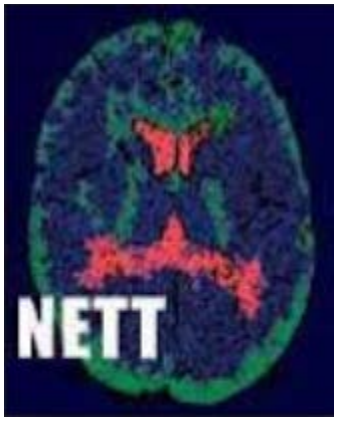
NETT Program Evaluation

Executive Summary



Neurological Emergencies Treatment Trials

Prepared for the National Institute of Neurological Disorders and Stroke

National Institute of Neurological Disorders and Stroke

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OVERVIEW OF NETT

The Neurological Emergencies Treatment Trials (NETT) network was formed in 2006 with a mission "to improve outcomes of patients with acute neurologic problems through innovative research focused on the emergent phase of patient care." NETT carries out this mission principally through the conduct of large, simple phase 3 clinical trials of interventions aimed at neurological emergencies. NETT has three principal components. The first is a Clinical Coordination Center (CCC) at the University of Michigan led by Dr. William Barsan that organizes, manages, and oversees clinical trials. The second is a Statistical and Data Management Center (SDMC) at the Medical University of South Carolina led by Dr. Yuko Palesch that constructs study databases, receives data, and analyzes results. The third is a network of 17 hubs with funded infrastructure throughout the United States and a sub-network of two to six spokes per hub. The spokes and hubs are responsible for recruiting, enrolling, and assessing study participants.

Through fiscal year 2014, NINDS has provided NETT $60 million in funding for infrastructure and $91 million in funding for six clinical trials of which three have been completed (**Table 1**). The studies funded for implementation in NETT are independently reviewed by NINDS and generally come from outside the network. These trials have been among the largest and most impactful in the field. The RAMPART trial, which evaluated the use of intramuscular midazolam versus intravenous lorazepam (previous standard of care) for the treatment of status epilepticus in the field, was a landmark study for its use of exception from informed consent (due to emergency nature of the treatment), rapid enrollment (far ahead of schedule), use of an intervention that relied on emergency medical personnel in the field, and results demonstrating the non-inferiority of midazolam. The study was published in the *New England Journal of Medicine*,[1] received the Society for Clinical Trials Trial of the Year Award for 2013, has changed clinical practice for civilian and military populations, and likely has substantially improved health. Other trials in NETT have not had as dramatic impact as RAMPART to date but have or are evaluating common interventions to common neurological emergencies with high morbidity and/or mortality.

Table 1. Clinical trials within NETT

Study	Intervention	Target N	Result/status*
RAMPART	Pre-hospital treatment of seizures with IM midazolam vs. IV lorazepam	1024	IM midazolam was at least as safe and effective as IV lorazepam
ALIAS 2	High dose IV albumin vs. IV saline for acute stroke	1100	Stopped for futility (after 841 enrollees)
ProTECT 3	IV progesterone vs. placebo for acute traumatic brain injury	1140	Stopped for futility (after 882 enrollees)
POINT	Clopidogrel + ASA vs. ASA for TIA and minor stroke	5841	Currently enrolling (2477 enrolled)
SHINE	IV insulin (strict control) vs. sliding scale insulin (standard care) for acute ischemic stroke	1400	Currently enrolling (503 enrolled)
ATACH 2	IV nicardipine (intensive blood pressure control) vs. standard care in intracerebral hemorrhage	1280	Currently enrolling (717 enrolled)

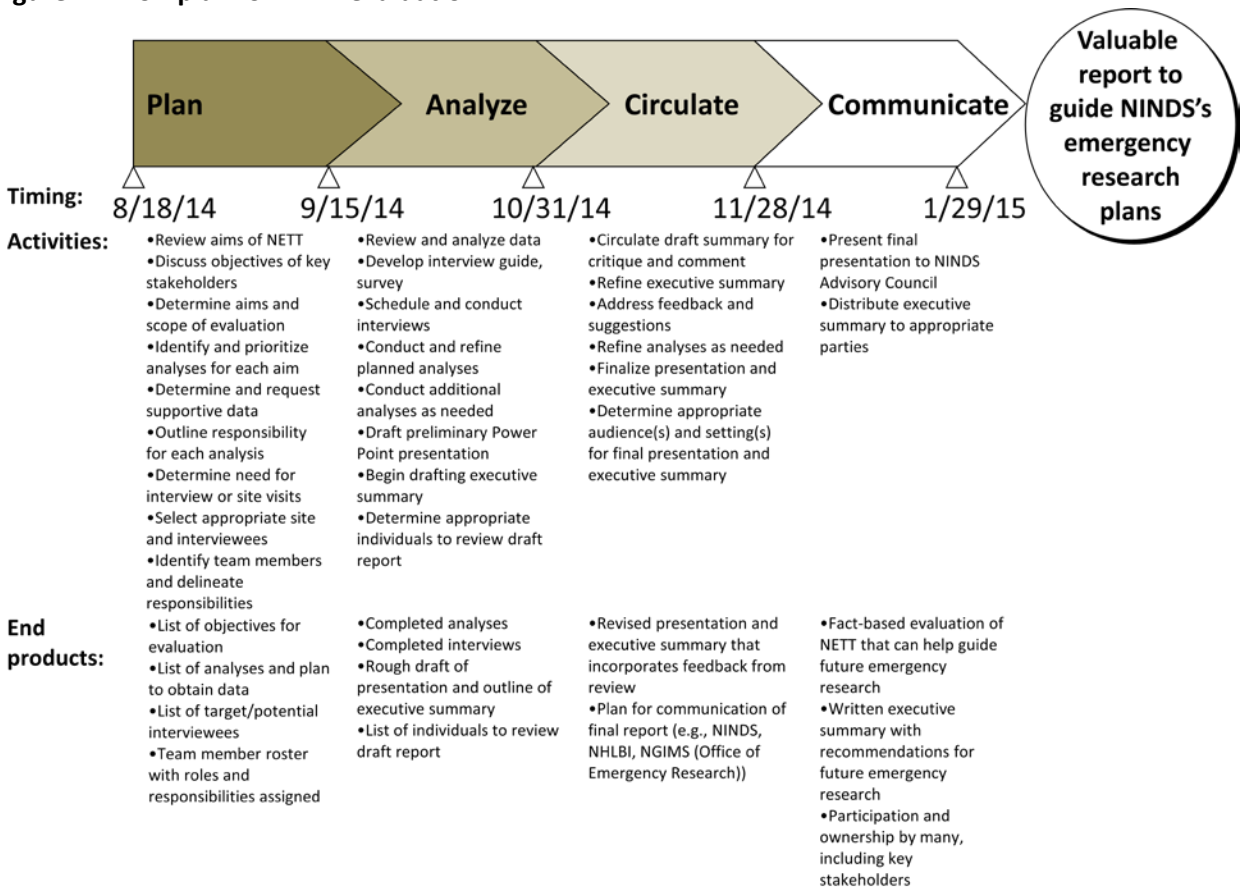
* Enrollment as of December 2014

With the creation of StrokeNet (a clinical trials network dedicated to stroke), the closing of the Resuscitation Outcomes Consortium (ROC, a NHLBI-funded clinical trial network focused on pre-hospital cardiopulmonary arrest and severe traumatic injury), and the upcoming tenth anniversary of NETT, NINDS sought to engage an independent consultant to assess the impact and efficiency of NETT and develop recommendations for the network for the future.

EVALUATION OF NETT

To evaluate the NETT as it approaches its tenth year of funding that is coming to a close, 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 1**). The evaluation had three principal components. The first was an online, 13-question survey emailed to individuals involved in NETT as a project coordinator, trial investigator, a hub or spoke investigator, or an investigator in the Clinical Coordination Center or Statistical and Data Management Center. "Anyone with enough engagement" in NETT was encouraged to respond. The response rate was 46.6% with 149 respondents.

Figure 1: Workplan for NETT evaluation



The second part of the evaluation process was semi-structured interviews with nine leaders of emergency neurology research who have participated in NETT. The interviewees were selected by

NINDS and included individuals who had participated in NETT, other emergency clinical trial networks, other NINDS-funded efforts, and an individual whose hub was not re-funded. All interviews were conducted by the independent consultant. The interviewees are listed in **Appendix Table**.

The third part of the evaluation process was analysis of the outcomes, efficiency, and performance of NETT based on publicly available data, surveys, and data from NETT itself. This portion was conducted by NINDS staff and the independent consultant with the independent consultant reviewing all data.

The evaluation was led by Ray Dorsey, MD, Professor of Neurology and Director of CHET (Center for Human Experimental Therapeutics) at the University of Rochester and supported by Katie Pahigiannis, PhD in the NINDS Office of Science Policy and Planning, directed by Paul Scott, PhD. As part of the work plan teleconferences were held on August 18, September 26, October 28, and November 21, 2014 with a committee made up of leadership and staff of NINDS, NIH Office of Emergency Care Research, and NHLBI Division of Cardiovascular Sciences. Additional, more frequent teleconferences were held with a subgroup of the internal committee.

Impact of NETT

NETT has had a profound impact on emergency neurology research. Multiple interviewees spoke of how NETT has changed the nature of emergency research, fostered research collaborations among specialties where little previously existed, developed a robust infrastructure for clinical trials, and conducted impactful studies. For example, NETT has been a "landmark" for emergency medicine, "broken ground in (developing) close collaboration with neurology colleagues," and "demonstrated how a federally funded network can be successful in implementing clinical trials."

A survey of NETT participants revealed that NETT had fulfilled its key goals as laid out in its original request for applications, including improving outcomes of patients through research (4.4 on a 5-point Likert scale), encouraging collaborations between emergency medicine and neurology (4.5), and developing infrastructure for emergency neurology research (4.7). NETT received similarly high marks for its impact on emergency care research (3.7 on a scale from 0 to 4) and public health (3.5). While two clinical trials were stopped prematurely for futility, these studies investigated a previously commonly used (and more expensive) intervention (intravenous albumin for acute stroke) that is now rarely used and a potentially promising treatment (progesterone) that failed to work for a condition (traumatic brain injury) that has a large unmet therapeutic need. Its three current studies are evaluating important approaches to the treatment of ischemic and hemorrhagic stroke.

The leadership and infrastructure of NETT are highly praised. The leadership of the Clinical Coordination Core is described by interviewees as "the best people you will ever find" and as "superb." Similarly, the Statistical and Data Management Center's leadership is called "stellar" and its data management software as "very user friendly." Praise in general for the hubs and spokes is high ("some rock stars") with a "superb" emergency medical services capability. However, performance among the hubs and spokes was more variable ("real winners, real losers (among hubs)"). While enrollment in clinical trials conducted within NETT has generally followed projections in contrast to most previous NINDS-funded clinical trials, some hubs have outperformed others in recruitment, timeliness to study launch, and quality of data submitted.

Efficiency of NETT

The success of NETT in building new relationships, creating a strong clinical trial infrastructure, and conducting high quality clinical trials has been expensive. Total (direct + indirect cost) funding through

fiscal year 2014 for NETT's infrastructure and for the clinical trials conducted through NETT has been $151 million. Peer comparisons are difficult to find, but data on two other emergency clinical trial networks funded by NHLBI (ROC) and HRSA (Pediatric Emergency Care Applied Research Network, PECARN) are provided in **Table 2**.

Table 2. Comparison of emergency clinical trial networks

Network	Current focus	Years	Total funding through FY2014	# of sites	# trial participants	Network
NETT	Large phase 3 clinical trials for neurological emergencies	2006-16	$151 million	17*	4,135	NETT
ROC	Phase 2, 3, and 4 out-of-hospital clinical trials and registries for cardiopulmonary arrest and severe traumatic injury	2004-15	$143 million	10	42,746	ROC
PECARN	Pediatric emergency care for acute illness/injury trials, registries, and screening tools	2001-15	$128 million	18	2,400	PECARN

The average cost (beyond infrastructure) of the three phase 3 clinical trials completed within NETT was $19 million. Comparable data for large scale clinical trials for emergency research are hard to find, but the funding is in line with an estimate of $26,000 per participant for phase 3 clinical trials (that may have more assessments, but a lower cost setting, than in clinical trials for emergent conditions)[2] and is far less than published estimates for average out-of-pocket expenditures for phase 3 trials ($106 million).[3]

While the economic efficiency of NETT is likely favorable but harder to establish given the lack of comparable data, the operational efficiency of NETT is clear. While NINDS-funded clinical trials were recently criticized for their delays in recruitment and resulting extensions in budgets,[4] studies in NETT have largely recruited in line with projections. One clinical trial (ALIAS 2) originally began outside of NETT, but due to slow enrollment was moved within NETT at which point recruitment rapidly increased. By the end of the trial, despite starting later 12 of the 13 largest enrolling sites were NETT hubs.

Future of NETT

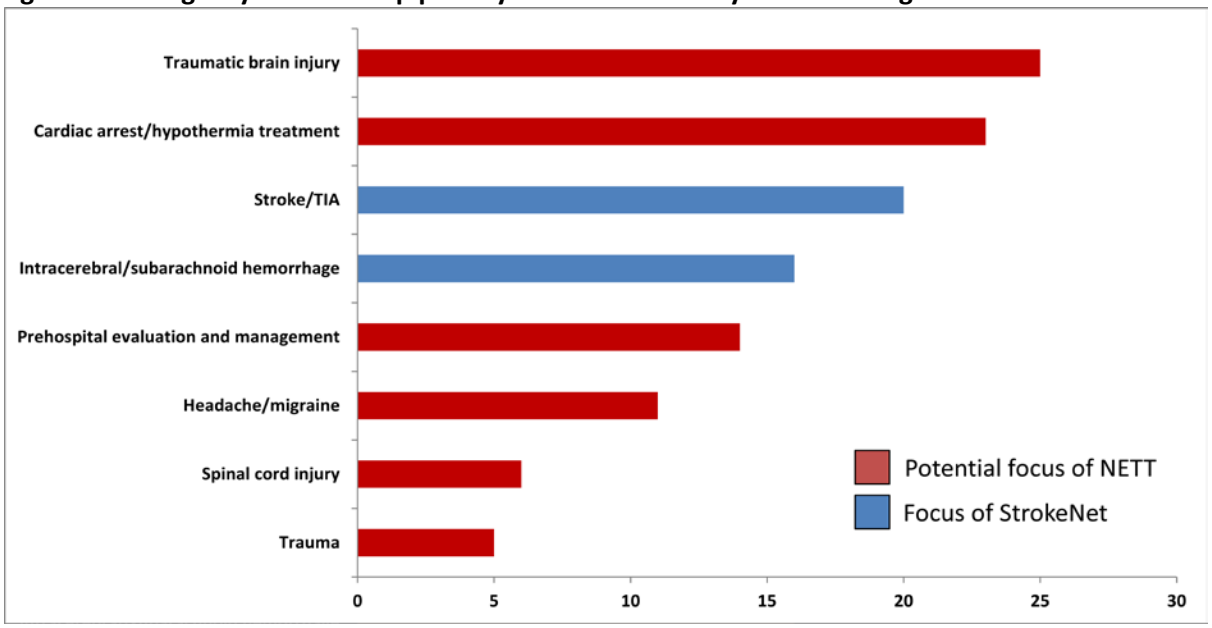
While NETT has been largely successful in fulfilling its mission, the network has ample opportunity for improvement in its capacity, processes, engagement, and scope. All interviewees thought that NETT's infrastructure could support more clinical trials, which could result in greater operational efficiencies and take advantage of many hubs' desire for additional trials. In addition to more trials, some of NETT's operations, especially payments of spokes could be improved. Currently, payments to spokes flow from NINDS through the clinical trial's principal investigator's institution then to the Clinical Coordination

Center at the University of Michigan then to the spoke's hub and finally to the spoke. At each step in the process, indirect costs are assessed resulting in progressively less money reaching the spoke investigator. Implementing payment contracting processes that are in place for StrokeNet and NeuroNEXT could help fund spokes more efficiently. Similarly, start-up funds for spokes could help them launch trials without incurring deficits. Finally, longer duration (rather than one year) contracts could reduce needless waste and delays in payment of spokes.

NETT has recruited a large number of minorities through its hubs for its clinical trials. On average, approximately half of participants in its clinical trials come from minority populations and for the two trials (RAMPART and ProTECT) that operated with an exception from informed consent approximately two-thirds of participants were from minority groups. By contrast, approximately 70% of participants in other NINDS-funded clinical trials are non-Hispanic whites. While NETT has successfully engaged diverse communities in many of its efforts related to the exception from informed consent, very few of its leaders are from minority groups and none of its current hubs are Minority Serving Institutions. In addition to engaging minorities, NETT's leadership is at times perceived as too "Michigan-centric," and many hub investigators are looking for a more active role (e.g., on steering committee, in writing publications, in suggesting ideas for clinical trials) in the network beyond leading recruitment efforts at its hubs and spokes. Similarly, while not an original focus of NETT, the network could create greater opportunities for developing the next generation of emergency neurology investigators.

With the creation of StrokeNet and the closing of ROC, the scope of NETT will have to continue to address non-stroke neurological emergencies and consider the void in cardiopulmonary arrest and trauma. Such a shift should not be difficult given the unmet need of many neurological emergencies (e.g., traumatic brain injury), the common nature of neurological emergencies (headache and back pain are two of the ten most common emergency department complaints), and a survey of the NETT investigators and coordinators that readily identified priority areas beyond stroke ready for investigation (**Figure 2**).

Figure 2. Emergency research top priority areas identified by NETT investigators and coordinators



Finally with the increasing attention to public health emergencies from fungal meningitis outbreak in 2012 to the more recent cases of enterovirus D68, NETT should consider its role in conducting research in this area, which has no clear champion. In a 2013 *New England Journal of Medicine* piece[5] entitled "Research as part of a public health emergency response," Drs. Nicole Lurie, Francis Collins, and colleagues said, "[Additional] research, done in parallel with and after the response itself, is often essential to address the most pressing knowledge gaps presented by public health emergencies and to ensure that they are addressed by the time another similar disaster strikes. Recent events have also illustrated gaps in planning for, and rapidly executing, scientific research in the context of disaster response."[5] The recent Ebola virus experience only reinforces this point.

NETT may have the interest, experience with emergency medical services, and some of the capability ("when have a well functioning network, addressing pandemics, epidemics makes perfect sense to me") to conduct research on public health emergencies. Additional capabilities (e.g., remote assessments, specialized resources) and relationships (e.g., with CDC, public health specialists) will have to be developed. However, a highly capable research network currently focused on emergency neurology research may be well positioned to address critical public health issues. As Dr. Lurie and colleagues advised, "Just as preparedness is a continuous, ongoing activity, so too is the effort to plan for the effective conduct of research before, after, and especially during an emergency."[5] NINDS, the Office of Emergency Research, and NETT all may want to consider what role a highly successful emergency clinical trial network could and should play in addressing future public health emergencies.

References

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3. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, The price of innovation: new estimates of drug development costs. J Health Econ, 2003. 22(2): p. 151-85.
4. NINDS Strategic Plan, Clinical Panel Report. Available at: http://www.ninds.nih.gov/about_ninds/plans/NINDS_strategic_plan.htm. Accessed November 24, 2014.
5. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as part of public health emergency response. NEJM 2013;368:1251-5.

Appendix Table: List of Interviewees for NETT project evaluation

Interviewee	Institution	Role in NETT
Dr. William Barsan	University of Michigan	Principal investigator of NETT and the clinical coordinating center (CCC)
Drs. Yuko Palesch and Valerie Durkalski-Mauldin	Medical University of South Carolina	Principal and co-principal investigators of statistical and data management center (SDMC)
Ms. Katherine Lamond	University of Pennsylvania	NETT hub project manager
Dr. Art Pancioli	University of Cincinnati	NETT co-principal investigator
Dr. Claiborne "Clay" Johnston	UT Austin	Principal investigator of POINT trial within NETT
Dr. Roger Lewis	Harbor UCLA	Principal investigator in ADAPT-IT project within NETT
Dr. Tom Aufderheide	Medical College of Wisconsin	Hub principal investigator
Dr. Kurt Denninghoff	University of Arizona	Hub principal investigator, whose funding was not renewed
Dr. Michael Hill	University of Calgary	Co-principal investigator for ALIAS trial within NETT