this process include continuous communication with the FDA, including a pre-IND meeting.

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Clinical Trials

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Phase I/II – Design and Analysis

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Ultimately to bring new medical breakthroughs and therapies to the public, high-quality data are necessary to show convincing clinical benefit. Such medical evidence is only acquired via the gold standard double-blinded, randomized phase III clinical trial.

A phase III trial is complex and elaborate and should be designed to provide definitive, pivotal proof of efficacy. Unfortunately, in some fields of neurology the medical science has not advanced to the point to where it is possible to effectively design and execute a phase III trial, and so a phase I or II study may be necessary in order to acquire the information needed for the eventual definitive phase III trial. For example, a treatment may only be effective in some forms of a disease, at certain doses or when given in a specific regimen and these issues should be well specified before a phase III trial is attempted. The practical day-to-day conduct of a multicenter trial requires extreme organization. Ethical considerations preclude experimenting on large numbers of patients before appropriate preclinical and phase I/II data are obtained. Thus, a series of trials, each with achievable goals and a place in establishing a cumulative pattern of evidence and confidence should precede the definitive phase III trial.

Many investigators are under the mistaken impression that for a phase I or II trial, a statistician can be used on a consultant basis – probably after the trial data have been collected. Designing a progressive series of projects, each enabling the later ones, requires a professional statistician who is a full collaborator with a scientific stake from the conceptual beginning of the trial.

In a clinical trial, one gathers randomly sampled data that may or may not match the reality in the larger population. Typically, the phase III trial is designed to definitively answer an important clinical question regarding whether a particular treatment or intervention is effective. Drugs/devices have to go through a stepwise process to achieve the data necessary to proceed to the phase III trial. Therefore, the purpose for the phase I/II trial is to provide specific data needed to design a subsequent, adequately powered phase III trial. Feasible goals for a pilot phase I or II trial are: (1)

		Our data indicate that treatment is	
		effective	ineffective
In reality, treatment is	effective	Success	Type II error
	ineffective	Type I Error	Success

Fig. 1. Possible outcomes after drawing data.

studies of safety and tolerance, pharmacokinetics or drug activity, (2) studies to optimize the intervention strategy, that is, optimal dose or duration of dosing, (3) studies to select the best of several possible interventions or dosages, based on tolerance or markers of activity and (4) studies to define the target population, that is, ischemic stroke or intracerebral hemorrhage or both, or futility.

It is perfectly appropriate to use biomarkers or other types of well-characterized surrogate outcomes for some phase I and II studies, but such markers should be used with caution in phase III trials. In designing a phase II study, it is important to avoid the trap of simply comparing an A versus B outcome that would be typical of a properly designed phase III trail, since this leads in essence to an underpowered trial that carries a high risk of type II error: incorrectly abandoning a treatment that would have proved effective. Such pseudo-phase II/III studies often end up wasting the money invested in the trial as well as the investigator and community resources devoted to it, and it may make it practically difficult for other teams to recruit patients with the same disease to better designed trials. Worst of all, the likely negative result may prevent that treatment from attracting resources for later, more adequately equipped investigators.

It is important to remember that statisticians do not employ separate sample-size tables for phase II trials than for phase III. In either case, the same sample is required to gather usable information – with adequate protection against type I and type II errors. Pilot studies should not purport to enable go/no go decisions based on clinical efficacy.

A trial can be seen as a success when there are enough data that lead to conclusions that agree with the population outside the sample. Statistical design is a way of determining how much insurance there is to reach a definitive conclusion. Even when the treatment is proven ineffective (assuming that it actually is), the trial can be considered a success because the new information will curtail wasting effort and resources on the intervention/treatment and move on to something that might work.

From a statistical perspective, there are 2 different ways that trials fail: type I error (false positive conclusion) and type II error (false negative). This is schematized in figure 1. Both types of failure play important roles and require careful attention in trial design so as to be avoided. It bears emphasis that the p value expresses the probability that an ineffective treatment will be falsely deemed effective (type I error).

Table 1. Problems with the pilot trials as surrogates for phase III trials

- Study sites and subjects enrolled may not be representative of the population and thus not generalizable.
- The typical small number of subjects enrolled eliminates or limits stratification by race or gender or other factors.
- Employing a small number of the best sites, recruitment might be higher in these and unrepresentative of other centers in the country.
- A pilot trial may have different, more stringent entry criteria than one would be used for the phase III trial.
- Subjects agree to a short-term study, when what may be more important is longer-term follow-up and outcomes as in the phase III study and thus, subjects are used inefficiently.
- Frequently, in pilot trials surrogate outcomes are used which are not validated as a relevant clinical endpoint for a phase III study.

Statistical power is the degree of protection from deciding against a treatment that is, in reality, effective (type II error). More generally, the statistical test shows whether 2 treatments are different – not necessarily in clinical efficacy but in safety, in ability to influence a biomarker or in any other respect of interest.

One of the reasons the phase I/II trial should be used for very specific applications is that there are some inherent problems with the ways in which some would use pilot studies. Some of the key problems encountered in using phase II trails as mini-phase III trails are summarized in table 1. Because large phase III trials are large, complicated and expensive, investigators sometimes use the pilot to estimate the administrative and 'process of disease' parameters in a miniature controlled trial, the results of which lead to an overinterpretation of the treatment effect. A key question raised by such logic is, for example: If a controlled pilot trial is significant, why do a large phase III trial when the pilot would suffice? However, a pilot trial usually is not sufficient to change practice, which a phase III trial of a large, more heterogeneous study sample with a positive result would likely do. Worse, it could change practice when the effect was observed only in a small relatively homogeneous sample of a pilot study. If a concurrently controlled randomized pilot trial is not significant, there may not be any impetus to do the definitive phase III trial. However, if the pilot study was underpowered by design, the likelihood of a negative result is high to begin with, and by not proceeding to a phase III trial, the potentially effective treatment may be prematurely discarded. Therefore, an underpowered concurrently controlled pilot study often provides worse information than one would obtain from a single-arm design, yet would require many more subjects.

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Biomarkers in Neurology

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Most clinical decision making is based on methodologically sound clinical trials demonstrating an impact of therapy on important patient outcomes such as mortality and health-related quality of life. Phase II studies, used to establish safety and demonstrate mechanistic data to support the potential of efficacy, are generally smaller studies and do not have adequate power to detect significant differences in clinical endpoints. In these cases, surrogate outcomes for the clinical endpoints can be employed, allowing execution of smaller, more efficient trials [1].

A Biomarkers Definitions Working Group that included members from the FDA, NIH, universities and industries recently refined definitions for surrogate outcomes, biomarkers, pharmacodynamic markers and clinical endpoints [2]:

- 'A biological marker (biomarker) can be defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic process or pharmacologic responses to a therapeutic intervention.
- A pharmacodynamic marker specifically refers to a biomarker of pharmacologic response.
- A surrogate endpoint is defined as a biomarker intended to substitute for a clinical endpoint and is expected to predict clinical benefit, lack of benefit or harm. It is based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.
- A clinical endpoint is a characteristic or variable that reflects how a patient feels, functions, or survives'.

Pharmacodynamic markers and surrogate endpoints are, therefore, subsets of biomarkers (fig. 1). The extent to which a biomarker is appropriate for use as a surrogate endpoint in evaluating a new treatment depends on the degree to which the biomarker can reliably predict the clinical benefit or harm of that therapy, compared to standard therapy [3]. There are relatively few biomarkers that qualify for the status of surrogate endpoints. Although the approach may seem straightforward, the use of biomarkers and surrogates carries with it a number of practical problems and pitfalls [4].

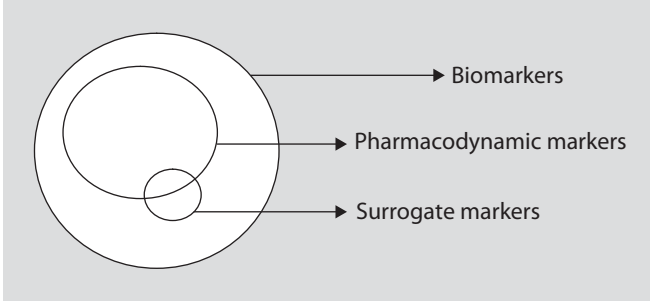

Fig. 1. Venn diagram representing pharmacodynamic markers and surrogate outcomes as subsets of biomarkers.

Pitfalls in Choosing Biomarkers

A proposed biomarker may be integral to the pathophysiology of a disease outcome, have correlation to but not be straightly linked to the disease outcome or be completely independent of the the clinical outcome of a disease.

In the example in figure 2, biomarker X reflects one of the pathophysiologic steps leading to a disease outcome. Biomarker Y is directly correlated with one of the steps leading to the disease outcome, although not directly linked to it, while biomarker Z does not have any correlation with the disease outcome. Confirmatory studies could show that X and Y are suitable biomarkers that might be used as surrogate outcomes. In contrast, a rational for considering Z a reasonable biomarker does not exist.

An example of biomarker X would be total cholesterol levels and low-density lipoprotein (LDL) cholesterol as a surrogate outcome in coronary artery disease. Although it is reasonable to think that cholesterol levels could be a potential pharmacodynamic marker of the action of lipid lowering drugs, it was essential to prove by a controlled clinical trial that lipid lowering drugs not only decreased cholesterol levels but also decreased overall mortality [5]. Sometimes the results of several phase III clinical trials are required in order to identify clinical useful biomarkers.

Logic alone does not guarantee that a biomarker can be used as a surrogate outcome. A reasonable association between a biomarker and clinical outcome does not mean for sure that a treatment effect on this biomarker will imply in improved clinical outcomes. An example of how clinical reasoning was not translated into an effective surrogate is the control of arrhythmias in patients post-myocardial infarction. As 75% of sudden deaths after myocardial infarction are due to ventricular tachycardia, it was thought that the prevention of complex ventricular tachycardia with drugs could decrease mortality after a myocardial infarction. In fact, a randomized controlled trial revealed that mortality was increased by the use of antiarrhythmic medication after myocardial infarction. Biomarker Z could, therefore represent preventing cardiac arrhythmias post-myocardial ischemia [6].

A clinical outcome may be time dependent and this should be considered when using biomarkers as surrogate outcomes. One example is the use of phosphodiesterase-3

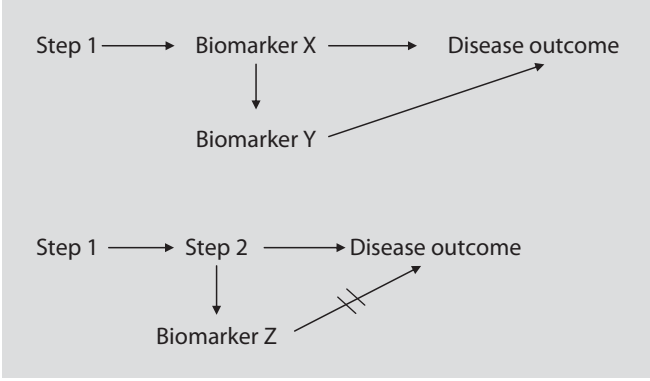

Fig. 2. Possible correlations of proposed biomarkers and disease outcome.

inhibitors (amrinone, milrinone) that can increase cardiac contractility in patients with cardiac failure but increases mortality if chronically used [7].

Another important pitfall in the implementation of biomarkers is error in anticipating a realistic effect size and standard deviation of biomarkers in order to ensure adequate power to detect a significant difference [4]. The literature has several examples of underpowered biomarker studies. It is impossible to know how many would have emerged as important surrogates, had the studies not been flawed by type II errors [3].

Biomarkers in Neurodegenerative Diseases

Detecting presymptomatic central and peripheral nervous system dysfunction is an important target in neurodegenerative disorders [8]. The development of disease-modifying drugs would be greatly facilitated by the use of surrogate markers in phase II trials. Neuroimaging, neuropsychological and cognitive testing in addition to new technologies such as biochemical, proteomic, metabanomic and gene array profile of biofluids are among the many potential tools. Examples of current biomarkers being used in different neurodegenerative diseases are described in the table 1 [9].

Biomarkers for neurodegenerative diseases should have certain specific characteristics: simple to quantify in accessible tissue, stable in the general population, unaffected by comorbid factors, and quickly and reproducibly measurable at different times or centers [9]. Biomarker levels should vary linearly (either negatively or positively) with disease progression and in response to a disease-modifying therapeutic intervention. One biomarker is unlikely to fulfill all these criteria. However, diagnostic and disease progression biomarkers could be coupled in a clinical trial. The combination of more detailed clinical assessments, in addition to imaging and biochemical profiling, is likely to be a successful approach [9].

Table 1. Current biomarkers used in different neurodegenerative diseases

Neuroimaging	
Structural [10–13]	Medial temporal lobe measurement in AD Hemispheric measurements in AD Ratio of the midbrain to pons areas (PSP) Rates of striatal atrophy in HD Voxel-based morphometry for WMD measurement
Functional imaging	
fMRI [9, 14]	BOLD responses in presymptomatic gene carriers in HD BOLD activation in the hippocampal and parahippocampal regions in MCI
Magnetic resonance spectroscopy [9, 15]	*N*-acetylaspartate to creatine ratio in conversion from MCI to AD and in cognitive decline in PD
PET and SPECT [9, 16]	Fluorodeoxyglucose PET reduction uptake in AD and MCI Correlation between reduced glucose uptake and apolipoprotein E4 gene dose in cognitively normal adults Compounds developed to image amyloid in vivo Decline in striatal D2 receptor binding in HD Dopamine processing in PD
DNA microarrays [9, 17]	Gene expression profiling to identify mRNA changes in postmortem brain from patients with incipient AD Common gene expression changes in skeletal muscle from HD mouse models and patients Upregulated mRNAs which were able to distinguish controls, presymptomatic HD gene carriers and symptomatic HD patients
Proteomics approaches [18]	Identification of unique protein profiles in AD, PD, HD and ALS
Metabonomic profiling of tissues and biofluids [9, 17]	Metabolic phenotype definition in the brain of a transgenic mouse model of spinocerebellar ataxia 3
Biochemical biomarkers identified in cerebrospinal fluid and serum [9]	Decrease in the A42 peptide in AD Increase in total protein in AD and decrease in FTD Reduction in orexin in CSF of HD
Clinical biomarkers [8, 9]	Comprehensive neuropsychological battery to discriminate early FTD from AD Visual and verbal memory span scores to identify the earliest cognitive deficits in elderly patients at genetic risk of AD Attention and executive function testing for disease progression in HD Cognitive dysfunction evaluation in PD

AD = Alzheimer's disease; PSP = progressive supranuclear palsy; HD = Huntington's disease; WMD = white matter disease; BOLD = blood oxygen level dependent; MCI = mild cognitive impairment; PD = Parkinson's disease; PET = positron emission tomography; SPECT = single positron emission computerized tomography; ALS = amyotrophic lateral sclerosis; CSF = cerebrospinal fluid; FTD = frontotemporal dementia.

Biomarkers and Stroke

Although an excellent rationale exists for the assumption that lowering total and LDL cholesterol should have a role in the prevention of stroke, this hypothesis was only recently validated. The Stroke Prevention by Aggressive Cholesterol Levels trial recapitulated the Scandinavian Simvastatin Survival Trial in atherosclerotic disease and proved that in patients with recent stroke or transient ischemic attack and without coronary heart disease, and in association with a significant reduction in levels of LDL, 80 mg of atorvastatin daily reduced the overall incidence of stroke and cardiovascular events. This is one of the first trials that elevates a biomarker to a surrogate endpoint for future studies [19].

In acute stroke trials, thrombolytic therapy is based on the recanalization hypothesis; the premise that opening occluded vessels will improve clinical outcome through regional reperfusion and salvage of the threatened brain tissue. Recanalization is a biomarker, but its value as a surrogate endpoint has been challenged. Recanalization may occur too late to salvage ischemic tissue, or be superfluous, if adequate collateral blood flow sustained the tissue without recanalization. Reperfusion injury and persistent distal embolism may exacerbate injury despite adequate recanalization. The landmark study that proved rt-PA improved clinical outcomes in acute stroke did not use recanalization as an endpoint [20]. Only recently, a formal meta-analysis confirmed the strong correlation between recanalization and outcome in acute ischemic stroke, demonstrating association with improved functional endpoints and reduced mortality. This analysis elevates recanalization to a surrogate endpoint status that could be used in early-phase trials of thrombolytic treatment [21].

The association between hemorrhage expansion and poor outcome in primary intracranial hemorrhages (ICH) is well defined. Hematoma enlargement, therefore, would be a logical surrogate outcome in trials of acute ICH treatment. With this rationale, a phase II trial using a hemostatic drug (factor VIIa) was designed to test efficacy in preventing hematoma enlargement, showing a trend toward better clinical outcomes in those treated with factor VIIa when compared to placebo [22]. Unfortunately, in this case, the biomarker did not make an effective surrogate. A subsequent phase III trial using factor VIIa in the acute setting of ICH, although able to prevent hematoma enlargement, did not demonstrate any significantly reduced mortality or improved quality of life at 90 days [23].

Conclusion

Surrogate markers have not fully come of age for use in neurological studies. Few biomarkers have been properly validated. Surrogate outcomes are now considered a necessary component of development and technology assessment, and efforts should be implemented to define valid biomarkers in neurological conditions [8].

Although biomarkers can help reduce uncertainty about adverse effects and increase level of confidence about outcomes in clinical trials, it is unlikely that a single measurement could capture all dimensions of clinical outcomes for a given neurological disorder. Evolving to a multidimensional and continuous model, rather than the current one-dimensional model which uses binary outcomes, will further strengthen the utility of biomarkers in clinical trials.

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FDA Investigational New Drug Requirements

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When a clinical trial involves the use of an investigational agent, the FDA has authority over the research through its programs for investigational new drugs (IND) and investigational devices. This authority also applies to marketed drugs and devices if the clinical trial involves the use of a new dose regimen, a new indication or a new population. At least 30 days prior to initiation of a clinical trial, an IND application (21 CFR 312) must be filed with the FDA. The IND, which may be submitted either by an industry sponsor or a physician-investigator, includes a copy of the clinical trial protocol. A full description of the contents of an IND submission is provided in the federal regulations, and also in FDA form 1571. This and all other FDA forms are available on the FDA website (http://www.fda.gov/opacom/morechoices/fdaforms/cder.html). FDA may notify the sponsor at any time of concerns related to the clinical trial and may place a clinical hold on the trial until these concerns are addressed and resolved. If no response is received from FDA within 30 days following their receipt of the initial IND submission, subjects may be enrolled in the trial.

Clinical trials must be conducted in accordance with the standards on good clinical practice (GCP) developed by the International Conference on Harmonization. These standards, which were developed to provide an international ethical and scientific quality standard for trials that involve participation of human subjects, are outlined in the FDA guidance document 'E6 Good Clinical Practice: Consolidated Guidance' (1996) (http://www.fda.gov/cder/guidance/959fnl.pdf). Key points in the GCP guidelines are also highlighted in FDA form 1572, which outlines the responsibilities an investigator agrees to assume in order to conduct a clinical trial. A signed form 1572 must be submitted to the FDA for each principal investigator who participates in a clinical trial.

The following commitments are made by an investigator when completing and signing FDA form 1572:

- The investigator will not deviate from the protocol without the agreement of the sponsor and the prior review and documented approval of the institutional review board (IRB). The only exception is when the change is necessary to eliminate an immediate

hazard to trial subjects. If such a deviation occurs, the investigator should submit as soon as possible a written justification for the implemented deviation or change to the IRB, the sponsor and, if required, the FDA.

- The investigator will personally conduct or supervise the trial. He/she must have sufficient time to properly conduct and complete the trial, should be able to demonstrate the potential for recruiting the required number of eligible subjects and should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial.
- The investigator will inform all subjects of the investigational nature of the trial and will ensure that the requirements related to obtaining informed consent (21 CFR 50) and IRB approval (21 CFR 56) are met [see chapter by Woodbury-Harris, this vol., pp. 121–123].
- The investigator will report to the sponsor all adverse experiences that occur in the course of the trial in accordance with 21 CFR 312.64. The sponsor is under a similar obligation to report both serious and unexpected adverse experiences to all concerned investigators, institutions, IRBs and the FDA. Note that the investigator is also the sponsor in the case of an investigator-sponsored IND.
- The investigator will be thoroughly familiar with the appropriate use of the investigational agent, including the potential risks and side effects, as described in the protocol, investigator's brochure and other supporting documentation.
- The investigator will ensure that all associates and employees assisting in the conduct of the trial are qualified and are adequately informed about the protocol, investigational agent and their duties.
- The investigator agrees to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection. The GCP guidelines provide a detailed list of the documents that should be located in the investigator's files before, during and after the completion of a clinical trial. The documents that the investigator must maintain include the following:
  - Investigator's brochure (contains all evidence that supports the potential efficacy of the intervention including all animal studies and, if relevant, phase I and II data)
  - Signed protocol and amendments
  - Approved informed consent form
  - Any written information or advertisements used for subject recruitment
  - Financial and contractual agreements
  - All IRB correspondence
  - Documentation that the IRB is constituted in agreement with regulations
  - Curriculum vitae or other documentation of qualifications of the principal investigator and all subinvestigators
  - Certification of good laboratory practices for all testing facilities
  - Labeling, shipping and handling instructions for the investigational agent
  - Any updates or revisions to the above material
  - Monitoring visit reports
  - Study-related communications
  - Signed informed consent forms
  - Source documents that substantiate the integrity of the data
  - Signed, dated and completed case report forms

  - Reports of serious adverse events and other safety information
  - Progress or continuing reports submitted to the IRB and/or FDA
  - Final monitoring report and clinical trial report documenting the completion, results and interpretation of the trial

  In the case of an industry-sponsored IND, the investigator will typically be given a notebook or 'regulatory binder' in which these required documents can be filed for ready access. In addition, the sponsor will perform regular monitoring visits, during which the contents of this binder will be reviewed and updated as necessary. In the case of an investigator-sponsored IND, it would be prudent to create a similar notebook to organize these documents.
- The investigator will ensure that an IRB complies with the requirements of 21 CFR 56 and will be responsible for the initial and continuing review and approval of the clinical trial. The investigator will also agree to promptly report to the IRB all changes in the conduct of the clinical study and all unanticipated problems involving risks to the human subjects.
- The investigator will comply with all other requirements of clinical investigators as outlined in 21 CFR 312. Clinical trials that are under the regulatory authority of the FDA are subject to auditing. During audits, the FDA checks compliance with FDA regulations, protocol adherence and institutional operating procedures. The FDA audits investigator's study files and IRB documentation to determine compliance with the investigator's responsibilities outlined on form 1572.

The FDA requires anyone who submits a marketing application for a new drug, biologic or device to provide information concerning the compensation to and financial interests of any clinical investigator who conducted clinical trials submitted in support of the application. Therefore, industry sponsors of clinical trials always obtain financial disclosure forms from the principal investigator and all subinvestigators. This practice should also be followed for investigator-sponsored INDs. Financial disclosure forms are typically filed in the regulatory binder, and investigators should assure that completed forms are available for all parties by the time the study is completed. Details regarding this requirement are provided in the FDA guidance document 'Financial Disclosure by Clinical Investigators' (2001) (http://www.fda.gov/oc/guidance/financialdis.html).

In summary, clinical trials that use an investigational agent, or a marketed agent outside of the approved labeling, must adhere to FDA regulations as outlined in 21 CFR 312. All trials must be performed in accordance with GCP standards, and investigators must comply with all commitments outlined in FDA form 1572. For an industry-sponsored IND, the sponsor will typically provide a regulatory binder for organized filing of all required paperwork. In addition, representatives of the sponsor will make routine monitoring visits to assure that the investigator is following all applicable regulations, that all paperwork is complete and up to date, and that all data are being recorded accurately with appropriate source documentation. The same standards apply to clinical trials conducted under an investigator-sponsored IND. Therefore, it is essential to create organized files and procedures to assure that the

trial is conducted in compliance with all applicable regulations and that the data are valid. All trials conducted under an IND are subject to FDA inspection. Significant problems uncovered during an FDA audit can ultimately lead to invalidation of the clinical trial data.

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European Union Regulatory Requirements

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Legislation Governing Clinical Trials Evaluating Medicinal Products in the European Union

Until recently, each member state of the European Union (EU) followed its own set of clinical trial regulations. In recent years, however, the laws pertinent to clinical trials in the EU have been harmonized by the European Medicines Agency (EMEA), a European agency responsible for the evaluation and supervision of medicinal products (http://www.emea.europa.eu). The single most important legislative document governing clinical trials in the EU is the so-called clinical trials directive (CTD), also known as directive 2001/20/EC [1]. The CTD, published on May 1, 2001, required each member state of the EU to publish new national clinical trial legislation incorporating the principles contained in the CTD by May 1, 2003, and to make the new legislation effective by May 1, 2004. The goal of the CTD has been to harmonize and simplify the regulations pertaining to clinical trials involving medicinal products by making compliance with the principles of good clinical practices (GCP) and good manufacturing practices (GMP) for medicinal products a legal requirement across the EU.

The CTD rules apply to commercial and noncommercial interventional trials of any phase, evaluating investigational medicinal products (IMPs). A clinical trial is defined as any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more IMPs and/or to identify any adverse reactions to one or more IMPs and/or to study absorption, distribution, metabolism and excretion of one or more IMPs with the object of ascertaining its (their) safety and/or efficacy [1]. An IMP is defined as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form' [1]. Further information on IMPs is provided in detailed guideline documents (see below).

An Overview of the EU CTD

The CTD lays out the ethical rules of the protection of clinical trial participants in accordance with GCP and the Declaration of Helsinki, including rules for special protection of vulnerable subjects and provisions for data protection. The directive requires that each clinical trial has an EU-based sponsor (or legal representative when the sponsor is not based in the EU) who assumes legal responsibility for the trial and ensures that the trial is conducted according to the GCP and GMP principles. Prior to the commencement of a trial, the sponsor (or a designate) must apply for authorization to the competent authority (CA) in each member state concerned (CA is the state's agency that regulates clinical trials), and must obtain a single, favorable opinion from the ethics committee (EC) in each relevant member state. The sponsor is also responsible for notifying the CA and the EC about substantial amendments in the protocol and about the end of the trial. The CTD lays out the basic principles of safety monitoring and pharmacovigilance in clinical trials, including the requirement for reporting to CA and EC the suspected unexpected serious adverse reactions (SUSARs). The sponsor is also required to make arrangements for indemnity or compensation in the event of injury or death attributable to the trial, and any insurance or indemnity to cover the liability of the investigator or sponsor. IMPs must be manufactured packaged, labeled, stored and analyzed according to GMP principles, in licensed facilities, and a professional with appropriate expertise, called the qualified person must certify every batch of IMPs for compliance with GMP. IMPs require authorization for manufacturing in a member state, or import authorization if manufactured outside the EU. IMPs and any devices necessary for their administration must be provided free of charge by the sponsor. The CTD calls for the development of detailed guidelines to assist in the implementation of the CTD, GCP and GMP principles, and several such guidelines have already been developed. Each member state must appoint inspectors and make provisions for inspections of clinical trial sites and manufacturing facilities to ensure compliance with GCP and GMP regulations. The CTD makes provisions for suspension or termination of a trial due to infringements of CTD regulations.

The CTD also calls for the formation of central databases to hold information about all clinical trials conducted in the EU, and associated pharmacovigilance data. In response to this requirement, the EMEA established and administers 2 linked central databases. The databases were developed to facilitate communication between the authorities regarding clinical trials conducted in the community and to allow for enhanced oversight of clinical trials and protection of clinical trial subjects. One of these databases is the European Clinical Trial Database (EudraCT), which contains information on every trial under the purview of the CDT (http://eudract.emea.europa.eu). Sponsors wishing to apply for clinical trial authorization to the CA of any member state must begin by registering the trial in the EudraCT and obtaining a protocol-specific EudraCT number. EudraCT also provides the application form and instructions. EudraCT is interfaced with a pharmacovigilance database, called EudraVigilance-Clinical Trial Module

(EV CTM) (http://eudravigilance.emea.europa.eu/human/index.asp). Only EMEA, CAs and the European Commission have access to the data contained in the 2 databases; however, there are plans for providing access to certain types of information in the 2 databases to other stakeholders, including marketing authorization holders, clinical trial sponsors, healthcare professionals, and the general public [2, 3] (see also description of contents of Chapter V in volume 10 of the Eudralex, below).

Key Directives, Guidance Documents and Instructions for Application to CA and EC

The directives and guidelines on clinical trials in the EU are available in volume 10 of EudraLex, a set of rules and regulations governing medicinal products in the EU (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/). A brief overview of the contents of volume 10 is provided below.

Volume 10 of the EudraLex consists of 6 chapters. Chapter VI, 'Legislation', contains the CTD and 2 additional directives. The 3 directives jointly provide the legal basis for clinical trial guidelines in the EU. Directive 2005/28/EC provides further guidance on the implementation of GCP in clinical trials as well as requirements for authorization for the manufacturing and importation of such products. Directive 2003/94/EC lays down the principles and guidelines for GMP pertinent to medicinal products and investigational medicinal products for human use.

Chapter I, 'Application and Application Form', contains the application form and detailed instructions for the application for authorization of a clinical trial to CA and EC (the same form for both), and forms for notification of substantial amendments and declaration of end of trial. The application packages to CA and EC consist of the cover letter with the EudraCT number, the application form, the protocol, the investigator brochure and the IMP data. The application to the EC also contains information on recruitment arrangements, subject information and informed consent procedure, suitability of the investigator and quality of the facilities, insurance and indemnity for compensation in case of injury or death of a trial subject and to cover the liability of the sponsor and investigator, information on financial transactions and compensation to subjects and investigator/site as well as information about proposed other sites and countries involved. Chapter I provides guidelines on additional member state-specific items that must be included in the application to the CA and EC. In addition, chapter I provides instructions on how to notify the CA and EC of substantial amendments, urgent safety measures and declaration of end of trial. The CTD requires that assessment of the application for clinical trial authorization to the CA and EC does not exceed 60 days. Some countries require a 30-day review timeframe. For certain types of products, the review time may be 90 days or longer. Applications to the CA and EC may proceed in parallel.

Chapter II, 'Monitoring and Pharmacovigilance', contains a detailed guidance document on the collection, verification and presentation of clinical trials-related adverse reaction reports. The document outlines the pharmacovigilance responsibilities of

investigators and sponsors, and provides instructions on recording, evaluation and reporting of adverse events. The investigator is required to report all severe events immediately to the sponsor except for those events that, according to the protocol and the investigator brochure, are not required to be reported immediately. In case of the death of a trial subject, the investigator must provide the sponsor with additional information upon request. The sponsor must keep detailed records of all adverse events and must submit them on request to the concerned member states. Sponsors are required to report SUSARs to the CA and EC of the member states in whose territory the clinical trial is conducted. SUSARs that result in death or are life threatening must be reported to the CA within 7 days, with follow-up information sent in within an additional 8 days. All other SUSARs must be reported within 15 days. Sponsors must also inform all investigators about any findings that could adversely affect the safety of study subjects. Every year, the sponsor is required to provide a list of all SUSARs that have occurred during the year to the CAs and ECs. The SUSARs must be entered into the EV CTM database. Chapter II also provides detailed information on the EV CTM.

Chapter III, 'Quality of the Investigational Medicinal Product', contains guidelines building on GMP requirements contained in directive 2003/94/EC. The key guidance document in chapter III, 'Good Manufacturing Practices, Annex 13, Manufacture of Investigational Medicinal Products, July 2003' discusses the detailed requirements on the production of IMPs, quality management, required documentation and release of batches by the qualified person. Chapter III also contains documents on manufacturing and import authorization, a compilation of procedures for inspections and exchange of information among authorities, and a guideline on the chemical and pharmaceutical quality documentation concerning IMPs in clinical trials. In addition, there is a document in chapter III clarifying the definition of IMPs and providing guidance on noninvestigational medicinal products (NIMPs) used in clinical trials (such as concomitant or rescue medications).

Chapter IV, 'Inspections', provides detailed guidelines on the qualification and training of GCP inspectors and on inspection procedures to verify compliance with GCP. New guidelines have recently been added to Chapter IV, to cover various aspects of GCP compliance, preparation of GCP inspection reports, and communication on inspections and findings.

Chapter V, 'Additional Information', provides the text of the International Conference on Harmonization (ICH) GCP guideline: recommendations on the content of the trial master file and archiving; and a recently developed guideline on the data fields from EudraCt that may be included in the publicly accessible European database on Medicinal Products (http://eudrapharm.eu). A question and answer document in chapter V provides useful information on a number of topics, such as the roles and responsibilities of sponsors (or their legal representatives) and investigators, and a decision tree to establish whether a clinical study is a 'clinical trial' as defined in the CTD. Chapter V also provides a recently developed guidance on ethical considerations for clinical trials on medicinal products with the pediatric population.

Challenges in the Implementation of the CTD and Future Directions

There have been numerous reports indicating that the goal of harmonization of clinical trials regulations in the EU has not yet been achieved, and that the CTD has resulted in significant increases in administrative burden and trial costs, decline in the number of new trials and delays in implementing trials. The effects of the CTD have been felt particularly acutely in academic settings, due to limited resources available for noncommercial trials [3, 4]. In response to these difficulties, a new organization called the European Clinical Research Infrastructures Network has been formed to improve harmonization of clinical trials practices and to facilitate the conduct of multinational studies in Europe [5]. In addition, the European Commission and the EMEA organized a conference in the fall of 2007 to provide an overview of the experience with the EU clinical trial legislation to date. The conference resulted in a comprehensive report and a set of recommendations for addressing the problems in the implementation of the CTD [6]. A major conclusion of the report is that the problems that have been encountered appear to be a consequence of different interpretations and different implementation in the national legislation of the member states. The recommendations call for solving the problems through issuing additional guidelines or developing new legislation, when appropriate.

Disclaimer

The views expressed in this chapter do not necessarily represent the views of the National Institutes of Health, the US Department of Health and Human Services or the United States.

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Adaptive Clinical Trials

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The last 2 decades have been a time of growing interest in the use of adaptive clinical trial designs. An adaptive design uses accumulating data to decide how to modify aspects of the study as it continues. The modifications to the trial are not done on an ad hoc basis but according to prespecified rules and in a manner that preserves the validity and integrity of the trial. The goal of adaptive design is to learn from the accumulating study data and quickly apply what is learned to optimize the next stage of the trial. This flexibility can result in minimizing exposure of subjects to ineffective treatments, a smaller total sample size, faster clinical development and better use of available resources.

A well-known example of an adaptive trial utilizes a data monitoring committee (DMC) or data safety and monitoring board (DSMB) to monitor interim study results by group sequential methods. When employing a group sequential design, the DMC/DSMB reviews the accumulated study data at several predetermined stages during the course of the trial to determine if one or more treatment arms of the trial should be terminated at the current stage because the study question has been answered, an arm has been shown to be harmful or it is likely the trial will be futile. The integrity of the trial is upheld by the fact that only the DMC (and not the investigators and sponsor) are privy to the unblinded interim data. The validity of the trial is assured through the use of statistical methods that preserve the overall type I error (or false positive) rate despite the multiple interim looks at the emerging data.

There are a number of different types of adaptive designs. These include designs that allow for a change in (1) how subjects will be allocated to the available treatment arms (for example, assign fewer subjects to what looks to be an inferior arm), (2) the number or types of subjects to be entered into the next stage of the trial, (3) the conditions under which to stop the trial and (4) how the data will be analyzed (for example, switching from superiority to noninferiority). The Pharmaceutical Research and Manufacturers of America (PhRMA) recently convened an Adaptive Designs Working Group to promote understanding and use of such trial designs. The working

group has published a classification of the different types of adaptive trials and an evaluation of the benefits and challenges associated with these designs [1]. For phase II/III trials, there are 2 important types of adaptive designs which may prove very useful: the first plans for re-estimation of the sample size at a predefined point in the study; the second allows for a seamless transition from phase II to phase III while modifying the design of the phase III component based on the phase II results. These approaches are discussed in the following sections.

Sample Size Re-Estimation

Investigators interested in the clinical development of a new intervention for a disease will eventually want to implement a phase III (efficacy or confirmatory) trial of the new intervention versus a control. Before the phase III trial can be effectively designed, however, there are 2 general sets of questions that need to be addressed. The first set of questions deals with practical or administrative issues such as whether the intervention is feasible to administer and whether outcome evaluations can be obtained in a standardized manner. Such issues are best addressed in standalone pilot (phase I and II) clinical trials. On the other hand, investigators also may have questions about sample size design parameters for the phase III trial such as:

- What is the variance of the outcome variable (for continuous outcome variables)?
- What is the event rate in the control group (for binary outcomes)?
- What will be the accrual rate (for time-to-event outcomes)?
- What will be the treatment compliance, treatment crossover, and loss-to-follow-up rates?

Investigators typically make use of data from previous trials, epidemiologic studies and expert opinions to estimate these parameters. But often these parameter projections are substantially incorrect due to changes in the study population characteristics, concomitant medications and outcome definitions, among others. As a result, phase III trials may end up being underpowered and the results inconclusive.

An adaptive clinical trial design provides a solution to the problem of insufficient preliminary data by estimating these parameters as best one can, implementing the phase III trial with a preliminary sample size estimate of N and incorporating an internal pilot study. An internal pilot study, first introduced by Wittes and Brittain [2], constitutes the initial stage of a trial using an adaptive design. Data obtained from a predefined number of subjects initially enrolled are used to refine the phase III design parameters and recalculate the sample size to obtain a new estimate, N^*. Recruitment of subjects then continues until a total of N or N^* subjects is enrolled, whichever is greater. Importantly, the subjects in the internal pilot stage are continued into the second (final) stage and utilized in the overall phase III analysis.

Some important practical considerations concerning the use of internal pilot studies include the following:

- Re-estimation of the sample size is not a substitute for careful trial planning. The initial sample size estimate (N) should be calculated as accurately as possible.
- The study protocol should specify that the sample size will be recalculated based on an internal pilot study.
- It is generally recommended that the subjects enrolled in the internal pilot cohort represent a sizeable fraction of the total N so that the parameter estimates will be stable when calculating N*.
- An upper limit should be set on N* before the trial is started. It may not be feasible to complete a trial if N* is substantially larger than N.
- It is inadvisable to downsize a trial if N* is less than N, for this may preclude assessment of secondary outcomes and subgroup analyses. In addition, it would be a major disappointment if, at the end of the trial, the treatment effect is not deemed statistically significant because the sample size was decreased.
- The internal pilot approach will not work well if recruitment is fast and the outcome variable is long term. This could result in a long time gap between the recruitment of the internal pilot subjects and the remaining subjects; for various reasons, the two cohorts of subjects may differ in their characteristics and outcomes.

In recent years there have been many methodological developments in the field of sample size re-estimation [3, 4]. Methods have been proposed that allow for either blinded or unblinded re-estimation of design parameters. In addition, there is methodology for updating the sample size estimate based on interim assessment of the size of the treatment effect. Reservations have been expressed about some sample size re-estimation procedures. First, there is concern that recalculating the sample size based on data from the trial may lead to inflation of the type I error rate. Second, some unblinded re-estimation methods may enable back-calculation of the study's interim results. Both of these concerns have been addressed through the development of re-estimation methods that do not jeopardize the statistical validity and scientific integrity of the trial. In light of this, and given the importance of avoiding an underpowered study, a plan for sample size re-estimation should be incorporated into every phase III trial.

Adaptive Seamless Phase II/III Trials

Another type of adaptive design is the seamless phase II/III design which combines into a singe trial objectives traditionally addressed in separate phase II and III trials [4, 5]. Seamless designs avoid the usual delays between phases II and III (for example, due to new grant application and review, IRB review, FDA review, loss of momentum on the part of the clinical sites). An adaptive seamless design uses the data from the phase II stage of the trial to modify the design of the phase III stage. Subjects enrolled in the first stage of the trial are included in the analysis of the overall trial, making the trial inferentially seamless. Thus, these designs make more efficient use of subjects and accelerate obtaining final phase III results.

A typical example of an adaptive seamless design combines the selection of the best dosage from among several dosages of an investigational drug and a control treatment (phase II) to carry forward into an efficacy evaluation (phase III). After the dosage is selected based on a short-term endpoint, the subjects on that dosage and the control group continue to be followed during the phase III portion of the study, which will compare this dosage against the control treatment on the basis of a long-term clinical endpoint. New subjects are enrolled into the phase III portion and randomized to the control group or to the dosage group identified in phase II. Subjects on the terminated dosages typically are discontinued from study. Of course, besides dosage selection, other possible phase II objectives might be to choose the most promising of 2 or more surgical procedures or to identify which of several patient subpopulations is most responsive to treatment, among others.

Due to their flexibility, analyses of adaptive seamless phase II/III designs may require complicated statistical methods. A particular concern is that the analysis of the overall results must adjust for selection bias unless the phase II endpoint is totally distinct from the phase III endpoint. For example, suppose the phase II endpoint selects one of several dosage groups based on toxicity, while the phase III stage compares the selected dosage against the control treatment based on an efficacy outcome. In this case, no statistical correction is needed. On the other hand, if the phase II portion of the study selected a dosage on the basis of an early biomarker response, and the biomarker was used because it was thought to be correlated with the phase III clinical outcome, some statistical correction would be needed; this correction could be minor, however, if only a small fraction of the total phase II/III trial sample size consisted of the subjects enrolled into the phase II stage.

Compared to running separate phase II and III trials, the use of adaptive seamless phase II/III designs can expedite the clinical development process for a new intervention by eliminating the downtime between study phases, require a smaller total number of subjects by incorporating phase II subjects into the phase III evaluation, and provide longer-term follow-up data by the end of the phase III portion of the trial from the continued observation of the subjects from the phase II portion. However, these adaptive designs are complicated and require careful planning to implement. Seamless designs are best suited to situations where the phase III portion of the project including the endpoint can be fully planned, apart from the selection of the dosages (or treatments or subpopulations) that results from phase II. The efficiencies of the adaptive seamless design can best be realized when subject enrollment is rapid and when the phase II portion of the trial is short relative to the total trial follow-up; otherwise enrollment of new subjects into the phase III stage will be delayed.

Challenges in Adaptive Designs

There are a number of logistical and statistical challenges in implementing adaptive designs. Rapid data collection is necessary in order to take advantage of their

flexibility and efficiencies. Thus, these designs are most suitable for studies where the outcomes on which the adaptations are based occur early relative to the overall duration of the trial. Implementation of an adaptive design requires close coordination between data management, data analysis, randomization procedures, clinical sites and the investigational product supply center, in order to ensure efficiency at every stage. The key statistical concern for most adaptive designs is the preservation of the type I error rate, as there is often repeated significance testing, multiple comparisons (for example, among treatment arms) and use of early data to make late decisions, all factors which tend to inflate the type I error rate. Fortunately, there is now well-developed statistical methodology for designing and analyzing most adaptive designs [4]. In order to facilitate the interpretation and acceptance of the final study results, however, it is important to prospectively specify the scope of possible adaptations and decisions, the objectives of the adaptations, and how the adaptations are expected to affect the type I error rate and power of the statistical analysis.

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Design and Analysis Plans

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For phase III trials, many options for study design exist, including the most commonly used parallel design. Other designs that are encountered in neurological clinical trials are factorial design, crossover design (mainly for chronic, nonprogressive conditions, such as epilepsy) and a variety of adaptive designs [1, 2] that allow changes to the design due to new information from internal and/or external sources during the course of the trial.

In choosing a study design, the first and foremost consideration is the research question. Is it to be shown that an agent or device of interest is better than placebo, better than another active treatment currently in use or better if used in addition to the current standard of care? Or is the trial to establish that the agent or device of interest is equivalent to or as good as the current standard of care? The former set of questions leads to a superiority hypothesis and the latter to a noninferiority hypothesis. One can use any of the aforementioned study designs for either type of hypothesis. However, the statistical hypotheses and analysis methods will depend on these research aims.

For a study that wishes to show superiority, the set of statistical hypotheses are: H_0: $\mu_A = \mu_B$ versus H_A: $\mu_A \neq \mu_B$ for a two-sided test or H_0: $\mu_A = \mu_B$ versus H_A: $\mu_A > \mu_B$ for a one-sided test, where H_0 is the null hypothesis and H_A is the alternative hypothesis, and μ_A and μ_B are the mean values of the specified primary outcome measure for treatment groups A (the test agent or device) and B (the placebo or control agent), respectively, and where we assume here that the larger the value of μ, the better the outcome. Some of the examples of μ are the difference from baseline National Institutes of Health Stroke Scale score at 3 months for an acute ischemic stroke study and the decrease in the number of seizures from pre-baseline 3 months to a 3-month period at some time after randomization in an epilepsy study. For a study that uses a binary outcome (such as treatment success or failure), one can substitute μ with π, where π represents the expected proportion of subjects with good or successful outcome. If one rejects the null hypothesis, that is, p value is less than the conventional 0.05, one would conclude that the agent or device of interest is more effective as measured by the primary outcome. If one fails to reject the

null hypothesis, one cannot conclude in the equivalence of the two groups, but merely note that there is insufficient evidence to show the superiority of the test agent or device.

For a study that wishes to show noninferiority, the set of statistical hypotheses are H_0: $(\mu_B - \mu_A) \geq \delta$ versus H_A: $(\mu_B - \mu_A) < \delta$, where δ is referred to as the margin of noninferiority which is a quantity that is usually less than the minimum clinically important difference (MCID). If the null hypothesis is rejected, we conclude that the new agent or device is indeed as good as the current standard. Noninferiority test is always one-sided and usually tested at the α-level of 0.025 instead of 0.05. Because of these parameter values, noninferiority studies generally require a much larger sample size than the superiority trials. The rationale for the noninferiority studies is to identify an agent or device that is nearly equivalent or at least as effective (within a specified margin) as the current standard, but have some beneficial qualities over the current standard, such as causing less side effects, easier administration or promoting better compliance by the patients and costing less. Sometimes, a trial will test for noninferiority of the new agent or device, and if and only if the null hypothesis is rejected, then it will proceed to test for superiority of the new agent or device. The closed testing procedure [3, 4] allows one to test the superiority hypothesis at the traditional α-level of 0.05 in this situation.

Once the research question is translated into statistical hypotheses, the following items are required to design a phase III study: (1) the primary outcome variable, including what (for example, the ordinal modified Rankin Scale (mRS) score or dichotomized mRS score), when (for example, at 1 or 3 months after randomization), how measured (for example, in person or by telephone) and by whom (for example, a stroke neurologist or anyone who is certified in mRS assessment); (2) the anticipated value of μ (and its variance) or π in the control group; (3) the MCID (for a superiority study) or the δ (for a noninferiority study); (4) the α-level, which is conventionally 0.05; (5) the desired minimum statistical power to detect the MCID (acceptable range being 80–95%); (6) randomization scheme (for example: 1:1 or 2:1 ratio; simple, blocked or adaptive; with or without stratification); (7) planned statistical analysis for the primary outcome. A strong collaborative effort between the clinical and statistical investigators to quantify these items yields a solid design.

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Behavioral/Neuropsychological Outcomes and Quality of Life Endpoints

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The surge in clinical trial research over the last decade has led to an increased demand for cognitive evaluations. Once utilized solely as an intellectual screen, cognitive assessments are now more widely employed and have been shown to be useful (1) as primary or secondary outcome measure(s), (2) in evaluating whether a participant meets entry criteria for a study, (3) in determining whether a neuropsychological deficit would exclude a participant from a study, (4) as an independent variable to define group membership (demented versus demented) and (5) as a means of documenting adverse effects following treatment. The increased demand for careful cognitive testing in clinical trial research has also led to a greater need for consensus batteries, namely those that include a core group of measures where there is widespread agreement regarding a minimum standard for assessing outcome.

Defining Behavioral Outcome

Central to all clinical trial research is a working definition of behavioral outcome. For the purposes of this chapter, behavioral outcome is conceptualized as an overt action, an observable behavioral consequence that can be operationally defined and measured [1]. An investigator may have an understanding of which outcomes are to be assessed, such as fatigue or memory loss or inattention, but these outcomes are of little use without knowing how to correctly assess the construct.

Choosing a Test Battery

There are several factors that should be taken into consideration when deciding which measures to include in a test battery for a clinical trial. First and foremost,

test selection should be driven by the research question. For some trials, the emphasis will be on demonstrating the presence or absence of mental status impairment, whereas in other trials, the focus will be on characterizing specific neurocognitive deficits. In the latter case, the investigator needs to have a clear idea, based on the literature, of which cognitive domain or functions should be most closely examined and choose measures that are sensitive to the representative group of skills under investigation. For example, a clinical trial examining the efficacy of stimulant therapy in children would want to focus on attention and not, for example, visuospatial skills. Other times, it may not be possible or practical to target a specific cognitive domain and a more generalized assessment is needed. In this situation, the choice is either to employ a screening measure, or to construct a more extensive battery that samples a wide range of cognitive skills. One approach increasingly recognized in clinical trial research is the use of a consensus battery. These batteries have a number of advantages because they allow investigators to pool data, standardize the protocol, utilize the same normative sources and work together in the context of a multicenter investigation. The National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards are one such recent example [2]. The Neuropsychology Work Group collectively proposed overall clinical and research objectives, recommended standards for studying vascular cognitive impairment and developed 3 protocols, a 5-, 30- and 60-min assessment that emphasized key cognitive abilities.

A test battery should be designed so that it can be realistically incorporated into a clinical trial while still allowing for a representative sampling of neurocognitive function. What is meant by 'representative' encompasses an array of abilities conceptualized in terms of cognitive domains. These include general intellect, language skills, visuospatial/visuoperception, attention, learning and memory, abstraction and executive functions as well as motor skills. While most neuropsychologists agree on which domains comprise a comprehensive evaluation, opinion varies as to what tests are best representative of a given skill, the optimal length of the test battery and the number of measures required in any given study.

It is generally accepted that extensive batteries tend to be more sensitive in detecting subtle cognitive dysfunction, but shorter batteries may be more useful for serial assessments [3]. There are a number of published cognitive screening batteries, all of which purport to be sensitive for detecting impairment. Even if a clinical trial only permits a brief cognitive screen, it is always important to use guided hypotheses to select which functions or group of functions will best address the research question under investigation. Brevity, ease of administration, lack of age, educational and other sociodemographic bias as well as diagnostic sensitivity are important features of a useful screening measure. One caveat is that while a screening test may be shown to be effective in detecting impairment, the same instrument is not necessarily equally responsive in detecting change over time [4]. There are a number of reviews comparing various screening measures and their psychometric properties [5–11].

Fixed batteries, including the renowned Halstead-Reitan and the Luria-Nebraska, share one advantage: they can be purchased as a group of preselected tests, complete with instructions and normative data. However, such fixed batteries are not practical because they are expensive, time consuming, inflexible and lack specificity [12]. It is better for investigators to have a clear idea of which cognitive functions to target and then work with a qualified expert to identify and administer the measures that will most likely yield meaningful information. Heaton et al. [13] suggest that one strategy for keeping the length of a test battery down is to omit tests that assess similar attributes.

Tests with multiple forms that have been shown to be comparable and those with minimal practice effects should be emphasized over those that are easily remembered and lack alternate forms. This becomes important for all prospective clinical trials. Practice effects, defined as improvement in performance resulting from repeated exposure to the test material or in some cases the task demands, are present on most neuropsychological measures in normal participants as well as those with neurologic impairment [12, 14]. Furthermore, research indicates that practice effects vary according to the skill being assessed, the test-retest interval and other subject variables such as age and overall competency [15]. Use of alternate testing forms reduces practice effects but does not completely eliminate them [15].

Tests with norms corrected for demographic factors such as age, education and, when possible, acculturation should be given priority over those that lack these corrections. This topic is addressed in further detail on the following pages.

Testing Standards

Neuropsychological tests should meet rigorous psychometric standards. The psychometric properties of published instruments are provided in the test manuals along with the standards for administration, scoring and interpretation. It is important that testing instruments are reliable and valid and demonstrate sensitivity and specificity. These concepts are briefly reviewed, but for a more extensive explanation of psychometric standards, the reader is referred to Cronbach and Meehl [16] and Smith [17].

Reliability is a measure of consistency. Internal consistency means that the items on a particular scale measure similar properties. Validity refers to whether a given test assesses what it purports to measure. In clinical trials, test validity should be considered a prerequisite condition for reliability, meaning, that if a test is not valid there is no reason to examine other psychometric properties.

A word of caution: a test can exhibit high face validity but in fact have low construct validity. This means that a test can look, on the surface, as though it measures a certain skill (that is, face valid) but turns out to measure a different construct. For example, a timed test of a visuospatial construction that requires rapid processing may in fact be measuring speed of processing and not visuospatial skills in individuals

with motor slowing such as those with Parkinson's disease. Thus, it is important to make sure that face validity mirrors the construct under investigation.

Test sensitivity refers to the proportion of true positives that are correctly identified by that measure. For example, when employing a mental status screen, the number of people categorized as demented, who in fact have dementia, reflects the test's sensitivity. Test specificity refers to the proportion of true negatives, that is, the number of people who do not have dementia and are correctly identified as such. Since an individual test can have high sensitivity and low specificity and vice versa, it is important to investigate both statistical indices when evaluating a test's utility.

Test Selection

A recent survey examining assessment practices among doctoral level clinical neuropsychologists revealed that the majority of respondents reported using a wide variety of instruments, with an average of 12 tests per battery [18]. Most use a flexible approach to test selection, as opposed to a fixed, prestandardized battery. In addition, while respondents reported using a large number of instruments to assess a given cognitive domain, the majority indicated that they use the same select group of measures. That is, despite the large number of tests to examine, for example, memory (in this survey respondents reported using 273 instruments), the Wechsler Memory Scale and California Verbal Learning Test, were reportedly used by over half the respondents [19, 20]. The most frequently examined cognitive domains are mentioned below.

Language

Language function can be assessed using a standardized aphasia battery or by measuring discrete verbal subskills. Brief aphasia screening tests are also available that can identify the existence of a problem but should not be used to characterize the type of language disturbance. Detailed reviews of numerous test batteries and tests for aphasia are readily available and will not be reviewed here [21].

Visuospatial Functions

There is a lack of consensus as to how to define the term visuospatial, also loosely referred to as perceptual functions. It is a heterogeneous domain, comprised of multiple skills including, but not limited to, facial recognition, spatial memory, visual analysis and synthesis, visual discrimination, visual recognition, personal space, spatial planning, visuomotor integration, visual spatial navigation of personal and extrapersonal space, visual attention as well as visual orientation [22]. Since many of the

measures require manual dexterity and are timed, these may not be optimal for clinical trial participants with movement or speed of processing disorders [23]. Under this circumstance, an investigator may want to consider utilizing only untimed or motor-free visuospatial tasks. A typical battery will include a minimum of 1 or 2 tasks, in which at least 1 assesses either graphomotor or assembling visuoconstruction, using, for example, the Rey Complex Figure Test or Block Design, respectively [19, 24].

Attention, Vigilance and Tracking

Attention, vigilance and tracking may be thought of as conceptually different, but they are difficult to assess as separate skills [12]. Most neuropsychologists include measures of simple and sustained attention not only because they are considered to be important in any test battery, but also because intact attention is a necessary precondition for even the most basic assessment. If subjects cannot demonstrate an ability to follow the task instructions and attend to the relevant task demands, the test results will be confounded, leading the investigator to conclude that a trial participant exhibits an impaired skill when, in fact, the reason for failure was inattention. Therefore, attention is both a skill to assess in its own right as well as a variable that needs to be established so that it does not interfere with the interpretation of the test results. There are numerous tasks that measure attention, but the most widely used are Trail Making and Digit Span [25, 19]. Other span tests, using letters, words and blocks are also available, as are continuous performance measures. In addition, cancellation tasks, using letters, numbers and shapes, are employed as measures of attention.

Memory and Learning

Memory involves the ability to store, retain and retrieve information. It is not a unitary skill; rather, memory is assessed on multiple levels, using a wide range of stimuli presented under different conditions. A mnemonic measure may utilize visual, auditory, tactile or other sensory stimuli to assess one or more memory abilities, which are referred to in the literature as working memory, learning and learning efficiency, immediate and delayed recall, remote memory, recognition memory, autobiographical memory and source memory. There is general agreement that there are many types of cognitive deficits that are subsumed under the heading 'memory impairment' and no one assessment strategy will be able to characterize this heterogeneous and complex construct. While memory testing is an integral part of any neuropsychological examination, a comprehensive memory evaluation is time consuming and often impractical for clinical trial research. Therefore, many investigators will focus on some aspect of memory that is most suitable for their research objective,

and then select one or more measures that directly assess that subskill. There are a number of excellent reviews on memory and techniques to evaluate memory-related skills [26, 27].

Executive Functions

Executive functions refer to the complex of behaviors involved in anticipating, planning and formulating goals, self-monitoring as well as using feedback to guide and modify behavior [28, 29]. This domain is considered to be an essential component of neuropsychological testing. Specific executive functions include verbal and conceptual reasoning, generating problem-solving strategies, planning and formulating abstractions, planning and monitoring performance, utilizing feedback, incorporating novelty, managing multiple tasks at the same time ('multitasking'), set shifting and the ability to ignore competing stimuli while focusing on relevant task demands. It is possible to measure various components of the executive functions without employing a test labeled as such because many tasks of higher cortical function rely on one or more executive components. Since measures of attention directly involve executive skills, they are often grouped together under one domain. However, it is also important to be aware of the executive demands integral to other language, memory and visuospatial measures. A common pitfall is to misinterpret an executive deficit as another type of impairment. For example, poor performance on a word-reading test may not be due to a language problem per se, but to difficulty staying on task or problems shutting out competing task demands.

Motor/Psychomotor Skills

Psychomotor performance and speed of processing are skills that are often incorporated into neuropsychological testing protocols because they are easily administered, do not require a grasp of the English language and have minimal practice effects. In addition, they do not rely on complex instructional demands or a specific level of education or acculturation. Motor performance is typically assessed examining one hand (usually the dominant, followed by the nondominant) and can provide data pertaining to lateralized deficits and asymmetry of function. The most widely used measure is the tapping test, also referred to as Finger Oscillation Test [25]. Pegboard placement, timed motor sequencing and grip strength are also used to assess motor function. Although tasks of psychomotor function are considered to be generally reliable and reproducible, age effects and gender differences have been reported [13, 30, 31]. Age interactions with education effects are also demonstrated, with higher education associated with faster tapping performance among older but not younger subjects [32].

Measuring Quality of Life

Quality of life (QoL) is defined as the set of capacities used to engage and experience satisfaction from socially and psychologically meaningful thought and behavior [33]. Health-related quality of life (HRQoL) measures are those dimensions of QoL that are impacted by health status and may be affected by health care [33]. HRQoL questionnaires are administered as part of a clinical assessment that emphasizes patients' feelings of well-being as well as their perception of their own capacity to work, complete activities of daily living and engagement in recreational activities [33]. More recently, HRQoL is being used as a prospective measure of patient status over time and as a means to evaluate the effectiveness of intervention.

QoL measures can be conceptualized as either generic or disease specific and each has its advantages [34, 35]. Generic instruments are designed to have breadth and to be applicable across a wide range of patient groups, diseases and interventions. Examples of generic measures are the Sickness Impact Profile and the SF-36 Health Survey, two instruments that have received much attention in clinical trials [36–38]. A major advantage of using generic instruments is that they have been used on so many different research samples and there is very sound and reliable information on the psychometric properties of these measures. Disease-specific QoL instruments have an advantage over generic measures because they can focus on features that are specific to a given disease or condition. Domain-specific measures focus on a single disease entity, but can be used with a broad range of patients (that is, dementia populations). Disease-specific measures are designed to target a specific population of patients (that is, those with Parkinson's disease). However, a shortcoming of disease-specific QoL measures is that they have not been as thoroughly developed and adapted as generic measures because they are less flexible, and do not, by definition, have a broad application [35]. As a result, an investigator may wish to combine instruments, supplementing a generic measure with another that is disease specific.

Computerized Assessment of Neuropsychological Function

Interest in computerized assessment of psychological functions began in the 1960s and is steadily growing [39]. Early studies were limited by expensive, heavy cumbersome machines and the lack of adequate normative data. Currently, there is a rapidly expanding market of highly portable computerized batteries that are commercially available and some have gained wide acceptance as research batteries. There is also a slowly emerging market that centers on developing computerized measures that are available on the internet. When used in the proper context, computerized assessment may offer a cost-efficient and practical method for evaluating cognition.

There are distinct advantages to using computerized assessment. Test stimuli can be presented in a highly rigorous fashion without concern regarding interrater

differences. In addition, responses and response latency patterns can be systematically recorded and analyzed. Other advantages include: the results are automatically tabulated and analyzed without having to check for clinician errors, reports can be immediately generated and the data readily stored for future use. Finally, large numbers of participants can be screened easily without multiple practitioners or having to test for examiner bias.

However, there are distinct disadvantages associated with computer-based assessments. Some computerized tests do not meet established testing standards. A recent study by Broglio et al. [40] examined 3 computerized assessment programs designed to assist in concussion diagnosis and management following a head injury and found only low to moderate test-retest reliability. In addition, computerized assessments are not appropriate for clients with neurobehavioral difficulties that require flexibility in the presentation of stimuli. Problems involving motor control, cognitive processing speed or sensory deficits may interfere with a participant's ability to solve a task. Individuals who are not motivated or exhibit suboptimal effort cannot be easily differentiated from those who have cognitive impairments. Another consideration is that while computerized testing may be user friendly for young and middle-aged individuals, the elderly are typically less familiar with computers and may be unnecessarily penalized [40].

A major problem is that computerized testing is largely confined to testing performance through auditory and visual modalities, thus limiting the scope of the examination. The most serious limitation related to its systematic application is that the computerized tabulation of the subject's response, the score, tells the examiner only whether an item was passed, not how the problem was solved or failed. While this may not be problematic for trials where the goal is to detect the presence of impairment, it can be critically important when the investigator is trying to understand the reason underlying task failure and the emphasis is on obtaining information pertaining to different cognitive profiles or identifying patterns of cognitive deficits [12].

Although computerized tests are useful and have been developed to mirror traditional measures, they may not provide comparable information. Despite the automated testing format, computerized assessments do not necessarily result in high test-retest reliability. It has even been suggested that the automated presentation of stimuli, coupled with reduced interaction between the examiner and examinee, bares little resemblance to traditional assessment and that the two forms of testing will never be shown to be equivalent [41].

Study Participants

Minority Assessment

Most researchers and clinicians are well aware of the pressing need to address the issues and challenges associated with employing neuropsychological measures to assess cognition among ethnic minorities. There is widespread agreement that the

overwhelming majority of cognitive measures, developed by and standardized on Caucasian samples, are biased and not appropriate for use among linguistically and culturally diverse populations. Furthermore, US census projections indicate that net immigration will be the leading factor underlying future population growth, a finding that suggests assessment challenges will only continue to grow as racial and ethnic diversity increases [42]. Currently, minorities comprise 28% of the US population, but this figure is expected to increase to 50% by 2050. There is little doubt all of these factors will impact clinical trial assessment.

Currently, there is a lack of consensus as to how to best address this problem and there are no empirically based guidelines [43]. Depending on the clinician/investigator, different approaches have been followed, including the use of culturally adapted and verbatim translations of the most widely used cognitive measures. Although a recent national survey of clinicians serving bilingual and monolingual Hispanic clients indicated a tendency to choose the latter, including the use of personally translated versions, it has been shown that this approach is biased and flawed. Artiola I Fortuny et al. [44] closely examined the testing material published in Spanish, that is, questionnaires and test protocols, manuals, test instructions and individual test items and found numerous instances of incorrect language and, overall, many of the translations to be of unacceptable quality [44]. In some cases, the back translations (originally published in English, translated into Spanish and then back into English) were incomprehensible to a native speaker, rendering the test invalid. The use of nonverbal tests to reduce cultural bias is not necessarily the solution either. Although they may reduce the linguistic burden, many nonverbal skills have large education effects [45].

This situation is further complicated by research showing that other educational and cultural factors influence neuropsychological test performance, including length and experience in the US, the country where one is educated, an individual's preferred language, the age at which English was first learned, and reading ability [46, 47]. In one study, an archival data set obtained from Caucasians, African Americans, Hispanics and Asians referred to an outpatient neuropsychology clinic in Los Angeles was used to examine the association between ethnicity and cognitive performance [48]. The neuropsychological battery consisted of those measures frequently encountered in neuropsychological settings. Although the groups were roughly equivalent in terms of the frequency of clinical diagnoses (indicating that the groups were similar in the nature of their presenting illness) and the test scores were adjusted for age and education, there were still significant ethnic group differences on neuropsychological testing on a third of the measures, which included tests of naming, digit span, visuoconstruction and nonverbal processing speed.

It has also been suggested that the use of Caucasian normative standards leads to overpathologizing among non-Caucasians, further emphasizing the need to employ racial and ethnic norms corrected for age, education and gender. Although in some cases this results in improved sensitivity and specificity of certain cognitive tests, Manley [68] has argued that this approach is also problematic, as racial and ethnic

norms tend to be outdated, and set more lenient standards. However, even more significant is that using racially separate normative standards does not address the underlying factors that may be causing the test discrepancies [43]. At this juncture, it is recommended that investigators seek out the best available method, whether it is well-standardized tests suitable for the minority group(s) under investigation or carefully translated measures. Most important, careful thought should be given when selecting a norm reference group for each clinical trial. This selection directly impacts test sensitivity and specificity, and it will also set the standard for how impairment is defined for minorities in clinical trials.

Testing the Very Old

Census projections indicate that the population aged 85 years and older is growing most rapidly compared to the other large age groups [42]. It has also been estimated that, as the population ages, 1 in 3 will have a stroke or dementia [2]. Unfortunately, the oldest age groups have been the least well studied and there is a striking lack of standardized measures and normative standards to evaluate the very old. Yet, this is a vulnerable age group that carries with it considerable controversy as to which cognitive and sensory changes should be considered pathologic versus those that reflect the 'normal' aging process. Nevertheless, investigators often include subjects who are above 80 years of age but use tests and norms developed for their younger counterparts. For these studies, an investigator should either check the manual for each measure to make sure there are representative age corrections or make sure the study design incorporates an age-matched control group.

Testing Considerations

Depression and Mood Disorders

There are several important reasons to assess mood state when examining mental status change. First, depression, anxiety and apathy can directly impact cognitive performance and confound a study, masking a subject's true ability. Second, an investigator may want to measure mood state to exclude subjects exhibiting clinically significant symptomatology. Although including individuals with mood-related symptoms is well justified in certain clinical trials, it is not recommended to include participants that express severe psychological distress. The problem is that extreme symptoms are not always readily apparent. A total score on a depression screening measure may fall below the clinical cutoff for severe depression, but the seriousness of one's psychological distress only becomes evident when the individual items are examined. Third, mood states often mirror cognition and may serve as an important indicator of mental status change. For example, participants who exhibit frontal lobe disturbance, whether stemming from trauma, epilepsy, infection or a degenerative disease, will typically exhibit predictable cognitive deficits as well as marked personality change,

which may range from excessive emotionality to marked apathy. For all of the above reasons, it is recommended that clinical investigators include at least a brief emotional screen in their test battery.

Measuring Premorbid Abilities

An investigator's ability to determine whether a deficit exists depends in part on a participant's premorbid level of cognitive functioning. The simplest strategy to estimate premorbid ability is to utilize the best-performance method, a technique based on the assumption that the highest score or group of scores represents the best index of an individual's original cognitive potential.

Ideally, previous test scores, educational and occupational records, and well-documented historical information are the best index, but rarely, if ever, are these data available. Most investigators estimate premorbid ability using one of several approaches as described by Lezak [12]. One strategy is to rely on tests of mental ability that are known to be relatively resistant to the effects of aging and generalized brain insult. Historically, the most commonly used measure is vocabulary test performance, an ability that correlates highly with education and is known to be relatively resilient to the effects of aging. The most frequently used vocabulary measures are the Wechsler Adult Intelligence Scale III (WAIS-III) and the Shipley Hartford Institute of Living (SILS) [19, 49]). While the WAIS-III vocabulary subtest is used extensively, it requires an oral definition and should not be used with patients with expressive language difficulties. The SILS is based on a multiple choice format and uses recognition rather than recall to assess vocabulary.

Another strategy is to use word reading as an estimate of premorbid ability. Word reading is directly related to level of education and may be more sensitive than using a grade level to estimate premorbid IQ because the ability to pronounce an irregular word requires a facility with the English language that is directly related to reading skills and overall verbal ability. The National Adult Reading Test (NART), a measure that requires oral reading of 50 phonetically irregular words that increase in difficulty, was originally developed in Britain [50, 51]. The North American Adult Reading Test (NAART) has been adapted for use in the US and Canada [4, 52]. This test uses 61 words and has been shown to correlate with WAIS-R VIQ and FSIQ. Other adapted versions include the American National Reading Test (ANART), a 50-word version developed for ethnically diverse US populations and the Short NART, a form recommended for individuals who fail more than 5 of the first 25 items [53].

Another word reading test is the Wide Range Ability Test (WRAT-READ), a test that uses phonetically regular and irregular words to assess premorbid IQ. Research comparing various versions of the NAART and WRAT-READ indicate that while both are generally adequate measures of premorbid verbal ability, the latter test may be more useful with participants who score in the lower ranges of VIQ. A problem with vocabulary test performance and word reading is that both are vulnerable to brain disorders that involve verbal ability.

Drugs and Alcohol

A careful assessment of drug and alcohol usage is an essential component of the screening process. Admittedly, there are limitations as to how rigorous an investigator can be in assessing the influence of prescribed medications and recreational drugs on neuropsychological test performance. There are other problems associated with addiction, including deficient nutrition, unemployment, and poor health, all of which are associated with poor test performance. Although often not reported, older adults are especially at risk for potential complications and disorders associated with the use of prescription and over the counter drugs [54]. It has been estimated that individuals over 65 years consume nearly a third of all prescription medications. These factors notwithstanding, it is important to acquaint oneself with the scope of cognitive deficits associated with chronic usage of particular substances with particular attention paid to age-related changes in pharmacodynamics, especially among the elderly [55]. A thorough review of medications, recreational drugs and alcohol usage will also allow the investigator to statistically control for potential confounders that may interfere with the treatment under investigation.

The drugs that have received the most attention in terms of their impact on neurocognitive performance are antidepressants and antiepilepsy medications [54]. The cognitive sequelae associated with these medications are well described and have been the subject of much research [55–59]. There is also a burgeoning literature demonstrating cognitive impairments following long-term use of antianxiety drugs, especially the benzodiazepines [54, 60].

Recreational drug usage is more difficult to monitor. Even when the investigator makes an attempt to record the number, type and frequency of substance use, the obtained information is not always accurate. Nevertheless, every attempt should be made to evaluate and control for this variable, as it remains a potential confounder in clinical trial research, particularly among younger trial participants.

Studies examining polydrug users indicate combining two or more drugs may have additive negative effects. For example, if cannabis is used in combination with MDMA (ecstasy) or alcohol is used in combination with cocaine, more pervasive cognitive deficits are likely to persist after abstinence [61–64].

Burden of Neuropsychological Testing on Recruitment and Retention

Consent to Participate and Attrition

Subject attrition is present in all clinical trials and investigators need to plan ahead accordingly. There is a body of research showing that (1) subjects who agree to participate in clinical trials may be different from those who refuse and (2) subjects that drop out of studies are different from those who elect to continue their participation. Factors such as median family income, distance of one's home from the testing site, work-related disability and physician approval, whether explicit or implicit, has been

shown to impact recruitment [65, 69, 70]. With regard to attrition, subjects who drop out tend to be older, show more cognitive impairments at baseline and be less socially active [66, 67].

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Clinical Endpoints

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Defining and measuring 'clinically meaningful' endpoints is a major challenge for late stage phase II and most phase III clinical trials in neurological disorders. By definition, a clinical endpoint is a characteristic or variable that reflects vital status, level of functioning or quality of life [1]. Certain clinical outcomes, such as death, recurrent stroke and recurrent headache are widely accepted and have standard definitions that may incorporate clinical features, laboratory values and neuroimaging [2]. Quantitative outcomes (such as tumor volumes, degree of white matter disease and erythrocyte sedimentation rate) are useful for objectively monitoring disease activity. For many neurological conditions, however, markers of progression, regression and outcome may be more difficult to define. Chronic conditions, such as Parkinson's disease, Alzheimer's disease and peripheral neuropathy, may have outcomes defined by rating scales, but their effect on quality of life is more difficult to gauge.

The threshold for 'meaningful' is subjective, but should be substantiated based on the severity of the outcome and the potential impact for the larger population. For instance, a 1% reduction in death for a common condition, such as stroke, would translate into thousands of lives saved each year in the United States. For a rare condition with potentially devastating effects (such as meningitis), again, small reductions in morbidity and mortality may be compelling. For quantitative outcomes, thresholds which correlate to changes in category of function (for example ambulatory vs. non-ambulatory or independent vs. dependent) may be appropriate. When there remains uncertainty about how clinicians or patients would value changes in health status, surveys can be a useful way to establish consensus. Establishing the range of a clinically significant effect is an essential step in calculating the requisite sample size. Phase III trials must be adequately powered to detect a clinically meaningful difference, or they will not provide meaningful data once completed.

Although trials should be designed based on a primary clinical outcome or composite clinical outcome, secondary outcome measures are useful to provide additional information on the robustness of effect.

Classification

Outcomes assessing severity can be classified as shown in table 1 [3, 4]. Handicap and health-related quality of life are the 2 outcomes that resonate most with patients, but they are much more difficult to define, validate and consistently assess in research studies. Clinical trials, especially phase III trials should, nevertheless, attempt to measure disability, handicap or health-related quality of life. In phase II trials, since the aim is to establish that the treatment under study influences the disease process, it is appropriate to use impairment scales, but clinically relevant disability and handicap scales should be included, since they will be useful in designing the phase III clinical trial [5].

Clinical Outcome Scales

Rating scales used in neurological conditions facilitate standardization across trials, allowing comparison of baseline severity and the magnitude of effect. A clinical scale must be both clinically useful and scientifically sound. To be clinically useful, it must be practical to administer. A scientifically sound scale must be reliable (interrater, intrarater and test-retest reliability), valid and responsive to changes in a patient over time or to differences between patients. There are 2 types of scales in use [6].

(1) Single-item scales: single-item scales assess a single disease feature or outcome and are simple and quick to administer, easy to score and easy to interpret. Their main disadvantages are that they have limited ability to differentiate between patients, or even a single patient, over time and they are prone to observer error and have low interrater reliability.

(2) Multiple-item scales: multiple-item scales aim to measure more complex, multidimensional outcomes such as disability and quality of life. These scales are usually composed of a list of categories designated by numbers to form an ordinal scale. The advantage is that since they combine various items, the chance of a random error in each item is negated and reliability is higher. The main disadvantage is that they are more difficult to interpret than single-item scales.

The development of a multiple-item scale is similar to the processes involved in the design of a clinical trial. The first step requires deciding on the domains to be measured (definition of the construct and subconstructs). Secondly, the individual disease features or outcomes are generated. Next, the outcomes are assessed in a sample of patients and the results used to develop reliable and valid constructs and subconstructs. The last step is examination of the scale in a new group of patients [6]. Most large phase III clinical trials should employ outcome scales that have already been validated and are well accepted for the disorder under investigation.

Table 1. Outcome classifications for clinical trials

Outcome	Definition	Examples of scales
Impairment	Evidence of underlying pathology	Glasgow Coma Scale Folstein Mini Mental State Exam NIH Stroke Scale
Disability	Functional consequence of impairment	Barthel Index Glasgow Outcome Scale Modified Rankin Scale
Handicap	Social impact of the disease	Viitanen Scale
Health-related quality of life	Social impact of the disease	Nottingham Health Profile Stroke Impact Scale
Quality of life outcome in epilepsy	Social impact of the disease	2OLIE

Health-Related Quality of Life

Health-related quality of life is increasingly being accepted as a relevant endpoint and outcome criterion in evaluating the effects of therapeutic interventions in clinical trials. There are 2 core sets of outcomes that should be included in a quality of life assessment: (1) physical, intellectual, emotional and social functioning, and (2) degree of satisfaction derived from performing these activities [7].

Quality of life indicators have a particularly important place in assessing outcomes under specific conditions, such as [8]:

- The intervention has a potential effect on symptomatology without affecting the natural history
- The intervention results in a high frequency of extremely unpleasant adverse reactions
- Prevention trials in which untreated subjects have few symptoms, low morbidity/mortality and the interventions have undesirable side effects
- Trials of new drugs that are not superior to standard therapy, but have fewer adverse effects or lower costs

The Need for Patient-Reported Outcomes

Patient-reported outcomes measure the overall impact of a treatment on health, incorporating both the direct treatment effects (for example, decreased physical functioning due to surgical complication in an epilepsy patient who has undergone temporal

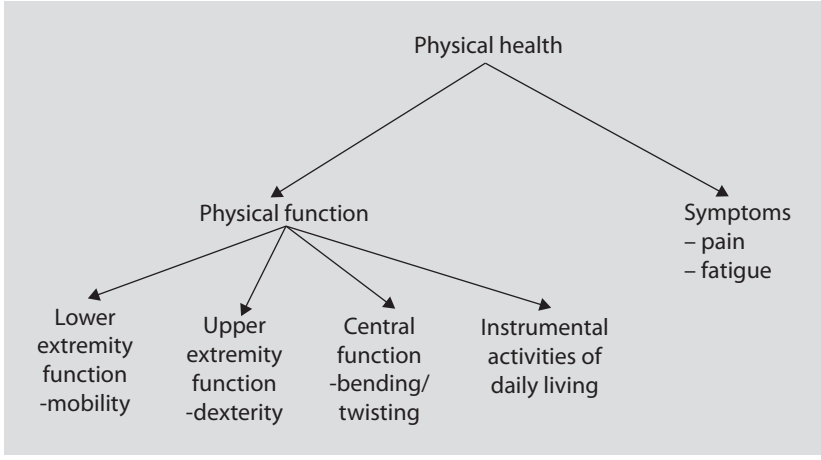

Fig. 1. The framework proposed by PROMIS for outcome assessment questionnaires.

lobectomy) and indirect ones (for example, return to employment, ability to retain a driver's license or improved social functioning as a result of seizure reduction) [9]. Using current investigator-derived scales, it is difficult to know if, for example, the proportion of stroke patients receiving active treatment are able to function independently in their activities of daily living after 1 year, if headache patients are spending fewer days away from work as a result of treatment or if Parkinson's disease patients' symptoms are declining more slowly as a result of clinical management decisions. In the future, these types of measures, outcomes important to the patient, should be included as endpoints for clinical trials [9].

Patient-Reported Outcomes Measurement Information System

The NIH's Patient-Reported Outcomes Measurement Information System (PROMIS) initiative is a 5-year multicenter cooperative program designed to develop, validate and standardize item banks relevant to common medical conditions, especially chronic ones. The aim is to enable efficient and interpretable clinical trial and clinical practice applications of patient-related outcomes [10]. An item bank is composed of carefully calibrated questions that define and quantify a common concept and provide operational definition of a trait [11, 12]. Valid, generalizable item banks can standardize clinical research across NIH-funded research organizations dealing with patient-reported outcomes. Existing outcome assessment questionnaires use a framework that includes concepts of physical function, mental health, social function and symptoms (fatigue, pain). PROMIS experts refined the framework by specifying unidimensional subdomains [10]. An example of this approach is shown in figure 1.

Conclusion

Clinical outcome measures should be carefully considered in the design of a trial. Trials must be adequately powered to detect clinically significant effects of study-specific interventions. To date, few studies have used patient-reported outcomes measures to evaluate new therapies, but these have tremendous potential in neurological conditions.

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Data Management and Quality Assurance

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Data management encompasses the acquisition and maintenance of study data. Data management activities are important to any study because data are the medium by which the study results are processed, interpreted and reported. The conduct of any clinical study requires a substantial investment of financial and human capital. A comprehensive data management strategy represents thoughtful stewardship of these limited resources. Moreover, the quality of any study rests heavily on the quality of its data management effort.

Study data management activities should focus on ensuring that: (1) data are of the highest quality, (2) participant safety and confidentiality are protected and (3) study staff has tools that facilitate efficient and effective conduct of the study.

An effective data management strategy identifies the data to be collected, provides a comprehensive design of the data collection, editing, storage, quality control and management processes, and delineates delivery of a quality data set to the study statistical team for analyses.

Key components of an effective strategy include:

- Identification of the data elements required to address the study hypotheses
- Design of the study data collection forms to capture data elements in an objective format with mutually exclusive responses
- Description of the randomization system and related automated tools (for example screening log)
- Description of the clinical data management system that will collect, store and edit the data as well as provide performance and quality reports on the data
- Delineation of data collection flow, editing and correction processes
- Delineation of the processes to capture safety data and reports coming from external sources, such as laboratory data
- Description of all quality control steps and reports
- Delivery of data to statistical team for analyses

The components of an effective data management strategy are the same for a single-site phase I study or a multicenter phase III efficacy study. However, the approach may differ as the size and number of study sites increase. To assist clinical researchers in implementing clinical studies cost-effectively and efficiently, the National Institute of Neurological Disorders and Stroke (NINDS), NIH, has introduced common data elements and core forms that are critical to any study. The elements and forms will be available on the NINDS web site (http://www.ninds commondataelements.org/CRF.aspx) in a modifiable format to facilitate study-specific customization.

Data Management Team

Two key components required to ensure an effective data management strategy are (1) a skilled data management team and (2) comprehensive planning. If either of these components is lacking, the data management effort can be critically handicapped and could result in costly recollection of data or unanswered study questions.

Given the array of data issues that must be addressed, a data management team is most often required to develop an adequate and comprehensive plan. The following areas of expertise should be represented within this team:

- Computing hardware support – to ensure there is adequate computing equipment to support the entire data effort, allowing for secure data acquisition, generation and management of data queries and status reports, analyses, and archiving/data-sharing requirements
- Systems programming – to ensure the computing hardware involved possesses appropriate software and it is being properly programmed and maintained;
- database programming – to ensure the data collection and/or housing tool is functioning properly
- Statistical/supplemental analysis – to ensure data are collected in a manner that supports effective analysis in accordance with the stated analysis plan (note that this implies that the analysis plan should be developed ahead of, or in parallel with, the data management plan, but not afterwards)
- Administrative support – to ensure adequate support of all clerical and administrative needs with respect to managing the data, such as development and/or distribution of reports and data instruments
- General oversight – to ensure all data management components are working as a cohesive unit and to provide general direction

These skills are diverse and it is often difficult to identify a single individual who will have sufficient expertise to mount a data management effort alone. Thus, a team approach is recommended, headed by a knowledgeable individual who has experience in clinical data management. This individual will interact frequently with the other study team members to ensure that the data management strategy addresses the study requirements.

Data Management Plan

Once the data management team is identified, they should work to develop a comprehensive data management plan. After careful consideration and planning, the data management plan should be produced in written form and explicitly include descriptions of the following components:

- Infrastructure – who the members of the data management team are and where the effort will be housed
- Data elements to be collected – in dictionary format, the name, type and intended use of all data elements to be collected in conjunction with the study
- Data flow – how, and by whom, all data are to be collected, stored, cleaned, analyzed and archived
- Computer hardware and software components that are required
- Maintenance procedures – general security procedures, backups and computer software upgrade policy
- Quality control procedures – checks for data accuracy and consistency.

Another consideration for the data management plan is the introduction of administrative logs and tools that can assist the coordinators in study operations. Examples of such tools include:

- Screening log – documents all individuals screened for the study as well as their disposition
- Laboratory tracking form – documents date samples sent to the laboratory for a study participant and can be used to assure results are received
- Protocol exception log – documents out of window, missed visits and other activities that may not be consistent with the protocol

For studies that will be submitted to the Food and Drug Administration (FDA), additional federal regulations (CFR 312, part 11) must be addressed in the data management plan.

Often, the data management plan needs to be reasonably well developed before approaching a major funding source, such as the NIH or a biopharmaceutical company. The earlier such details can be determined, the greater the likelihood of attracting the funding to successfully launch the project.

It is imperative that the data management team develops the plan in collaboration with the study clinician(s), including the principal investigator and the study coordinator, or their representatives. Their input is necessary not only to define the data elements to be collected but also to review the study forms and assess the data flow. Clinicians are often on the front line with respect to the data collection effort, and their input can help ensure that the data collection strategy is not awkward, burdensome or impractical. Quite simply, it is counterproductive to develop a sophisticated data management plan that does not support the efficient and effective functioning of the clinical staff.

Quality Assurance and Quality Control

Quality assurance, as applied to clinical trials, is any method or procedure for collecting, processing or analyzing study data that is aimed at maintaining or enhancing their reliability or validity [1]. Data integrity refers to the consistency of data throughout a study, from the source documents through reporting of results. The quality of a study is dependent on data accuracy in all stages from data recording to publication of the results.

Quality assurance encompasses internal quality control, study monitoring and external audits or assessments. Internal quality control are those ongoing, built-in strategies that an investigator or coordinating center employs to ensure the accuracy of the observed, recorded, abstracted, entered or reported data. The study forms, operations manuals, data dictionary, data management plan, training programs and reports are examples of internal quality control mechanisms. It is also important to delineate quality control steps that will prevent data issues, assist in identifying potential issues and identify a corrective action plan.

Prevention Activities

Comprehensive quality control steps are required to prevent study quality issues. Such prevention activities should include documentation, such as the data management plan, that should include data and study flows (described in the next section), study communications and checklists. Quality control activities increase with the amount of data to be collected, the variety of elements and the number of study sites.

Data and Study Flows

A data flow, a sample of which is shown in figure 1, is part of the data management plan and provides an overall picture of how study data will be captured. The data flow is to include an explicit description of how each of the following data tasks is to be accomplished:

- data capture from study participants – paper, direct electronic capture or others;
- secondary data capture – from laboratories and external diagnostic reading centers;
- transmission to and from central repository for storage and processing – mail, telefax or electronic transfer;
- data storage – where and how data will be stored, including location and software platform;
- process and flow for correcting data from coordinating center to and from clinical sites – electronic mail, web site, fax or mail, as well as tracking of the corrections;
- flow of data extraction for reports and analyses – to statistical coordinating center or from coordinating center.

It is also often helpful to develop a flow that describes how an individual proceeds through the study as shown in figure 2. The development of the flow provides a check on the protocol details to assure that key steps are described and that data management details will be addressed. For example, in some studies the receipt of data from a central laboratory was not fully specified, resulting in the laboratory transmitting

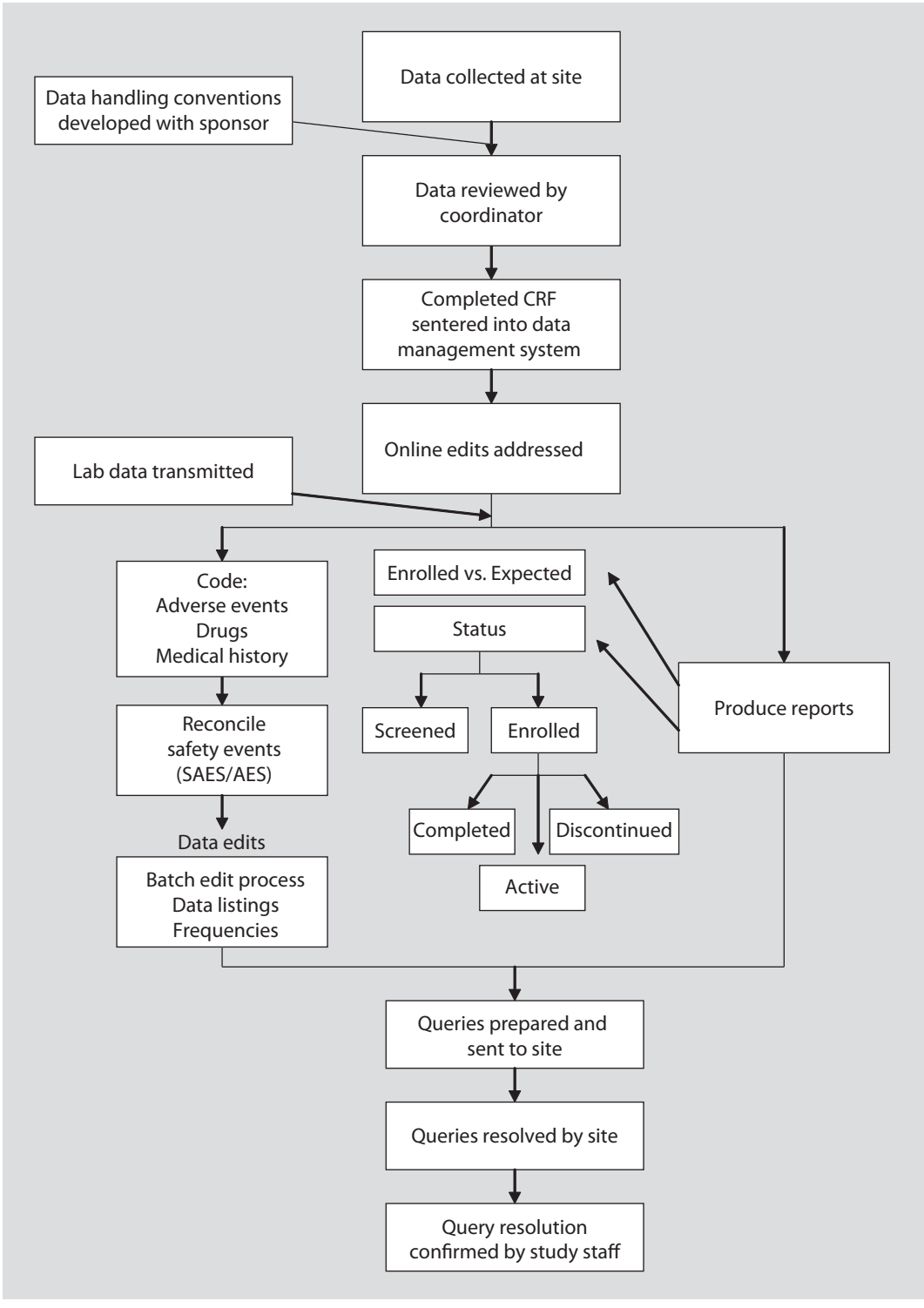

Fig. 1. Sample data flow. CRFs = Case report forms.

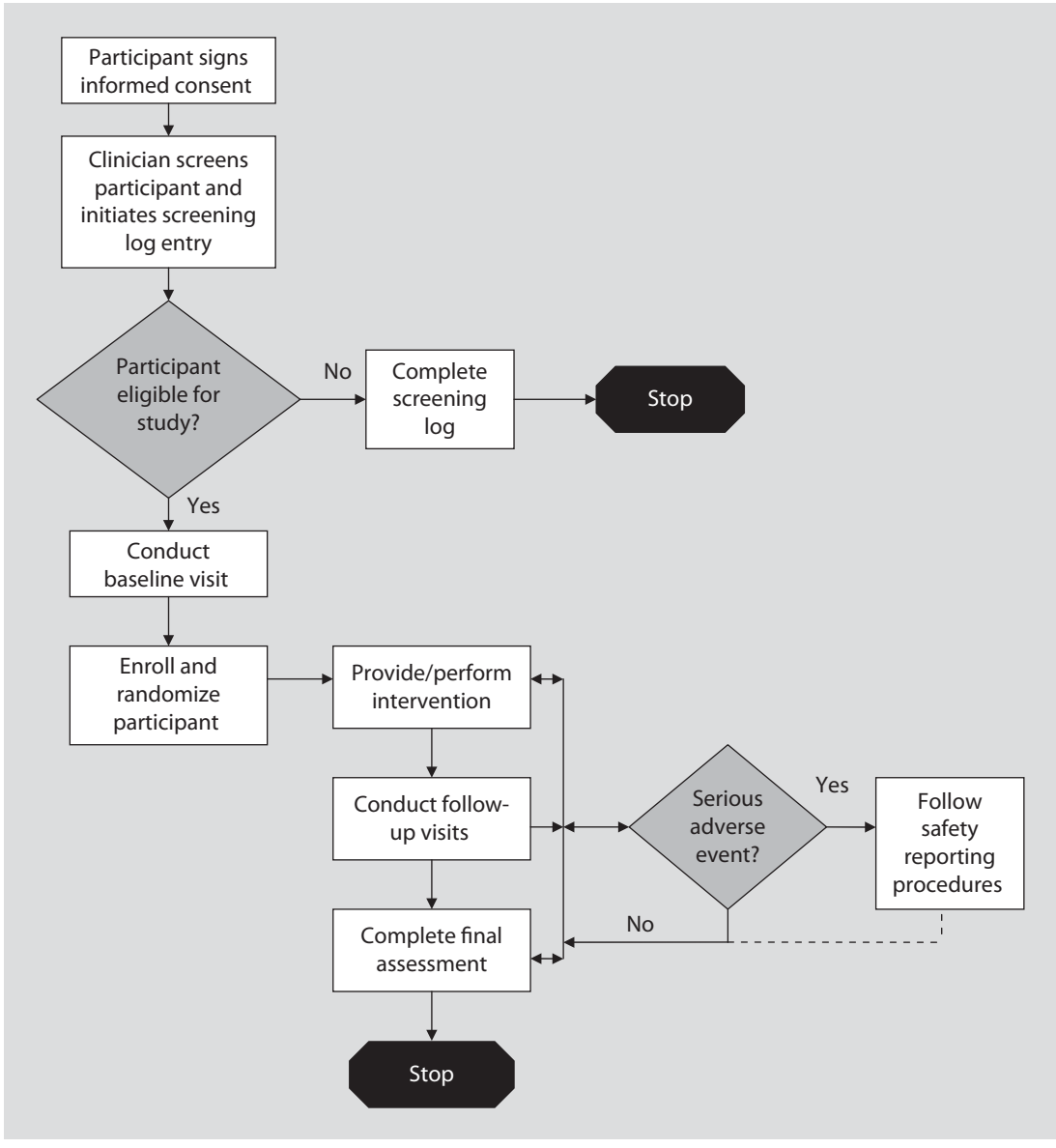

Fig. 2. Sample participant flow through study.

results in a series of idiosyncratic strings that was quite expensive to decipher and caused lost data for some of the study participants.

Communications

Ongoing and routine communications among study staff in a single-site study and among the coordinating center, clinical sites and sponsor in multisite studies are important mechanisms for: (1) clarifying study procedures, (2) developing a 'team

spirit' that encourages ongoing recruitment and retention of study participants and (3) sharing successful strategies among sites.

Communications, which can include telephone conference calls, newsletters and/or dedicated web site postings, help to prevent study issues that can compromise quality.

Identification of Potential Issues

Data edits, routine reports and site visits each help to identify potential study issues.

Data Edits

Automated data edits that identify missing data, implausible values and inconsistent entries (for example pregnant male) should be performed by the study's computer system to identify data issues. The edits generate data queries that are sent to the study site for resolution. A mechanism for tracking the queries sent and resolved by the sites is important to ensure that all issues are resolved or determined that they cannot be resolved.

Reports

Reports that describe site performance, study forms, data, status and safety and other potential issues are an excellent way to identify potential study issues. Performance reports are typically generated by a coordinating center and focus on study sites. Reports describe actual against expected enrollment, forms entered, missing study visits, forms and/or data queries sent to the site as well as unresolved queries. Coordinating center performance reports describe forms received and entered, queries generated and resolved, and progress toward study completion. Study status reports that describe individuals screened, enrolled, active, discontinued from study treatment and completed provide a study summary. These reports can provide an early warning of quality control problems, allowing for the timely implementation of preemptive and corrective procedures.

Aggregate data reports by site explore categorical data response frequencies and grouped continuous data items (such as age groups). These reports help to identify missing data items and anomalies, and can aid in assessing individual site performance. Descriptions of data items over time by individual study participants illuminate implausible values as well as potential site and/or data issues.

Frequency of report generation is determined by such factors as number of sites, enrollment projections and duration of study. In studies with large numbers of sites and active enrollment, weekly reports are useful.

Site Visits

Visits to the study site help to assure that data are collected according to the protocol, individual identifiers are not stored with the study forms and informed consent is appropriately administered. Some site visits include a data audit that compares the

study forms and data in the database to source data to ensure that the data are accurately represented. Site visit reports summarize findings and provide a mechanism for the site to correct and document any identified issues. Although site visits can be costly and require a considerable investment of human resources, they are quite useful in assessing overall site performance and maintaining a high level of quality within the study.

Issue Resolution

Study issues can be resolved through the query process and site visit reports. Additional training is sometimes introduced as a mechanism to resolve issues. Sites that do not enroll or continuously do not address quality issues even after warnings and training may need to be discontinued from the study.

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Multidisciplinary Trial Design

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Current Multidisciplinary Trends in Clinical Neurology

The constant technical progress of diagnostic and therapeutic procedures has led to a steady change in the management strategies of a large variety of neurological diseases over the last thirty years. The progress of neuroradiological imaging tools from pneumencephalography through early angiography to noninvasive CT and MRI provides one of the most spectacular examples on how our diagnostic armory has advanced to less invasive but more informative techniques. Similarly, interventional procedures trend towards minimally invasive treatment strategies, including microneurosurgery and image-guided interventions, endovascular techniques, stereotactic radiotherapy, etc.

When it comes to actual clinical care, however, strategies to improve neurological patient management trend towards higher levels of complexity, shifting from single-discipline treatment to multidisciplinary management (fig. 1). Many neurological core entities, such as multiple sclerosis, epilepsy, neurovascular disease and degenerative disorders, are usually diagnosed and managed by a multidisciplinary team involving neurology, neuroradiology, neuropathology, neuropsychology, internal medicine and many more, depending on disease entity and individual patient profile. Some disorders have been a multidisciplinary challenge since their initial description, as they involve multiple organ systems via metabolic links (such as Wilson's disease) or multiple locations (Rondu-Osler-Weber disease). Several clinical domains expand from neurology into other domains like, for example, neurosurgical treatment for epilepsy or Parkinson's disease, while others extend from neighboring disciplines towards neurology, such as the management of neurovascular patients with carotid stenosis, brain arteriovenous malformations, cerebral cavernous malformations and intracranial aneurysms.

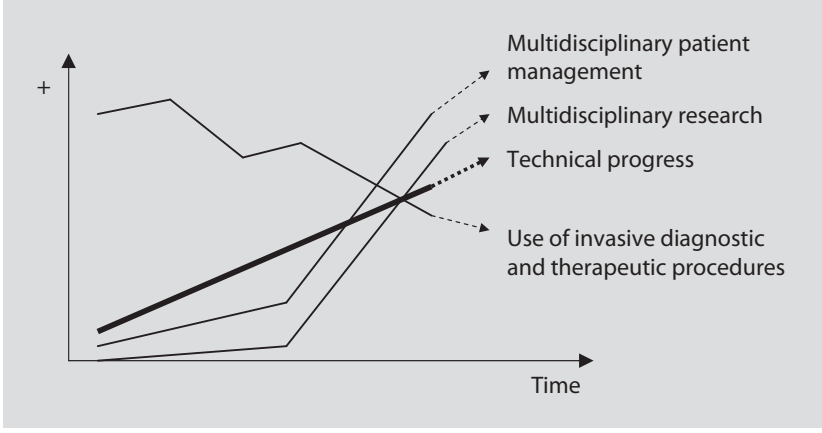

Fig. 1. Idealized graphical illustration showing technical progress fostering ongoing trends towards less invasive diagnostic and therapeutic procedures along with increasing sophistication and multidisciplinarity of clinical care and research strategies.

Multidisciplinary Clinical Trials – General Concepts

The current trend towards multidisciplinary management strategies is mutually inspiring for all major segments of academic medicine, including collaborative patient care, shared teaching programs and joint research protocols. The concept of the multidisciplinary clinical trial design emerges as a direct consequence of the changing clinical practice patterns. It responds to the increasing need to test the presumed benefits and potential risks of changing management algorithms and new treatment approaches in a collaborative, that is, multidisciplinary, setting.

As in patient management, the changing algorithms are associated with increasingly complex designs, as an increasing number of collaborators share the responsibility for joint study protocols. While in the past, clinical trials for Parkinson's disease focused on medication alone, multidisciplinary perspectives test the safety and efficacy of stereotactic surgical intervention compared to pharmacological therapy. Recent trials on secondary stroke prevention in a setting of a symptomatic carotid stenosis compared the clinical efficacy of carotid surgery versus endovascular intervention and involved surgical, neurointerventional and neurological co-investigators. Therefore, any multidisciplinary trial structure will ideally allow collaborators to act as equal partners, rather than as ancillary or adjunct disciplines. This involves all stages during the building up of a clinical trial, from the initial planning phase, protocol and endpoint definitions, intervention and follow-up modalities, the composition of the various supervising board for case adjudication and safety monitoring, as well as members of the executive and steering committees. Study site recruitment may depend on the availability of treatment modalities involved, and study initiations naturally include appropriate protocol application and eventual monitoring through

various disciplines. Multidisciplinary investigators have to share domain-specific expertise, but split responsibilities between those for 'intervention' and those for 'evaluation'. While the neurologist may or may not administer therapy in one of the study arms, neurology certainly plays a key role when it comes to the clinical evaluation of neurological function.

Multidisciplinary Clinical Trials – The Specific Role of Neurology

The multidisciplinary trial design is based on the principle of shared expertise in patient management and trial performance. Naturally, participating neurosurgeons will provide experience and expertise for neurosurgical interventions in the invasive treatment arm, interventional neuroradiologists for endovascular procedures, neurologists for patient assessment and the use of clinical scales and scoring systems, and so on.

Active involvement of a study neurologist is now considered common standard in controlled clinical trials whenever the study outcome includes assessment of neurological function (table 1). Nonetheless, the principle of independent neurological outcome evaluation has not always been applied, even in recent trials that specifically evaluated clinical outcome of invasive treatment modalities; for example, neither the International Subarachnoid Aneurysm Trial (ISAT) [1] (comparing the safety and efficacy of endovascular coiling versus neurosurgical clipping of ruptured aneurysms) nor the n-BCA trial [2] (evaluating the effectiveness and safety of N-butyl cyanoacrylate embolization of brain arteriovenous malformations) included independent neurological outcome assessment.

Conceptually, the specific role of the neurologist in a multidisciplinary clinical trial is based on several principles (table 2).

First, there is the neurologist's expertise in the assessment of neurological function. The evaluation and analysis of neurological syndromes and deficits is the neurologist's daily work and should be his or her mission in the collaborative setting of a multidisciplinary trial. Sharing domain-specific expertise in collaboration with other disciplines, the neurologist may serve as a clinical referee deciding on whether a lesion or condition is considered symptomatic or asymptomatic (for example, carotid stenosis). The neurologist may further judge possible syndrome progression (for example, Parkinson's disease) or symptom recurrence (such as TIA, stroke, epilepsy and migraines), and may help defining treatment indications and therapeutic thresholds allowing patient enrollment in a clinical trial according to clinical inclusion criteria (such as qualifying clinical events or syndrome severity).

Neurology's genuine interest in the epidemiology, natural history and long-term follow-up of specific disease entities makes the study neurologist an ideal observer of interventional versus noninterventional comparison groups depending on the explicit trial design. The neurological co-investigator as part of the multidisciplinary study team may add to a positive center/patient interaction and may be ideally placed

Table 1. Multidisciplinary trials with neurological endpoint evaluation

Subject	Multidisciplinary study	Complementary disciplines
Carotid stenosis surgery	• NASCET [12] • ECST [13] • ACAS [14 • ACST [15]	• Neurology, vascular surgery/ neurosurgery
Carotid stenosis surgery versus endovascular	• SPACE [16] • EVA-3S [17] • CAVATAS [18] • CREST [19]	• Neurology, vascular surgery/neuro-surgery, interventional neuroradiology
Cardiac sources of ischemic stroke	• SPAF trials [20] • CLOSURE [21] • PICSS [22]	• Neurology, cardiology
Craniectomy in malignant MCA infarction	• DECIMAL [23]	• Neurology, neurosurgery, neuroradiology
	• DESTINY [13]	• Neurology, neurosurgery
	• HAMLET [24]	• Neurology, neurosurgery
Management of unruptured intracranial aneurysms	• ISUIA [25]	• Neurology, neurosurgery
	• TEAM [26]	• Interventional neuroradiology, Neurology
Management of unruptured brain AVMs	• ARUBA [27]	• Neurology, neurosurgery, interventional and diagnostic neuroradiology, radiotherapy
Parkinson's disease:	• Neurostimulation versus medical management [28]	• Neurology, neurosurgery

MCA = Middle cerebral artery; AVMs = arteriovenous malformations.

to provide independent informed consent information for trials comparing different types of intervention.

In interventional trials, self-audit of postoperative risks has proven unreliable [3]. In this context, the neurologist's role helps to assure an independent endpoint evaluation of neurological function, either as part of a blinded study protocol or as an independent bystander in an open trial evaluating 2 or more types of invasive therapy. Most importantly, study neurologists are generally trained and certified in the use of specific outcome scales for stroke (such as NIHSS, Rankin Scale [4] and Barthel index [5, 6]), multiple sclerosis (such as EDSS [7] and MSFC [8]) and Parkinson's disease (MDS-UPDRS [9]), but also quality of life instruments (SF-36 [10], EuroQol [11]) to name but a few.

Table 2. Principles of neurological participation in multidisciplinary research protocols

Clinical expertise
– Neurological status
– Symptomatic versus asymptomatic lesions
– Syndrome progression
– Therapeutic threshold (inclusion criteria)
– Treatment indication
Specialty-specific interest
– Neuroepidemiology
– Natural history
– Long-term follow-up
– Positive center/patient interaction
– Independent informed consent information for intermethod comparison
Independence
– Clinical endpoint evaluation
– Disease-specific outcome scales (stroke, Parkinson's disease, etc.)
– Data quality

Overall, the neurologist's complementary role (fig. 2) may help to improve the data quality of a multidisciplinary trial protocol throughout the various steps of patient screening, enrollment, follow-up and outcome evaluation.

Multidisciplinary Clinical Trial – The Principle of Equipoise

In general, conducting a controlled clinical trial is justified when scientific data suggest clinical uncertainty regarding equivalence or superiority between 2 or more therapy options. If clinical equipoise can be assumed between study arms, randomization is the currently best available algorithm leading to unbiased allocation of eligible patients to parallel comparison groups. Clinical equipoise, however, is a lack of consensus within the clinical community, not between individual physicians, as it is the medical community, not individual doctors, who establishes standards of practice. The multidisciplinary clinical trial provides an ideal platform allowing participating disciplines to settle a pressing clinical question within (and on behalf of) the medical community.

The history of internal carotid artery disease management constitutes one of the most encouraging examples on how the medical community through multidisciplinary clinical studies succeeded in implementing neurological and morphological decision criteria for treatment of both symptomatic and asymptomatic lesions. The carotid surgery trials (NASCET, ECST, ACAS and ACST) not only established

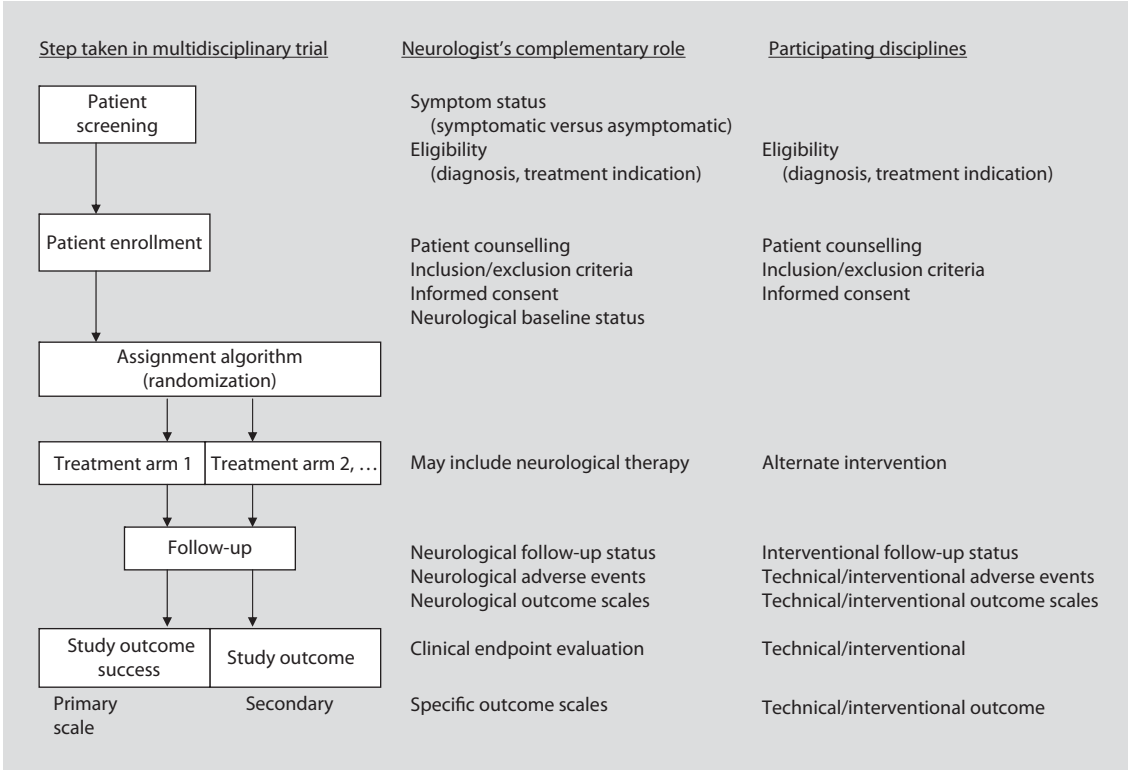

Fig. 2. Neurological participation in multidisciplinary clinical trial designs.

proven clinical benefit of interventional treatment in defined subgroups at risk, but also helped to foster the idea that multidisciplinary decision making is the gold standard of neurovascular patient management (table 1). Carotid stenosis trials have now successfully passed on to the stage of comparing risk/benefit profiles of coexisting treatment modalities; community equipoise has provided the basis for the multidisciplinary CAVATAS, SPACE, EVA-3S, and CREST studies comparing surgical versus endovascular therapy via independent neurological outcome assessment.

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Design and Analysis Issues

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The Primary Efficacy Analysis

When it comes to statistical analyses, more or repeated is not better. For each statistical test there is a chance of error. A trial that might be fair, with a controlled risk, becomes unfair if repeated statistical testing is allowed until a preferred or desired result is obtained. It is common to accept a 0.05 risk of type I error. This means that there is a 1 in 20 chance of a false-positive result. However, the combined risk of a false-positive result rises with the number of tests.

The honesty of statistical testing depends on stating ahead of time a precise, uniquely defined set of circumstances in which the null hypothesis is to be rejected. If the statement is vague, so that more than one actual procedure or more than one outcome measure can fit it, then the outcome will not be definitive. Thus, each phase III trial must have a single, unambiguously stated primary efficacy analysis. The primary analysis could be sequential or complex, containing multiple hypotheses – but in such circumstances the probabilities have to be explicitly adjusted by a professional statistician in order to maintain the overall p value.

There may be other, secondary analyses, but even when prospectively stated, they do not carry the same weight of scientific evidence as the primary analysis does. Rather, secondary analyses are suggestive and may be used to generate hypotheses for new studies. However, a statistician has no scientific way of quantitatively assessing the reliability of secondary analyses.

Striking a Balance between Focus and Believability

Many study designers prefer to focus closely on the primary analysis, and there are good reasons for this practice. In a strictly statistical sense, it makes the study clearer,

more decisive and more compelling. It also means that the data collected can be simpler: less time consuming and burdensome at the bedside and therefore more likely to get compliance and accuracy from personnel who feel that their primary job is giving medical care. Simplicity of data can also mean far less complexity and time in data entry, quality monitoring and analysis. All this has a major impact on the practicality and reliability of a given study.

However, there can be drawbacks to this approach. Although statisticians and administrators crave cleanliness, the medical colleagues reading reports of a study are likely to have questions: frequently, others will have a different interpretation of the results. If the outcome is positive, there will be people who wonder if the results are artifactual and arising from measurement procedures or if they are driven by an effect in a large population subgroup that is not replicated in smaller groups. Thus, there have even been instances where a positive study did not change clinical practice. If the outcome is negative, other types of questions are common, such as if the treatment or intervention might have worked if given later or if restricted to a certain type of patient.

Therefore, although there may be no requirement to do more than the primary analysis, it is wise to balance the economy of minimalism with the need to answer enough subsidiary questions to make the medical community comfortable and ready for a new stage of research.

Power Analysis

The power analysis section is one of the most central components in the proposed trial. It provides quantitative assurance that the project (assuming that the experimental treatment is effective and that the basic design captures the medical reality) is likely to result in data with a statistically valid outcome.

Power has 2 complementary aspects that require careful scrutiny:

- Is there enough of it? It has become semi-traditional in the medical community to test at 80% power, but this is often not enough. From the statistical point of view, using 80% power has a simple meaning. Of every 10 projects that have effective treatments, 8 can be expected to have positive outcomes and 2 to fail. Considering the negative consequences in the community of casting needless, random doubt on potentially beneficial therapies, this seems like a poor idea. Therefore, 90 or 95% power would be optimal.
- Is the effect size adequately small? As discussed in a previous section on the fallacies of setting the sample size by using optimistic estimates of the effect size, it may not be correct to use pilot data. It is also not correct to start with determining the sample size that is administratively practical and then adjusting the effect size accordingly. The only criterion is clinical judgment, not statistics, as to what is the smallest effect that patients, families and caregivers would notice and appreciate.

Interim Analyses

The rules for sample size suggested in the previous paragraphs are prudent ones. However, they are likely to lead to sample sizes that are very large and suggest that pilot data will often be unnecessary. What is the solution for this dilemma?

Often the most reasonable strategy is to use interim analyses. There is a chance of stopping early and if the effect size is as large as hoped. But the trial can be continued in case the effect size is modest, but clinically worthwhile.

Many proposals provide for interim analyses, but unfortunately too often analyses that would not be useful. Using interim analyses requires that the p values at each analysis be adjusted to maintain the overall significance level of the trial as a whole. There may be some incidental loss of power, but the significance level for the whole trial still adds up to 0.05, it is only divided up differently. If interim analyses are included, the power should be computed and the chance of stopping early presented.

Recruitment

The power calculation defines the sample size that is needed. This estimate has to be complemented with believable, documented calculations indicating that the appropriate number of subjects can actually be recruited during the time period for the trial.

Sensitivity to Assumptions

The nature of the power calculation should be described in enough detail that a statistical reviewer can reproduce such calculations. As just explained, the calculation will be based on assumptions, always including different levels of power, effect size and recruitment. The proposal can be made more believable through a sensitivity analysis that gives tables illustrating the effect of departures from these as well as any other assumptions specific to the project.

Covariates and Subgroups

In many projects, the population may be divided into subgroups or there may be covariates that depend on the individual subject. These factors may be numerous and striking and may affect both the natural history level of outcome variables and the response to treatment, and these possibilities complicate planning and analysis.

One potential problem is randomization imbalance. In extreme cases, if the experimental treatment is assigned a disproportionate number of patients from a worse

performing group, then even if there is a treatment effect in both groups, the imbalance may cause an artifact that appears to nullify or even reverse the trend. Many investigators feel that, in a large enough sample, randomization should eliminate any large bias. In principle, this is true. In practice, it would be more convincing if the argument is accompanied by numerical calculations explaining the meaning of 'large enough'. When there are several such factors, the chance of an imbalance in at least one of them rises, and the combined effect of several small or large imbalances may be difficult to predict. When the final reports of the study are published, any actual imbalances could lead to inconclusive debate.

However, more important than the potential for randomization imbalance is the potential for differential effect in different subgroups. Even if the randomization balances, different effect sizes in subpopulations can upset the power calculation, leading to potential failure.

Further, if there were a difference in effect depending on the patient, then this is useful therapeutic information that the community would wish to know.

Imbalance can be controlled to some degree by stratified randomization. However, there are limits to this approach. If there are too many strata, then it becomes too likely for small clinical centers to be able to complete randomization blocks, and a high proportion of incomplete blocks tend to nullify randomness. Imbalance and differential effect can both be modeled by including factors in the primary analysis (the one that has scientific weight). Again, this has limitations, since an analysis with too many factors tends to become too complex, too tricky, thereby leading to a lack of credibility. A sincere effort to model the underlying clinical reality can be difficult, but it can also have its rewards.

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Strategies for Recruiting and Retaining Minorities

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The directories from the National Institute of Health mandate that significant efforts are made to include minorities in clinical trials [1]. However, recruitment, enrollment and retention of minorities in clinical trials present significant challenges. These barriers include, but are not limited to, poor impressions of potential minority study participants by the research staff [2], narrow professional relationships between the medical staff of tertiary care medical facilities and referring physicians in predominantly minority communities as well as a disproportionately low number of minority research staff with established relationships within the minority community. Increasing participation of minorities in clinical trials is critical for advancing knowledge about disease and decreasing healthcare disparities.

Multiple studies indicate that physicians' poor perceptions of potential African American study participants is a significant limitation in the recruitment of this population into clinical trials. Specifically, physicians and research staff report the following negative views regarding potential African American study participants: unable to understand complexity of trials, unable to see value in participation, fear of the health care system and general undereducation regarding medical treatments. Although some of these perceptions have a contextual foundation, generalization to the entire African American community is without merit [2–7].

Clinical trials with successful recruitment of African Americans can overcome some of these perceived and real barriers. One example of this is recruitment to the African American Antiplatelet Stroke Prevention Study (AAASPS), a landmark NINDS-/NIH-funded clinical trial which set out to determine the efficacy and safety of aspirin and ticlopidine to prevent recurrent stroke exclusively among African-American noncardioembolic ischemic stroke patients [8]. The race-disease disproportionate of affected individuals is especially high for stroke, with African Americans being about twice as likely as Whites to experience strokes, yet as noted above, African Americans have been traditionally underrepresented in clinical trials [8].

Table 1. AAASPS strategies for community-based recruitment

• Development of a community advisory panel at main study site
• Encourage satellite sites to develop community advisory panels
• Community service coordinator to raise awareness
• Internet postings about the study
• Involvement of church healthcare coordinators
• Community volunteer corps to promote study
• Involvement of minority health professionals to identify potential participants
• Use of media to popularize study
• Support from churches and major African American legislative groups

A hallmark of the AAASPS study design was that it was carefully planned to meet the needs of the African American community during the early and main phases of the study. For example, surveys were performed in target communities to better understand African American sensitivities in relation to clinical trials given the legacy of past medical abuses which happened in this community [9]. When awareness of barriers to entry into clinical trials were identified, steps were taken to systematically resolve these challenges and to apply a plan uniformly across all study sites. Cultural sensitivity tapes were developed and shared with local study staff at site investigator meetings. The importance of spending adequate time and developing a trusting relationship with potential study participants, serving as their advocate during the study and involvement of study staff from the community were emphasized as primary features of the trial. Other strategies used by the AAASPS are listed in table 1 [10].

These strategies helped the AAASPS successfully recruit and retain 1,809 African American stroke patients from 62 sites. The success of the study provides direct evidence that large clinical trials can successfully recruit African Americans. Lessons learned from AAASPS suggest that the approaches listed below will portend success for recruitment in other high-risk understudied race-ethnic groups:

- Careful pretrial planning
- Involvement of the target community in planning phases of the study
- An understanding of community sensitivities
- Development of excellent communication and trust with community members
- Involvement of target community in study staff

The methods used in the AAASPS trial and others can be supplemented with suggestions made by African Americans or other relevant minority focus groups regarding clinical studies. Multiple focus groups composed of African American individuals have addressed perceived barriers to clinical research. The principal recommendations from these efforts regarding increased clinical trial involvement include many of the common features expected of a trusting physician-patient relationship, including honest and respectful communication, complete information on risks/benefits of the trial ahead of time and sufficient time to review informed consent [5, 7].

All evidence to date suggest that the foundation needed to establish minority participation in clinical trials is no different than the basis for a good patient-physician relationship in nonminority populations, namely reciprocal respect coupled with the good will to do well for others. Emphasizing these relationships, either in a clinical setting or in a community-based model like that used for the AAASPS, will increase the number of African Americans and other underserved minority subjects participating in medical research.

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Informed Consent and HIPAA

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Protection of human subjects is of utmost importance in clinical trials. All clinical trials require study-specific monitoring procedures to assure safety of participants and integrity of data. These objectives are accomplished by the informed consent process and by data and safety monitoring of the participants in the trial. This section will focus on the informed consent. The purpose of the informed consent process is to ensure that the participant fully understands the information about a clinical study/trial in order to make an informed decision to enter or not. It is important for both the participant and the investigator to remember that informed consent is an ongoing process throughout the trial/study. Informed consent is based upon 3 components: information about the proposed research study, comprehension of that information and voluntary participation. The consent form must be approved by the institutional review board (IRB) and is governed by the FDA in 45 CFR 46.116 and 21 CFR 50.20.

The principal investigator (PI) of the study or senior study staff member will first describe the purpose of the study, the study procedures, explain the risks and benefits of participation and compensation if any that may be provided. The PI or staff member will then go through the consent form with the potential participant. The subject is allowed time to go through the consent form and ask questions. Once the form is signed and dated by the participant, it is called the informed consent document. The participant receives a copy of the document and the document is saved in the participant's folder. Only then can the study treatment activities proceed [1].

The informed consent form should be in clear, simple language, between a 4th and 8th grade reading level, and contain the following elements [2]:

1 A statement that the study involves research
2 An explanation of the purpose of the research, an invitation to participate and explanation of why the participant was selected, and the expected duration of the participant's participation
3 A description of procedures to be followed and identification of which procedures are investigational and which might be provided as standard care to the participant in another setting; use of research methods such as randomization and placebo controls should be explained

4 A description of any foreseeable risks or discomforts to the participant, an estimate of their likelihood and a description of what steps will be taken to prevent or minimize them; as well as acknowledgment of potentially unforeseeable risks
5 A description of any benefits to the participant or to others that may reasonably be expected from the research and an estimate of their likelihood
6 A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the participant
7 A statement describing to what extent records will be kept confidential, including examples of who may have access to research records such as hospital personnel, the FDA, and drug sponsors
8 For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if participants are injured through participation; where further information can be obtained, and whom to contact in the event of research-related injury
9 An explanation of whom to contact for answers to questions about the research and the research participant's rights (including the name and phone number of the PI)
10 A statement that research is voluntary and that refusal to participate or a decision to withdraw at any time will involve no penalty or loss of benefits to which the participant is otherwise entitled
11 A statement indicating that the participant is making a decision whether or not to participate, and that his/her signature indicates that he/she has decided to participate having read and discussed the information presented

When appropriate, or when required by the IRB, one or more of the following elements of information will also be included in the consent document [2]:

1 If the participant is or may become pregnant, a statement that the particular treatment or procedure may involve risks, foreseeable or currently unforeseeable, to the participant, or to the embryo or fetus
2 A description of circumstances in which the participant's participation may be terminated by the investigator without the participant's consent
3 Any costs to the participant that may result from participation in the research
4 The possible consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation
5 A statement that the PI will notify participants of any significant new findings developed during the course of the study that may affect them and influence their willingness to continue participation
6 The approximate number of participants involved in the study

There are groups that are designated vulnerable populations for which the FDA determines requirements for consent; the IRB determines the requirements for individual trials. These groups requiring special protections for maintaining their rights and safety include: children, pregnant women, fetuses, prisoners and the mentally challenged. The investigator must be aware of the laws applicable to his or her study under federal, state and local law. While there are no specific regulations for the cognitively impaired individual, investigators need to especially sensitive to these potential participants. While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is necessary for

research involving these individuals. Additional time for the process, use of a surrogate and treating the informed consent process as a continuing effort to inform the participant are warranted. Cognitive ability should be assessed as the study progresses to ensure the right to withdraw participation is fully understood by the participant [1].

The Health Insurance Portability and Accountability Act (HIPAA). also impacts clinical research. Within the HIPAA there are privacy and security rules governing protected health information (PHI) that can identify the individual. It applies to research involving medical treatment and medical records research or chart review. Investigators are required to obtain the participant's permission before using the PHI for a clinical trial. If the consent form contains the required authorization, it is HIPAA compliant. It is possible to have a separate document that the participant will sign authorizing use of PHI in the clinical trial. The IRB, state regulations or the institution will make this determination. The privacy rule itself does not require an IRB to review the separate authorization form nor is it required to review or approve the proposed use or disclosures of PHI. The authorization form focuses on privacy risks, and states how, why, and to whom PHI will be used and disclosed. The signed form will only be valid for the specific study in which the subject will participate. There are 9 basic core elements which must be addressed in the authorization form.

1 Description of the information to be used and disclosed
2 Who is authorized to make the use or disclosure (PI and research team)
3 Who is authorized to receive the PHI (sponsor, contract research organization, central labs)
4 Description of the purpose of use or disclosure
5 Expiration date; a duration of the use must be defined
6 Signature of the subject and the date it is signed; subject receives copy
7 Individuals have the right to refuse to sign; if they do refuse, they cannot participate in the research study.
8 Individuals have the right to rescind the authorization at any time; it must be in writing
9 PHI redisclosures are not protected

In summary, the informed consent document ensures that the subjects' rights are protected when they elect to participate in a research study; HIPAA ensures that their PHI will only be disclosed under strict conditions.

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Committees for Multicenter Clinical Trials

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The structure of a multicenter clinical trial is complex and includes participating centers that screen, enroll and treat patients, a clinical coordinating center that is responsible for the overall conduct of the trial including interactions with the local centers and sponsors as well as developing reports, and a data coordinating center that is responsible for quality control measures, managing and scrubbing of the data, interim data analyses as well as the final data analyses. In addition, most large clinical trials also have a committee structure that provides advice to the principal investigator, helps in the overall conduct of the study, performs some components of the research, organizes and supervises publications, and executes independent safety monitoring.

Figure 1 demonstrates the overall design of a large multicenter clinical trial including the committee structure. Most trials are governed by an executive committee (steering committee/coordinating committee) that is chaired by the principal investigator, who usually is a clinician. Other members of the committee include the senior statistical investigator, coordinators for the trial's clinical and data management centers, other senior clinical investigators, and often representatives of the sponsor. Some the members of the executive committee may be local principal investigators who often have rotating and time-limited terms. The executive committee meets regularly to assess the progress of the trial and to respond to issues related to the conduct of the trial. The executive committee authorizes modifications to the protocol or operations manual, approves recruitment of participating centers, selects members of other committees, responds to issues that arise in the conduct of the trial, and interacts with sponsors and governmental bodies such as the data safety and monitoring board (DSMB). A core group of the executive committee, often including the principal investigator, senior statistical investigator, fiscal managers as well as senior staff of the clinical coordinating and data management center usually meets to address day-to-day issues related to the trial.

Most trials also have an advisory committee that includes experienced and major researchers in the field; this committee may have internal (from the local institution)

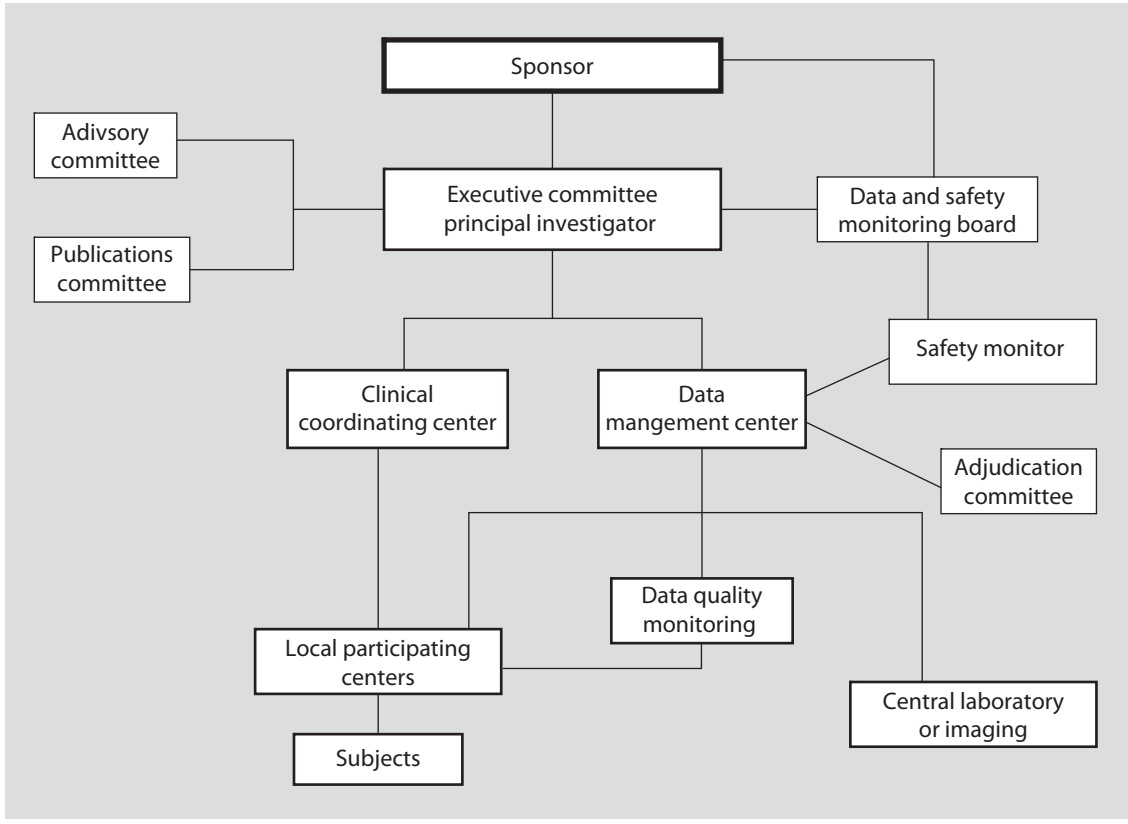

Fig. 1. Overall design of a large multicenter clinical trial.

or external (from other centers) members. The members of the committee usually have expertise in the disease that is being treated, the intervention that is being tested, clinical trial design and conduct as well as data management and analyses. This committee provides recommendations to address major problems that the trial faces.

The executive committee also appoints other committees or groups of investigators that perform specific duties. A publications committee usually includes members of the executive committee and local investigators who are particularly active in the trial. The publications committee, which usually is chaired by the trial's principal investigator, is responsible for authoring major papers emanating from the trial. In addition, the publications committee usually develops guidelines for and screens proposals for publications using data collected in the trial.

Most trials also have an adjudication panel (committee) that is responsible for the determination of major endpoints or outcomes in the trial or establish eligibility of some subjects in the trial. Members of the adjudication panel are unaware of treatment assignments. The panel has a specific charter and uses predetermined or prespecified definitions for determining safety and efficacy endpoints. In addition, the

panel has a plan for the resolution of disagreements in endpoint diagnoses. The panel is a particularly important component of a clinical trial, such as one testing a surgical intervention, in which a double-blinding design cannot be used. In general, the trial's statistical plan is based on the use of the adjudicated diagnoses for the analyses of the results of the trial. Besides adjudicating clinical endpoints, many trials have panels of physicians (for example, a neuroradiology center or electrophysiology center) that judge imaging or other laboratory data.

The external DSMB is a key component trial that is independent from all other components of the trial [1]. The committee, which usually includes clinical and statistical experts, is appointed by the sponsor. The committee usually meets once or twice a year, but it can be activated if an unanticipated or unusual adverse experience related to the trial occurs. The DSMB usually has a charter that includes ground rules that are agreed upon with the investigators, sponsor and regulatory bodies [2]. The committee monitors individual subject's adverse experiences and aggregate safety data that occur in the individual treatment arms. As such, it interacts closely with the data management center, which provides reports for the DSMB, and the trial's safety monitor. The DSMB is also charged to maintain the scientific integrity of the research and, as a result, it reviews and approves changes in the protocol or design of the trial. In addition, the panel usually has the charge to perform one or more interim analyses for efficacy. In these circumstances, the trial will have predefined rules for stopping the trial for lack of safety, strong evidence of efficacy or futility. Based on the results of these analyses, the DSMB may halt a trial because exposing additional subjects to the study intervention is no longer appropriate.

In summary, vibrant and proactive committees that interact with all other components of the trial are an important element in the design of modern clinical trials.

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Interim Monitoring of Clinical Trials

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Prudence and good clinical research practice dictates that clinical trials be scrutinized at interim stages, as data and experience with the study is accumulating, as opposed to doing so only at the study's conclusion [1]. Performing interim evaluations of a trial affords the capability of making midcourse corrections in study aims and/or procedures if necessary. Such corrective actions reduce the chance of squandering precious resources such as funding, time and effort. An interim evaluation of a clinical trial's functioning is generally referred to as an interim monitoring or interim analysis. Such an assessment should be comprehensive in that all aspects of the trial and its protocol should be scrutinized, including inclusion/exclusion criteria, recruitment, general study procedures and preliminary analyses of the accumulated study database. Depending on the size and scope of the trial, a comprehensive interim monitoring plan may be mandated by the funding source (such as the NIH or a pharmaceutical company).

The Interim Monitoring Plan and Report

Effective interim monitoring of a clinical trial requires a considered and formalized plan. The plan should include the timings and scope of these interim evaluations. A central component of any interim evaluation is the construction and review of a broad-spectrum status report on the conduct of the study thus far. The principal investigator assisted by lead study staff typically author this report. Areas addressed in a thorough interim analysis report include:

- Principal investigator update (describing major challenges and/or triumphs encountered in conducting the study thus far)
- Recruitment (number of enrollees and when/where they were enrolled, number screened for enrollment as well as reasons for refusal and/or rejection)
- Enrollee follow-up (number of study visits completed by enrollees, number of late visits, number of missed visits and attrition, that is, number of enrollees who have volun-

tarily withdrawn, were lost to follow-up or were involuntarily withdrawn from the study)
- General data management (contemporary snapshot of the size/scope of the study database, number and description of data queries and corrections encountered, amount/type of late and missing data)
- Enrollee safety (number, type, and comprehensive description of reported adverse events)
- Protocol changes (changes in the study protocol suggested by the study investigators or mandated by a recognized authority, such as the FDA or NIH)
- Baseline characteristics of the subjects enrolled to date (sociodemographic data and other key covariates, presented overall and by relevant subgroups)
- Statistical interim analysis of key endpoints (see below)

Interim monitoring reports are often compiled for, and reviewed by, an external body that is charged (by the principal investigator or the funding source) with overseeing the effective, safe and efficient conduct of the trial. Use of an external group is generally recommended (and often required) to provide objectivity and to maintain confidentiality (and blinding) with respect to interim study results. This external group, sometimes referred to as data and safety monitoring board (DSMB), can include as members experienced clinicians, statisticians and participant representatives or advocates. The DSMB can be vested with the authority to modify or even prematurely end a clinical trial. Reasons a DSMB may recommend discontinuation include a determination that the trial places participants at undue risk of harm or there being little chance that current results will change should the trial continue.

Why Include an Interim Monitoring Plan?

An interim monitoring plan is often mandated by the funding institution or source. Such is usually the case with respect to phase II and III trials. There are compelling reasons to incorporate an interim monitoring plan in every clinical trial, even if one is not mandated by the funding source. Interim analyses provide formalized occasions to fully scrutinize a trial's functioning and even to determine whether or not it should continue. Stopping a trial early due to participant safety concerns or relative little chance of observed results changing in the future is both ethical and prudent insofar as efficiently and effectively utilizing precious resources.

Periodic and systematic review of clinical trial operations and its accumulated database also allows for the detection of problems while there may be time to correct them. Problems such as slower than expected recruitment, poor parameter estimates (such as poorly estimated event and attrition rates), overly restrictive entry criteria and key covariate imbalances between comparison groups often can be corrected when detected in early stages of a trial. Interim monitoring also provides DSMBs the opportunity to give the study investigators objective, practical and timely advice for

improving trial operations and its procedures. By regularly monitoring trial safety data, these interim reviews can also play a crucial role in ensuring the overall safety and effective care of trial participants. This is particularly true when, as is often the case, DSMBs are authorized to review safety data and primary endpoint data, in an unblinded fashion.

More subtle benefits of including an interim monitoring plan in the conduct of a clinical trial include providing a powerful incentive for the study team to become more intimate with the nuts and bolts of the trial and its accumulating data. The process of constructing a comprehensive status report on a trial and presenting (maybe even defending) it to an experienced oversight panel forces investigators to ponder and respond to very practical questions:

- Is the study protocol feasible and appropriate?
- Is the study protocol being uniformly followed?
- Are trial operations (clinical management, administrative, data management) running efficiently and effectively?
- Were pretrial assumptions (parameter estimates, resource needs) reasonably accurate?
- Is the data analysis plan reasonable (sufficiently comprehensive, pertinent and doable)?
- Are there any unforeseen circumstances and, if so, how should they be addressed?

Producing and presenting such interim reports act as rehearsals and warm-ups for the final study report or definitive results manuscript. Although such a final report will be more expansive than the interim reports, much of its primary message will have been honed already.

Statistical Issues

Statistical analysis of outcome data that has accumulated thus far is often another key component of a comprehensive interim monitoring plan, especially in phase II and III trials. Performing statistical tests in this way, in a repeated fashion as data is accumulating, allows detection of significant benefit, harm or futility sooner than at the trial's end. Such statistical evidence can provide support for early discontinuation of a trial. Of course, other important factors must be considered as well. However, one cannot simply employ a statistical test multiple times within a clinical trial, as data is accumulating, without quantitatively allowing for such multiple uses. In short, the type I error rate of a statistical test increases as it is repeatedly used on accumulating data. There are a number of statistical strategies to address this problem and allow for such multiple testing [for a review, see 1]. A frequently used strategy involves use of a so-called α-spending function to apportion the overall statistical significance level, α, over all the multiple tests, including the final analysis. The spending function takes into account the inflation of type I error that occurs over multiple uses of the test statistic. In this way, one can control the proportion of the overall α that is 'spent' at the

occasion of the final analysis, thereby controlling how conservative the interim tests will be.

There is no established upper limit on the number of statistical interim analyses that can be performed within one trial. However, the typical desire to have much of the statistical significance level, α, 'spent' at the final analysis (that is, establishing that statistical significance is reached at an interim monitoring stage only if dramatic evidence is observed) and the large amount of time and effort required to perform such statistical analyses typically translate into a range of 3–5 analyses altogether (including the final analysis). This consideration does not necessarily limit the number of general, or administrative, interim monitorings that can occur during the trial. Large clinical trials typically produce interim monitoring (administrative and/or statistical) reports every 6 months. Thus, not all of these interim monitoring times must (or should) include an interim statistical analysis of outcome data.

Frequency and Timing Issues

The number and frequency of interim monitoring times within a trial can vary quite a bit, but are often determined based on calendar and resource feasibility. Because the reports are so comprehensive, it is often not very practical to produce them more frequently than every 6 months or so. In some large studies or those in which safety is especially a concern, there may be administrative monitorings performed in which only, say, procedural aspects of the trial and/or safety data is evaluated, without reviewing/analyzing primary event data. Such partial or streamlined interim monitoring may be performed more frequently.

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Medical Monitoring

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Subjects in a clinical trial are placing themselves at some risk for anticipated or unexpected adverse experiences that could lead to death or disability. Thus, the sponsor and investigators have an obligation to include a detailed plan for monitoring the trial for the safety of the subjects. Assuring maximal safety of subjects is an ethical underpinning for any clinical trial. Institutional review boards and governmental regulators also mandate that any trial be monitored for potential adverse experiences or safety concerns. In order to meet these responsibilities, the trial must have a detailed plan to assure subject safety, including an ongoing program to monitor reported adverse experiences. The safety of subjects is especially relevant in trials testing interventions in neurological diseases that are associated with impairments in cognition or consciousness. In these circumstances, the subject may be enrolled though surrogate consent obtained from an authorized representative. In addition, subject safety is very important for trials enrolling children.

In general, a clinical trial has 2 levels of safety monitoring, a local safety monitor and an external and independent data safety and monitoring board (DSMB). The safety monitor usually is a senior clinician who has expertise in the disease and knowledge about the intervention being tested including potential adverse experiences. The safety monitor usually is a senior clinician who is otherwise independent of the study. The safety monitor may be located at an institution that is enrolling patients or may be outside the institution. The advantage of being 'within' the center is the rapid availability of safety information. The advantage of being at another center is that the perception of independence is clearer. The safety monitor is aware of treatment allocation and interacts with the unblinded component of the data management center and the DSMB. The safety monitor periodically reviews accumulating data with an emphasis on serious adverse experiences and submits reports to the DSMB. The safety monitor evaluates aggregate data and information from individual treatment groups. The safety monitor also looks at serious and unanticipated adverse experiences for individual subjects, but does not examine efficacy data. The safety monitor is charged to notify the DSMB if a

safety concern is identified. The concern could be a major difference in adverse experiences between the treatment groups or the result of a single serious adverse experience.

The DSMB is appointed by the sponsor to serve independently from other components of the trial [1–3]. Members of the DSMB include both clinicians and statisticians, and sometimes other professionals who have expertise in the design and conduct of clinical trials and have no financial or other conflict with the study investigators. The DSMB also includes a supporting statistician to perform independent analyses. The committee meets at regular intervals to evaluate aggregate and individual subject safety data. A major charge is to assure the safety of subjects in the trial. The committee sees aggregate data and information separated by treatment arm (A/B). The DSMB may elect to keep itself blinded to the identity of 'A' and 'B' or they may decide to become aware of the actual treatments (control or active treatment). If the committee does not already know the nature of the treatments, the DSMB should have information available, so it can be 'unblinded' if a situation warrants immediate knowledge of treatment allocation. The DSMB is also activated on an emergency basis if a serious and unanticipated adverse experience is reported. Depending upon the data, the DSMB proactively makes recommendations. The advice may be: (1) the trial should continue recruitment without any change of the protocol; (2) the investigators should modify the trial and protocol, for example changing inclusion or exclusion criteria, timing of assessments or other follow-up activities; (3) the trial should suspend enrollment because of a safety concern; (4) the trial should be halted. Evidence of the lack of safety with the intervention being tested or the presence of strong evidence that the new intervention is superior to standard treatment (in effect a safety concern for the control group) is among the leading reasons for prematurely halting a trial. The DSMB usually interacts with the sponsor, the principal investigator and the trial's executive committee. The executive committee and sponsor share the DSMB recommendations with the local investigators, individual institutional review boards and regulatory bodies.

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Budgets for Clinical Trials

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Developing the budget is typically the last task undertaken as an investigator plans a clinical trial. It is often done hurriedly, grudgingly and superficially by those who have little experience and even less interest in doing one. Yet an adequately planned budget is absolutely critical for the successful outcome of the clinical trial. In our experience, it is the most neglected aspect of planning a clinical trial.

Clinical trial budgets can be considered from the differing perspectives of the research initiator (that is, the principal investigator), the clinical site investigator in a multicenter trial and the institutional or practice administrator. Further, trials can be sponsored by federal and/or nonprofit agencies versus pharmaceutical or device manufacturers, with the latter often including a profit margin. Due to space constraints, we will focus on selected aspects of clinical trial budget preparation for multicenter trials. Budgets for individual sites for industry-sponsored clinical trials have been described elsewhere [1, 2].

Clinical trial budgets are inherently complex (table 1). Investigators must start budget preparation early, preferably as soon as the protocol is taking shape (table 2). Ongoing interaction with institutional officials (that is, grants management) and the research sponsor is critical, seeking advice and input. Since clinical sites cannot and will not lose money by participating in a multicenter trial (the old days when medical schools underwrote many expenses are gone), many trials have failed due to poor budget planning.

Indirect costs to the clinical sites represent a large line item expenditure, and this is typically negotiable. Sponsors often have policies, as do individual institutions for clinical research activities (in contrast to higher NIH-negotiated facilities and administration rates). Indirect cost rates of 20–30% are typical; it is important to establish in advance at each site what these monies will cover (that is, among other things, office space for research personnel and general office supplies).

Personnel costs at the clinical sites are another large expenditure. Consider what level of training is required for local research coordinators as well as salaries by region

Table 1. Steps and components of clinical trial budgets

	I. Clinical site budget
1	Review the protocol and manual of operations in detail
2	Prepare a flow sheet of types of personnel (that is, level of training) and time requirements for each step in the protocol
3	Estimate costs of clinical procedures (standard clinical charge versus discounted 'research' rate)
4	Add in indirect costs: use a typical average of 25–30%, but these must be aggressively negotiated for each individual site
5	After calculating the total cost of carrying out the research for entire sample size, decide how to distribute on a per patient recruited and/or per participant visit basis
	Occasionally overlooked components:
1	Fees for clinic space
2	Site 'start-up' expenses including training and IRB preparation
3	Pharmacy fees
4	Local publicity/advertising/posters
5	Participant transportation and parking
6	Data entry (personnel, time, computer or fax)
7	Time/personnel to respond to data queries
8	Cost of living increases for personnel for multiyear trials
9	Time/personnel/space for site monitoring visits and FDA audits
10	Institutional review board fees
11	Phlebotomy supplies and fees, specimen preparation and shipping (dry ice)
12	Office space for research personnel/general office expenses (telephone/fax)[1]
13	Investigator meetings (time away)
14	Training procedures: teleconference or in person (and retraining due to personnel turnover during the course of the study)
15	Periodic teleconferences with the coordinating center to review local progress and issues
16	Indemnification issues (some foreign sites have specific requirements)
	II. Clinical coordinating center budget
	Occasionally overlooked components:
1	DSMB expenses (meetings, honoraria)
2	Medical safety monitor
3	Site inspection (carried out by investigators or private CRO)
4	Regular preparation of detailed reports for the study sponsor
5	Travel coordination for investigator meetings, DSMB meetings, site visits, steering committee meetings, training workshops
6	Event verification committee activities
7	Administrative costs for maintaining current IRB certification/federal assurance numbers for all sites (especially onerous for international sites)
	III. Drug acquisition (including placebo) and central drug distribution (if applicable)
	Occasionally overlooked components:
1	International sites have unique rules and requirements adding substantially to headaches and expenses
	IV. Data management and biostatistical support
1	Usually provided by the data management group
2	Go over line-by-line to reduce costs and beware of occult overlap

IRB = Institutional review board; DSMB = data safety monitoring board; CRO = clinical research organization.
[1] Variably included with indirect costs.

Table 2. Che's shibboleths for budgeting of clinical trials

1	You can never start too early to prepare the budget.
2	You can never justify the proposed expenditures too much.
3	The trial will invariably cost more than you anticipated when you drafted the budget.
4	Principal investigators who delegate budget preparation because it is 'not scientific' will eventually get double the pain.

and in selected large urban centers. Successful clinical trials increasingly include international sites, but foreign sites have special issues related to ongoing certification, drug shipping and accountability, travel expenses as well as indemnification that must be considered in budget planning.

Some tests or procedures that are required per protocol can be considered standard of care, and hence are not paid for by the research. Because standard of care often varies, and improper billing for research activities is unethical and illegal, such tests/procedures justified as standard of care must be thoroughly justified. When participants return for clinic visits required by the study protocol, separate billing for ancillary care given at the clinic visit is generally not allowed. This aspect should be thoroughly explored as part of budget planning, and individual site investigators counseled [3]. In certain circumstances, Medicare/CMS and even third party insurers may reimburse some costs for the randomized intervention. For some surgical procedures and devices, these potential cost savings can be very substantial [3].

Budget planning is only one facet of the complicated process of organizing and initiating a clinical trial, and researcher leaders sometime seek to delegate most or all of such planning, since it does not require their scientific acumen. This is not appropriate (table 2). An adequate budget requires intense, ongoing collaboration between the principal investigator(s) and administrative colleagues.

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Institutional Review Boards and Ethical Issues in Randomized Clinical Trials

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Institutional review boards (IRBs) for the protection of human subjects are charged with applying the federal regulations, a mixture of the Common Rule (US Code of Federal Regulations, Title 45 – Public Welfare and Human Services, Part 46 – Protection of Human Subjects, Subpart A – Basic HHS Policy for Protection of Human Research Subjects) and FDA regulations [the FDA version of the Common Rule appears in 2 pieces, at 21 Code of Federal Regulations Part 56 (the rules for IRBs) and at 21 Code of Federal Regulations Part 50 (the rules for informed consent)]. These sets of regulations govern the conduct of research involving human subjects. The specific tasks of the IRB are: to determine that the risks to subjects are minimized or that the 'risks to the subjects are reasonable in relation to the anticipated benefits' and that the selection of subjects is equitable [1]. The IRB must also ensure that proper informed consent is obtained. Ethical considerations, while not the sole purview of IRBs, are also weighed in the context of calculating the risks and benefits. Clinical trials are vital to gaining approval for new therapies as well as for determining the optimal therapy for an illness. History is replete with examples of treatments that were thought to be effective but turned out to be harmful (for example, steroids for head trauma [2]). However, clinical trials pose their own difficult ethical issues. Some are generic to all clinical trials and some are particularly common in clinical trials in neurology and neurosurgery due to the nature of the diseases that encompass these specialties. The space does not permit comprehensive coverage (for detailed reviews, see Coleman et al. [1]), but we will summarize some of the important issues regarding the IRB and clinical trials.

Placebos

The most efficient way to conduct a clinical trial is to compare the therapy to placebo, since active control comparison will require a much larger sample size to be

adequately powered. A comparison arm is needed to assess effect in most phase III trials and, in the US, the regulatory agencies generally require one arm to be superior to the other to demonstrate efficacy. However, the use of placebos in serious disorders is increasingly problematic now that effective therapies are available. For example, no IRB would approve a placebo-controlled trial of first-line therapy for status epilepticus in the emergency department. This is why studies of abortive therapy to terminate seizures have focused on acute repetitive seizures as an alternative. The classic trial of Alldredge et al. [3] included a placebo arm because in that jurisdiction, the standard for the ambulances was not to give benzodiazepines, which meant that the placebo arm was receiving the standard of care. Once effective treatments for serious life-threatening disorders are available, there are major ethical issues in using placebo. In fact, the revised Helsinki Declaration expressly prohibits this sort of design, though its precise intent remains a matter of some debate [1, 4]. The statement was largely directed at AIDS studies in Africa, where, as in the study by Alldredge et al. [3], placebo was the standard of care, but in the context of AIDS was not felt to be ethically justifiable [1].

Sham Procedures

New emerging treatments such as direct injection of stem cells or viral vectors into the brain require a neurosurgical procedure. One negative trial of stem cells for Parkinson's disease [5] created much controversy by using sham neurosurgery with burr holes for the placebo group. Many, but not all, ethicists argued that this was unethical [6]. Some, including a cogent argument by the investigators, argued that this sort of placebo-controlled trial was necessary to determine effectiveness. In fact, this trial demonstrated that the intervention was not effective and saved patients from an ineffective and potentially toxic treatment. Similar problems exist with implanting deep brain stimulation devices, but these can be ameliorated by having everyone receive the device and use effective versus sham stimulation for a defined period following which everyone gets the proposed intervention in the open-label phase [7].

Vulnerable Populations

One of the ethical principles in research is that, within reason, competent adults can consent to more than minimal risk procedures without direct benefit to themselves. However, neurology and neurosurgery are full of examples where the IRB needs to exercise extra care. The regulations affecting children are beyond the scope of this chapter (see Coleman et al. [1]) and are not unique to neurological disorders. Such regulations are meant to protect children and do not allow for risky procedures such

as burr holes except for direct therapeutic benefit. However, there are other settings where subjects could be considered vulnerable and deserving of extra thought and protection.

Emergent Situation Does Not Allow Time for Informed Consent

The need for an informed consent process in all settings would clearly preclude certain clinical trials. This has been the case for status epilepticus and, from a practical point of view, for acute head trauma interventions. In 1996 [8], HHS announced, under section 46.101(i), a waiver of the applicability of the requirements for obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained [1]. This waiver provides a third route through which IRBs may approve research in this class. Unfortunately, not all IRBs have set in place those community procedures that would permit this route. Patients in emergency situations are now available for research if the IRB has complied with the applicable regulations.

Patients Unable to Give Informed Consent due to Temporary or New Incapacitation in a Previously Competent Subject

Clearly, status epilepticus and acute head trauma fall under this umbrella. Many but not all acute strokes [9, 10] as well as intracerebral hemorrhage will fit. The procedures described above were designed to conduct clinical trials without individual informed consent in an emergency setting where there is no time to obtain consent. Unfortunately, there are no provisions in the federal regulations except for children for generalized surrogate consent [1]. OHRP has recently (September 2007) asked for comment and consultation on this issue [11]. In the state of New York, the Commissioner of Health has recently asked the New York State Task Force on Life and the Law to address this important lacuna in the research structure [Dubler N, a member of the Task Force, pers. commun.].

Impaired Capacity

Many patients with stroke, even if technically competent, are impaired [9, 10]. In a dominant hemisphere stroke, they may be aphasic. If nondominant, they often have neglect and are therefore incapable of understanding what is wrong with them. Even if neither of these is applicable, these patients are clearly under great stress in a setting where their ability to give a full informed consent is compromised. Stroke is one such important example but is clearly not the only such situation. The IRB will treat these as a vulnerable population deserving extra protection [1].

Table 1. Ethical issues in clinical trials in neurology and neurosurgery

Issue	Examples
Use of placebos	epilepsy, status epilepticus, all surgical procedures, Duchenne's
Sham surgery	Parkinson's disease, dystonia, degenerative disorders, epilepsy
Impaired capacity	dementia, acute neurological conditions (such as stroke and trauma)
Future impaired capacity	dementias, neurodegenerative disorders
Quality of survival	dementias, neurodegenerative disorders

Dementia

Protocols involving consent in individuals with dementia are another concern. Generally, mildly demented individuals, especially those living in the community, are capable of giving consent for low-risk protocols [1, 9, 11]. High-risk protocols are more problematic [1]. However, many of these individuals will progress over the course of a clinical trial of preventing progression and may subsequently become sufficiently demented to have lost capacity. While the informed document is signed once, IRBs view consent as an ongoing process and if a subject is no longer able to consent this may be an issue. Some proposed solutions to this dilemma have included long-term, long-range consent [12], where a competent patient with a progressive disorder (for example, Huntington's or Alzheimer's disease) states that it is his or her wish to continue in the research even after no longer being capable of giving consent. These contracts are widely used in Alzheimer's disease and, at least for minimal-risk research, are well respected. There are also 'Ulysses' contracts, obtained while the subject is competent, that envision holding the patient down and forcing compliance over active refusal in the future [12]. These are far more problematic.

It is not possible to more than highlight the issues in this overview. Table 1 summarizes some of the specific issues relevant to specific classes of neurological and neurosurgical disorders. The additional caveat is that patients with progressive neurological disorders and their families are often quite desperate and willing to try almost anything. Particularly with aggressive therapies that are aimed at prolonging life, quality of survival or of death must be weighed carefully [13]. It is the role of the IRB and the principal Investigator of the clinical trial to design a study that will provide a valid scientific answer without placing subjects, including those in the placebo arm, at undue risk and to be sensitive to the unique ethical issues raised when brain function, which is the substrate for cognition and behavior, is compromised.

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Financial Conflict of Interest

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Close relationships between academic investigators and the private sector help to accelerate the translation of discoveries into potential therapies for patients. However, such arrangements may also create concurrent professional and financial interests. The primary concern in such a situation is that a financial conflict of interest (COI) could diminish investigator objectivity and may compromise human subject safety, data credibility, and public trust in clinical trials.

The clinical research community widely recognizes that financial interests related to clinical trials deserve special attention. Several prominent professional organizations have developed financial COI guidelines [1–5]. The Federation of American Societies for Experimental Biology offers a COI toolkit [6] to help clinical investigators recognize and manage relationships that may present financial COI. Publishers' organizations, such as the International Committee of Medical Journal Editors, have developed manuscript submission requirements that include financial COI disclosures for authors, editors and reviewers [7].

Clinical investigators should also be aware of a number of federal regulations and guidance documents that apply to federally funded or FDA-regulated research.

- The Department of Health and Human Services (DHHS) issued regulations [8, 9] to promote objectivity in research supported by the Department's Public Health Service (PHS) agencies, including the National Institutes of Health. The regulations require institutions to ensure there is no reasonable expectation that the design, conduct or reporting of PHS-funded research will be biased by financial COI.
- The DHHS Office for Human Research Protections provides guidance on financial relationships and interests in research involving human subjects [10]. The guidance offers issues to consider when dealing with financial COI in human subjects research.
- The FDA guidance on financial disclosure by clinical investigators [11] requires anyone who submits a marketing application to certify the absence of certain financial interests of clinical investigators, or to disclose them. Failure to disclose such interests can result in FDA audits, requests for additional studies or rejection of the study data as the basis for an FDA decision.

Most academic institutions have developed policies and procedures for identifying and managing investigator financial COI. Although individual institutions may have stricter standards, the DHHS regulations [8, 9] provide minimum standards. 'Significant financial interest' is defined in the regulations as anything of monetary value related to the research, including but not limited to, salary or other payments for services (such as consulting fees or honoraria), equity interests (such as stocks, stock options or other ownership interests) and intellectual property rights (such as patents, copyrights and royalties from such rights), with some exceptions.

The same DHHS regulations define 'investigator' as the principal investigator *and* any other person who is responsible for the design, conduct or reporting of research funded by the PHS or proposed for such funding. The FDA considers 'clinical investigator' to mean any listed or identified investigator who is directly involved in the treatment or evaluation of research subjects. With regard to financial COI, the definition of 'investigator' generally includes the investigator's spouse and dependents.

To handle financial COI appropriately, clinical investigators should be aware of COI issues when entering into financial arrangements that relate to their research activities. It is critical for investigators to work closely with the institution's established financial COI process. In some cases, managing the COI means restructuring or eliminating the financial relationship, or changing the conflicted investigator's role in the clinical trial. In many cases, however, the transparency provided by full disclosure is a sufficient management strategy. When this approach is used, disclosures are usually made in both the informed consent process and in any trial-related publications or presentations.

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Clinical Trials in Progressive Neurological Diseases

Recruitment, Enrollment, Retention and Compliance

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Progressive neurological diseases, as discussed in this chapter, are rare, idiopathic, degenerative conditions which lead to marked disability, and often shorten survival. Some examples are amyotrophic lateral sclerosis (ALS), Alzheimer's disease, various types of hereditary peripheral neuropathy, Huntington's disease, mitochondrial neuromyopathies, multiple sclerosis (MS), various types of muscular dystrophy, multiple system atrophies, Parkinson's disease, primary lateral sclerosis, spinocerebellar atrophies and spinal muscular atrophy. The authors of this chapter are most familiar with ALS, and thus most of our illustrations will come from this particular disease.

Clinical trials are especially important in progressive neurological diseases. While symptomatic care has improved dramatically in many of them in recent years [for an overview of ALS symptomatic care, see 1], there remains no effective disease-modifying therapy for most. In ALS, for example, there is just one disease-modifying therapy available, riluzole, and this prolongs tracheostomy-free survival for only a few months [2, 3]. Advances in genetics, proteomics, metabolomics and high-throughput drug screening have led to an impressive pipeline of potential disease-modifying candidates for many of the progressive neurological diseases; in ALS, for example, there are more than 30 promising compounds in various stages of development [4]. Clinical trials are the only valid means of sifting through these compounds. While we wait for effective disease-modifying therapy, clinical trials also offer real health benefits to participants [5–7] as well as hope.

Among the many challenges to clinical trials in progressive neurological diseases, this chapter will focus on recruitment (bringing potential subjects in contact with trials), enrollment (providing consent for participation), retention (keeping subjects in the study) and compliance (getting subjects and study personnel to follow the study protocol). Surprisingly little specific research has been done to compare different strategies for handling these challenges; thus, in many cases, our suggestions are based upon research in other fields (cancer, for example) or our experience.

Prerequisite

Even before subjects can be recruited for a trial, they must be diagnosed with the disease of interest. This is not straightforward. Diagnosis in most progressive neurological diseases is unfortunately cumbersome and time consuming. While some of these conditions have a specific diagnostic test (a measurable gene defect in Huntington's disease, spinocerebellar atrophies or spinal muscular atrophy, for example), most have to be diagnosed clinically (by symptoms and signs). As a result, there can be considerable delay between symptom onset and diagnosis, and thus, considerable neurologic deterioration before recruitment is possible. In ALS, the interval between first symptoms and a diagnosis that is certain enough to allow entry into a trial is typically about a year [8]. In FALS1 animal models, earlier administration of therapies is often much more effective than later administration. Rapid diagnostic tests for the progressive neurologic diseases that facilitate earlier recruitment to trials are thus sorely needed. Biomarkers are being developed that may someday minimize this problem [9].

Recruitment

Following diagnosis, the challenge is referral of potential subjects with progressive neurological diseases to clinical trial sites. Most progressive neurologic diseases are rare; ALS and MS, for example, each have an incidence of around 1–2 per 100,000 per year [10]. As a result, centers have emerged which concentrate expertise in disease management, including multidisciplinary care teams. These centers are where most of the trials take place. Surprisingly, there is evidence that many potential subjects with progressive neurological diseases are not attending these centers. In a registry of 1,359 American veterans with ALS [11], for example, only 609 or 43.7% were ever seen in such centers [11a]. The reasons for this are not immediately clear but are under investigation. While we wait for the results, it seems prudent to remind referring physicians of the many benefits of specialized, multidisciplinary clinics for patients with progressive neurological diseases; these include enhanced quality [12] and length [13] of life as well as access to clinical trials.

Enrollment

The next surprise is that even diagnosed patients attending centers with trials are not enrolling as one might expect. At Duke University, for example, 739 unique patients with ALS were seen since over the past 6 years, 544 by the Director of the Duke ALS Clinic (R.S.B.). Over this time period, only 73 of 739 (9.9%) patients enrolled in an ALS trial at Duke. During the start of a recent trial at Massachusetts General Hospital, there were 268 active patients with ALS. Only 6 of 268 (2.2%) patients ultimately

enrolled in the trial. Some of the patients in these two clinics would not have been eligible for a trial, but even considering only those who potentially qualified, the numbers are disappointing. At Massachusetts General Hospital, after prescreening of patients with ALS, 81 patients were sent a letter inviting them to be screened for the trial. Less then half responded, and again, only 6 of 81 (7.4%) were ultimately enrolled.

Slow or suboptimal enrollment delays the development of potential ALS therapeutics. Additionally, slow-enrolling trials are more resource intensive and may end prematurely without an answer due to insufficient power. Trial-eligible patients who do not enroll may pursue alternative ALS treatment programs; these may range from obtaining available trial medications outside of trials to entering programs with little or no scientific rationale (such as chelation therapy or prolonged antibiotics for seronegative Lyme disease). In such pursuits, patients not only forgo the benefits of participating in trials [5–7], but may also suffer further financial, emotional and even physical harm. It is not easy to predict or track harms that occur outside a well-designed trial, for example, many patients with ALS may had received off-label topiramate and/or minocycline outside of trials for some time before it was realized that these medications unexpectedly worsen functional scales and cause side effects [14, 15].

To better understand enrollment, we recently performed a critical review of recent ALS and MS trials [15a]. We were able to find enough data to calculate an enrollment rate (participants/site/month) in 36 ALS trials and 20 MS trials. The mean ALS trial enrollment rate was 2.1 participants/site/month (SD = 1.9, range 0.1–7.5). The mean MS trial enrollment rate was 2.9 participants/site/month (SD = 3.6, range 0.4–13.2). Enrollment rates did not appear to change over more than a decade of clinical trials. The reasons for these low but highly variable enrollment figures are not yet clear.

Suboptimal enrollment is not unique to trials in progressive neurological diseases, and is more thoroughly studied in cancer trials. Less than 5% of adult cancer patients in the United States participate in clinical trials, a rate that has not improved in more than 20 years [16–18]. Reasons for failing to enroll have been broken down into useful categories [19] including 'trial factors', 'patient factors' and 'doctor factors.' We looked at trial factors that might influence enrollment in ALS trials and were unable to find an effect based upon choice of endpoint, presence of a placebo, ratio of active to placebo groups, invasiveness of administration, availability of study intervention outside the trial or geographic site of enrollment.

Among patient factors influencing enrollment in cancer trials, one surprising finding was a reported lack of awareness regarding the availability of clinical trials as an option for therapy; in one study, 85% of 6,000 cancer patients surveyed said they did not participate in a trial because they were unaware that this was an option for them [20]. This is only part of the story though, since even among cancer patients who were aware of trials, 71% did not participate [20]. Fear of insurance denial was identified

as a common reason for declining a trial [20, 21]. Other reasons included the need to travel long distances, liability for out of pocket costs, the fear of 'being a guinea pig', perceived loss of control over decision making and the possibility of 'not receiving the best available care' especially with placebo-controlled designs [20, 21]. Most disturbing of all, the provided reason was patient confusion over the purpose and methods of a potential trial. This was magnified by the complexity of trial consent forms; surveys of cancer consent forms found less than 5% to be readable at the desired eighth grade level, with most at the college level [22]. Even among patients who provided consent to participate in some cancer trials, the majority were unable to state the purpose of the trial or their alternatives [23, 24].

Faced with confusion and uncertainty, cancer patients often turn to their local physicians for guidance. Unfortunately, many physicians surveyed in the cancer literature were not referring their patients for trials [21]. The most common reasons identified included lack of awareness of open trials [21], 'concern for the doctor-patient relationship' stemming from loss of control over choice of therapy and discomfort with the concept of uncertainty implicit in a comparison trial [19]. Others expressed doubts about the relevance of study questions and the choice of therapies, and, citing limited resources, felt that trials were not worth the additional time and effort they would have to expend to get their patient into a trial [19, 20].

Patient factors or doctor factors that might influence ALS trial enrollment have not been studied. Nonetheless, in the meantime, it is reasonable to target these potential factors, as has been done in oncology trials, in hopes of improving ALS trial enrollment. Better education of patients regarding trials, specifically targeting the misperceptions seen in cancer patients, seems prudent. Indeed, studies comparing 'intensive education with consenting' compared to 'standardized consenting' resulted in more knowledgeable participants and a doubling of enrollment in cancer trials [25, 26]. Equally important will be better education of our physician colleagues regarding the availability and utility of trials, and the dangers of alternatives. Indeed, most cancer patients participating in trials state that their doctor had the greatest influence on their participation [20].

Retention

A proportion of subjects with progressive neurological diseases entering a clinical study will not complete it. There are a number of reasons this might occur. In previous ALS trials, for example, we have lost subjects due to death, progression of disease to the point where subjects can no longer travel to the center and/or complete outcome measures, treatment-related side effects, loss of faith in the trial, the seeking of an alternative therapy and loss of contact. Some of these reasons for subject dropout are inevitable and must be taken into account in designing the trial. Others are more controllable. Unplanned dropouts may lengthen the duration

of the study. They may also affect the generalizability of study results, since the characteristics of the subjects who remain may be very different from those that drop out. At worst, they can invalidate study results, since the study may wind up underpowered.

With many of the progressive neurological diseases, death during a trial is unavoidable and should be planned for in trial design. Prior trials in the disease of interest utilizing similar enrollment criteria and study durations are used to estimate dropouts due to death, and sample size calculations then take this into account. To minimize loss of subjects due to death, end-stage subjects who will have lifespans less than the study duration should be excluded from enrollment. In ALS trials, we try to accomplish this in 2 ways: hard measurements that predict poor survival (such as forced vital capacity below a certain cutoff or inability to swallow study medication) and gestalt, investigator-predicted survival of less than the study duration. Progression of disease is also inevitable, and for some this will result in loss of ability to travel to the trial center. Selecting subjects near the trial site can decrease this. Selecting outcome measures that can be obtained over the phone, the internet or through local physicians and laboratories can also be effective. Most ALS trials, for example, now employ an outcome measure called the ALS functional rating scale-revised (ALSFRS-R). This measure has been validated for phone use [27].

With regard to more 'controllable' sources of dropout, a recent publication reviewed retention strategies in clinical trials from a variety of disciplines [28]. Successful strategies were categorized under 'respect for patients', 'tracking' and 'study personnel'. Respect for patients referred to establishing a positive rapport, including acknowledgement of patient ideas and time commitment to the study. Specifics included birthday cards, newsletters updating study progress, 'check in' phone calls between visits, flexibility in visit scheduling and visit reminder letters. Financial incentives were suggested to cover travel costs, though caution was suggested with the size of these to avoid the perception of coercion. Under tracking, the emphasis was on collecting comprehensive contact information during the initial study visit, including multiple contacts. It was recommended that these multiple contacts be informed of the study by the subject to minimize reluctance on their part to provide the subject's location in the future. An explicit 'cascade of contacts' should be developed in conjunction with the subject at an early study visit. Frequent phone or internet contacts throughout the study appeared to maximize the investigator's ability to track. If frequent contacts are not possible, attempts should start several weeks prior to study visits. Some studies even used Department of Motor Vehicle records to help locate lost subjects [29]. Finally, there was the study personnel category. Personnel who were compassionate and enthusiastic were better at retaining subjects. Personnel must also be highly motivated, available and flexible to subjects needs. Overall, use of these strategies facilitated a follow-up rate of 86% at 5 years in 109 survivors of adult respiratory distress syndrome and a follow-up rate of 98% at 8 years in 454 healthy men [28, 29].

Compliance

Even a well-enrolled study with a high retention rate can have subjects or study personnel deviate from the protocol. These deviations, which range from minor (barely missing an allotted window for a study visit) to major (failure to take or deliver the allotted treatment or to complete critical study outcomes accurately) must be accurately recorded. Strategies for measuring subject compliance include clinician impression, subject reporting, pill counts, prescription records, assessment of pharmacological response and assay of drug or metabolite in body fluid [30]. The first 4 of these are usually simpler and less expensive, but less accurate than the last 2, and may overestimate compliance [30]. When pill counts are used, as they frequently are in trials in progressive neurological diseases, some studies recommend using a device to monitor removal of tablets from the container, though this strategy does not guarantee ingestion. Measurement of noncompliance by study personnel are usually undertaken by the coordinating site and by independent medical monitors.

In ALS trials, in addition to reasons given above for subject dropout, we have seen subject noncompliance due to apparent forgetting and to disease progression to the point where opening or swallowing study medication becomes difficult. We have seen study personnel noncompliance as a result of forgetting details of the protocol as well. Both types of noncompliance are potentially very serious problems. Subject noncompliance with medication can substantially reduce the power of the study; if 30% of patients fail to appropriately use the study medication, for example, the number of patients needed to attain the same α- and β-levels is reportedly doubled [30]. In a study comparing 2 treatments, even equal degrees of subject noncompliance in the 2 groups may bias the study results toward 1 group; missing a dose of a long-acting drug, for example, would have less of an effect than missing a dose of the shorter-acting drug. Noncompliance by study personnel creates extra work for the coordinating center and, if frequent or severe enough, can result in closure of the study at the site or at all sites, or in failure of acceptance of trial results by a journal or the FDA.

Strategies for maximizing subject compliance overlap with those used to minimize drop out (see the respect for patients, tracking and study personnel categories above). To address the problem of forgetting, one study on vitamin intake showed that calendar blister packs can be more effective than bottles with pill organizers [31]. For progressive neurological diseases that impair strength, dexterity and/or swallowing, patient-friendly packaging and medication that can be crushed or given parentally should be considered.

Comparisons of strategies for maximizing compliance by trial personnel are lacking. However, one interesting study recently looked at factors associated with site investigator compliance in a large Japanese cardiovascular trial [32]. Investigators were classified as being 'compliers' or 'noncompliers', with the latter group needing assistance from the coordinating center on 50% or more of their expected data. Eleven predictors were examined in a regression model and 3 were found to be predictive of

noncomplier status: prior participation in a clinical trial (those with prior participation were unlikely to be noncompliers), favorable investigator opinion of the support system for case registration and follow-up (those who liked the system were unlikely to be noncompliers) and number of patients enrolled (surprisingly, those enrolling less than 10 patients were more than twice as likely to be noncompliers). Thus, coordinating centers should plan for extra efforts toward investigator compliance when taking on inexperienced trial sites. Sites that do not like the system being used in the trial and those that have a history of poor enrollment in the disease of interest should be avoided.

Conclusions

Clinical trials in progressive neurological diseases have many challenges, including diagnosis, recruitment, enrollment and compliance. These challenges can be managed using the lessons learned from our own experience and from published studies in other fields. Advances in biomarkers and efforts to educate referring physicians are underway which should further facilitate important clinical research in this deserving population.

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Genetics in Clinical Trials

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Clinical trials provide the 'evidence' in evidence-based medicine. Despite their cost and complexity, clinical trials save society billions of dollars [1]. Recent advances have enabled genome-wide analyses of single nucleotide polymorphisms in complex diseases. Such analyses require large sample sizes and thus depend on collaborative efforts. Genetics ancillary to clinical trials benefit from recruitment by numerous investigators at diverse institutions. Additionally, clinical trial subjects are well characterized via trial eligibility screening, and baseline characteristics and outcomes are collected via validated, standardized measures. This allows genotype-phenotype, genotype-outcome and treatment-response analyses. Banking DNA only marginally increases costs relative to the cost of the trial itself.

The disadvantages to ancillary genetic studies in clinical trials are also clear. Typically, trials do not recruit disease-free individuals necessary for genetic controls. As a result, historical control subjects, who may have incomplete, differentially acquired phenotypes, are frequently used. Trial eligibility criteria result in collections that are not representative of the disease-affected population. For example, PROACT II, a study of intra-arterial thrombolysis, randomized subjects representing 1.5% of those screened [2]. Such small samples can render subcollections useless, even in the absence of recruitment bias.

Although pharmacogenetics is subject to hyperbole, the underlying concepts are traditional. Clinicians consider treatment based on ethnicity, gender and other factors, all of which are the result of gene expression. Malignant hyperthermia [3], long QT syndrome [4], venous thromboembolic disease [5] and tardive dyskinesia [6], among others, have associated underlying genetic risk factors. New tools including microarray technology [7], high-throughput screening and bioinformatics, when combined with large simple trial infrastructure, allow a better understanding of pharmacogenetics.

Finding the High-Responder Subgroup in Clinical Trials

Defining subgroups of high responders in clinical trials might allow more cost-effective treatment. However, the subgroup must represent a substantial proportion of the disease-affected population and testing must be practical. Subgroup analyses are often underpowered because the parent study test is powered to the primary hypothesis. High-responder subgroups might not be easily identified via purely clinical criteria. For example, it was hypothesized that those with cardioembolic stroke represented a subgroup responsive to acute anticoagulation [8]. Subsequent studies failed to confirm this [9]. Determining genotypes associated with adverse outcomes may be useful in planning or monitoring treatment. For example, about 20% of Whites carry different CYP450 mutations causing warfarin sensitivity, suggesting that CYP2C9 genotypes may be helpful in deciding warfarin dosing [10].

Alzheimer's Disease

The epsilon 4 allele of apolipoprotein E *(APOE)* is a well-established, prevalent risk factor for Alzheimer's disease. *APOE* testing has been used to determine subgroup responsiveness to acetylcholinesterase inhibitors, with mixed results (table 1). *APOE* genotyping has also been used to explore novel classes of treatment agents. This strategy allows useful data on therapeutic targets to emerge, even from negative trials. For example, a randomized trial of the peroxisome proliferator-activated receptor-γ agonist rosiglitazone in subjects with mild to moderate Alzheimer's disease [11] demonstrated no significant treatment effect on cognition overall, but an exploratory analysis showed improvement in cognition for the *APOE4*-negative, but not for the *APOE4*-positive group. Results of such a finding will need to be confirmed in further trials.

Pharmacogenomics in Antiepileptic Drugs

About 30% of patients with epilepsy are refractory to therapy, despite the availability of numerous antiepileptic drugs. Two hypotheses have emerged regarding how genetics influence refractoriness: transporter and target [12]. In testing the transporter hypothesis, much attention has focused on P-glycoprotein, encoded by the *ABCB1* gene. An early association study found a significant relationship between refractory epilepsy and the *ABCB1* single nucleotide polymorphism C3435T [13], but attempts at replication yielded mixed results. The target hypothesis, less appealing from a clinical perspective because it assumes that genetic variation in responsiveness is drug-specific, argues that refractoriness occurs due to variations in genes encoding for drug targets such as sodium channels and GABA receptors. Currently, no definitive

Table 1. Studies where APOE status has been used to attempt to identify high-responder populations in Alzheimer's disease trials

Ref.	Drug	Trial design	Findings
[11]	rosiglitazone	randomized, placebo controlled	exploratory analyses demonstrated significant improvement on ADAS-Cog in *APOE* ε4-negative patients treated with 8-mg dose
[19]	galantamine	randomized, placebo controlled	*APOE* ε4 genotype did not affect improvements in cognition, global rating, function or behavior
[20]	tacrine	randomized, placebo controlled	non-*APOE* ε4 carriers on tacrine improved more versus placebo than patients with APOE ε4 on tacrine versus placebo
[21]	metrifonate	pooled analysis of 4 randomized trials	interactions of *APOE* genotype and metrifonate effect on cognition were not significant
[22]	tacrine	prospective case series blinded to genotype	no significant differences in response to treatment were seen based on *APOE* genotype
[23]	sabeluzole and galantamine	pooled analysis of 4 randomized trials	sabeluzole was not effective overall or in any subgroup stratified by ε4 allele count; galantamine produced cognitive and functional improvements that were not affected by ε4 allele count
[24]	rivastigmine	pooled analysis of 2 randomized trials	no significant differences in response to treatment were seen based on *APOE* genotype
[25]	donepezil	prospective case series	*APOE* ε4 carriers had improved or unchanged scores at retesting for visual and verbal memory, visual attention, inductive reasoning and Mini Mental State Examination; these favorable effects were not observed in the ε4-negative group
[26]	donepezil	prospective case series	no significant differences in response to treatment were seen based on *APOE* genotype
[27]	citicoline	randomized, placebo controlled	possible improved response to treatment in the epsilon 4 carriers
[28]	tacrine	randomized, placebo controlled	intention-to-treat analysis of patients with available genotypes did not reveal response differences by genotype
[29]	selegiline	randomized, placebo controlled	*APOE* genotype did not influence therapeutic outcome
[30]	tacrine	prospective case series	*APOE4*-positive patients had declined more than ε4-negative patients on treatment

genotype-response relationship has been discovered [14]. Despite intensive research, no molecular basis for pharmacoresistance to antiepileptic drugs has been identified yet.

DNA Banking

Clinical trials are designed to test the primary hypothesis, and some argue that failing to adequately test the primary hypothesis because of an inadequate sample size is unethical, exposing subjects to risks without the benefits [15]. Excessively powering a study may also be unethical. Clinical trials should maximize the subjects' contribution; genetic studies, of minimal risk, are therefore worthwhile. A genetic substudy allows the possibility of therapeutic target discovery, even in negative studies.

Recent technological advances coincide with increasing recognition of the importance of very large cohorts for studying complex genetics [16]. Genetic studies that rely solely on analysis of samples collected in the trial risk inadequate power. Genomic approaches increase the likelihood that useful information will be gained by an ancillary genetic study, but even phase III trials risk being underpowered for genetic results. The number of subjects needed for gene discovery depends on several factors, including gene number and effect size, disease heterogeneity and study design, but is estimated between 2,000 and 10,000. Moreover, replication depends on the availability of independent populations. Limited access to biomaterials collected by individual projects is a roadblock to genome-wide analyses. In response, efforts in gene banking (NINDS repository: http://ccr.coriell.org/Sections/Collections/NIGMS/?SsId=10) have been undertaken. Underpinning uniform public access are bioinformatics solutions, and DbGaP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) offers a resource for genotype-phenotype data.

Summary

Pharmacogenetics is founded on longstanding traditions in clinical practice, where therapies are selected based on history and physical findings in order to maximize benefit and minimize risk. Genetic tools allow increased sophistication in patient profiling and treatment optimization. Pharmaceutical companies are aware of the value of collecting genetic data during their clinical trials [17, 18]. Pharmacogenetics research is bidirectional with clinical trials: efficacy data are correlated with genetic polymorphisms, which in turn define subjects for treatment stratification. Currently, pharmacogenetics is in its infancy. Nonetheless, we anticipate that the identification of disease-specific genes will result in earlier diagnostic measures, disease progression markers and targets for therapeutic discovery.

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Randomized Clinical Trials in Children

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Randomized clinical trials specifically designed to target infants and children are critical to developing optimal treatment for childhood neurological disorders. Brain growth is dynamic during the first 2 decades of life, and cerebral maturation is accompanied by developmental changes in regional volumes, synapses and receptors. The clinical manifestations of childhood neurological disorders often evolve over time, reflecting this maturation. Some disorders such as infantile spasms, febrile seizures and muscular dystrophy occur exclusively in childhood, and therefore therapeutic trials cannot be extrapolated from adult studies. Other disorders such as spinal muscular atrophy (SMA), absence seizures and head trauma occur in a variety of ages, but are likely to have different clinical manifestations and outcomes in children than in adults.

In addition to the numerous regulatory issues discussed in the chapters by Hall and Traystman [this vol., pp. 10–33] and Hemmen and Zivin [this vol., pp. 39–45], there are particular challenges unique to performing randomized clinical trials in infants, children and adolescents. These include not only enrollment issues, but a variety of issues summarized in table 1. Furthermore, there are unique genetic and outcome issues for investigators proposing randomized clinical intervention trials on children with neurodegenerative disorders such as Duchenne's dystrophy or SMA. To illustrate some of these issues, we describe 3 examples of pediatric randomized clinical trials.

Hypothermia Trials in Neonates

Investigators proposing randomized clinical interventions for critically ill neonates are faced with several unique challenges: providing a rigorous definition of disease, enrolling subjects and instituting intervention in a timely fashion, and defining outcomes that include both short- and long-term parameters. The published outcome

Table 1. Issues relating to pediatric trials

Regulatory issues
Special rules for children as they are unable to give consent
Drug formulations
Wide ranges in dosages
Changing doses with age (such as mg/kg)
Need for different formulations (liquids, tablets) while maintaining blinding
Laboratory measurement
In young infants blood drawing is difficult and amounts are limited
Implies that randomized controlled trials need fewer labs and microtechniques
Norms in children often not well established
Objective measures such as MRI may require sedation
Cognitive measurements
Psychological measures are age dependent
Many measures (strength, attention) are difficult to assess in young children
Outcome
Outcome measures may change over time in developing brain
Long-term follow-up is needed to assess recovery/outcome

data for infants believed to be suffering from moderate to severe hypoxic ischemic encephalopathy (HIE) suggest that over 60% will experience death or disability at 18 months of age and 30% of survivors will develop cerebral palsy [1, 2]. Several investigators have performed randomized controlled trials of hypothermia instituted within 6 h for HIE with outcome measured at 18 months [3–5]. These trials provided encouraging results which suggest that, if instituted early, hypothermia improves the neurodevelopmental outcome of neonates with HIE. Furthermore, these trials have provided the impetus for the large multicenter Infant Cooling Evaluation trial in which hypothermia is started in the field in infants with HIE.

Pediatric Epilepsy Trials

Childhood absence epilepsy is the most common form of childhood epilepsy, accounting for 10–15% of all cases [6, 7]. It is now recognized that, while seizure outcomes are often favorable, many of these children have significant difficulties in attention, executive function and school performance that may persist even when seizures are controlled [8]. While there are several effective therapies, we do not know which is optimal. The childhood absence epilepsy trial, which will enroll over 450 subjects, compares head to head 3 first-line treatments, ethosuximide, lamotrigine and valproate. Efficacy is based on both lack of clinical absences and confirmation by a 1-hour video electroencephalography. Neuropsychological and quality of

life measures are also used. Primary outcomes are based on 'freedom from failure'. Pharmacokinetic and genetic studies are also performed.

The study illustrates many of the difficulties in performing pediatric trials. Because the age range is 3–12 years, some children can swallow tablets, but others cannot. In addition, the weight range is very large, resulting in a wide range of doses. This led to challenges in the drug formulations as multiple dose forms were needed to maintain the blinding. Particularly in the younger children, weight changes occurred during the course of the study that resulted in a change of dosing after reaching stable dose. Given the large range of ages, measures of psychological tests were chosen that are adaptable to the different ages, but some measures such as attention could not be administered to the youngest children. While the study illustrates the challenges, it is also an excellent example of how a properly designed adequately powered pediatric study can be done that will yield valuable information [9–11].

Trials in Children with Neurodegenerative Disorders

SMA is an autosomal recessive disorder that affects spinal cord neurons and is caused by homozygous absence of the SMN1 gene. SMA is clinically characterized by muscle weakness and genetically by mutations in the SMN gene. Outcomes vary from death in early life for those with type 1, severe orthopedic and pulmonary complications for those with type 2 and progressive weakness and loss of motor ability even in those with the milder type 3 who do eventually walk. Because of the devastating nature of this disorder, numerous preclinical and clinical studies have attempted to halt progression of the disease [12].

Challenges in conducting such trials include the variable nature of the disease and thus difficulties in classifying subjects accurately, reliable assessment of progression of disease, and the difficulty of translating biochemical and molecular results from bench to bedside. The former 2 difficulties resulted in the development and validation of a functional motor scale [13]. The latter has resulted in numerous pharmacologic trials for SMA based upon in vitro data. Recently, since phenylbutyrate was known to increase SMN transcript expression in both fibroblast cultures and leukocytes from patients with SMA and an open-label pilot trial performed on nonambulatory patients with SMA suggested a significant increase in muscle strength, and subsequently, a phase III randomized controlled trial was proposed [14, 15]. This trial, recently published, enrolled 107 children aged 30–154 months who were randomly assigned to receive phenylbutyrate (500 mg/kg/day) or matching placebo on an intermittent regimen for 13 weeks. Although the medication was well tolerated, the regimen studied proved to be ineffective. A randomized clinical trial of phenylbutyrate for neonatal SMA is now ongoing.

Recent review of the numerous treatment trials in the United States and abroad suggests that SMA may be considered a developmental disorder and that early

intervention may be possible; thus, the identification of presymptomatic SMA by newborn screening may warrant further investigation for future intervention trials [12]. Furthermore, randomization based on genetic analysis may be needed as severity of the disease is linked to SMN2 copy number [16].

These are selected examples intended to illustrate both the need for pediatric trials and the challenges in performing them. With the increased recognition that adult data are not universally applicable in children, even when the disease may be similar, we expect and hope to see an increased number of pediatric clinical trials in the future.

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Neurological Emergencies

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Neurological emergencies are common and particularly devastating in terms of disability and mortality. Every 28 s, a person in the US is victim to one of the 8 most common neurological emergencies and every 2 min, someone in the US dies from one of these conditions [1–22]. These most common neurological emergencies (acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, bacterial meningitis, status epilepticus and anoxic brain injury) are responsible for more than USD 115 billion per year in US healthcare spending. Despite their impact and prevalence, therapeutic options in the emergent phase are often limited or nonexistent, in part because of the difficulties in performing clinical trials in this challenging patient population. Despite pathophysiological differences in these conditions, the common unifying principle related to clinical trials is that each of these conditions has a rapidly progressive course and the window of opportunity for emergent treatment is narrow and often limited to the first few minutes to hours after symptom onset. While many of the challenges in performing research in neurological emergencies are common to other neurological clinical trials, there are 4 areas which are unique and deserve special mention: (1) patient identification, (2) accessibility of the research team, (3) necessity of a multidisciplinary research team and (4) unique consent issues.

Patient Identification

Stroke syndromes (acute ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage) are sudden, often catastrophic, and occur at any time and in any place. Likewise, traumatic brain injury, spinal cord injury, status epilepticus and anoxic brain injury occur suddenly and randomly. These disorders affect all groups and the loss of neurological function often makes the patient incapable of seeking medical attention independently and necessitates a dependence upon others for recognition

of the problem and access to the healthcare system. The planning of interventional clinical trials for neurological emergencies requires a complete understanding of how the healthcare system is accessed in each of these conditions. For many neurological emergencies, emergency medical services (EMS) are typically the first point of access. For some disorders, access to early treatment is best when EMS are the patient's first contact with the healthcare system [23]. Recognition and treatment are delayed when patients call their personal physicians or seek to access the healthcare system on their own. There has been considerable effort to educate the public about the need to call 911 for acute stroke and these efforts have had some success in accelerating the arrival of acute stroke patients to the emergency department [24]. Faster treatment happens when EMS notifies the emergency department prior to the patient's arrival at the hospital [25].

Depending upon the nature of the intervention and the neurological emergency, certain treatments can be started in the prehospital phase (e.g. FAST-Mag) [26, 27],although more commonly interventions will occur in the emergency department. For any emergency condition studied, investigators need to have a thorough understanding of the typical time of onset, the likely first point of access to the healthcare system and the existing protocols for management of patients with symptoms of the targeted disease. For example, many patients with intracerebral hemorrhage will access the healthcare system through EMS, but the chief complaint may vary from headache to vomiting to altered mental status to 'found down' [28]. Investigators therefore need a thorough understanding of the specific dispatch and EMS protocols for each of these complaints. If the patient does not arrive at the hospital through EMS, the emergency department still typically becomes the first point of access. It is critical to understand the operations of the emergency department including the triage process, level of expertise of emergency care providers and operational protocols to devise the best process for identifying patients who may be eligible for clinical trials [25]. To enact certain clinical trials, the operational and triage protocols in the EMS or emergency department may need to be changed to enable rapid identification of these patients at the earliest possible time.

Accessibility of Research Team

One of the greatest difficulties in conducting clinical trials in neurological emergencies is that the patient may present at any time, day or night, and the time window for intervention is typically short. Because recruitment windows are tight, the patient care research team has to be available whenever the patient presents with the target disease and must be able to respond quickly after the patient is identified. A main criticism of many previous negative trials for treatment of neurological emergencies is that the disease was not treated in the proper time window. Ischemic stroke is a good example. The NINDS trial, which treated 50% of the patients within 90 min of symptom onset

and 50% between 90 min and 3 h after symptom onset, showed clinically significant benefit from tissue plasminogen activator, whereas European trials which treated up to 6 h after stroke onset were negative [29]. Observational trials of patients with intracerebral hemorrhage have demonstrated that hemorrhage growth will occur in a high percentage of patients within hours of symptom onset and treatment strategies to reduce hemorrhage growth should be applied within this narrow time window [30, 31].

The research team clearly needs to be available 24 h a day, 7 days a week and 365 days a year to enable successful patient recruitment. After the patients have been successfully identified, rapid notification of the research team is critical. Level 1 trauma centers in the US have adopted a classification system tied into rapid notification for alerting the patient care team. This method has been adopted in many centers for ischemic stroke treatment and clinical trials using a 'code stroke' approach [32]. Typically, there is a single page or a phone number to call at all times which can trigger a rapid response from the interventional team. This approach needs to be seamless and reliable at any time of day or night. The criteria for notifying the investigational team must be simple and clear. The notification of the research team should occur at the earliest possible time, which may be before the patient has arrived at the hospital.

Automated identification systems are being studied, whereby information in the triage record is automatically scanned and electronically directed to investigators without the need for human identification and classification [33]. Any system that is used should purposely overtriage so that the research team is often notified about patients who are not eligible for the trial but eligible patients are not overlooked.

Multidisciplinary Research Team

The diagnosis and care of neurological emergencies encompass a broad spectrum of medical specialties, including neurology, neurosurgery, neurointervention and critical care. By virtue of the fact that these conditions are emergencies, the prehospital care system and emergency department are almost uniformly involved in all of these. Emergency physicians are the 'boots on the ground' for most of these conditions, since they are already present in the emergency department at all times and will be involved in the emergent care for all of these patients. Specialist involvement is likewise critical, since these patients will typically require hospital admission and standardization of routine care for these conditions is critical in any clinical trial. The specialists are clearly the people who will be caring for these patients during their hospital stay and their input is necessary to ensure the success of clinical trials in neurological emergencies. Clinical trials in neurological emergencies may work best when the research team is a combination of specialists and emergency physicians who work together to streamline patient entry into clinical trials [34]. Many clinical trials in neurological emergencies will require long-term follow-up of patients which the specialists are in the best position to provide.

Consent Issues in Emergency Research

Respect for subjects is the cornerstone of clinical research ethics as formulated in the Belmont report and elsewhere. A key manifestation of respect for subjects is usually recognition of their autonomy in the form of informed consent processes. Emergency research in general and neurological emergency research in particular create special challenges to performing meaningful and adequate informed consent processes. Patients with emergency conditions and their families are usually in a stressful and emotional situation that is not conducive to carefully receiving and contemplating the complex information that may be needed to consider participation in a clinical trial [35, 36]. Furthermore, the interventions being tested in trials of emergency care usually need to be delivered within minutes of patient presentation, so there is very little time for patients or families to consider the decision of whether or not to participate in the trial. Finally, neurological emergencies in particular usually involve impaired mentation such that patients themselves cannot engage in a discussion of what they want. In such situations, either families must decide for patients or alternative processes must be used in place of the consent process. Approaches to the challenges posed by informed consent in neurological research depend on a more detailed understanding of the underlying principles upon which autonomy are based. This section will briefly explore these principles, discuss some specific barriers and techniques, and examine the use of exception from consent for emergency research when the principle of autonomy remains silent.

Purpose and Importance of Consent in Neurological Emergency Trials

The importance of informed consent is rooted in the principle of autonomy, but under this umbrella one can consider consent as having 2 somewhat distinct purposes.

The first, more explicit, purpose involves engaging an individual in a rational deliberative decision-making process based on his or her own individual values. The underlying notion is that individuals generally know what is best for themselves and that even if they do not, they are entitled to make their own mistakes when it comes to their own body and health. Certainly, individuals are likely to be ideally motivated to make decisions in their own interest and to protect themselves from inappropriate risk. This purpose of consent can thus be considered primarily an individualized safeguard against undue risk that also considers such things as differing tolerance to risk.

A second purpose of the informed consent process is implicit and involves recognition that the mere act of involving a person in his/her own decision making is an inherently humanizing gesture of respect. The consent process is a mutual transaction between 2 moral agents, the subject and the investigator. As such, it helps correct the power imbalance that inherently results from an investigator's expertise and a patient's illness. By engaging investigators with their subjects, the consent process also works against the objectification of patients that can often occur in the practice

of modern medical care. Simply put, sitting down with patients demonstrates respect and helps remind investigators that subjects are real people.

The 2 purposes of consent are complementary, but independent. Their relative importance varies by situation. Attention is more commonly focused on the former purpose, perhaps because those engaged in the conduct and regulation of clinical research have personality types that more easily relate to its explicit and rational elements. In the emergency environment, however, the importance of the second purpose of consent is paramount. In the emergency department, the rapidity of the necessary decision making and the subject's situational impairment makes meaningful fully informed decision making extremely difficult and unreliable. At the same time, the emotional context of the emergency environment makes the second purpose of consent even more valuable. Unlike other clinical environments in which there may be an established physician-patient relationship that precedes consideration of an investigator-subject relationship, emergency department patients are usually being treated by doctors they have never seen before, at a time that they are sicker than ever before. Furthermore, the brisk pace of care usually required in high-acuity situations tends to objectify patients more than in other care environments. Emergency research consent processes should maximize both described purposes, but it is appropriate to focus attention on the latter.

Specific Solutions to Barriers and Limitations in Consent in Neurological Emergency Trials

Effective consent processes depend on conscientious researchers and many other elements, but a few specific solutions to some common barriers exacerbated in the emergency environment are worthy of discussion.

As mentioned above, emergencies make it even more difficult to provide subjects with all the knowledge they may need to make fully informed decisions. This is an exacerbation of a problem common to medical consent processes in all environments. Indeed, Carl Schneider, a legal ethicist, has suggested that consent can never be adequately informed because medical decision making always involves professional expertise and a depth of knowledge impossible to summarily convey to lay patients, and that the attempts to make patients responsible for decision making may be bad for patients by diminishing the value and purpose of the physician's expertise [37]. It has been argued, however, that patients have expertise too. They are (or may be) experts on themselves, including their own values, risk aversiveness and fear of uncertainty. In the emergency environment, rather than trying to convey too much medical detail about a clinical trial, it may be useful to provide basic medical information, and then inquire about the patient's relevant values and feelings regarding clinical research. An informed consent process structured in this manner may help guide subjects to a personally acceptable decision, that is, a person that finds known risks and a known chance of benefit more acceptable than unknown risks even if offset by a chance at improved outcomes, may not want to participate in research, whereas a

person willing to accept added uncertainty for a chance at a better outcome may be encouraged to participate.

Other consent problems exacerbated in emergencies are those in which patients feel that they will not get the best care possible if they do not consent to participate in a proposed clinical trial. These are known problems in many research environments, but are often intensified by the heightened acuity, fear and suddenness of emergencies. These problems include therapeutic misconception and the perceived need to cooperate to get treated well. Therapeutic misconception is the difficult-to-dissipate notion in which subjects believe that a new experimental therapy must be better than standard therapy by virtue of it having been selected for study [38]. Even if told otherwise, patients also can feel that they will not get optimal treatment if they 'disappoint' their doctor by choosing not to participate in an offered study. This perception may be more likely in the emergency department, where they are being treated by a doctor that they just met and did not select. Some techniques proposed to address these problems in other venues, including questionnaires or 'teach backs' to assess understanding, are not amenable to the emergency setting. A better solution in the emergency department is, whenever possible, to differentiate the clinical care team and the research team. This is best accomplished by having on-call investigators or coordinators respond to the emergency department to offer enrollment to patients, and by explicitly introducing themselves as researchers distinct from the care team. When this is not practical, other methods of exaggerating the distinction between clinical care and research should be considered in the emergency setting.

Finally, regulatory efforts created to protect research subjects have often become barriers to meaningful informed consent processes, and these problems are also amplified in the emergency department. Indeed, written informed consent documents in many institutions have become so lengthy and complicated that the majority of patients believe that the intention of the form is not to protect patients, but rather to protect researchers and their institutions [39]. Although problematic in all clinical trials, 15-page consent forms written at a 12th grade level are particularly likely to fail to protect subjects in the emergency setting. A national effort to improve the accessibility and content of informed consent documents and their attendant processes is underway [40]. It has been recommended that informed consent forms be limited to only the information required by 45 CFR 46.116 and to about 1,250 words presented at an 8th grade level in a highly readable format [40]. Adoption of these recommendations would substantially improve informed consent efforts performed in emergency situations.

Exception from Informed Consent in Emergency Research

In the emergency setting, meaningful informed consent is sometimes not just difficult, but impossible. Patients with neurological emergencies often require immediate medical care but are comatose and without family or other surrogate decision makers.

In neurological emergencies, some treatments need to be given within the initial minutes after the brain injury to be effective. Current guidelines in research ethics and research regulations acknowledge the situation in which there is a compelling need for clinical research to determine the best emergency care for critically ill and injured patients, but in which subjects cannot practicably make their wishes known. In such cases, the majority of patients surveyed support conducting the needed research, individual autonomy is silent and the ethical principles of beneficence and justice prevail. The requirement for informed consent is excepted or waived in these limited extraordinary circumstances, but such trials are conducted in the US under special regulations.

In 1996, federal agencies responsible for the oversight of clinical research worked together with other interested parties and published the Final Rule describing characteristics of research that could be conducted when informed consent was not possible and the requirements of trials conducted in this manner [41]. The rule is described in detail in the regulations at 21 CFR 50.24 'Exception from Informed Consent in Emergency Research', covering trials under FDA jurisdiction. For trials not overseen by the FDA, but funded by the NIH or otherwise regulated by HHS, the secretary published a waiver of informed consent under 45 CFR 46.101(i), permitting that such trials could be conducted if they met the rules laid out for FDA trials at 21 CFR 50.24 with the added stipulations that they not enroll prisoners or patients known to be pregnant. The terms 'exception from informed consent' and 'waiver of informed consent' are often used interchangeably.

Exception from informed consent for emergency research is applicable to a relatively narrow spectrum of clinical trials. Eligibility requires that the condition being studied is life threatening and one in which current treatments are inadequate or unproven. Further, proposed trials must have the potential to benefit the subjects enrolled. Finally, it must be impracticable to perform the trial without an exception to informed consent. Definitions of these terms and conditions are not included in the regulation. In 2000, the FDA issued a guidance that helped clarify some terms but that still left considerable latitude in the hands of the institutional review boards (IRBs) reviewing these proposals. A revised guidance document has been drafted by the FDA and subjected to public comment, but has not yet been released in a final form.

If a trial is eligible, the following special provisions must also be accomplished. Investigators must notify the public about the trial and that it will be conducted with exception from informed consent. Public notification is required prior to conducting the trial, and again after the results have been reported. The regulations do not specify the form or extent of notification, but trials conducted under these guidelines use a variety of methods, including press releases, print and broadcast advertising, public service announcements, and web- and e-mail-based announcements. Investigators are also required to conduct community consultations. Unlike public notification, which is a one-way communication to the general public, community consultation is an exchange of information between the research team and the community from

which subjects may be enrolled. The draft FDA guidance suggests that community be defined in 2 ways. One as the geographic community from which subjects will be enrolled, and the other is a community suffering from, or at high risk for, the pathology or conditions being studied. The format of community consultations is not defined in the regulations, but previous efforts have included town hall format meetings, visits to community groups and religious groups, presentations to local governments, use of community liaison committees, formal focus group assessments and random digit-dialing telephone surveys [42].

In addition to these major provisions, there are other requirements in the regulations. If consent is practicable for some subjects in a trial using exception, the regulations still require an informed consent process for that subset. The regulations also require that consent to continue in the study be obtained from subjects or families after enrollment when it becomes practical to do so, even though that will often be after the intervention is completed. Given the relatively low risks of continuation in a trial after the emergency intervention is over, and the risks of inadvertent bias inherent in postrandomization/postintervention exclusion of data, it may still be permissible to use some limited data, like mortality (which is publicly available), in subjects that do not consent to continue. Clearly, further interventions, assessments and use of particularly sensitive data would not be allowed in these patients. Further clarification is needed and the FDA has been asked to provide this in the upcoming final version of the guidance statement [43].

The exception from informed consent regulations has caused substantial consternation and concern among both investigators and IRBs, primarily because the requirements for community consultation and public notification are unfamiliar and somewhat vague. Lack of specificity in the regulations, however, allows flexibility in their implementation which is important since trials conducted with exception can vary considerably in their design, level of risk, sensitivity and other important factors. It is problematic because it is hard to know how much consultation and notification effort is enough. Assessing the sufficiency of these processes is best accomplished by determining the purpose of community consultation and public notification. In the absence of any published regulatory intent, we propose an underlying ethical basis for these regulations, from which their purpose can be derived and the success of implementation can be assessed.

Community consultation and public notification requirements are best justified on the basis of the purposes initially outlined to explain the value of consent processes. These include understanding, respect and transparency. Understanding is best enhanced by community consultation processes that focus on improving investigators' as well as IRBs' knowledge and awareness of the variety of values and beliefs present in the community. This understanding comes only from talking to people. The stimulus for discussion in community consultation is the trial being proposed, but the follow-up question is not 'What do you think about the research?' but rather 'Which of your values and experiences seem most relevant to this research?' Community

consultation is not practical as a means of 'community consent' or as similar form of deliberative democracy. Respect is likely the best reason for community consultation. If the consent process is a moral transaction between investigators and subjects, then community consultation is a process that lets investigators demonstrate respect, that is, engage in their half of the moral transaction, even in the absence of the specific identified subject. Giving respect is as important as being respected, and having investigators sit down and talk to people who could theoretically become subjects engenders respect for and grounding in the humanity of their subjects. Transparency is the purpose of public notification. Note that this is very different from the purpose of public education per se. Transparency is a public communication aimed at controlling the behavior of the investigator, the sender of the message, who is dissuaded from doing anything that he/she would not be willing to have spotlighted to the world. In contrast, public education is intended to change the behavior of the recipients of the message. Public education is successful if lots of people pay attention and learn something new, but transparency is successful if it prevents anybody from surreptitiously proposing any clinical research exempt from consent that the public would pay attention to, care about or object to [44].

Focusing on understanding, respect and transparency improves the value of community consultation and public notification to subjects, and allows IRBs to focus on more meaningful assessments of these processes. The focus is not 'Did the public understand and like the research?', but rather 'Did the investigator listen and learn something about the community?' It does not ask 'Was enough of the community respected?', but 'Did the investigator provide enough respect?' Not 'Did enough people learn about the trial?', but 'Did the investigator shout about the trial loud enough?' Assessments of the adequacy of efforts, therefore, require measures of what the investigators did, their processes, rather than their impact on the community. Ultimately, informed consent, the moral basis for exception, lies in the process, not the result.

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Clinical Trials of Surgical Devices for Neurological Disorders

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The widespread availability of commercially approved implantable devices has revolutionized the field of functional neurosurgery. While traditional neurosurgery would focus upon removing lesions such as tumors or repairing damage from vascular anomalies, the ability to modulate the function of neural structures using adjustable devices has created opportunities to treat disorders which ordinarily would be considered medical diseases.

The devices used for these therapies have generally fallen into 2 categories. The first and most broadly applied classes are neurostimulation devices. These include systems for peripheral nerve stimulation (including vagus nerve stimulation, VNS), spinal cord stimulation (SCS) and deep brain stimulation (DBS). Each of these are programmable, such that stimulation parameters, including contact utilization, pulse width, pulse amplitude and frequency, can often be individually tailored to optimize therapy and minimize stimulation-related adverse events. Pulse generator technology for these systems has evolved recently, with rechargeable batteries now available for spinal stimulation from several vendors. Each of these have been approved for specific applications within the nervous system, and as a result they have also been used recently for a variety of experimental applications which will be reviewed here. The other major class of devices is infusion devices. Currently, the only approved application of such devices is for infusion of drugs into the spinal subarachnoid space for spasticity or chronic pain, but the evolution of biological therapies in the brain is requiring development of experimental intracranial infusion systems. This chapter will focus upon the clinical trials with either justified currently approved applications of a variety of neurological devices as well as more recent trials testing experimental applications of approved or new devices for a wide range of functional neurological disorders.

Pain

Electrical SCS has been used for decades for treatment of pain. The best results reported are for treating pain of peripheral or spinal nerve injury, rather than pain caused by injury to the central nervous system. The response is thought to be based on a variation of the gate control theory wherein stimulation of large fibers entering the spinal cord inhibits activity in smaller fibers which carry pain information. The FDA approved spinal cord stimulation several years ago based on the numerous available publications and broad general practice in treating these conditions. Similar 'grandfathering' of DBS for chronic pain was not granted and this indication is still not officially approved for use.

Movement Disorders

In the US, DBS is currently approved for general use only for movement disorders. The first approved indication was for essential tremor, where DBS was found to be extremely effective at controlling the action tremor characteristic of this disorder [1]. However, the most frequent application of this technology is in the treatment of Parkinson's disease (PD), where high-frequency electrical stimulation is presumed to block transmission of electrical signals from the stimulated area, similar to what would occur if lesions were created. Thus, most DBS applications have been based upon prior success with lesioning. The 2 primary targets for DBS in PD are the subthalamic nucleus (STN) and globus pallidus interna (GPi) [2]. A recent multicenter randomized trial comparing STN DBS with best medical therapy demonstrated that STN DBS reduced the amount of time spent in the symptomatic 'off' state and reduced side effects of medical therapy (motor fluctuations and involuntary dyskinesias), while also reducing the total amount of medicine required to maintain benefit [3]. This reflects a general view in favor of the STN as the target of DBS for most PD patients, however, there are no good data which strongly supports one target over the other. Currently, there is a multicenter study which is randomizing patients to either STN or GPi DBS, which should clarify the rationale for choosing a particular target.

DBS has also been trialed for a variety of other movement disorders. Dystonia is a disorder characterized by twisting, writhing involuntary movements thought to be mediated by basal ganglia dysfunction, and can manifest as either focal, regional or generalized disease. Currently, DBS for dystonia has received conditional approval for use by the US FDA, but this still requires submission of an investigational device exemption to use in routine practice. GPi DBS is the main target for primary dystonias, based upon prior success of lesions (pallidotomy) [4]. Many small series and open-label studies have supported the efficacy of pallidal DBS in dystonia, although demonstrable benefit may not occur for several weeks or months compared with the relatively immediate response of PD and tremor symptoms to DBS. Recently, however, randomized

studies have been reported in which control patients are studied for a period of time with the DBS system off and these have also demonstrated significant improvements in objective motor symptoms and quality of life scales [5]. Primary dystonias appear to respond well to DBS, with some evidence that genetic forms of primary dystonia have the best therapeutic response. Cervical dystonia also seems to respond well to DBS in a recent small, single-blind multicenter series, but others have reported more variable results [6, 7]. Results with secondary dystonias (often resulting from ischemic or traumatic events) have been less encouraging, although some successes have been reported with GPi as well as thalamic DBS. However, there have been no substantial, definitive studies to clarify the role of surgery in secondary dystonia. Other applications of DBS include Tourette's syndrome, which has both a compulsive and a motor component [8]. Definitive trials to test the efficacy of DBS in this disease remain to be completed.

Epilepsy

Surgical intervention has long been an important therapy for medically refractory epilepsy. This has mostly involved ablation or resection of an identifiable focal brain abnormality. Many forms of epilepsy do not fall within this category, and there are also many lesions which cannot be safely resected even when demonstrated to be the cause of epilepsy. With this clear need for alternative therapies, and the lack of major advances in novel medical treatments, a larger variety of devices has been tested as epilepsy therapies than for any other neurological disorder. The most well-known epilepsy device, and the only device currently FDA approved for general use in epilepsy, is VNS. Although the mechanism of action remains unclear, some retrograde signal generated by unilateral electrical stimulation of the vagus nerve in the neck is clinically effective as a therapy for certain types of epilepsy. Several progressively larger and more definitive clinical trials demonstrated clear efficacy of this therapy, which led to FDA approval and widespread use over the past several years in routine clinical practice. One intriguing difficulty with the definitive studies was the slight change in vocal tone induced by stimulation of the vagus nerve. While not disabling, this does result in a notable change in voice, thereby obviating the possibility of performing a randomized trial with a blinded stimulation-off group. As a result, the randomized studies which led to device approval used a low-intensity stimulation group as a control, which also resulted in vocal changes but in theory was not therapeutically effective compared with the higher-intensity group [9]. While this did reveal a significant difference, the ultimate magnitude of potential benefit of VNS remains unclear, since a confounding influence of mild therapeutic benefit at low stimulation intensity cannot be eliminated.

In order to more directly intervene at the site(s) of seizure generation or propagation within the brain, 2 intracranial devices are currently being testing in large, multicenter studies. The same DBS device approved for treatment of PD is currently undergoing testing as a therapy for epilepsy [10, 11]. The target is the anterior nucleus of the thalamus,

which is in the center of Papez' circuit whereby seizures often propagate to the rest of the brain. Electrical stimulation in this area is not intended to stop seizure generation but rather block spread, such that a mild initial aura would be self-limited and not progress to a disabling generalized seizure. Following some promising preliminary data in small, open-label series, a large, multicenter study is currently near completion. For the first several months following bilateral implantation, patients were randomized in a double-blind fashion to either sham stimulation or to a single, standardized stimulation paradigm. Unlike VNS, DBS is blinded, since most patients have no noticeable persistent consequences of stimulation which might influence the integrity of blinding. Once the blinded phase is completed, stimulation is adjusted in an open-label, individualized manner in patients who are followed for the next 9 months. Data for the blinded phase are anticipated soon, but one concern with this approach is the possibility that even a successful trial may underestimate the effect size from the blinded phase if a single stimulation paradigm is not optimal for every patient. Another issue is the fact that simply by placing electrodes into this brain region causes seizure frequency decrease in some patients prior to electrical stimulation. Thus, a comparison between implantation with and without stimulation might not show a significant benefit if part of the beneficial effect occurred with damage to the anterior nucleus during electrode insertion.

The alternate approach is a novel responsive neurostimulation device which is being tested for the first time in human patients. While DBS stimulates tonically, based upon stimulation parameters input into a programmable pulse generator, responsive neurostimulation devices sense the onset of aberrant electrical activity and then fire electrical pulses in an attempt to quench the development of a frank seizure. This is the first device being tested which not only has an effecter component (a stimulator), but also a sensor component operationally linked to control the output. In the future, this concept could be broadly applicable to a variety of diseases where therapy can be delivered on demand based upon some physiological change in the brain. In this case, either a deep brain electrode and/or a surface cortical electrode can be attached to the combined sensor/pulse generator [12–14]. When a local electrical abnormality is transmitted through the electrode to the sensor, the spread and development of a full seizure is aborted. The sensor/pulse generator is not placed in the chest as with a DBS device, but rather it is curved and inserted into a recess which is drilled out of the skull so that the device remains local within the head. Pilot studies have shown some promise, and more definitive studies are currently underway [12–14]. Limitations to this approach include the sensitivity of seizure detection algorithms within the sensors and the accuracy of localization of the seizure focus.

Depression

Major depression is among the largest public health problems and a significant number of patients can be sufficiently refractory to medical therapy that more aggressive

intervention may be justifiable. Two devices are currently being applied to patients with major depression. The only device which is FDA approved for general use is the same VNS device used to treat epilepsy [15–17]. Since this does not involve intracranial surgery, it has been somewhat attractive from the standpoint of risk assessment. However, the relevance of the benefit reported in studies which led to FDA approval continues to be questioned. As a result, despite FDA approval following a somewhat controversial process, many insurers currently do not cover the use of VNS for depression. This highlights the importance of performing studies which not only result in FDA approval for a new device, but which are designed with endpoints which would be convincing to most practitioners and to third-party payers if met.

DBS is also being tested for depression. Functional imaging in human have identified several potential areas which are abnormally active in depression. Two of these, the subgenual cingulate cortex and the anterior limb of the internal capsule, have been targets for pilot studies of DBS for depression. Clinical data from pilot patients treated with subgenual cingulate DBS have been promising, along with appropriate improvements in functional imaging, with no major adverse events [18]. The anterior limb of the internal capsule has long been a target for both lesioning and DBS in patients with obsessive-compulsive disorder [19, 20]. While DBS had variable effects on the major symptoms of this disorder, demonstrable mood elevation was noted repeatedly in treated patients. Based upon this, several patients with depression have now been treated in a pilot study with DBS in the anterior limb of the internal capsule [20]. Larger pilot studies and eventual multicenter randomized trials are currently planned by at least 2 manufacturers to test DBS at both sites as treatments for major depression.

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Gene Therapy Clinical Trials in the Human Brain

Protocol Development and Review of Current Applications

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Gene therapy has long held great promise as a cutting edge technology to improve human disease. The completion of the human genome project and ongoing advances in understanding the molecular pathophysiology of many disorders provides opportunities to directly impact upon these mechanisms using genetic manipulation. Despite problems with public perception and isolated celebrated complications, gene therapy in the central nervous system (CNS) has evolved substantially in recent years and now is among the leading organ systems for new human gene therapy clinical trials. The surprisingly large number of clinical trials undertaken to test gene therapy in the human brain include treatments for brain tumors, Parkinson's disease (PD), Alzheimer's disease (AD) and 2 lethal pediatric neurogenetic disorders. This chapter will outline the basic science of gene therapy and the agents used for gene delivery, discuss the unique regulatory issues which influence progression of promising preclinical gene therapy results into a human clinical trial and then finally review the current state of human gene therapy clinical trials for CNS diseases.

Basic Science of Gene Therapy

Gene therapy methods can be generally subdivided into 2 classes: ex vivo and in vivo gene therapy. Ex vivo gene therapy involves genetic modification of cells outside of the body, usually in cell culture, prior to implantation into the patient. In the CNS, this has generally involved transplantation of genetically modified fibroblasts into a brain region to secrete a bioactive factor. In vivo gene therapy involves introduction of a gene directly into cells in the body to modify their function or influence survival. Naked DNA does not transfer well into cells and therefore application to humans

is limited. Similarly, lipid encapsidation of DNA (liposomes) has been used, but the technology remains fairly inefficient and there are some concerns regarding toxicity following introduction of large quantities of a liposome reagent which can sometimes act as a detergent and possibly dissolve myelin. Therefore, by far the most common method of gene delivery for in vivo gene therapy has been the use of genetically modified viruses as agents (vectors) for transfer of genetic material into host cells. Viruses exist largely to transfer their own genetic material efficiently into cells, where they then utilize and subvert cellular machinery to replicate and create thousands of new viral particles, which can then spread to other cells. The major accomplishment that has facilitated translation of in vivo gene therapy into human clinical trials, thereby harnessing the power of viral particles for efficient gene transfer, is the elimination of any toxicity due to viral replication or inflammatory reactions to viral proteins.

Regulatory Approval

Gene therapy is perhaps the most highly regulated area of human research in the US. For most areas of new research, an initial single-center clinical trial often requires only approval from an institutional review board. For certain types of new drugs or devices, additional approval from the US Food and Drug Administration (FDA) may be required before initiating even a preliminary or safety study. Both of these are in fact required for human gene therapy protocols. However, any study involving introduction of recombinant genetic material (DNA or RNA) into humans for any purpose (which includes any type of gene therapy) requires additional review by the Recombinant DNA Advisory Committee (RAC), which is an advisory committee of the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA). Any work involving recombinant DNA, regardless of whether it involves human, animals or simply cells, requires approval by an institutional biosafety committee, and therefore this is additionally required for human gene therapy studies and is not obviated by all of the other regulatory processes. Detailed guidelines for the RAC review process are available at http://www4.od.nih.gov/oba/. FDA review and approval guidelines are available for the office which regulates human gene therapy, the Center for Biologics Evaluation and Research (CBER), at http://www.fda.gov/CBER/gene.htm.

CNS Gene Therapy Applications in Human Clinical Trials

Brain Tumors

The first clinical application of gene therapy in the CNS was to treat brain tumors. One major approach to human brain tumor gene therapy is delivery of prodrug-activating genes to tumors. These gene products convert otherwise inert molecules into antineoplastic cytotoxic agents in situ, theoretically exposing tumor cells to very

high levels of active drug. The earliest and most popular such gene is the herpes simplex virus (HSV) thymidine kinase (TK) gene [1, 2]. This gene is the target of antiviral therapies such as acyclovir and gancyclovir, thymidine analogs which can be phosphorylated by HSV-TK. Once modified, these activated analogs can incorporate into growing DNA chains and block elongation, thereby selectively killing dividing cells. Another advantage of this approach is the so-called bystander effect, whereby the activated prodrug can diffuse out from transduced cells to nontransduced cells, thereby providing amplification of the antitumor efficacy [3, 4].

The first trials of HSV-TK gene therapy involved transfer of the gene into tumor cells using retroviral vectors. Most of these studies were phase I or II studies, and they primarily involved transplantation of retroviral producer cell lines into the cavity created following surgical resection of the tumor. Although some promise was seen in isolated patients in early-phase studies, neither complete regression of residual tumor nor the less restrictive measure of stability of disease were seen at any greater rate than conventional adjuvant therapies following surgery in most cases [5–10]. This was validated in a phase III study as well, which also showed an increased rate of intracranial hemorrhage and other complications in the gene therapy patients compared with controls [11]. Subsequent studies have used infusion of purified adenoviral vectors harboring HSV-TK in lieu of retroviral producer cells [12–15]. This approach has shown encouraging results and was even superior to the retroviral approach in a direct comparison in one clinical trial, while a subsequent randomized study demonstrated an increased survival in patients with resected gliomas followed by adenoviral HSV-TK gene therapy compared with control patients undergoing resection followed by conventional therapy [12–17]. This approach continues to be investigated.

Oncolytic virus therapy is another therapeutic approach that attempts to exploit the dividing nature of tumor cells against a background of nondividing, differentiated neurons and minimally dividing, replaceable glial cells [18, 19]. Many viruses destroy cells following replication, with the newly produced virions being released to infect surrounding cells, thereby amplifying the cytotoxic effect. Oncolytic viruses are modified such that they will replicate selectively in dividing cells so that they will destroy tumor cells while sparing normal tissue. The first clinical trials of oncolytic virus therapy in human brain tumors have utilized modified HSV [20]. Initial studies using different HSV mutants revealed fairly similar results, with good safety profiles and reduced tumor volume and/or extended lifespan beyond the expected in isolated patients [21, 22]. Although there have not been large follow-up studies with either virus, there is robust ongoing preclinical development of oncolytic HSV vectors which are adding potentially therapeutic genes to the viruses to amplify any effect while minimizing toxicity. A modified adenovirus called ONYX-015 contains a deletion in the adenovirual E1B-55K gene, which permits replication only in cells which do not have a functional p53 tumor suppressor gene [23]. Since most high-grade gliomas have extensive deletions or inactivating mutations in p53, and based upon results in other cancers, ONYX-015 was tested in human glioblastoma in an early-phase trial.

Although the safety profile was good, there was little evidence of therapeutic efficacy [23]. The avian Newcastle disease virus has also been modified for selective oncolytic activity within tumor cells, and this has been tested in a recently reported phase I/II study in 11 patients with glioblastoma [24]. Unlike other gene therapy studies for brain tumors, this oncolytic virus was administered via systemic intravenous infusion. No significant toxicity was encountered and no maximum tolerated dose was identified, despite evidence of profound immune responses to the virus within 1 month of treatment. There was evidence of a good response to therapy in several patients, with 1 patient having complete regression of tumor. If this were ratified in more rigorous follow-up studies, it would be a shift in traditional approach to brain tumor gene therapy, providing a nonsurgical option for patients.

Parkinson's Disease

Aside from cancer, gene therapy has been tested in human PD more than any other disorder. There are currently 3 active clinical trials of gene therapy for PD, with additional studies in planning phases. PD is characterized by the loss of dopaminergic neurons in the substantia nigra, leading to a reduction in dopamine inputs to target cells within the striatum and dysregulation of the downstream basal ganglia circuitry which regulate movement [25, 26]. While the cause of neurodegeneration in PD remains unknown, the anatomy and physiology of this disease is better understood than for many other neurological diseases. This permits the design of rationale therapies such as gene therapy.

Three approaches to gene therapy for PD are currently in clinical testing. All of these use adeno-associated virus (AAV) vectors as the gene delivery vehicle. In fact, the first demonstration that AAV vectors can be safe and effective for long-term gene transfer in the brain was performed in an animal model of PD nearly 15 years ago [27]. The first human trial of in vivo gene therapy for any adult neurodegenerative disorder involved infusion of an AAV vector with the glutamic acid decarboxylase (GAD) gene into the subthalamic nucleus (STN) [28]. GAD is the rate-limiting step in the synthesis of GABA, the major inhibitory neurotransmitter in the brain [29]. Following loss of dopaminergic input to the striatum, there is a dysregulation of the basal ganglia circuitry. The goal of this approach is to deliver the GAD gene to STN neurons, thereby allowing these neurons to produce GABA which would be released locally as well as through efferent connection to targets such as the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr). This should then re-establish GABA transmission not only to the local STN target but to larger portions of the basal ganglia circuitry in order to normalize the flow of information to subsequent structures such as the thalamus and cortex. The concept was validated by measuring evoked GABA release into the SNr following STN AAV-GAD gene therapy in a rodent model of PD [28]. Given the difficulty in translating some experimental therapies to success in humans, this approach attempts to capitalize on successful STN surgery in human PD, such as deep brain stimulation and lesioning [30–32].

A phase I study of AAV-GAD gene therapy for PD has recently been completed and detailed results have been reported [33, 34]. This study involved 12 patients with advanced PD who would normally have met criteria for deep brain stimulation. Since this was the first time that in vivo gene therapy was attempted for an adult neurological disorder, only unilateral therapy was approved based upon the belief that an unanticipated adverse event might be more devastating if an injury occurred to the same structure bilaterally. Since all patients had bilateral but asymmetric disease, the untreated symptomatic hemisphere was available in each patient for both clinical and functional imaging comparison. Thus, while not a blinded or placebo study, this was in fact a controlled study to the extent that a control was available for comparison, thereby offering an unusual opportunity to more extensively analyze functional outcomes in a phase I study designed primarily to determine safety. The primary outcome of this study demonstrated that infusion of AAV-GAD into the STN appears to be safe at the doses tested [33]. There also was a significant improvement in clinical ratings as measured by part III of the Unified Parkinson's Disease Rating Scale (UPDRS). The total body score significantly improved beginning at 3 months after surgery and continued for 1 year, both off and on medication. When analyzed by body side, the effect was largely restricted to the hemibody opposite the treated hemisphere in both conditions over the same time period. Functional imaging with flourodeoxyglucose PET scans also demonstrated significant improvements in the pathological metabolism of motor circuits in these patients over time, again restricted to the treated hemisphere [34]. This approach is currently beginning a phase II trial which will involve a blinded, control group with a partial-thickness burr hole to investigate possible placebo effects which were not addressed in the phase I study.

The second approach to gene therapy for PD is delivery of the neurturin gene to the striatum using an AAV vector. Neurturin is a growth factor in the GDNF family, which acts upon a primary receptor which is not present on dopaminergic terminals in the striatum, but which can also act very effectively upon GDNF receptors at somewhat higher doses [35–37]. Development of GDNF gene therapy for human use became difficult since the company controlling the intellectual property for this gene did not permit further development of any GDNF therapies after the failed recombinant GDNF infusion trial. Therefore, neurturin was pursued in an attempt to continue development of growth factor gene therapy for human PD without possible legal obstructions. Neurturin gene therapy appears to yield production at sufficient levels to be productive in the striatum, since both rodent and primate models have demonstrated substantial preclinical efficacy without any obvious adverse effects [35–37].

Based upon this preclinical success, AAV-neurturin has been tested in human clinical trials. The phase I study has been completed, exploring bilateral striatal infusion of AAV-neurturin in patients with advanced PD who were divided into low and high treatment doses. As with AAV-GAD, this appeared to be safe with no clear adverse events related to the therapy. Results have not yet been published, but presentations at national meetings have suggested significant improvements in numerous clinical

ratings in treated patients, including off medication UPDRS as well as improvements in total on time. Given the strong safety and encouraging efficacy profile, this study progressed to a phase II study and is the first gene therapy approach for PD to enter phase II. The study design is a 2:1 design, with 1 treated patients for each control, with controls again receiving only partial-thickness burr holes. At present, enrollment in this study has been completed and follow-up is planned for 1 year, at which time results will be unblinded and analyzed.

The final gene therapy approach in active human clinical trials again utilizes AAV to transfer the gene for aromatic acid decarboxylase (AADC) into the human striatum. AADC converts the dopamine precursor L-dopa to dopamine, and is the enzyme which is imaged with F-dopa PET [38]. Evidence suggests that increased striatal AADC can increase dopamine transmission in the striatum which can improve both the magnitude and longevity of response to L-dopa drug therapy [39–42]. A phase I study is currently ongoing using a single injection of AAV-AADC into the human striatum bilaterally. While clinical outcome data is still being evaluated and appears to be encouraging, some impressive functional imaging data has been presented at scientific meetings. F-dopa PET was used here, which is in fact a direct measure of gene transfer, since F-dopa is only retained following conversion to dopamine by AADC. So far, several patients appear to have substantial increases in striatal F-dopa uptake, particularly in areas targeted for gene therapy, suggesting ongoing gene expression and increased striatal dopamine production. The design of future studies based on this therapy at present remains unclear and likely will follow more extensive presentation of outcome data.

Alzheimer's Disease

AD is an age-associated neurodegenerative disorder which clinically manifests as a progressively severe dementia. Coincident with the primary AD pathologies is the loss of cholinergic neurons in the basal forebrain. These project to key regions responsible for learning and memory, and the drug therapies currently available to treat AD are in fact designed to increase cholinergic transmission in the brain [43, 44]. Nerve growth factor (NGF) has long been known as a powerful neurotrophic factor for basal forebrain cholinergic neurons, and this has resulted in the development of 2 gene therapy approaches which have reached human clinical trials.

The first trial involved ex vivo gene therapy and was the first trial of any type of gene therapy for an adult neurodegenerative disorder [45, 46]. In this phase I study, 8 patients were enrolled and underwent skin biopsies to obtain fibroblasts, which were then modified to express NGF and were then expanded. Patients initially underwent stereotactic injections awake, but 2 patients developed intracranial hemorrhages which appeared to be caused by movement during surgery. One of these patients died several weeks later from a cardiopulmonary event, and subsequent patients were more heavily sedated or anesthetized during surgery with no further complications. There were no complications referable to the cell transplantation or the gene. The methodology for performing ex vivo gene therapy is technically very complex,

difficult and costly, however, and standardizing creation of cell lines from skin biopsies for each patient is nearly impossible. Since inception of this trial, AAV gene therapy technology advanced substantially over time and had already been utilized in 2 other human CNS gene therapy clinical trials. Therefore, based upon these facts and the above results, a second phase I study was initiated which used AAV to deliver the NGF gene directly into neurons of the basal forebrain [47]. Results of this study have not yet been published but appear to be encouraging, and a subsequent phase II study using this approach is expected to be initiated soon.

Summary

The longstanding promise of gene therapy of all types has yet to be fully realized. After a difficult period, however, developments in recent years have created a resurgence of interest in the clinical utility of this unique technology. To the casual observer, the number of studies in the brain which have entered clinical trials is often surprising. The excellent safety record of the numerous studies outlined above and several others not reviewed here, combined with encouraging preliminary efficacy data suggests that gene therapy will continue to evolve as a therapeutic option in clinical trials for CNS disease. With the explosion in human trials for these disorders, it is very possible that the next few years will finally see sufficient success in advanced trials of one or more approaches to justify FDA approval and use in general clinical practice.

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Magnetic Resonance Imaging for Surrogate Outcomes and Patient Selection

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The role of magnetic resonance imaging (MRI) has been rapidly developing and expanding in the evaluation, treatment and investigation of neurologic diseases. Neuroimaging is employed in clinical trials in a variety of ways. For example, imaging studies can be used to confirm diagnosis, to provide insight into prognosis and to monitor disease progression. A particularly exciting area of development is the use of MRI in clinical trials of new therapeutic agents for neurologic disease. The most promising applications of advanced neuroimaging in this setting are: (1) as surrogate outcome measures of treatment response and (2) to optimize patient selection for therapies.

MRI as a Surrogate Marker of Neurologic Disease

Neuropathologic MRI findings in diseases including dementia, multiple sclerosis and ischemic stroke are actively being evaluated as biomarkers and potential surrogate outcome measures for use in clinical trials. In dementia, MRI hippocampal volume measurement is the most studied imaging variable with a number of phase III trials of stabilization therapies using MRI atrophy measures, both hippocampal and whole brain, as secondary outcome measures [1]. Quantitative MRI lesion volume measurements have also been used as a measure of progression in vascular dementia.

Atrophy measures of both gray and white matter have also been used extensively in treatment trials for multiple sclerosis (MS) and are currently considered the preferred marker for monitoring MS-related neurodegeneration [2]. Importantly, atrophy progression correlates with increasing disability. However, existing therapies have shown little effect on atrophy progression, and the study duration and sample sizes necessary to demonstrate a therapeutic effect on this slowly progressing marker have not been extensively evaluated.

On the other hand, gadolinium (Gd)-enhancing and T2-weighted lesions have been demonstrated to be reliable surrogate markers of inflammation and acute relapse, and have become the standard primary outcome measure for phase II MS trials of anti-inflammatory agents. However, the utility of this surrogate marker is limited by a lack of clinical correlation with evolution of disability. Moreover, these neuroimaging markers have not been sufficiently replicated, standardized and validated to serve as primary outcome measures for phase III therapeutic trials [2].

In acute ischemic stroke, MRI provides clinically important information including confirmation of the diagnosis, demonstration of stroke location and potentially stroke subtype, and identification of the site of vascular occlusion. It is also helpful in predicting prognosis based on MRI findings including size and location of infarct and perfusion abnormality, presence or absence of vessel recanalization, and burden of prior cerebrovascular disease. Moreover, initial diffusion lesion volume correlates well with final infarct volumes and has also been demonstrated to correlate with clinical and functional outcomes, particularly in the anterior circulation [3, 4]. Baseline MR perfusion lesion volumes also correlate well with final infarct volume and clinical outcomes, and in fact correlate better than baseline diffusion lesion volumes [4]. Therefore, perfusion- and diffusion-weighted imaging are being explored as surrogate markers of outcome in phase II clinical stroke trials to detect a signal efficacy. For example, in trials of neuroprotective and recanalization therapies, it is expected that an effective treatment would lead to smaller final infarct volumes compared to placebo. The use of surrogate markers can serve to substantially reduce the sample sizes necessary to demonstrate 'proof of concept' in order to determine if a larger phase III trial should be pursued [5].

MRI for Patient Selection

MRI as a tool to optimize selection of candidates for therapies may be particularly useful in settings such as acute stroke where the number of patients who will benefit from recanalization therapies decreases progressively over time. Therapeutic decisions can be based on individual patient pathophysiologic information including presence of an ischemic penumbra, target vessel occlusion and exclusion of hemorrhage. Several recent or ongoing ischemic stroke clinical trials include MRI criteria for patient enrollment. The phase II Desmoteplase in Acute Ischemic Stroke (DIAS) trial selected patients for treatment who had a diffusion-perfusion mismatch on baseline MRI and demonstrated a positive dose-response relationship for good clinical outcome and reperfusion following IV demosteplase within 3–9 h from onset [6].

However, the optimal study design to prove the clinical utility of this imaging-based selection approach is to have all eligible subjects undergo a baseline MRI and then have treatment randomization assigned according to MRI presence or absence

of diffusion-perfusion mismatch or ischemic penumbra; the key feature being that all subjects are included for treatment assignment, regardless of MRI pattern. This design was used for the Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study that treated subjects with intravenous recombinant tissue plasminogen activator 3–6 h after onset, though it did not include a placebo arm [7]. The DEFUSE investigators demonstrated that of patients with a baseline diffusion-perfusion mismatch those who had early reperfusion were more likely to have a favorable clinical response than those who had not. Furthermore, subjects with a large diffusion lesion and/or a large perfusion lesion with severe delay, termed 'malignant profile', had a low rate of favorable clinical response and experienced fatal intracranial hemorrhage following early reperfusion. In the MR and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, a multivariate model is used for determining ischemic penumbra, incorporating variables from both the diffusion and perfusion imaging data (presented at the 2007 International Stroke Conference, San Francisco, Calif., USA). Acute ischemic stroke patients within 8 h of onset are randomized to mechanical embolectomy or standard medical management stratified by penumbral pattern to test the hypothesis that the presence of substantial penumbral tissue on baseline MRI predicts the subjects most likely to respond to recanalization by mechanical embolectomy.

Clinical stroke trials like DIAS, DEFUSE and MR RESCUE represent the new approach of studies testing the utility of advanced MRI techniques for patient selection in the setting of evaluating the efficacy and safety of acute stroke therapies.

Future Directions

Newer techniques including MR spectroscopy and functional MRI have potential as tools for monitoring neurologic disease activity and therefore for use in drug development, but will require additional validation and correlation with clinical symptomatology [1]. Other advances including an MR contrast agent with ultrasmall particles of iron oxide which uptake in macrophages are beginning to be explored as biomarkers of neurologic disease as well [2].

Summary

The development of advanced MRI techniques has not only improved our ability to diagnose neurologic disease, but has also allowed us to move beyond the limitations of external clinical signs and symptoms in monitoring disease course or testing new therapies. Having a window into the active disease pathophysiology through MRI has fostered clinical trial designs that have the potential to be more efficient and successful in expanding our therapeutic options.

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Computed Tomography

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Computed tomography (CT) was first introduced by Godfrey Hounsfield in 1972. The advent of CT proved to be a major advance in neuroimaging, dramatically augmenting the power of the clinician to detect and diagnose diseases of the brain and spinal cord. Although magnetic resonance imaging (MRI) has superseded CT in many areas of neurology due to its advantages (better image resolution, no use of radiation and less toxic contrast agents), brain CT still plays a critical role in neurology because of its lower cost and widespread availability. CT is particularly useful in the emergency setting where rapid image acquisition is critical. With the development of helicoidal technique and multidetector scanners, CT has remained a powerful tool and is essential for the management of cerebrovascular and other diseases.

In designing a clinical trial, the decision to use a CT platform, as opposed to MRI or some other imaging, may be intrinsic to the science (for example, CT remains superior for evaluation of bony structures) or be related to generalizability (CT is widely available) or cost considerations.

Ischemic Stroke

In the hyperacute phase of evaluation of stroke-like symptoms, a noncontrast CT (NCCT) is usually ordered to exclude or confirm intracerebral hemorrhage (ICH). CT has high sensitivity for detection of hemorrhage and is the most cost-effective strategy in this setting. NCCT is less sensitive for detecting hyperacute ischemic changes. The sensitivity of NCCT for brain ischemia increases after 24 h, but in a recent review of 15 studies, early signs of ischemia were detectable in 61% (standard deviation: ±21%) of the studies done in the first 6 h after symptom onset [1]. Early signs of infarction include hypoattenuation of the cerebral parenchyma, obscuration of the lentiform nucleus, loss of gray-white matter differentiation in the basal ganglia, cortical sulcal

effacement, loss of insular ribbon, obscuration of the sylvian fissure and hyper-attenuation of large vessels ('hyperdense middle cerebral artery sign'). These signs not only help in the diagnosis and therapeutic decision making, but also have prognostic significance in predicting a poor outcome [1, 2]. Mistakes are common, though, occurring in 20% of cases even in an optimal setting [3]. Standardized methods have been developed to achieve a better rate of recognition and reduce the interobserver variability. The use of a semi-quantitative scale, such as the Alberta Stroke Program Early CT Score (ASPECTS) [4], improves sensitivity and specificity for predicting functional and radiographic outcomes [5, 6]. ASPECTS can predict the patients likely to benefit from intra-arterial therapies. Unfortunately, ASPECTS has limited utility, too. Recent data suggest that using the ASPECTS analysis of NCCT does not identify patients who will benefit for thrombolysis, nor is the ASPECTS score a predictor of symptomatic intracranial hemorrhage in patients treated within the 3-hour time window [6].

There are many reasons to image the extracranial and intracranial vasculature in stroke patients including identifying and grading vascular stenoses, diagnosing vascular diseases such as aneurysms, vascular malformation and dissections, and evaluation of the dural sinuses. Vascular imaging can be accomplished through several methods including transcranial Doppler, MR angiography and CT angiography (CTA). The first helical CT scanners developed for this purpose became available in 1988. Since then, there has been considerable progress with novel contrast injection schemes, rapid postprocessing algorithms and the emergence of new multidetector technology using 16-, 32- and, most recently, 64-slice scanners. This breakthrough in technology has sparked a true renaissance in this area. The greater availability of CT scanners, rapid image acquisition times and less susceptibility to motion make CTA a very attractive tool for better managing acute stroke patients. In the acute setting, multislice CT scanners provide tremendous benefit by identifying patients with large vessels occlusions who might benefit from more aggressive reperfusion interventions.

Although there was some concern in the past about the safety of using contrast agents in patients during the acute phase of stroke, published data demonstrate that the use of nonionic contrast agents is safe and does not adversely affect the prognosis [7]. The risk of contrast-induced nephropathy is very low, and it is extremely rare for CTA-induced contrast-induced nephropathy to precipitate renal dysfunction requiring dialysis [8].

CT perfusion techniques also offer the opportunity to obtain quantitative blood volume maps. By tracing the first pass of contrast through the brain, maps of relative cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume can be constructed. CBF is the volume of blood flow through the vessels, including the large conductance vessels, arteries, arterioles, capillaries, venules, veins and sinuses. Cerebral blood flow is expressed in units of ml/min/100 g of tissue. Cerebral blood volume is the volume of blood in the vasculature, and is expressed as milliliter/100 g tissue. Blood traverses the vessels through different path lengths and different resistors; therefore, the transit time from the arterial inlet to the venous outlet

is not uniform. Rather, there is a distribution of transit times averaged to yield the MTT. MTT increases in ischemic brain due to the flow of blood into ischemic tissue via collateral flow. Stratification of patients according to CBF at the time of onset may provide a better indicator of the risk of hemorrhagic transformation, the major complication of thrombolytic therapy [9, 10].

Intracerebral Hemorrhage

Up to 15% of first-ever strokes are due to ICH. The 30-day mortality rates are high, 35–52%. NCCT remains an important tool in the evaluation of patients with ICH and is equivalent to MRI in identifying the presence and location of acute bleeding, quantifying the size of hemorrhage and monitoring hematoma growth (which is associated with a poorer prognosis). In order to identify patients who would be good candidates for future therapies aimed at preventing hematoma expansion, it is important to have a marker to predict hematoma growth. It has recently been suggested that contrast extravasation during CTA predicts hematoma expansion in ICH [11]. Although the specific mechanism of contrast extravasation remains unclear, CTA now has a potential role in risk stratification as well as diagnosis.

Subarachnoid Hemorrhage

NCCT remains a key study for the diagnosis of subarachnoid hemorrhage. The sensitivity is near 100% when performed in the first 12 h of bleeding and declines in a stepwise fashion to approximately 58% by day 5. NCCT can miss small quantities of hemorrhage and thus the technique used is very important. Very thins cuts (3 mm) through the base of the brain and a scanning plane parallel to hard palate are helpful in minimizing the false-negative results [12]. CTA is extremely useful for the detection of cerebral aneurysms and has significantly reduced the need for conventional transfemoral angiograms. In some centers, it has replaced conventional angiography as a diagnostic tool, as multislice technology rivals digital subtraction angiography diagnostic for accuracy [13].

Conclusion

CT still remains a useful diagnostic tool for evaluating cerebrovascular symptoms due to its speed, simplicity and accuracy. The advent of the multislice technology has created novel applications which have enhanced vascular imaging and created a multitude of research opportunities for exploration of this technology in outcome prognostication and selection of cases for specific interventions.

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Positron Emission Tomography Imaging

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In this chapter we are going to explore the role of positron emission tomography (PET) imaging biomarkers in clinical trials. The basic requirements for a successful radiotracer biomarker are: (1) sensitivity and specificity to treatment; (2) if the biomarker is sensitive to normal aging during long-duration studies, then a well-defined relationship that can be incorporated during data analysis; (3) ease of use, including radiotracer availability and a study design that involves minimal demands on the patient for increased compliance; (4) simplified data analysis, preferably objective computer-aided algorithms; (5) understanding of tracer pharmacokinetics and pharmacodynamics for increased confidence in data interpretation; and finally (6) using imaging to help select a homogeneous patient population for increased power (minimal number of subjects required). Even though we will discuss the application of PET techniques in the field of Parkinson's disease (PD), similar approaches to other neurological diseases can be inferred.

With a high prevalence rate and an aging population, PD has been the focus of a variety of treatment strategies including drugs, stereotaxic surgery, embryonic and stem cell replacement procedures, and lately, gene therapy. For all of these treatment options, it is important to establish biomarkers that reflect the efficacy of the procedure. Efforts are underway to develop novel imaging biomarkers that include parameters derived from new radiotracers as well as different analytical procedures to quantify changes in brain network activity as indices of the treatment response.

One handicap of clinical trials of new therapeutic agents for PD has been the inclusion of atypical parkinsonian patients who often do not respond to treatment. We will present screening approaches to identify such patients prior to randomization.

Diagnosis of PD

PET studies measure the uptake and conversion of [^{18}F]fluorodopa (FDOPA) to [^{18}F] fluorodopamine by the enzyme dopa decarboxylase in the striatal dopaminergic nerve

terminals. A number of prior studies have shown that the assessment of nigrostriatal dopaminergic function using FDOPA PET yields quantitative parameters, which correlate with independent disease severity measures and can discriminate early-stage PD patients from normal control subjects [1]. More importantly, it has been shown that in vivo striatal FDOPA measurements correlate with dopamine cell counts measured in postmortem specimens [2].

The development of radiotracers which bind to the dopamine transporter (DAT) on nigrostriatal dopaminergic terminals has led to another means for directly imaging the nigrostriatal dopaminergic system with PET or single photon emission computed tomography. The most extensively studied agents in this category are the cocaine analogues, such as 2-β-carbomethyl-3β-(4-iodophenyl) tropane and its fluoroalkyl esters [3]. DAT is expressed on dopaminergic nigral terminals, and quantification of striatal DAT appears to be directly related to the extent of nigral cell degeneration [4]. Since DAT may not be as subject to upregulation as dopa decarboxylase, it may be a more sensitive marker for nigrostriatal cell loss in parkinsonism and normal aging [3].

The presynaptic vesicular monoamine transporter (VMAT) is involved in the packaging and transport of monoamines to storage vesicles located in nerve terminals. Radioactive ligands that bind to VMAT sites such as [^{11}C]dihydrotetrabenazine can be used as a reliable measure of monoaminergic and nerve terminal density [5]. VMAT binding appears not to be affected by antiparkinsonian dopaminergic medications such as levodopa, giving it potential advantage over FDOPA and DAT. However, this method has comparably low signal to noise and may not be specific for dopaminergic terminals [6].

Radioligands such as [^{11}C]raclopride (RAC) and [^{11}C] N-methylspiperone can provide sensitive measures of local D_2 receptor density. However, RAC is easily displaced by endogenous dopamine. Indeed, changes in striatal RAC binding may reflect endogenous dopamine levels instead of D_2 receptor density [7]. Nevertheless, this attribute may allow RAC to be utilized with pharmacological and behavioral activation as a means of assessing endogenous dopamine levels. This application may provide information regarding the dynamic functions of the intact nigrostriatal dopamine terminals in movement disorders.

Differential Diagnosis and Computer-Aided Diagnosis

Atypical parkinsonian syndromes such as striatonigral degeneration, progressive supranuclear palsy and corticobasal ganglionic degeneration are often difficult to distinguish from PD on clinical grounds alone. However, these disorders appear to have specific regional signatures on fluorodeoxyglucose (FDG) PET imaging. On the other hand, striatal FDOPA uptake is reduced in both typical and atypical parkinsonian movement disorders [1].

One hundred and thirty-five parkinsonian patients were referred to our PET center for FDG PET to determine whether their diagnosis could be made accurately based upon their scans. Imaging-based diagnosis was obtained by visual assessment of the individual scans and also by computer-assisted interpretation. All image processing and analyses were performed using Statistical Parametric Mapping (SPM99; Wellcome Department of Cognitive Neurology, London, UK) [8]. The results were compared with 2-year follow-up clinical assessments made by independent movement disorders specialists who were blinded to the original PET findings. We found that blinded computer assessment agreed with clinical diagnosis in 92.4% of all subjects. Concordance of visual inspection with clinical diagnosis was achieved in 85.4% of the patients scanned. This study demonstrates that FDG PET performed at the time of initial referral for parkinsonism accurately predicted the clinical diagnosis of individual patients made at subsequent follow-up [9].

Accurate differential diagnosis is also of particular importance in the conduct of treatment trials in parkinsonism. Inadvertent inclusion of atypical patients into pharmacological trials for PD is likely to reduce statistical power by increasing the heterogeneity of the treatment cohorts. Thus, the use of imaging techniques like FDG PET may improve the power of future clinical trials by promoting group homogeneity.

Brain Networks

Although the primary pathological abnormality in PD is confined to the substantia nigra, the degeneration of dopaminergic projection neurons from the substantia nigra to the striatum results in widespread alterations in the functional activity of the basal ganglia. Specifically, the functional organization of the basal ganglia predicts that the loss of inhibitory dopaminergic input to the striatum results in increased inhibitory output from the putamen to the external globus pallidus, diminished inhibitory output from the external globus pallidus to the subthalamic nucleus, and functional overactivity of the subthalamic nucleus and internal globus pallidus resulting in decreased output from the ventrolateral thalamus to the cortex. These functional alterations in basal ganglia activity are accompanied by alterations in regional cerebral glucose metabolism and blood flow [1].

The measurements of local rates of metabolism or regional activation responses may not fully describe the complexities of neural systems (networks) involved in a neurodegenerative process and their modulation with treatment. These networks may be represented as patterns of metabolic covariation among spatially distributed brain regions, which can be altered by behavioral activation or the presence of disease.

Principal component analysis (PCA) has been used in the analysis of PET data to contrast groups in the same resting state and, more recently, in brain activation paradigms. One of these approaches, known as the scaled subprofile model, is a general form of the 2-way factor analysis of variance model [10]. In scaled subprofile

modeling of rest state data, PCA is employed to identify regional metabolic covariance patterns from metabolic scans obtained from combined samples of patients and normals. This form of analysis is blind to subject class designation and utilizes the variance across the entire population (normals and patients) to identify specific patterns associated with the disease state. These patterns reflect covarying regional increases or decreases in brain function relative to a baseline defined by the normal population.

The topographies of these covariance patterns correspond closely to specific physiological and anatomical regional networks known to be involved in disease processes and are highly reproducible across patient populations and tomographs [11]. Subject scores (PCA scalars) for regional covariance patterns can be computed on a prospective individual case basis from functional brain images and can be correlated with individual differences in independently measured clinical or physiological indices. The reproducible findings of relative lentiform-thalamic hypermetabolism in PD, associated with motor cortical hypometabolism, supports the hypothesis of excessive pallidothalamic inhibition as the main functional substrate of parkinsonian bradykinesia. This unique pattern can be used as an accurate marker for the differential diagnosis of parkinsonism.

We developed a modification of the original network algorithm to compute subject scores for a predetermined topographic profile from individual PD patient scans data on a prospective case-by-case basis [12]. This computational algorithm, referred to as topographic profile rating, is critical to the clinical application of network analysis in disease severity assessment and differential diagnosis.

Surgical Therapies

Quantitative functional brain imaging markers may be suitable as outcome measures for the surgical treatment of PD. Indeed, we have found that PET may serve as a useful tool in choosing optimal candidates for certain surgical interventions such as pallidotomy [13]. The therapeutic effects of this procedure, as well as the more effective and reversible deep brain stimulation technique, has been associated with significant PD-related spatial covariance pattern modulation [14]. Indeed, the degree of reduction in PD-related spatial covariance pattern expression with treatment has been found to correlate consistently with clinical improvement [14].

Dopamine Cell Implantation

The implantation of fetal mesencephalic dopamine cells into the striatum of PD patients has been considered as a neurorestorative treatment. We originally reported findings from a cohort of 19 advanced PD patients undergoing fetal nigral

implantation as part of a randomized blinded comparison with sham-operated controls [15]. Significant and similar increases in putamen FDOPA uptake were observed in both younger (≤60 years) and older (>60 years) subjects, but correlation with clinical outcome was significant only in the younger group [16].

Five of these subjects developed severe dyskinesias in the absence of or with only minimal amounts of dopaminergic medication. In addition to the posterodorsal zone in which a prominent reduction in uptake was present at baseline, the dyskinesia group also displayed a relative increase ventrally, in which preoperative dopaminergic input was relatively preserved [17]. This suggests that cell implantation should be confined to the dorsal putamen where larger preoperative decreases are observed.

Intraputaminal Glial Cell Line-Derived Neurotrophic Factor Infusion

Glial cell line-derived neurotrophic factor (GDNF) has potent restorative effects on dopaminergic neurons. Open-label trials in PD patients have been conducted in which GDNF was delivered into the putamen directly through surgically placed catheters. No serious side effects were observed after 1 year and a 39% improvement in off-medication motor subscore of the Unified Parkinson Disease Rating Scale was noted [18]. Medication-induced dyskinesias were reduced by 64% and were not observed off medication during chronic GDNF delivery. PET imaging with FDOPA demonstrated a significant 28% increase in putamen dopamine storage after 18 months. Based on this phase I trial, a double-blinded placebo-controlled study was sponsored by Amgen Inc. The results of this trial were not as promising and, in 2004, Amgen withdrew GDNF from all clinical trials [19].

Conclusion

An integrated approach utilizing network quantification methods and dopaminergic imaging can help elucidate the relationship between localized neuronal attrition and the expression of widely distributed functional brain networks. These complementary PET techniques may greatly advance the understanding of the pathophysiology of PD and the functional changes that occur with successful therapy.

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Clinical Research Training Opportunities and Elements

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Educational opportunities for elucidating the benefits of clinical trials to advance medical science as well as to aid in trial participation by physicians, recruitment of subjects to trials and implementation of trial results, happen at multiple levels of medical education including medical school, internship, residency, fellowship and into academic careers. Education of health care providers ranges from a few lectures per year to formal class work and from formal degree programs to passive education as a result of learning on the job via participation in multiple clinical trials. Such educational programs address concerns regarding the lack or ineffectiveness of clinical research training in medical schools and residencies. The larger problem of recruiting patients to clinical trials may reflect the views of nonacademic neurologists and neurosurgeons, who do not necessarily consider clinical research to be a part of the principal components of care of patients with neurological diseases. Barriers to implementation of educational programs include financial barriers and personnel resources as well as time, particularly during residency.

At the level of medical school education, articulating and demonstrating the opportunities in either basic science or clinical research by medical faculty helps to recruit students to academic careers and fosters clinical research participation even in those destined for nonacademic positions. A survey of 145 graduates from Penn State College of Medicine, participating in clinical research, found that as time spent actively participating in clinical research increased, the more likely those physicians would cite a medical school research experience as an important influence on their current participation in clinical research [1]. Simply having the opportunity to participate in clinical trials or having a research mentor in medical school was not, however, correlated with research participation status later in the individual's career. Such data do not prove or refute the benefit of such formative clinical research opportunities, but at least highlight an area of potential impact. Promoting active student participation in actual clinical trials is one simple way for neurologists and neurosurgeons to aid their own cause.

To establish a pervasive ethos that clinical research represents a valid treatment option beyond clinical practice and to encourage active participation about entering subjects into clinical trials, these attitudes should be encouraged at an early stage of medical education. This is particularly true regarding medical and surgical specialties that care for patients with many progressive and difficult-to-treat diseases where nihilism is pervasive. Some introductory level biostatics and epidemiology is usually taught in medical school. These courses could stress clinical research as a component of treatment options that aids in the advancement of medical science and is potentially beneficial for patients with medically refractory illnesses. Unfortunately, the typical level of training in medical schools does not effectively prepare students to become clinical researchers. This course work should be substantially expanded so as to foster clinical research by incorporating more comprehensive epidemiological and biostatistical methods. Such information should also become a part of United States Medical Licensing Examination testing so as to spur more in-depth training in medical school curricula. Consideration should be given for stand-alone programs for formal training in clinical training, such as an intervening year in medical school to be developed. Student fellowships in pathology that require an extra year of training already exist in many medical schools, and possibly this program could act as model for clinical research training programs.

In consideration of neurology and neurosurgery training programs, Residency Review Committee guidelines mandate that 'an active research component must be included in each program'. This requirement is fulfilled in various ways. As training programs include a spectrum from purely clinical to heavily NINDS-funded research, some programs require residents to do clinical research projects from initial conception to publication while virtually all programs at least rely on regular journal club events to review literature. An NINDS workshop focused on these issues in 2006 and led to the proposal of implementing several possible educational programs at the residency level.

Proposals included creating a mentor for enhancing clinical research awareness at each residency program. It was proposed that using resources such as the evidence-based medicine (EBM) tool kit being developed by the American Academy of Neurology, meant for programs without EBM faculty or a formal EBM curriculum, could be useful. Teaching modules could be developed and distributed for use in the journal club settings seen at most programs. Incentives for residents and the training programs could include monies for travel and registration at national meetings, coming from program training budgets or perhaps national organizations. The NIH, the Residency Review Committee (RRC) or the American Association of Neurology (AAN) could provide certification of competency in interpretation of literature and in understanding of the systems-based practice of clinical research. This system would have to rely on examinations and/or objective evidence of successful participation in clinical research. Analogous to broadening United States Medical Licensing Examination testing on clinical research topics for medical students, in-service and board examinations in neurology and neurosurgery could be similarly broadened to address the issue at the residency level.

Another proposal from the workshop was to create separate residency tracts for those interested in research and those interested in clinical practice. There was concern that the research tract residents might be favored, pushing the clinical tract residents further away from research. This approach may foster more clinical research careers, but it does not seem likely to promote improved referral or participation in studies from community neurologist and neurosurgeons.

One fundable approach to fostering clinical research awareness in neurology and neurosurgery training programs is through K30 awards. Clinical Research Curriculum Awards or K30 awards, awarded to over 50 academic institutions currently, are developing and improving didactic programs aimed at educating and training competitive clinical researchers. These programs are open to qualified candidates with various degrees, including MD or DO, and even others, including medical students 'who could benefit from a core curriculum for clinical research' [2]. These awards stipulate up to 2 years of formal coursework including a core curriculum of topics such as biostatistics, epidemiology, medical ethics, grantsmanship and clinical trial design. The educational credit hours fall short of the typical number of credit hours required for a masters degree in public health, but the program guidelines suggest institutions may provide support to complete master or doctoral level training. Participation can theoretically occur during medical school, residency and fellowship training or as new faculty member. Allowing residents to participate in these programs can present scheduling problems, since it may necessitate adding time to residency, perhaps an extra year, if clinical duties are not reduced. Subspecialty fellowships combining clinical training and masters degree programs in public health exist as well.

An excellent resource for physicians of all levels of education and practice is the website www.clinicaltrials.gov. This site includes summary lists of American and international clinical trials, both observational and interventional, with federal or private funding. Both physicians and patients can search for studies by key word and even by geographical criteria. Searching neurological terms such as multiple sclerosis, stroke or amyotrophic lateral sclerosis provides listings of over 2,000 trials. The ease of use and clinical utility make this site a resource that should be a part of any educational program to promote clinical research participation.

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Appendix

Protocol Outline[1]

The following sections should be included in the protocol:

- Précis
- Introduction
- Objectives
- A diagram of the subject entry from screening to end of study
- Inclusion and exclusion criteria
- Plan for monitoring subjects and criteria for withdrawal of subjects from the study
- Human subject protections
  - Rationale for subject selection
  - Recruitment plan and procedures
  - Justification for the exclusion of women, minorities and children (if applicable)
  - Evaluation of benefits and risks/discomforts of participation
  - Description of the consent process
  - Plan for maintaining privacy and confidentiality of subject records
- Adverse event reporting plan
- Data safety monitoring plan
- Protocol monitoring plan
- Data management/quality assurance plans
- Plan for research use and storage of human samples, specimens or data
- Statistical analyses to be carried out
- Remuneration/compensation
- Scientific references if applicable

Manual of Operations Outline[1]

The Manual of Operations details the study procedures and includes the following sections:

- Study protocol or synopsis
- Staff roster
- Study organization and responsibilities
- Training plan
- Communications plan
- Recruitment and retention plan
- Study design diagram
- Screening and eligibility criteria and processes
- Informed consent and Health Insurance Portability and Accountability Act

- Study intervention
- Blinding and unblinding (masking or unmasking)
- Evaluations and follow-up
- Concomitant medications
- Safety/adverse event reporting
- Data and safety monitoring responsibilities
- Study compliance
- Data collection and study forms
- Data management
- Quality control procedures
- Study completion and closeout procedures
- Policies
- Maintenance of Manual of Operations

Additionally, if the study involves a drug intervention, the package insert for an approved drug or the investigator's brochure for an investigational product must be included as an appendix.

Data Safety and Monitoring Plan[1]

The following sections should be included in the data safety and monitoring plan:

- Trial safety
  - Potential risks and benefits for participants
  - Adverse event and serious adverse event collection and reporting
  - Protection against study risks
- Interim analysis
- Data safety and monitoring
  - Frequency of data and safety monitoring
  - Content of data and safety monitoring reports
  - Data safety and monitoring board membership and affiliation
  - Conflict of interest for data safety and monitoring board
  - Protection of confidentiality
  - Data safety and monitoring board responsibilities

Resources

Common data elements[1]:
http://www.nindscommondataelements.org/CRF.aspx
Best clinical practices:
https://www.ctnbestpractices.org/proxy/training/training/ctnbp/Intro%20to%20Clinical%20Research/Start.html
Clinical trial toolbox[1]:
http://www.nia.nih.gov/ResearchInformation/CTtoolbox/

[1] These resources were developed by KAI Research.

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