NINDS vision for the next 5 years

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NINDS

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Coming together is a beginning. Keeping together is progress. Working together is success.
~Henry Ford

www.NIHStrokeNet.org
First five years / Next five years...

- Build
- Get first big win
- Establish pipeline
- Develop efficiency
- Maintain pipeline
- Utilize network
Working toward balance

- **Recovery**
  - Telerehab*
  - Transport 2
  - I-Acquire
  - SleepSmart

- **Prevention**
  - Crest2
  - Arcadia
  - Saturn
  - Aspire
  - SleepSmart

- **Treatment**
  - Defuse 3*
  - MOST
StrokeNet timeline (Oct 2018)

- **ARCADIA NOA N=1100**
  - 5/1/2017

- **TRANSPORT 2 NOA N=129**
  - 8/1/2018

- **MOST NOA N=1200**
  - 8/1/2018

- **ASPIRE NOA N=550**
  - 2/1/2019

- **ARCADIA ENDS**
  - 4/1/2019

- **NIH STROKENET CYCLE 2 ENDS**
  - 8/1/2022

- **MOST ENDS**
  - 8/1/2023

- **IAQUIRE NOA N=240**
  - 2/1/2024

- **SATURN ENDS**
  - 8/1/2023

- **SLEEPSMART ENDS**
  - 2/1/2024

- **TRANSPORT 2 ENDS**
  - 4/1/2024

- **SLEEPSMART NOA N=3062**
  - 8/1/2018

- **IAQUIRE ENDS**
  - 8/1/2022

- **SATURN NOA N=1456**
  - 8/1/2023

- **ASPIRE ENDS**
  - 4/1/2024
Plans in the works

- Athero research
- Hemostasis
- Genetics
- Behavior change
- Epidemiology
- Cerebrovascular biology

Prevention

Recovery

- Neuroplasticity
- Biology of Repair post-Injury
- Neural Regeneration

Acute Treatment

- Reperfusion
- Neuroprotection

Hemostasis
Take advantage of the network?

EVT Platform

Neuro-protection

Existing trials
Stroke Preclinical Assessment Network (SPAN)

A preclinical network to support translational studies for acute neuroprotection prior to endovascular reperfusion therapy in stroke
Targeting neuroprotection

- 2012 NINDS Stroke Research Priorities Meeting key priorities:
  - Accelerating the translation of stroke research in preclinical animal models into clinical studies of highly promising treatments.
  - Preclinical and clinical studies to achieve robust brain protection.
- European planning effort Multi-PART (Multicenter Preclinical Animal Research Team; 2012-2014) proposed a paradigm shift to perform preclinical studies with the same rigor and central coordination used in phase III randomized controlled human trials.
- NINDS workshop “Translational Stroke Research: Vision and Opportunities” recommendations (Stroke, 2017) included preclinical multi-laboratory trials of a putative treatment, with an agreed upon protocol, rigorous good laboratory practices, a centralized randomization and data center, and on-site source verification of data as a valuable approach before investing in a clinical trial.
- Stroke Treatment Academic Industry Roundtable (STAIR) 2017 meeting placed a high priority on evaluating agents that could further improve outcomes following endovascular therapy. Establishing the most promising agents to take into clinical trials is an important first step.
Objectives and structure of SPAN:

- Will test if neuroprotection can provide additional benefit to reperfusion alone (by either improving functional outcome or extending the therapeutic window of intervention), in an experimental controlled setting.
- Up to 6 leading academic sites with published expertise with the transient middle cerebral artery occlusion (tMCAO) model of stroke and related comorbidities will test interventions (including their own) in parallel.
- A Coordinating Center will provide overall study coordination, statistical analysis, randomization and blinding, data sharing, and monitoring of the individual sites.

Vision for SPAN:

To create a novel translational model that if successful, will accelerate the identification of the most promising neuroprotective therapies for future pivotal clinical trials and span the gap between preclinical and clinical testing, in a cost-and time-effective fashion.
• Rodent tMCAO
• 6 interventions in parallel
• Age, sex, comorbidities, + tPA

SPAN Network Infrastructure

- Site 1
- Site 2
- Site 3
- Site 4
- Site 5
- Site 6

Steering Committee

NINDS

External Advisory Board

Advisory Council

StrokeNet Ph. II Trial
Who may apply?

- **The network will include:**
  - Up to 6 preclinical network sites (RFA NS-18-033)
  - One coordinating center (RFA NS-18-034)

- **Eligible to apply:**
  - U.S. Organizations (Non-U.S. entities **are not** eligible)
  - Applicant organizations may submit more than one application, provided that each is scientifically distinct
  - Institution being awarded as a network site **cannot** be the SPAN CC (to avoid conflict of interest) and viceversa

- **PI qualifications:**
  - Published expertise in tMCAO model of ischemic stroke, neuroprotection, behavioral motor and cognitive outcomes, and preclinical models of stroke comorbidities (aging, hypertension, diabetes, etc.)
  - Neuroimaging capabilities
  - Documented expertise in leading multiple complex projects in parallel
  - Minimum of 3 person months effort
Funding Opportunity Title
Stroke Preclinical Assessment Network (SPAN) to Support Translational Studies for Acute Neuroprotection - Coordinating Center (U24 Clinical Trial Not Allowed)
U24 Resource-Related Research Projects – Cooperative Agreements

Key Dates
Posted Date
August 6, 2018

Open Date (Earliest Submission Date)
November 13, 2018

Letter of Intent Due Date(s)
November 13, 2018

Application Due Date(s)
December 13, 2018, by 5:00PM local time of applicant organization.
SPAN Network Sites: RFA NS-18-033

Stroke Preclinical Assessment Network (SPAN) to Support Translational Studies for Acute Neuroprotection (U01 Clinical Trial Not Allowed)

Activity Code
U01 Research Project – Cooperative Agreements

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Contact(s)
Francesca Bosetti, Pharm.D., Ph.D.
National Institute of Neurological Disorders and Stroke (NINDS)

Email future additional questions to SPAN@mail.nih.gov
NINDS StrokeNET-EVT Platform

Proposed Basic Structure of Trial to Assess “Which Patients should receive EVT”

Inclusion of Registry, Ancillary Studies, and Currently Funded Trials
Current Approach to Clinical Trials

- **MR Clean**
  - Does it work in the ultra early population?

- **DAWN/Defuse**
  - Does it still work when treating a little later?

- **Future Trial**
  - Another extension

- **Future Trial 2**
  - And another...
What is a Platform Trial?

An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment.
Strokenet Thrombectomy Platform – **STarting with Optimization of Eligibility**

- STEP-STONE
• Answers stand-alone question: Which patients should be treated with endovascular therapy
• Serves as “base” to launch ancillary studies for pre-, peri-, and post-EVT clinical trials
• Offers database to answer key scientific questions about endovascular therapy
• Stand-alone question of whether intervention works in EVT eligible patients
  • E.g. neuroprotection
• Ancillary study team largely retains control over ancillary study (scientific question, primary paper, etc.)
  • Need to work with EVT platform executive committee to coordinate studies
  • Must use parent protocol and CRFs for EVT data
  • Must allow for co-enrollment, sharing of information, harmonization of randomization scheme
• Works better if design is simple
**Basic Concept**

**Long-Term Platform Plan**

- **Pre-Procedural Treatments**
  - Neuroprotection
  - Lytics (TNK, tPA, ...)
  - Other Treatments

- **EVT Eligibility**
  - **Clinical**
    - Age
    - NIHSS
    - Pre-Stroke mRS
    - Time from Stroke Onset
  - **Imaging**
    - Clot Location
    - Core Size
    - Penumbra

- **Procedural Approaches**
  - Balloon Guide
  - Stenting Extracranial ICA
  - Timing of Stent
  - Pharmacological adjuncts
  - Sedation

- **Post-EVT Treatment Regimens**
  - DAP for Stents
  - BP Goals

**Consideration:**
- Do pre-procedural treatments modify eligibility?
- Do they modify eligibility only under certain procedural constraints?
- Which criteria predict outcome?
- Which criteria predict adverse events?
- Can imaging replace clinical criteria?
- Are procedural differences constant across allowed eligibility?
- Do they interact with pre-procedural treatments?
Next Steps

- Approval of platform concept with ESC in Nov
- 2019 submission of platform and ancillary trials
- Establish registry through network infrastructure
Plans in the works

Prevention
- Athero research
- Genetics
- Behavior change
- Epidemiology
- Cerebrovascular biology

Reperfusion

Acute Treatment
- Hemostasis
- Neuroprotection

Recovery
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- Neural Regeneration

Hemostasis

Plans in the works

NIH StrokeNet

National Institute of Neurological Disorders and Stroke
Single RCC Studies versus Multi-Center Studies (n=245)

- Acute
- Prevention
- Biomarker
- Recovery and Rehabilitation

- 11 or greater
- 2-10 Centers
- Single Center
Translational Gaps

Figure 3: The Two Valleys of the Research-to-Practice Continuum

- Valley 1: Basic Biomedical Research
- Valley 2: Health Decision Making and Clinical Practice

Research-to-Practice Continuum
Stroke Recovery Workshop:
Bridging the Translational Gap in Stroke Recovery & Rehabilitation Research
November 27-28, 2018
NINDS/NIH, Rockville MD, Neuroscience Center

Objectives
Identify gaps and opportunities to advance stroke recovery research through bi-directional translation between basic biomedical research and clinical science and practice. The goal of these discussions is to shape the best path forward for developing effective therapies for stroke recovery and rehabilitation.

- The workshop deliverable will be in the form of a white paper that describes what is needed to achieve key advances in the field, and will serve to:
  - Define what work is needed to achieve successful translation of restorative therapies from bench to clinic.
  - Establish an effective guidepost for future stroke recovery and rehabilitation research
Panel discussions around common themes

Animal models - Considering the limitations, how we can use animal models to address clinical gaps, better understand the molecular mechanisms of recovery, and exploit potential new targets to enhance spontaneous recovery?

Endpoints and Prognostication – How do we align clinical and preclinical patient-relevant outcomes and address what is meant when we say a person will benefit and what is needed to develop initial triage step at the time of discharge?

Modulator and co-variate factors in recovery – How do we use translational models to inform and address dosing and timing of interventions?

Biomarkers – How do we identify markers that cross the translational bridge?
Open round-table discussion of practical issues focused on generating transformative ideas for operation or implementation of stroke rehabilitation trials in StrokeNet

Are we missing opportunities to develop interventions for problems or symptoms in early phase recovery that are especially important to patients and community practitioners? Review of pre-workshop survey results.

How can rehabilitation trials better understand and collaborate with the community partners who are providing outpatient services and are affiliated with StrokeNet? Is there a role to work with professional organizations?

Are pragmatic, simple or adaptive trials feasible for stroke recovery and rehabilitation? How can the Network be leveraged to support such trials? Are there big data approaches that can be used to power trials in StrokeNet?
1) What do you see as the biggest practical barrier(s) to restoring function and health for stroke survivors after the acute management phase?

2) Which of the following stroke recovery and health-promoting technology-based solutions should be evaluated using the StrokeNet infrastructure?

3) If the StrokeNet Infrastructure was employed to evaluate and scale solutions to optimize recovery and health after stroke, which of the following would you select.

4) Which of the following is a major reason why we have so few large-scale stroke recovery/rehabilitation trials

5) What is your role in your healthcare institution?
Registration Link:

https://meetings.ninds.nih.gov/meetings/strokerehab/
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Plans in the works
Ideas:

• Embedding recovery questions in prevention trials
• 2019 workshop –
NIH
Transforming medicine and health through discovery