The 2008 William M. Feinberg Lecture
Prioritizing Stroke Research
S. Claiborne Johnston, MD, PhD

Abstract—Stroke is a tremendous burden to health worldwide both in the developed and developing world. Current levels of research funding do not adequately reflect this burden, particularly when expected increases in stroke rates are considered. Of course, an investment in stroke research is only justified if a return can be expected. The ultimate goal of stroke research is to reduce the burden of disease, and clinical trials are the clearest expression of the value of research because their results can directly impact health. In a review of stroke trials funded by the US National Institute of Neurological Disorders and Stroke, we found that the overall impact of the trials was dramatically positive and justified the entire research budget of the Institute. Nonetheless, there were obvious opportunities for improvement. Methods for selecting trials to fund could be improved and better aligned with disease burden and potential impact. Furthermore, clinical trial costs are increasing rapidly and reversing this trend must be a priority. More creative and systematic approaches to defining the research agenda and enhancing trial methods could substantially accelerate the rate of discovery and increase the impact of those discoveries on public health. To get there, we desperately need more research on research—meta-research—on topics not just relevant to stroke, but to the study of all disease. *(Stroke. 2008;39:3431-3436.)*

Key Words: cost of illness ■ health policy ■ research impact ■ resource allocation ■ stroke care

Research is an investment. Capital is spent and a return is expected, at least on average. In the private sector, identifying good investments consumes much of the financial services industry. Similar attention has not been given to the public investment in research. Funding decisions are often removed from consideration of the potential value of the return, and stroke research has suffered because of this. An ideal research portfolio should prioritize studies by their potential impact, recognizing that diversification is important, as it is in any investment portfolio, and that the costs and risks of these investments will vary. Of course, measurement of the return on the biomedical research investment is not trivial because the benefits may not be immediately obvious. Ultimately, biomedical research should improve health or reduce costs of care and its success should be measurable in these terms.

Placing stroke research into this framework, as one of many investment options in a biomedical research portfolio, 4 major questions are important in determining the position of stroke research: (1) Does stroke receive its fair share of the research investment? (2) What has been the return on the investment? (3) Can we do a better job prioritizing research? (4) Can we make research more efficient?

Does Stroke Receive Its Fair Share of the Research Investment?

For clinical research, the impact of a study is correlated, at least loosely, with the burden of disease. The more people with a disease, the greater the population that can benefit from the findings of a new study. Of course, diseases impact individuals differently, and those diseases that are more deadly and disabling will account for a greater overall burden.

Worldwide estimates of the burden of stroke are staggering. Stroke ranks as the number 3 killer worldwide with an estimated 5.7 million deaths in 2005, over twice the number attributed to HIV/AIDS.1 It is also one of the most disabling conditions with an estimated loss in 2005 of 51 million disability-adjusted life-years (DALYs), a measure of premature disability and mortality equivalent to 1 year of life without disability (Table).

Funding for stroke research has not fully reflected its burden of mortality and disability. Ten years ago, an analysis of funding from the US National Institutes of Health (NIH) showed that among several tested measures of disease impact, the burden of DALYs in the developed world most closely correlated with disease-specific research funding. By this metric, stroke was substantially underfunded with the $120

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From the Neurovascular Service, Department of Neurology, University of California, San Francisco, Calif.
Correspondence to S. Claiborne Johnston, MD, PhD, Department of Neurology, Box 0114, University of California, San Francisco, 505 Parnassus Avenue, M-798, San Francisco, CA 94143-0114. E-mail clay.johnston@ucsfmedctr.org
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million spent representing approximately half of what would be appropriate if funding were fully aligned with disease burden.² In contrast, funding for HIV/AIDS was approximately 10-fold greater and breast cancer approximately 5-fold greater than would be expected based on burden of DALYs. A similar disconnect has been reported for European countries with substantial research investments.³

In responding to public concerns about research funding priorities, the Institute of Medicine proposed in 1998 that the NIH track measures of disease burden and use them to strengthen the association with disease-related funding.⁴ We are currently re-evaluating the alignment between research funding and disease burden now a decade after this recommendation. In a preliminary analysis of these data, it appears that stroke remains underfunded, but the gap is closing, with $342 million in funding in 2006, 20% less than would be expected if funding were aligned with the burden of DALYs in the developed world.

One could argue that funding should anticipate future disease burden because results are delayed and more applicable to expected disease burden 10 or 20 years later. Such a delay could also explain why infectious diseases tend to receive a greater proportion of research funding. However, this argument does not appear valid. Stroke rates are increasing as the population ages with more dramatic shifts expected in the developing world. By 2030, the World Health Organization projects that deaths from stroke will increase by 37% to 7.8 million per year.¹ The World Health Organization estimates that stroke deaths will increase by 61% in the lowest income countries over the next 25 years compared with an increase of 11% in the highest.¹ In a separate analysis projecting trends in US stroke rates forward, unless existing treatments are used more effectively or new treatments are developed, stroke deaths in the United States would be expected to double by 2032 from rates in 2002 primarily due to the rapid aging of the population.⁵ Although deaths due to HIV/AIDS are projected to increase even more dramatically worldwide, stroke deaths still outnumber HIV/AIDS deaths in 2030 based on World Health Organization projections.¹ The story is a little different in terms of DALYs, with the expected impact of HIV/AIDS increasing more than 2-fold by 2030 and stroke increasing by 20% (Table), but these differences still would not account for the disproportionately large funding for HIV/AIDS and other infectious diseases. Projected disease burden in 2030 might account for triple funding of research for HIV/AIDS today compared with stroke, but in reality, the difference is 9-fold with 2005 NIH funding for HIV/AIDS research at $2921 million compared with $342 million for stroke.⁶

Thus, based on burden of disease and anticipated future burden, stroke research is underfunded. Of course, burden of disease is not the only factor that should influence funding levels. A perception that stroke research has less value in terms of its potential impact on disease could also explain underfunding.

What Has Been the Return on the Investment?

Biomedical research should ultimately lead to improvements in health and greater efficiencies in health promotion and care. For basic research, these benefits are distant and uncertain. However, for clinical research, and clinical trials in particular, the impact on health is more direct and potentially measurable. Furthermore, one can argue that basic findings are only translated to palatable benefits when they have been extended through translational studies to clinical trials. In fact, clinical trials account for a substantial proportion of the NIH budget. Currently, 4383 registered ongoing trials are funded by the NIH with overall expenditures of $2.8 billion in 2006, more than 10% of the NIH budget.⁶ ⁷ The National Institute of Neurological Disorders and Stroke (NINDS) spent $74 million on 26 randomized trials in 2004, several of which were stroke-related (Scott Janis, NINDS, personal communication). Thus, although it is currently impossible to measure the impact of the complete research portfolio, estimation of the impact of clinical trials is possible and is likely a reflection of the manifest benefits of a research program.

We previously evaluated the impact of the NINDS program of clinical trials.⁸ We found that the overall program was highly successful with substantial benefits in improved health well worth the cost of the research investment and the...
costs of the changes in healthcare delivery the trials dictated. For this current article, we used the original methods to evaluate the impact of stroke trials in particular and the subsequently stated results summarize our new findings.

Between 1966 and 1999, 12 of 28 trials funded by NINDS were devoted to stroke, accounting for $237 million of a total of $335 million in funding for trials converted to 2004 dollars. The stroke trials included 5 that found the intervention superior to control,\textsuperscript{9–13} 2 that found control superior,\textsuperscript{14,15} and 5 that found no difference.\textsuperscript{16–20} For 6 of these, data are available to estimate the impact of the trial on public health and economics (Figure).

The impact of the trials was dramatic. Over a 10-year period after funding completion, the trials improved health by generating an estimated additional 466 000 quality-adjusted life-years in the United States. Although they were responsible for increased expenditures of $3.2 billion during the 10-year period, including the costs of the trial and healthcare costs related to implementation of the findings, these costs were well worth the benefit in health by even very conservative valuations of health improvements. Valuing quality-adjusted life-years at gross domestic product per capita, a conservative approach that recognizes that greater expenditures result in an overall economic loss and are not sustainable for a society,\textsuperscript{21} the total return on investment was a net gain of $15.1 billion at 10 years for an investment of $237 million, a tremendous return unmatched by the best performing mutual funds. In the overall clinical trials portfolio of NINDS, stroke trials performed extremely well. This return is greater than the entire expenditures of NINDS, for basic and clinical research, during the period of study.

Private investment in biomedical research by the pharmaceutical and biotechnology companies has not produced the same returns for unclear reasons. More broadly, the overall success of pharmaceutical industry research has been disappointing in the last several years with funding increasing dramatically but very few new drugs and even fewer truly new drugs once the copycats and extended indications are eliminated from the count.\textsuperscript{22,23} The agents selected to take to clinical trials have not necessarily been those with greatest promise,\textsuperscript{24} but the true cause for the poor return on private investment in stroke research is unclear.

Thus, the public investment in stroke research has been very worthwhile with total returns justifying the entire research budget—basic and clinical—of the NINDS. Private investment has not yielded the same returns for unclear reasons.

Can We Do a Better Job Prioritizing Research?

Given the success of stroke trials and the NINDS portfolio of trials in general, the process for selecting trials appears to be working.\textsuperscript{25} However, results of 6 of the 28 trials included in our study accounted for nearly all the gains from the entire program. One wonders whether we could do an even better job in selecting interventions to test in trials and in prioritizing target populations and diseases. Science strives to be objective and measurement is one of the key tools in this quest. Metrics for public health impact of clinical trials are just now being developed.\textsuperscript{26} Although some are based on qualitative descriptions, newer methods have distilled results down to a few key measurable outputs.

The vast majority of trials funded by the NIH and NINDS are investigator-initiated, so the trial portfolio depends largely on their interests. This investigator pool doing trials is relatively small because there are few with adequate training, leadership skills, and foolhardiness to propose such randomized trials.\textsuperscript{22} Among the proposals received, favorable peer review may depend more on the qualifications of the principal investigator and details of the trial design than on the significance of the research question or the potential of the trial to impact health or scientific knowledge. Disparities between disease burden and research spending should not be a surprise, then, because there is little oversight of public health impact or distribution by disease.\textsuperscript{2} Thus, the current
processes for defining the portfolio of clinical trials are imperfect and fail to acknowledge the importance of these large investments and their potential to impact public health and costs.

Metrics used to evaluate the impact of trials such as those we used to estimate the impact of prior randomized trials can also be used to assess the potential impact of a planned trial. Whether a trial has occurred or is planned, the impact can be projected from estimates of the population affected, the impact per person, and the costs. Of course, the task is more difficult for planned trials because the model inputs are not derivable from observations but must come from opinion. For example, the probability that a trial will result in positive findings is obviously crucial to its value as an investment and expert opinion is the only viable source for its estimation. Inaccuracies and biases are common with expert prediction, so great care will be required in collecting and collating expert opinion to accommodate the uncertainty in prediction with as little bias as possible. Still, groups tend to predict results better than any specific expert. Therefore, methods of pooling opinions on predicted trial outcomes should be more reliable than proposers' estimates and than the opinions of a small number of peer reviewers.

The NINDS is leading the effort to make trial selection more rationale in its ImPACT pilot program. The program seeks to create validated models and procedures to systematize the estimation of potential trial impact. Although just getting started, the program may initially only produce more reliable estimations of impact for use by NINDS leadership or to better inform peer review. Once more established and validated, metrics from these models could also be used to evaluate briefer trial proposals, focusing initially on public health impact and portfolio balance and less on specific details of the trial design and leadership, which could be worked out more collaboratively later. Such an approach could increase the flow of ideas and proposals and improve the final quality of the trials funded.

Optimizing funding decisions for clinical trials could have a major impact on the overall public health effects of public trial funding. Even a small increase in the success rate, when considered as health and cost impact, of publicly funded clinical trials could generate substantial increases in the rate of discovery and in the overall benefits to society. The ImPACT program is clearly a step in the right direction in attempting to accelerate discovery and health benefits. A more rational approach to selecting trials is likely to benefit patients with stroke because more explicit modeling of the impact of research will illustrate the benefits of studying stroke given its great burden.

Can We Make Research More Efficient?
An investment is more attractive if, for a given return, the initial capital expenditure is lower. For the research investment, these costs include the initial underlying basic research, translational research, and clinical trials. There are opportunities to make each of these stages more efficient, but trial costs account for the largest proportion and may represent the easiest target for increasing efficiency.

Developing new therapies for neurological diseases is very expensive. For each new neurological drug coming to market, an estimated $1016 million is spent on development, including costs for failed drugs. Because less than one fourth of compounds tested in clinical trials actually make it to market, the total investment in making an effective drug is proportionally greater. Of course, the hit rate for stroke drugs has been even lower, but we will ignore that for now in the hopes of seeing this trend around soon.

Pharmaceutical companies devote more than half of development dollars to Phase I to III clinical trials with the rest spent on basic and translational research. It costs an average of $26,000 per patient enrolled in a Phase III trial, and trial costs are increasing rapidly. Over the last 20 years, development costs per drug have increased at a rate 7.4% higher than general inflation with clinical trials responsible for the greatest proportion of the increase. Greater complexity of trials probably accounts for most of this increase, although the underlying costs of health care have certainly contributed. Complexity is partially due to regulatory requirements such as site monitoring, adverse event reporting, and local Institutional Review Board (IRB) negotiations.

The high cost of clinical trials is eventually borne by all of us in the form of higher drug prices or greater expenditures by the NIH and foundations. It hampers further discovery by limiting the number of trials that can be done in the face of finite research expenditures. The high price of failure also encourages risk aversion with a tendency to do fewer trials or to focus on previously validated targets (ie, develop copycat drugs) rather than on truly novel agents. The true cost of harpered development may exceed those due to direct clinical trial expenditures.

At a trial site, performance of a clinical trial is not very different from providing routine patient care. A baseline history and examination is performed. A physician makes a decision about whether a patient is a candidate for a trial, just as is done for initiating any new therapy. Then the patient is followed, typically in the outpatient arena, during which the safety and efficacy of the new agent is evaluated as is done routinely in clinical practice.

Of course, trials differ importantly from routine clinical encounter in a number of ways. First, there are generally more forms to fill out in a trial than in routine practice. However, could not some of the data from trials be collected naturally from electronic medical records? Even more attractive, might the medical record be used as the actual instrument for data collection? Trials also typically require examinations that are not standard in a clinical encounter such as the NIH Stroke Scale score and the modified Rankin Score. However, these reliable and highly validated tools may actually work particularly well in routine patient care, even more valuable than some of the standard elements of the neurological examination, which have not been well validated and, in some instances, actually fail even simple tests of reproducibility. Is not reproducibility and validity important in clinical care as well? In this respect, maybe clinical notes should be modified to be more trial-like.

Regulatory requirements for clinical trials contribute greatly to complexity and costs. For example, prompted by
rare instances of investigators manufacturing data, the Food and Drug Administration requires site monitoring with extensive requirements for handling of data and quality assurance validations. Although these requirements likely increase study quality on average, they add tremendous cost and the benefits are unproven. Other forms of monitoring might be more efficient such as contacting patients directly to compare trial data with their reports. At least some rigorous evaluation of the various levels and types of monitoring seems advisable.

Central IRBs could help. The NIH has been trying to encourage sites to use central IRBs to approve performance of multicenter trials at all the sites in a trial, but most local IRBs have resisted and require independent reviews. This has led to substantial delays and prolonged negotiations at specific sites, probably with uncertain gain in the protection of subjects. Laws can be made and enforced at a federal level, overriding local law; why should IRBs be different? Is it impossible to constitute an appropriate single, central IRB that could fairly reflect the interests of the various subjects recruited? Delays in trials are very costly as are IRB reviews. Is local IRB review for multicenter trials really worth the cost?

Clinical trials frequently require follow-up evaluations and testing that goes well beyond what is necessary to demonstrate efficacy and safety. Clearly, there are opportunities to extend discovery beyond the primary hypothesis of a randomized trial, but this must be balanced with the overall efficiency of the trial. Complexity affects recruitment and labor requirements at a site. The Europeans have spearheaded a number of large simple trials that have cost a small fraction of what would typically be incurred in an NIH or industry trial, and many of these have had a tremendous impact on clinical practice. Can we learn from their example?

Validation and acceptance of surrogate markers could also increase the efficiency of stroke research. With new definitions of transient ischemic attack and stroke proposed, we are currently struggling with whether brain infarction regardless of symptom duration is a surrogate or really just a stroke. At the same time, we should be considering whether brain infarction is an adequate surrogate for clinical trials, particularly those of stroke prevention therapies. Whether a 1-mL infarction is symptomatic or asymptomatic depends predominantly on location, a factor that drugs for prevention would not be expected to impact differentially. Considering infarction, an appropriate surrogate could greatly increase the power of clinical trials by increasing event rates 2- to 7-fold. Similarly, other markers of disease activity and progression must also be developed and validated, and the Food and Drug Administration must be brought into discussions about acceptable levels of evidence for a surrogate.

There are a number of opportunities to make clinical trials more efficient, but there are few proponents for them and almost no rigorous study. Concerns about doing the best possible study and addressing peer reviewers and the Food and Drug Administration tend to add complexity and cost. Little push for balance exists on the other side, pushing for reduced costs and greater simplicity. Furthermore, very few investigators are interested in addressing the processes of clinical research as an appropriate and highly worthy topic for research in itself, perhaps in part because sources of funding for this metaresearch are essentially nonexistent.

The Future

We have done some great research in stroke over the last 30 years and this has led to substantial improvements in public health. Nonetheless, we are facing important challenges that are diluting resources and slowing progress. Most stroke researchers are still in training by the time they reach middle age and, given this degree of subspecialty training, it should not be surprising that the push is to drill down and focus on a specific area of study within the disease. Furthermore, models of success in prior generations demonstrate the value of “focus, focus, focus.” However, with this focus comes a loss for the appreciation of the forest. We desperately need investigators willing to pull back and re-examine broadly the processes, successes, and barriers to research. The lessons learned could greatly impact the pace and efficiency of stroke research as well as research in other areas. With investigators and funding addressing these fundamental issues about the way we get research done, the future could look very different from forecasts of rising costs and slowed progress.

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