# Division of Clinical Research Programs

<table>
<thead>
<tr>
<th>Clinical Trial Readiness</th>
<th>Phase I First in Human</th>
<th>Phase Ib First in target population</th>
<th>Phase Ila Proof of Concept (Biomarker)</th>
<th>Phase IIb Preliminary Efficacy (Clinical)</th>
<th>Phase III Definite Efficacy</th>
<th>Phase IV Post Marketing Surveillance</th>
<th>Dissemination Implementation CER</th>
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<tbody>
<tr>
<td>PAR CT Readiness</td>
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<td>PAR Exploratory Clinical Research</td>
<td>Cooperative Programs in Clinical Research PAR Phase II/III CTs</td>
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<td>PAR Dissemination Implementation CER</td>
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<td>SIREN</td>
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<td>NeuroNEXT</td>
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<td>StrokeNet</td>
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<td>HEAL EPPIC-NET</td>
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<td>Biomarker Discovery/Validation</td>
<td>Outcome Discovery/Validation</td>
<td>Clinical Trial Embedded Natural History Studies</td>
<td>Common Data Elements</td>
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Early Phase Clinical Trials: Current Portfolio

2018 Active Grants

- Stroke
- Multiple Sclerosis
- Traumatic Brain Injury
- Myasthenia Gravis
- Cryptogenic Peripheral Neuropathy
- Aromatic L-amino acid decarboxylase deficiency
- Charcot-Marie-Tooth type 1A
- Sleep deprivation
- Tuberous Sclerosis Complex
- Glucose transporter type 1 deficiency (GD1)
- Malaria
- Multiple system atrophy
- GNE Myopathy
- Huntington’s Disease
- Fragile X

Total: 21
Efficacy Clinical Trials: Current Portfolio

2018 Active Grants

- Traumatic Brain Injury
- Perinatal hypoxic-ischemic encephalopathy
- Muscular dystrophy
- Parkinson’s Disease
- Epilepsy
- Subarachnoid Neurocysticercosis
- Preterm birth
- Stroke

Total: 20
NINDS Networks

Pain
- HEAL
- Coming 2019

Phase II/biomarkers
- NeuroNEXT
- 2011-present

Exploratory Trial
- Phase I

Acute Care
- 2006-2018
- NIH SIREN Emergency Trials Network
- 2017-present

Phase II/III Trial
- Adaptive design

Phase III Trial
- Coming 2019

NIH StrokeNet
- 2013-present
NINDS Networks
Organizational and Funding Structure

• Increased trial quality
• Balanced portfolio
  – Allows logical ordering of incoming trials
  – Creates a pipeline for future trials
• Stable infrastructure and research capacity
  – Improved subspecialty input via working groups
  – Stable funding for research and training
• Improved data sharing
  – Single data center with uniform governance
  – Fosters the use of CDEs
• Manages trials competing for similar patients
  – Commitment to consider **ALL** eligible patients
• Coordinates with non-profits, industry, and international partners
• Trains the next generation of clinical trialists
NINDS Networks
NETT Clinical Trial Activities

• 2006-2018

• 22 Hub centers (17 funded) each with 3-5 satellite spoke hospitals, a coordinating center, and a data coordinating center

• Emergency neurology network that conducted large, simple, phase III trials for acute injuries commonly treated in the emergency room

Completed:
• RAMPART- Rapid Anticonvulsant Medication Prior To Arrival Trial (N=1024)
• ALIAS –Albumin Therapy for Neuroprotection in Acute Ischemic Stroke (N=841)
• ProTECT III - Progesterone for Traumatic Brain Injury (N=882)
• SHINE – Stroke Hyperglycemia Insulin Network Effort Trial (N=1151)
• POINT – Platelet-Oriented Inhibition in New TIA Trial (N=4892)
• ATACH II – Antihypertensive Treatment of Cerebral Hemorrhage (N=1000)
• ESETT- Established Status Epilepticus Treatment Trial (N=478)
NINDS Networks
Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)

Overview

• 2011 - present
• 25 regional sites, data and clinical coordinating centers
• Designed to advance the field by accelerating biomarker and therapy development

https://neuronext.org/
Completed:

- **SUPER BABY**  Spinal Muscular Atrophy Biomarker Study \(N=53\)
- **SPRINT MS**  Ibudilast in Progressive Multiple Sclerosis \(N=255\)
- **Beat MG**  Rituximab in Myasthenia Gravis \(N=52\)
- **RHAPSODY**  3K3A-APC in Acute Stroke \(N=110\)
- **STAIR**  SRX246 for irritability in Huntington’s Disease \(N=105\)

Ongoing:

- **CYTO-C**  Cytochrome C as Biomarker in Glioblastoma Multiforme \(N=200\)
- **FX LEARN**  AFQ056 (Novartis) for language learning in Fragile X \(N=100\)
- **Top CSPN**  Topiramate for Cryptogenic Peripheral Neuropathy \(N=125\)
- **MAGINE**  ManNAc for GNE Myopathy \(N=50\)
Overview

- 2013 - present
- 29 regional centers (24 funded) with 432 satellite stroke hospitals, a coordinating center, and a data coordinating center
- Phase 2 and phase 3 clinical trials and biomarker studies to advance acute stroke treatment, prevention, and recovery

http://nihstrokenet.org/
### NINDS Networks

**Population coverage of “Hub & Spoke” model**

#### Table: Population coverage by characteristic and distance from StrokeNet Center

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>20 Mile Radius</th>
<th>% of Total</th>
<th>40 Mile Radius</th>
<th>% of Total</th>
<th>65 Mile Radius</th>
<th>% of Total</th>
<th>Total (50 States)</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population</strong></td>
<td>120,758,337</td>
<td>38.3%</td>
<td>157,727,442</td>
<td>50.0%</td>
<td>189,572,542</td>
<td>60.1%</td>
<td>315,219,560</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Male (adult)</strong></td>
<td>44,518,863</td>
<td>38.1%</td>
<td>58,121,547</td>
<td>49.8%</td>
<td>70,121,776</td>
<td>60.1%</td>
<td>116,781,403</td>
<td>100.0%</td>
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<tr>
<td><strong>RACE</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>80,374,323</td>
<td>34.5%</td>
<td>109,783,222</td>
<td>47.1%</td>
<td>136,388,020</td>
<td>58.5%</td>
<td>233,168,413</td>
<td>100.0%</td>
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<tr>
<td>Hispanic/Latino</td>
<td>24,695,940</td>
<td>44.6%</td>
<td>29,719,245</td>
<td>53.6%</td>
<td>33,189,395</td>
<td>59.9%</td>
<td>55,429,828</td>
<td>100.0%</td>
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<tr>
<td>Black</td>
<td>18,115,454</td>
<td>45.9%</td>
<td>21,868,660</td>
<td>55.4%</td>
<td>24,323,226</td>
<td>61.7%</td>
<td>39,451,870</td>
<td>100.0%</td>
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<tr>
<td>Asian</td>
<td>9,952,233</td>
<td>65.3%</td>
<td>11,108,254</td>
<td>72.9%</td>
<td>11,888,761</td>
<td>78.0%</td>
<td>15,244,082</td>
<td>100.0%</td>
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<tr>
<td>Other</td>
<td>8,048,757</td>
<td>53.3%</td>
<td>9,567,560</td>
<td>63.3%</td>
<td>10,560,177</td>
<td>69.9%</td>
<td>15,111,418</td>
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<td>American Indian</td>
<td>509,505</td>
<td>20.0%</td>
<td>675,804</td>
<td>26.5%</td>
<td>866,548</td>
<td>34.0%</td>
<td>2,550,780</td>
<td>100.0%</td>
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<tr>
<td>Pacific Islander</td>
<td>197,664</td>
<td>37.6%</td>
<td>235,546</td>
<td>44.8%</td>
<td>267,158</td>
<td>50.8%</td>
<td>526,408</td>
<td>100.0%</td>
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</tbody>
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NINDS Networks
StrokeNet Clinical Trials Activities

Completed:
• **MISTIE-3**  Minimally Invasive Surgery for ICH evacuation trial ($N=500$) *
• **i-DEF**  Deferoxamine mesylate treatment for ICH trial ($N=293$) *
• **DEFUSE-3**  Delayed endovascular therapy for select patients ($N=182$)
• **TeleRehab**  Home based telerehabilitation stroke recovery trial ($N=124$)

Ongoing:
• **CREST-2**  Treatment of asymptomatic carotid stenosis ($N=2480$) *
  • **CREST-H**  Hemodynamic impairment ancillary study in CREST-2 ($N=500$)
• **ARCADIA**  Apixaban vs. aspirin for cryptogenic stroke ($N=1100$)
• **MOST**  Optimization of thrombolysis ischemic stroke trial ($N=1200$)
• **Sleep-SMART**  Treatment of obstructive sleep apnea ($N=3062$)
• **TRANSPORT-2**  Transcranial direct stimulation stroke recovery trial ($N=129$)
• **I-ACQUIRE**  Intensive infant rehabilitation for pediatric stroke ($N=240$)
NINDS Networks
Strategies to Innovate Emergency Care Clinical Trials Network (SIREN)

Overview

• Established in 2017
• Co-Funded with NHLBI
• 11 regional centers with 50 satellite ER sites, coordinating and data center
• SIREN improves the outcomes of patients with neurologic, cardiac, respiratory, hematologic and traumatic emergencies by identifying effective treatments administered in the earliest stages of critical care

https://siren.network/
Ongoing:

- **HOBIT**  Hyperbaric oxygen therapy in severe TBI (N=200)
  - Signal of efficacy: to determine whether there is a > 50% probability of hyperoxia treatment
  - Dose selection: to select the combination of treatment parameters (pressure +/- intervening normobaric hyperoxia)

- **BOOST**  Brain oxygen optimization in severe TBI (N=1094)
  - Whether PbTO2 monitoring vs ICP monitoring results in improved neurological outcomes measured by the GOS-E
NINDS Networks
HEAL: NINDS Early Phase Pain Investigation Clinical Network (EPPIC-NETT)

Overview

- FOA in Dec 2018
- Phase II studies
- Infrastructure applications in Feb 2019
- Anticipated funding in July 2019
- A cornerstone of the NIH’s Helping to End Addiction Long-term (HEAL) Partnership.
- Provides a robust and readily accessible infrastructure for the rapid implementation and performance of high-quality Phase 2 clinical trials to test promising novel pain therapeutics
Most trials completed enrollment ahead of schedule (N=3) or on-time (N=13), and without need for additional funding

Able to assess feasibility before funding trials

Efficient management of competing trials

Reduced need for de novo monitoring site visits

Workforce stability facilitates quicker trial activities initiation

Able to combine large meetings (e.g. Steering Committee and Investigator meetings) providing $100Ks in additional saving

Innovative master agreement contracting reduced F&A costs across trials

Successfully training fellows and junior faculty

Effectively involving smaller non-research hospitals in clinical research