SPOTRIAS Program Evaluation

Executive Summary

Prepared for the National Institute of Neurological Disorders and Stroke

by Ray Dorsey, MD, MBA and Paige Nichols, BA
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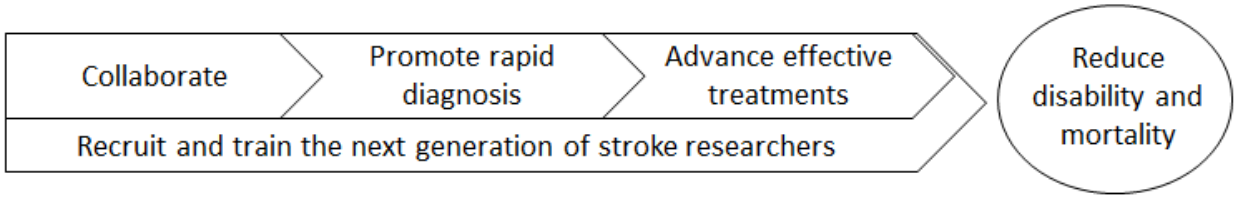
OVERVIEW OF SPOTRIAS

The Specialized Program of Transitional Research in Acute Stroke (SPOTRIAS) is a national network of centers that aim to perform early phase clinical projects, share data, and promote new approaches to therapy for acute stroke. The original solicitation issued in May 2001 called for the establishment of 10 SPOTRIAS centers funded using the P50 program project mechanism. The solicitation required that a center have a minimum of three translational projects supported by four cores (patient access, data management, training and career development, and tissue banking), clear evidence of involvement of emergency physicians with neurologists dedicated to stroke care, and the documented ability to treat a minimum of 12 patients a year with intravenous tPA within two hours from onset of symptoms.

During the 10 years of the program, the NINDS has been successful in incorporating 8 comprehensive stroke centers into the SPOTRIAS program. The current SPOTRIAS centers include: Columbia University, NINDS Intramural, Partners – Massachusetts, University of California – Los Angeles, University of California – San Diego, University of Cincinnati, University of Texas – Houston, and Washington University in St. Louis.

The goal of SPOTRIAS is to reduce disability and mortality in acute stroke patients through the development of improved treatment by laboratory investigation into the biology of stroke, clinical investigation of new therapies based on these laboratory studies, and assessment of outcome and improved application of effective therapies (Figure 1).

Figure 1:



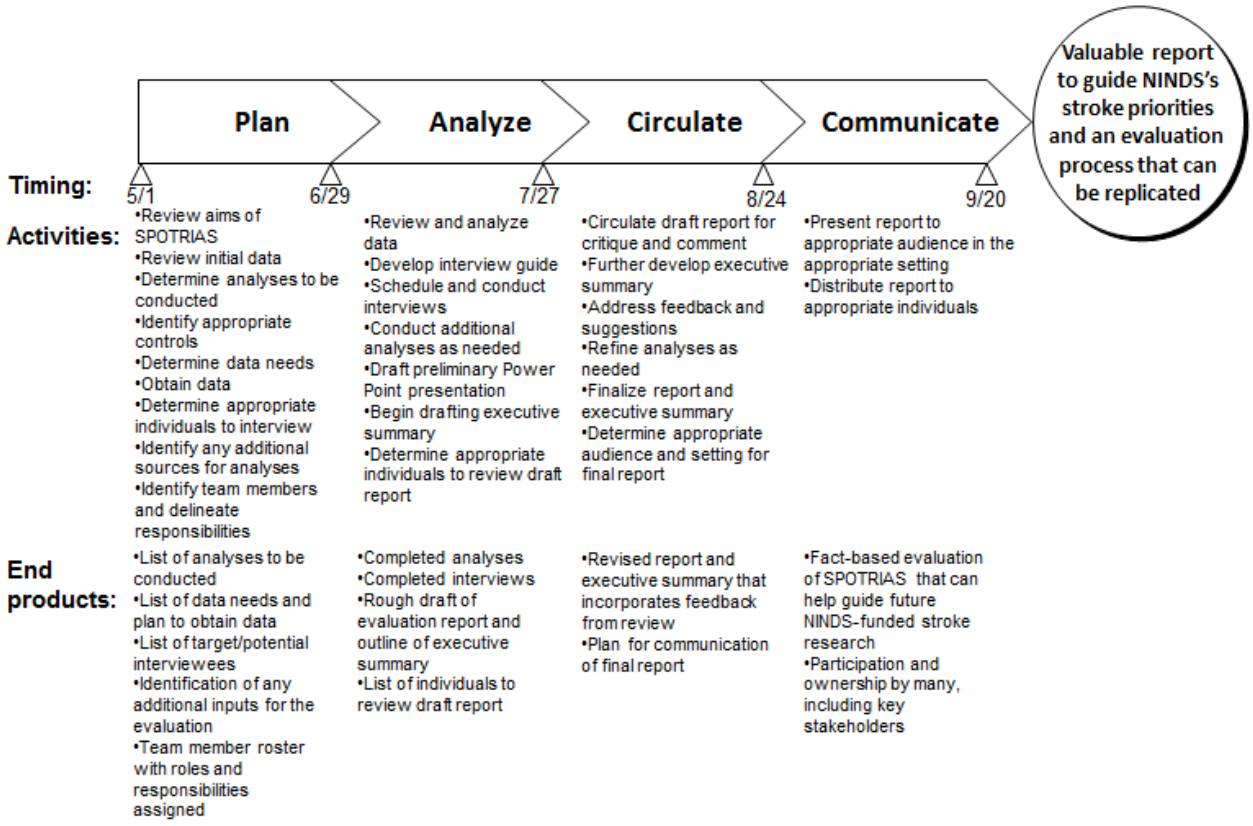
EVALUATION OF SPOTRIAS

To evaluate the SPOTRIAS project approximately 10 years after inception, the National Institute of Neurological Disorders and Stroke (NINDS) requested an evaluation of the program led by an independent consultant. A work plan was developed in discussion with NINDS leadership (Figure 2). As part of the evaluation process, the following individuals were interviewed as recommended by NINDS:

1) Joseph C. Broderick, MD, Chair of the Department of Neurology at the University of Cincinnati Academic Health Center (Current SPOTRIAS Principal Investigator)
2) Karen L. Furie, MD, MPH, Chair of the Department of Neurology at the Warren Alpert Medical School of Brown University (Previous SPOTRIAS Principal Investigator)
3) E. Clarke Haley, MD, Alumni Professor of Neurology and Neurological Surgery at the University of Virginia School of Medicine (Chair, SPOTRIAS grant peer review)
4) Christiana Hall, MD, Associate Professor of Neurology and Neurotherapeutics at the University of Texas Southwestern Medical Center (Former SPOTRIAS fellow)
5) Pooja Khatri, MD, MSc, Associate Professor of Neurology at the University of Cincinnati Academic Health Center (Former SPOTRIAS fellow and current SPOTRIAS Principal Investigator)

6) Patrick D. Lyden, MD, Chair of the Department of Neurology at Cedars-Sinai Medical Center (Former SPOTRIAS Principal Investigator)
7) Peter D. Panagos, MD, FACEP, Associate Professor of Emergency Medicine and Neurology at Washington University School of Medicine in St. Louis (Current SPOTRIAS Principal Investigator)
8) Jeffrey Saver, MD, Professor of Neurology at the David Geffen School of Medicine at University of California Los Angeles (Current SPOTRIAS Principal Investigator)
9) Robert Silbergleit, MD, Associate Professor of Emergency Medicine at the University of Michigan Health System (NETT Investigator)

Figure 2:



The evaluation was led by Ray Dorsey, MD, Associate Professor of Neurology at Johns Hopkins, and supported by Paige Nichols BA from Johns Hopkins and Katie Pahigiannis, PhD and Paul Scott, PhD from NINDS. As part of the work plan teleconferences were held on June 28, 2012, July 25, 2012, August 20, 2012 and an in person meeting on June 25, 2012 with leadership from NINDS.

KEY FINDINGS

Based on a systematic review of the SPOTRIAS program, including interviews with key leaders and participants in the program, SPOTRIAS has had tremendous success in fostering collaboration (especially across disciplines) and training the next generation of stroke researchers. Its clinical cores have enabled timely assessment, management, and incorporation of research into acute stroke. The program, however, has had more modest success to date in promoting the rapid diagnosis of acute stroke through new modalities and in advancing effective treatments for stroke.

Collaborate

From the outset, one of the aims of SPOTRIAS was to foster collaboration, initially across disciplines, especially among neurology, emergency medicine, and radiology, and later across SPOTRIAS sites. SPOTRIAS has achieved great success in meeting this aim. Among individuals interviewed for this evaluation, collaboration across specialties and centers, in what was previously a highly competitive environment, was identified as the greatest strength of the program. Collaboration with emergency medicine and radiology was apparent in many of the clinical cores and in the publications resulting from SPOTRIAS. In a random sample of SPOTRIAS publications, the proportion that included authors from emergency medicine or radiology increased five-fold from ~7% from 2003-2005 to ~35% from 2009-2012. Collaboration across SPOTRIAS centers was generally less evident (or more difficult to establish), but several SPOTRIAS clinical trials have involved collaboration across SPOTRIAS centers as well as with non SPOTRIAS sites.

One notable shortcoming in the effort to collaborate was the development of centralized resources. The data and biospecimen repositories were the most frequently identified weakness in SPOTRIAS by interviewees. In many cases, the quality of the data was "not good…[and] would not pass much for high quality journals as they were not all standardized and quality assurance was limited" leading to "grave concerns about how useful the samples are." In addition, few had utilized or could identify substantial advances resulting from these repositories. Recommendations for future repositories included having a clear hypothesis tied to them, standardizing the collection, and identifying a lead investigator to oversee the repositories.

Promote rapid diagnosis

The biggest contribution that SPOTRIAS has made to promoting the rapid diagnosis of acute stroke according to those interviewed has been the development of the clinical cores, which have allowed for timely diagnosis, treatment, and research participation among individuals presenting with acute stroke. According to one investigator, the clinical core helped "helped find, identify, and treat stroke early … a home run for me." Many cited these clinical cores, along with the requirement of SPOTRIAS applicant centers to treat 12 patients with tPA within two hours of symptom onset as laying the foundation for the development of primary stroke centers and comprehensive stroke centers that have fundamentally changed and enhanced the care of stroke nationally and beyond. The field of telestroke also benefitted from a rigorous study of its application funded through SPOTRIAS, but the assessment of its influence on the field was mixed.

While the clinical cores have helped promote the rapid diagnosis of acute stroke, the impact of the diagnostic studies in SPOTRIAS has been more limited. Although the MR Witness and MR Rescue studies hold promise, few of the imaging or biomarker studies in SPOTRIAS have changed clinical practice, are used in current clinical trials, or have resulted in intellectual property to date. In fact of more than 1000 patents issued for acute stroke since 2003, only one (methods for diagnosing ischemia by Huichun Xu and Frank Sharp) cited SPOTRIAS funding as a form of grant support.[1]

Advance effective treatments

Developing new therapeutics (drugs, devices, or other interventions) is resource intensive and risky. The estimated cost for developing a new drug now exceeds $800 million,[2] takes nine years[3] and only 20% of drugs entering phase I trials reach approval.[3] Phase I studies can take 12-22 months and phase II studies 26-30 months.[3] For neurological drugs, 73% entering phase I will reach phase II and only 47% will reach phase III.[3] Through its support of the development of tPA over a decade, the NINDS beat these odds and witnessed the FDA's approval of this therapy for acute stroke in 1996.

However, since the inception of SPOTRIAS, no new drug therapies for acute stroke have emerged from SPOTRIAS or elsewhere. During this time period, three devices for acute stroke have cleared the FDA, but only one, the Merci retrieval system, was part of a SPOTRIAS study, which was not instrumental in its clearance. Given the focus of SPOTRIAS on phase I and II clinical trials and the duration of the program, no new treatments would likely have emerged from the program. Of approximately sixteen pilot/phase II clinical trials in SPOTRIAS, one (6%) progressed to phase III. By comparison, in the 35 NINDS pilot/phase II clinical trials since 2002, three (9%) have gone on to start a phase III clinical trial. While the progression rates between SPOTRIAS projects and other NINDS projects are similar, both are below average in industry standards for neurology.[3] As a whole, 41% of ongoing or recent NINDS phase III clinical trials (n = 17) were preceded by NINDS-funded phase II and/or NINDS pilot studies.

The future may change as many of the most commonly identified promising treatments for stroke in development, including hypothermia and expansion of tPA applications (including three combination therapies) are have completed or are about to complete their investigation in SPOTRIAS and several potential phase III trials (e.g., ICTuS, argatroban plus tPA) are in the planning phase. One investigator noted, "The payoff (in terms of therapeutic advances) will come in the next 5 to 10 years and will be big." However, another noted that there have "not (been) a ton of success stories" in terms of therapeutic advances stemming from SPOTRIAS.

Recruit and train the next generation of stroke researchers

SPOTRIAS has been very successful in training the next generation of stroke researchers, which was the second most commonly identified strength of the program. Over 100 fellows from multiple disciplines have been trained through the SPOTRIAS programs. Based on a random sample of the fellows, these fellows have been highly productive during fellowship, publishing an average of 5.3 papers during this time, and have continued this productivity beyond fellowship, publishing 2.1 papers per year, on par with graduates of one of the country's top neurology residency programs.[4] One former trainee, who specifically sought out a stroke fellowship at a SPOTRIAS center, said SPOTRIAS "played a very tangible role in my career development. … (Training) is really one of the strengths of the program. It has put me on a first name basis with so many people that I enjoy working with. (It also has) made the NIH, (including the stroke program director) Scott Janis, much more accessible to me."

Several interviewees identified ways that the training program could be enhanced, including training more emergency physicians in stroke, increasing the didactic expectations of the program, and fostering even greater linkage across centers through having fellows spend time (~one month) at other training programs and expanding video conferencing applications across centers (e.g., journal club, lectures).

Reduce disability and mortality

The ultimate aim of SPOTRIAS was to reduce disability and mortality due to acute stroke. While this aim is unlikely to be realized over the course of the program to date, process measures suggest that SPOTRIAS has made progress. For example, the number of patients with acute stroke receiving tPA within two hours at the SPOTRIAS centers has generally increased over the duration of the program. In addition, an analysis of the Nationwide Inpatient Sample from the Agency for Healthcare Research and Quality[5] suggests that the proportion of patients presenting with acute stroke who received tPA was 8.4% in hospitals that were part of SPOTRIAS centers, 6.9% in hospitals that applied to be SPOTRIAS centers, and 3.7% among teaching hospitals generally. While these results do not demonstrate improved clinical outcomes, they do suggest that the process measure requirement to be part of

SPOTRIAS was influential in the selection of the sites and in their application of this treatment to the populations that the centers care for.

LESSONS LEARNED

Among the individuals interviewed who are (or were) part of SPOTRIAS, there was unanimous agreement that funding for SPOTRIAS should be continued and most thought that funding for the program should be increased. However, in the words of one investigator, "Clearly [SPOTRIAS] needs to be reformed. In its current state, (it is) not the most cost effective or scientifically efficient (program)."

The efficiency and effectiveness can be improved by focusing its resources on fewer studies across multiple centers with clear milestones and deliverables. In general, an emerging but not universal consensus was that the number of projects required (three) per SPOTRIAS center led to undesirable and sometimes inefficient competition for resources, attention, and potential research participants. These inefficiencies were compounded by inadequate project funding for larger scale trials. When comparing NINDS-funded largely phase II stroke trials within and outside SPOTRIAS, those funded within SPOTRIAS (average requested direct costs of ~$1.0 million per trial) generally received less financial support through SPOTRIAS compared to those funded outside SPOTRIAS (~$1.9 million). This was true even though SPOTRIAS studies generally targeted greater enrollment (an average of 106 participants per study) than stroke trials outside SPOTRIAS (73 participants per study). With fewer studies, more resources and attention could be focused on the timely execution of these studies, which should receive priority among participating centers. Efficiency may be further increased by centralizing some functions of SPOTRIAS, such as data management.

SPOTRIAS has developed into a collaborative stroke network poised to evaluate promising treatments across the spectrum of development, not just phase I and II studies. While NETT and NeuroNEXT offer the opportunity to conduct stroke trials and at least one investigator favored NETT for such a purpose, most felt that the expertise and experience in conducting stroke trials resided within SPOTRIAS centers. By focusing resources on developing clinical cores and training programs at additional SPOTRIAS centers (perhaps to a total of 12 according to one investigator), the capacity of SPOTRIAS to conduct larger scale phase III trials could be expanded efficiently.

These changes – expansion of centers with a focus on developing additional clinical cores and training programs, development of the network to include phase III studies, and a more stringent gating of trials moving forward – could help the NINDS and SPOTRIAS reach its objectives of promoting rapid diagnosis and advancing effective treatments that can reduce the disability and mortality due to acute stroke.

References

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