Overview

Fueled by the aging global population and economic growth of developing countries, the demand for new, safe, and effective therapeutics for neurological conditions in the US and globally will increase dramatically over the next generation. Scientific discovery and clinical investigation are critical for developing and evaluating new treatments and can have substantial public health benefits. However, several challenges confront the development of new therapies. Some of these are generic (e.g., rising costs of drug development, misaligned incentives, recruitment of research participants) and some are specific to neurological conditions (e.g., slow course of neurodegenerative conditions, limited availability of biomarkers). Along with these challenges are potential advances that could accelerate development, including scientific progress in the platforms that support discovery and development (e.g., in genetics and biotechnology) and in the more active participation of patients and advocacy groups that can help fuel the development of new treatments, even for the rarest of disorders. Beyond drugs for neurological conditions, clinical trials will examine other promising therapeutic interventions, including devices and procedures. Meeting the great need for effective therapeutics will not only require continued scientific discovery but also modifications in commercial incentives, improvements in the conduct of clinical trials, and advocacy and participation by the growing number of individuals affected by neurological conditions.

The burden of neurological disease is growing globally

The increase in life expectancy that occurred in the twentieth century has led to substantial increases in the number of individuals with neurological conditions, a trend that is expected to accelerate during this century. In China, for example, the number of individuals over 65 will more than double from 110 million in 2010 to nearly 240 million by 2030 (Figure 1.1) [1]. This change in population structure – occurring in many countries – will increase the burden of neurological disease globally [2]. Cerebrovascular disease currently accounts for the majority of global disability for neurological disorders as measured in disability-adjusted life years and will account for 4% of total disability-adjusted life years globally by 2030 [2]. Other conditions, such as Alzheimer’s disease and Parkinson’s disease, will see the number of individuals affected increase, and that increase will be greatest in developing countries [3], [4]. The number of individuals with Parkinson’s disease in the world’s most populous nations is projected to more than double from approximately 4 million in 2005 to over 8 million in 2030 (Figure 1.2) [4].

The growth in the burden of neurological disease coupled with the economic growth of developing economies, especially in Asia, will increase the global demand for neurotherapeutics. As the income of countries increases (as measured by per capita gross domestic product), countries tend to devote a greater proportion of their gross domestic product to health care [5]. Access to care for individuals with neurological conditions is severely limited in many parts of the world; however, with increasing income, a larger proportion of individuals in developing economies will have the resources necessary to benefit from current and future treatments for their conditions.

Clinical investigations can have a substantial public health impact

The development of new drugs and treatments is costly. The current estimate for the successful development of a drug, including opportunity costs, is $800 million,
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[6] and the estimate for the successful development of a new neurological drug exceeds $1 billion [7]. While the resources required to develop a new therapy are substantial, the societal return on this investment in improved health can be even larger.

One economic study suggests that the societal return from improved health on a handful of proven interventions would justify total US health care expenditures, including the research to produce the new therapies [8]. A detailed analysis of clinical trials funded by the National Institute of Neurological Disorders and Stroke found that the public return on investment in clinical trials has been substantial [9]. In that study, the investigators examined the costs associated with 28 clinical trials and resulting health care expenditures from adoption of interventions with benefit and compared those costs to resulting improvements in health over 10 years following completion of the trial. The study found that the total cost of the clinical trials was $335 million and that over ten years the total cost associated with the clinical trials and adoption of the beneficial intervention was $3.6 billion. However, the estimated net health benefit was $18.1 billion, which was calculated as the incremental health benefit from...
the intervention (measured in quality-adjusted life
years and then multiplied by the per-person annual
gross domestic product) projected over ten years. The
net societal benefit was, therefore, $15.5 billion ($18.1
billion less $3.6 billion), a 40-fold return on the research
investment.

The results of the study highlight two additional
important findings (Table 1.1). First, only a small
minority (6 of the 28 or 21%) of the clinical trials were
associated with any incremental societal benefit. And,
second, most (80%) of the societal benefit came from
two clinical trials. These points highlight the substan-
tial risk of drug development for neurological con-
tions and the need to reduce and spread that risk
effectively.

Developing new and novel drugs
is increasingly difficult

In addition to the inherent risks involved in clinical tri-
als, the challenges of translating scientific advances into
new therapeutic advances are increasing. From 1994 to
2003, funding for US biomedical research from industry
and government doubled [10]. Funding grew at a
slower rate from 2003 to 2008 and now exceeds $100
billion annually [11]. However, despite this increase
in financial support, the number of novel treatments
approved by the US FDA has remained relatively stagn-
ant [10, 11], even when allowing for time lags between
when the investments were made and when new prod-
ucts might be expected [12]. Thus, the return on the
research investment over at least the last 10 years –
measured as new therapies – is decreasing.

Coupled with the lack of increase in the number of
new drugs is the rising cost of drug development [13].
In 1979, the estimated cost for the clinical development
of a new drug was $54 million. By 2003, that number
had increased nine-fold to $467 million [6]. Larger
scale and longer duration trials may account for some
of the increase in costs.

Another large cost and barrier to the development
of new therapies is the recruitment of research partici-
pants [14]. Public participation may be the most crit-
ical challenge. Despite bearing the burden of disease
and expressing a strong desire to participate in clinical
trials, the public is not always encouraged to partici-
pate in research [15]. Only 7% of Americans report
their physician ever suggested that they participate in a
research study [15], and when they do participate, par-
ticipants often are not informed of the research results
[16, 17]. Dedicated efforts to informing individuals of
research opportunities, reducing the travel burden of
<table>
<thead>
<tr>
<th>Study Description</th>
<th>Treatment costs ($ per use)</th>
<th>Incremental net benefits ($ per use)</th>
<th>Quality-adjusted life years per use</th>
<th>Total net uses</th>
<th>Quality-adjusted life years</th>
<th>Incremental net benefits</th>
<th>10-year projections</th>
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<tr>
<td>Randomized Indomethacin Germinal Matrix/Intraventricular Hemorrhage Prevention Trial</td>
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<td>−2 857 340</td>
<td>1.00</td>
<td>6 038 099 978</td>
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<td>3 131 189</td>
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<tr>
<td>Diazepam for acute repetitive seizures</td>
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<td>3123</td>
<td>297 326</td>
<td>4038</td>
<td>955 140 007</td>
<td>4 288 862 203</td>
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<tr>
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<td>891 839 458</td>
<td>891 839 458</td>
<td>−891 839 458</td>
<td>−891 839 458</td>
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<td>−891 839 458</td>
</tr>
<tr>
<td>Asymptomatic Carotid Artery Stenosis Collaborative Study</td>
<td>0.75</td>
<td>6074</td>
<td>6074</td>
<td>−6074</td>
<td>−6074</td>
<td>−6074</td>
<td>−6074</td>
</tr>
<tr>
<td>Stroke prevention in atrial fibrillation</td>
<td>0.25</td>
<td>1 051 756</td>
<td>1 051 756</td>
<td>1 051 756</td>
<td>0.25</td>
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<tr>
<td>North American Symptomatic Carotid Endarterectomy Trial</td>
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<td>1819</td>
<td>1819</td>
<td>1819</td>
<td>35 457</td>
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<td>1819</td>
</tr>
<tr>
<td>Tissue plasminogen activator in ischemic stroke</td>
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<td>178 517</td>
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<td>−10 500</td>
<td>−10 500</td>
<td>−10 500</td>
<td>−10 500</td>
</tr>
</tbody>
</table>

NA: not available. Incremental net benefits include trial treatment costs, and quality-adjusted life years valued at 2004 per capita gross domestic product $40 310. Products of per use and net use data vary slightly from 10-year projections because of rounding.

The clinical trials are from a set of 28 phase 3 clinical trials whose funding was completed before January 1, 2000 and for which data on use, health benefits, and costs were available. Reprinted with permission from [9].

Table 1.1: Estimated use, health benefits, treatment costs, and incremental net benefits from eight clinical trials funded by the National Institute of Neurological Disorders and Stroke.
studies [18], and communicating research results [19] can facilitate participation in clinical trials.

The public is increasingly looking for roles beyond passive participation as research ‘subjects’ in clinical trials. Some, especially those affected by rare conditions, are creating their own research networks [20], funding their own studies [21], and even forming their own virtual biotechnology firms. Active participation by the public can lead to creative solutions to many of the challenges industry currently faces and may ultimately reduce the costs of development and increase the impact of proven therapies.

Developing neurotherapeutics has its own set of challenges

Many of the challenges of drug development are particularly acute for treatments of neurological conditions. Like biomedical research as a whole, increases in funding for neuroscience research have not translated into an increase in the number of novel treatments [22]. Particular challenges include a paucity of validated biomarkers [23] – with the notable exception of imaging for multiple sclerosis – that can assess efficacy (or lack thereof) of experimental therapeutics, longer duration of clinical trials [7], and higher failures rates due to lack of efficacy [24].

The scope of investigations for neurological treatments is growing

The scope of clinical trials for neurological conditions is rapidly expanding to address orphan indications, biologics, medical devices, surgeries, and comparative effectiveness studies. Interest in orphan drugs is increasing, due in part to advances in the understanding of rare neurological disorders and the high profile commercial success of some drugs for orphan indications. For example, the drug imiglucerase (Cerezyme) for Gaucher’s disease generated nearly $800 million of revenue in 2009 [25].

The design of the pivotal studies that have led to the approval of drugs for orphan indications within neurology differs from that for non-orphan indications, and this may reduce the costs of clinical development. For example, 68% of drugs with orphan indications did not have at least two pivotal studies that were randomized, double-blind, or placebo-controlled even though the standard regulatory requirements are the same for products with an orphan drug designation [26]. By contrast, 100% of pivotal studies for non-orphan indications included at least two randomized, double-blind, placebo-controlled studies.

Scientific advances have also led to the development of new biological therapies for neurological conditions. Some of these have addressed conditions with previously very limited treatment options (e.g., botulinum toxin for focal dystonia) and others have demonstrated substantial efficacy (e.g., natalizumab for multiple sclerosis). However, along with these benefits have come risks, including manufacturing and safety. The emergence of significant safety concerns (e.g., progressive multifocal leukoencephalopathy) with natalizumab [27] has led to restrictions on its use and has increased the need and interest for long-term safety monitoring of drugs [28].

In addition to drugs, clinical trials frequently evaluate devices for neurological conditions. The number of devices approved by the FDA is actually more than ten-fold greater than the number of drugs [29]. Part of this difference is due to the lower US regulatory threshold for the approval of devices compared to drugs [29, 30]. The FDA classifies devices into three levels. As described in more detail in the chapter on device regulation, Class I devices are generally low-risk devices and Class II devices represent an intermediate risk. Both are generally exempt from premarket review by the FDA unless the manufacturer desires to market the device for a new indication. Class II devices are evaluated by a Premarket Notification, or 510(k), process that only requires that the new device is as safe and effective (‘substantially equivalent’) to another marketed Class II device. Most 510(k) submissions, which the FDA has 90 days to review, do not require clinical data to demonstrate substantial equivalence. Class III devices, which comprise only 5% of products, are more complex and high-risk, and must demonstrate a ‘reasonable assurance of the safety and effectiveness’ for their desired indication [30]. Some class III devices, such as deep-brain stimulators, have undergone rigorous assessments in clinical trials [31, 32].

The scope of clinical trials for neurological interventions also includes surgeries. High quality data on surgical interventions, such as temporal lobe resections for epilepsy [33], are critical to understanding their relative risks and benefits in the target populations. The challenge, like that for drugs and devices, is that once benefit has been established for a given target population in a rigorous study, the intervention quickly spreads to populations for which the benefit is lower or...
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not established. For example, while carotid endarterectomy offers significant benefit for symptomatic carotid disease [34, 35], the vast majority are done for individuals with asymptomatic disease for whom the benefits are much smaller and less clear. Similar to outcomes of device trials, surgical outcomes in clinical trials is a function of the investigators – often the most experienced surgeons operating in the most experienced centers – which raises questions about the generalizability of results to the broader population.

A final frontier for clinical investigations in neurology is comparative effectiveness studies. Comparative effectiveness research ‘is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care [36].’ While comparative effectiveness has gained more attention recently due to the $1.1 billion dollars in funding for these studies as part of the American Recovery and Reinvestment Act of 2009 [37], comparative effectiveness studies in neurology are not new. For example, about half of the 31 trials the National Institute of Neurological Disorders and Stroke funded prior to 2000 could qualify as comparative effectiveness research [38]. Among these trials were the comparison of low-dose warfarin plus aspirin vs. standard warfarin for stroke prevention for those with atrial fibrillation and a comparison of valproate vs. phenytoin for seizure prophylaxis after brain trauma. Trials like these, including trials comparing ways health care is delivered, will likely become more common in the future, especially because many of the top priorities for comparative effectiveness research identified by the Institute of Medicine involve neurological conditions [37].

Conclusions

The need and impact of clinical trials for neurology will increase in the future. Demographic and economic factors will fuel this demand and increase the geographic reach of clinical trials, which will raise its own challenges [39]. Continued scientific advances will allow better characterization of clinical conditions, new biomarkers will provide for more efficient and informative investigations, and increased public participation will lead to more creative funding and organization of clinical trials. The scope of clinical trials for neurology is rapidly expanding and has moved past drugs to devices, surgeries, and comparative effectiveness research. The ultimate success of these expanded investigations will require continued attention to rigorous methodology, measures to reduce the burden of participation, and expanded collaboration among industry, other sponsors, and investigators.

Acknowledgement

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References

Chapter 1: The impact of clinical trials in neurology

Introduction

Clinical development can be described as a process of asking and answering specific scientific and operational questions at specific times to learn about the risks and benefits of drugs or devices that may be useful for human health. Good clinical development requires the involvement of skilled scientists from many different disciplines working together under the guidance of a thoughtful plan that describes the program of research that will provide the data to answer these questions. Because the human, monetary, and time resources required to initiate and complete a clinical development program are significant, every such plan involves careful articulation and sequencing of the questions to be answered.

It is especially important at the outset to state clearly the ultimate objective for a clinical program and how the approach being undertaken may improve on what is currently known or practiced. Is the purpose of the trial to improve prognostication, or provide a better understanding of disease or biomarkers? Is the objective to demonstrate efficacy, safety, or economic advantages of a drug or device over current standards of care? Is there an expectation that the approach will offer improved survival or long-term outcome? Each of these objectives requires a very different clinical plan and sequence of experiments.

Typically, clinical programs are described as involving several specific phases (phases I–IV). By convention, this scheme provides some understanding of the kinds of trials employed and the subjects being studied, but the specific phase does not provide a good basis for understanding exactly what kinds of questions are being asked. Trials typically thought of as being performed during a specific phase (such as a human volunteer study, phase 1) can be performed at multiple times during a development program. It is preferable when creating a clinical development plan to organize one's thinking into stages of information gathering that will accomplish specific objectives.

Table 2.1 provides an illustration of this concept and shows that, in the simplest way of thinking, clinical programs can be divided into early, middle and late stages. Although there is some overlap, each development stage has unique objectives that are required to progress further into development. The information collected at each stage builds upon what has already been learned and influences how decisions are made with respect to study design, population, indication, and program size.

What follows is a brief description of the questions that are typically asked and answered at each stage of clinical development and the kinds of clinical trials that are utilized in the effort. This chapter focuses specifically on the activities and questions that are involved in the generation of data to support the registration and approval of a drug candidate. The ultimate objective in this case is to demonstrate the use of a drug for management of symptoms or signs of an illness or to cure or slow progression of a disease. However, a similar framework and discipline can be used when ordering the sequence of questions for medical devices or for more academic clinical programs aimed at improving diagnosis, gaining better understanding of a disease state, or prevention of illness. Lastly, some important sources of information apart from the general scientific and medical literature are provided.
Table 2.1 Early, middle, and late development: objectives and examples of studies performed

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Early</th>
<th>Middle</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human pharmacology and biomarker exploration</td>
<td>‘First in human’, single and multiple ascending dose trials (‘phase 1’)</td>
<td>Targeted special safety studies in patients and volunteers</td>
<td>Special formulation pharmacology; drug-drug interaction studies; drug metabolism in renal and liver impairment</td>
</tr>
<tr>
<td>Exploratory efficacy and safety studies</td>
<td>Early, ‘first in patient’ studies</td>
<td>Dose-ranging efficacy and safety studies in patients (‘phase 2’)</td>
<td>Dose-ranging studies in new indications</td>
</tr>
<tr>
<td>Confirmatory efficacy trials</td>
<td>Seamless exploratory dose ranging and confirmatory efficacy</td>
<td>Pivotal confirmatory trials in primary indication; comparative efficacy trials (‘phase 3’)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic use studies, new indications expansion</td>
<td>Comparative efficacy trials</td>
<td>New indications, expanded population studies, combination trials (‘phase 4’)</td>
<td></td>
</tr>
</tbody>
</table>

**Early stage clinical development**

Early stage clinical research involves the design and conduct of studies aimed at understanding the basic human pharmacology of a drug. The program of early research is built upon knowledge gained from preclinical in vitro and in vivo experiments that define and justify an initial assessment of potential benefit and risk to human subjects. Clinical studies are then designed and performed to produce data that will enable initial determinations of safety and tolerability, pharmacokinetics, pharmacodynamics, and aspects of drug action and CNS penetration for the drug.

Every early stage clinical development program requires information derived from basic laboratory and animal experiments that define the fundamental pharmacologic properties of a drug. Basic information about the biological target, cellular pathways and the biochemical mechanism of action should be known. Information about the potency and selectivity of the compound for its target and the nature of concentration vs. response relationships is critical to the design of an early clinical program. Typically, data is available from more than one in vivo efficacy model that provides justification for exploration in humans. This data should include information about the time course of onset and duration of effect, dose vs. response characteristics, and the no-pharmacologic effect dose. Any information on biomarkers from in vivo models is also enormously useful at this stage.

In addition, safety and toxicology data from both in vitro and animal testing is needed to justify exposure in humans. Data from acute and chronic studies in animals as well as safety pharmacology studies help to define the dose range that can be used safely in humans and can highlight specific toxicity issues that may need to be monitored. In certain settings, special studies examining the potential for reproductive toxicity and carcinogenicity are required. Additional information on drug metabolizing enzymes, drug metabolites, the potential for drug interaction, and initial estimates of preclinical pharmacokinetics help to define parameters for early studies. When they are available, data from animals on pharmaceutical properties such as absorption and bioavailability are also useful in helping to design an early clinical program.

The main goals of early clinical studies are to provide initial assessments of safety, tolerability and pharmacokinetics and to estimate the dose range that will be deployed in later trials. This is usually accomplished through a combination of single ascending dose and multiple ascending dose trials that help to determine the maximum tolerated dose and regimen that provides adequate drug exposure for the proposed indications.

The key objectives of single ascending dose studies are to define safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. The dose range deployed usually covers approximately two logs and...
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is framed by a starting dose that is a fraction of the preclinical pharmacologic no-pharmacologic effect dose (NOPED) in the most appropriate or sensitive species and limited to a top dose that is guided by the preclinical exposure (drug concentration in plasma) at the no-adverse effect level (NOAEL). Although designs are highly variable, as many as 6–8 dose levels are used with dose increments typically >2-fold at the lowest doses and <2-fold at the highest doses. Commonly, about eight subjects are exposed in each dose cohort at a placebo-to-drug ratio of one to three. Close assessments of vital signs, hematology and blood chemistry, electrocardiography, and adverse events are collected in each cohort and advancement to the next dose level is allowed only after thorough review of these data. Intensive plasma sampling for pharmacokinetics is also performed in each cohort although these data are not available before advancement to the next dose level. At study end, an assessment is made of the overall tolerability and safety across the examined dose range along with any defined dose-limiting toxicity whether defined by adverse event or laboratory evidence. Detailed analysis of pharmacokinetic samples adds to the profile of the medication. This information is then used to help define design parameters for multiple ascending dose studies.

Multiple ascending dose studies extend observations on human pharmacology to longer periods of dosing. Again, the key objectives are to provide data on safety, tolerability and pharmacokinetics with prolonged dosing. In most studies, the duration of dosing ranges from 7 to 14 days with dosing frequency determined by the pharmacokinetic parameters defined in single-dose studies. Typically, 4–5 dose levels are examined in the single ascending dose study, with the dose range covering a little over 1 log.

Single and multiple ascending dose human pharmacology studies are usually conducted in healthy volunteers whose age may reflect the target population for the intended indication for the drug. Healthy volunteers are often preferred at this stage since the assessments of the tolerability and pharmacokinetic profile of the drug are less likely to be contaminated by disease-related adverse events and concomitant medications. However, there are several situations where early assessments of human pharmacology should be supplemented by data from the target patient population.

For some medications the tolerability profile in patients differs markedly from that in healthy volunteers. For example, patients with chronic epilepsy and schizophrenia who are chronically exposed to anticonvulsant or antipsychotic medications respectively, typically report fewer central nervous system adverse events than normal volunteers exposed to the same doses of a new medication. To ensure an accurate determination of the tolerable dose range, during early development both single-dose and multiple-dose studies are conducted in parallel in patients and normal volunteers. The combined data set provides the best overall initial picture of safety, tolerability and pharmacokinetics: studies in normal volunteers provide an assessment of normal human pharmacokinetics and determine which adverse events can reasonably be attributed to drug exposure; studies in patients provide a more accurate assessment of the tolerable dose range. Other studies specifically designed to characterize drug–drug interactions and effects on pharmacokinetic parameters can be performed to provide information about effects of concomitant medications used in patient populations.

Some initial studies in humans can only be conducted in patients. Medications with substantial potential toxicity risks such as cytotoxic or genotoxic drugs cannot be administered to normal volunteers and for this reason, early studies are conducted in patients. The most common setting where this occurs is in oncology drug development where initial single- and multiple-dose studies are virtually always conducted in cancer patients. Examples from neurological therapeutics include the use of specific B-cell depleting therapies for multiple sclerosis and immunotherapeutic vaccines for Alzheimer’s disease [1, 2].

Data generated from the kinds of experiments described thus far provide an initial picture of the human pharmacology of a drug. Ideally, early research efforts should also provide evidence of drug exposure at the target site of action over a period of time that is consistent with what is believed to be needed for efficacy in the human disease state. Further confidence is gained by demonstrating that the drug binds to the target at the site of action and that binding to the target results in a measurable pharmacologic effect. In these respects, wherever possible both single- and multiple-dose studies should include measures of central nervous system penetration and pharmacodynamic properties of drugs that are related to both primary and secondary mechanisms of action. Conducting these kinds of early assessments in patients rather than healthy volunteers may be easier to justify ethically and may generate data that is more relevant for decision-making.