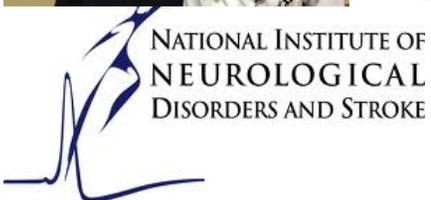


# NN Neuro NEXT

The NEXT Generation of Neurologic Treatments  
NIH-Network for Excellence in Neuroscience Clinical Trials





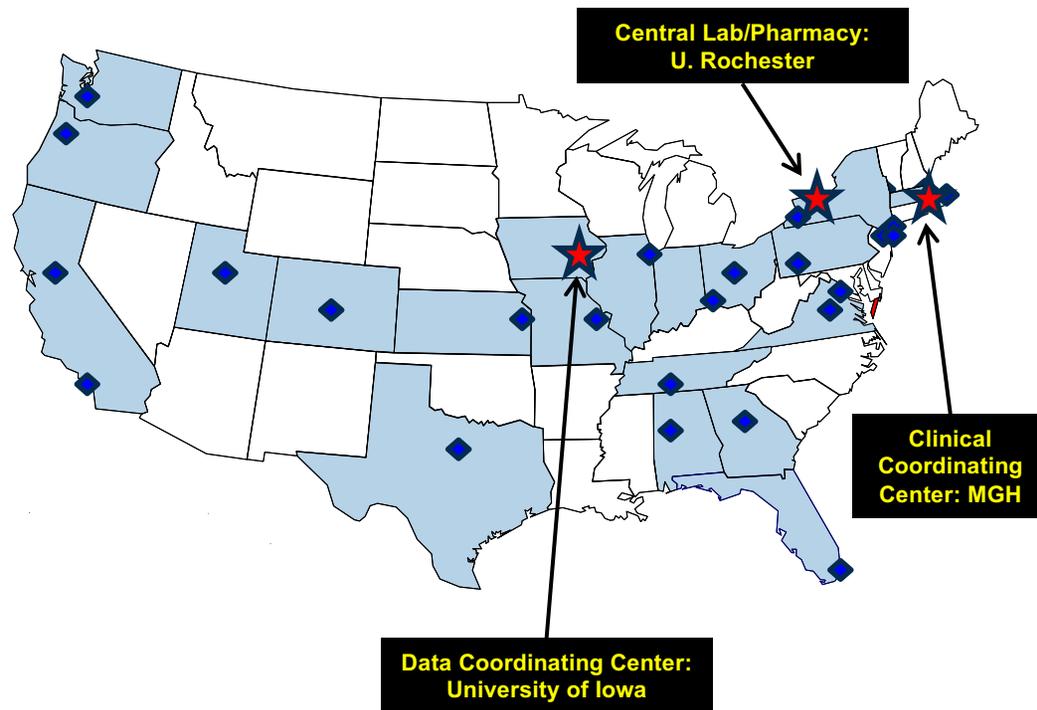
# NeuroNEXT Overview

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# Network Infrastructure

## NeuroNEXT Coordinating Centers and Clinical Sites



For additional information,  
visit: [www.neuronext.org](http://www.neuronext.org)

# Network Vision

Conduct studies in neurological diseases through partnership with academia, private foundations and industry

Expand the NINDS capability to:

- Respond quickly as new opportunities arise to test promising therapies for people with neurological disorders
- Test promising new therapies
- Increase efficiency of clinical trials before embarking on larger studies

# [ Novel Initiatives of Network

- Utilization of a Central IRB (CIRB) of record
- Pre-existing Master Clinical Trial Agreements (MCT) between the CCC and all clinical study sites
- **Availability of experienced trial design staff to assist with protocol and grant development**
- Experienced sites with full time funded coordinator and record of high enrollment and quality study conduct

# NeuroNEXT Applications (as of 12/1/16)

Over 165 Proposals received to date

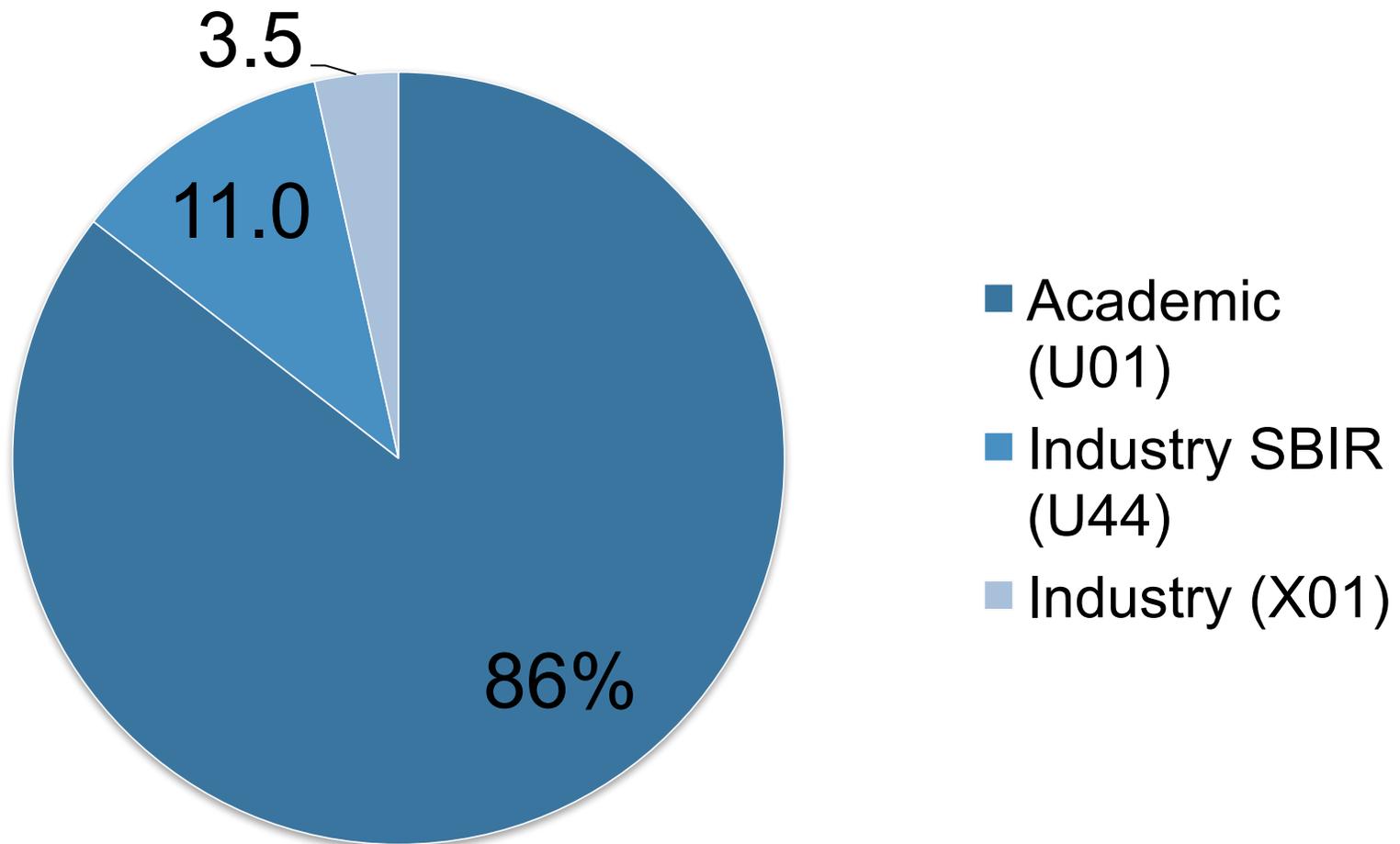


Most Frequent Indications	#
Stroke	19
Parkinson's Disease	17
Epilepsy	15
Autism	8
Multiple Sclerosis	8
Traumatic Brain Injury	8
ALS/PLS	7
Neuropathy	7
Charcot-Marie-Tooth	4
Duchenne Muscular Dystrophy	4
SMA	4
Cerebral palsy	4
Diabetic Neuropathy	3

*Several other indications had one or two proposals each*

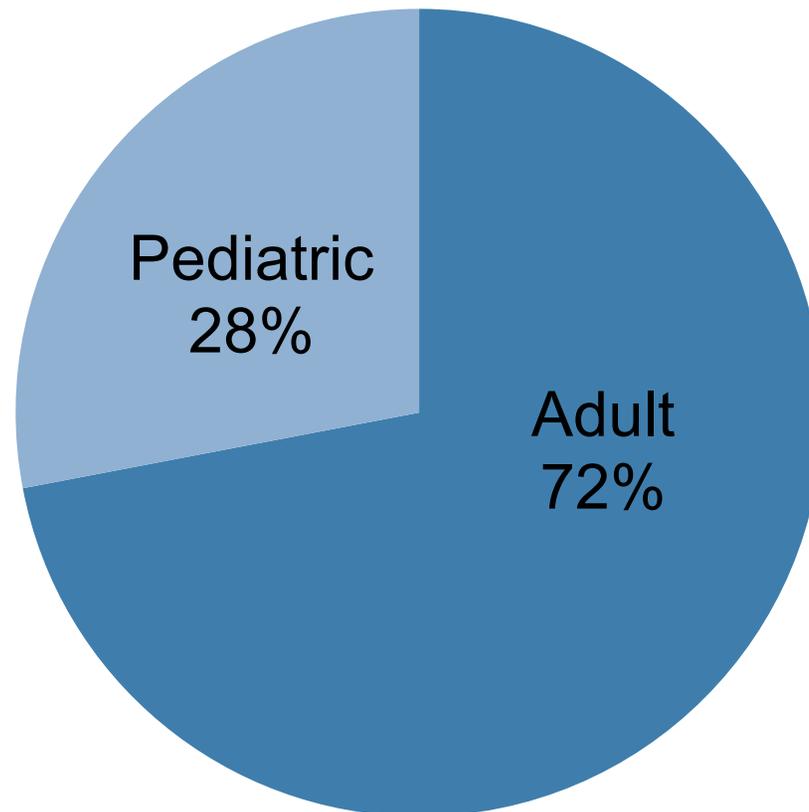
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# Who submits Proposals? (as of 12/1/16)



# Majority Targeting Adult Conditions

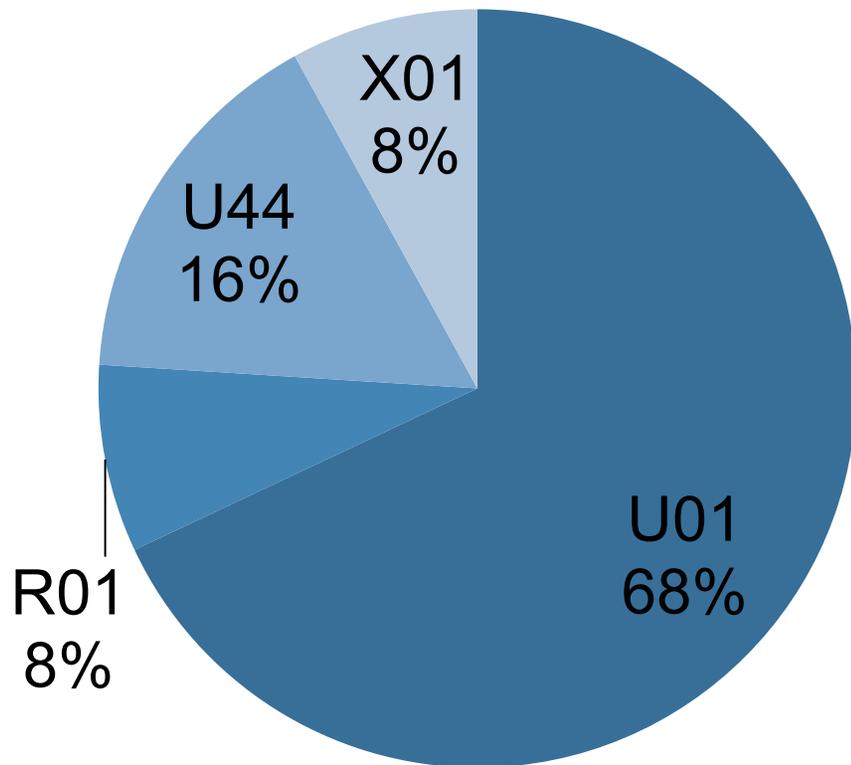
**% submitted to NEC for Review**



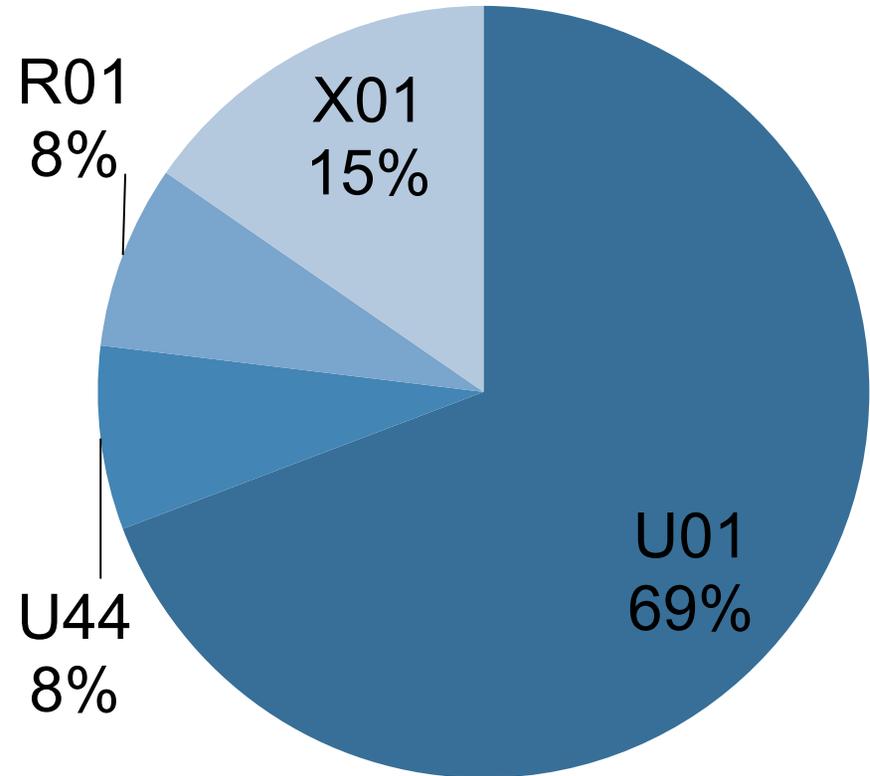
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# Grant Submissions (as of 12/1/16)

25 Initial Submissions



13 Re-submissions



# Timeline to grant submissions

- 25 Initial grants submitted – **1 funded!**
  - Median time from proposal submission to initial grant submission = **10 months**
  - Median time from NEC approval to initial grant submission = **8 months**
- 13 grants resubmitted – **8 funded**
  - Median time from proposal submission to grant resubmission = **19 months**
  - Median time from date initial reviews released to resubmission = **3.5 months**

# Summary Statements – Nonfunded

- Scientific Rationale/Significance: First or second reasons in 87%
  - # 1 reason in 16/23 (70%)
  - # 2 reason in 4/23 (17%)
- Dosing/PK/PD: First or second reasons in 47%
  - # 1 reason in 1/23 (4%)
  - # 2 reason in 10/23 (43%)
- Trial Design: First or second reasons in 30%
  - # 1 reason in 4/23 (17%)
  - # 2 reason in 3/23 (13%)
- Outcome Measures: First or second reasons in 26%
  - # 1 reason in 2/23 (9%)
  - # 2 reason in 4/23 (17%)



# Trial Design – Case Studies

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# Trial Design Overview

- **Confirmatory Designs:**
  - Large sample sizes
  - Many standard designs



- **Learning Stage Designs:**
  - Efficiency is critical
  - Carefully evaluate alternative designs



# [ Requirements – Any Clinical Trial

- 1) **Examine an important research question**
- 2) Use rigorous methodology to answer the question of interest
- 3) Assure that risks to subjects are minimized

Due to size limitations, meeting these requirements in early phase clinical trials can be a challenge.

As a consequence, the importance of study planning is magnified in these settings.

# [Phase I Studies

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Once a new drug has passed preclinical investigations, phase I trials represent the first application of a new drug on humans.

- Generally small: 20-30 subjects
- Risk of toxicity assumed to increase with dose
- Usually, benefit of new treatment also assumed to increase with dose
- Establish safety of new drug, and determine dose(s) to use in subsequent studies

# [Phase I Studies

---

Accurate determination of the MTD is critical, since it will likely be used as the maximum dose in future clinical development.

- If dose too low, a potentially useful drug could be missed
- If dose too high, participants in future studies could be put at risk

# NeuroNEXT NN104 Study



## ➤ NN-104 - RHAPSODY

- **PI:** Pat Lyden (Cedars Sinai)
- **Primary Objective:** To evaluate safety of multiple ascending IV doses of 3K3A-APC following tPA in subjects who have experienced moderately severe acute hemispheric ischemic stroke
- **Key Secondary Objective:** To evaluate effect of 3K3A-APC on presence of tPA-related bleeding (hemorrhage and microbleeds) in the brain as determined by MRI at Day 30

# NeuroNEXT NN104 Study

## Desired Study Parameters:

- Placebo group included for secondary comparison of intracranial bleeding rates
- Enroll approximately 100 subjects
  - 88 subjects in groups of four (3 treated / 1 placebo)
  - Default to placebo during safety review pauses
- MTD defined as highest dose with an estimated dose limiting toxicity (DLT) rate of 10% or less
- Four dose levels under consideration

# [ NeuroNEXT NN104 Study

## Best study design to achieve all objectives?

### 1) Conventional 3+3 Design:

- Simple and intuitive algorithm
- Easy to implement and monitor – requires no computer program
- Familiar to many clinicians

### 2) Continual Reassessment Method:

- First cohort treated at lowest dose
- Subsequent doses determined using re-estimated dose-response curve using all prior data to determine highest dose with estimated toxicity less than or equal to 10%.

# NeuroNEXT NN104 Study

To compare ability of designs to meet study objectives, conducted simulation study across range of scenarios:

Scenario	Prob. Of Correctly Choosing MTD		Prob. Of Overshooting MTD	
	3+3	CRM	3+3	CRM
1: All Doses Safe	91%	90%	--	--
2: Dose 4 MTD	86%	68%	--	--
3: Dose 3 MTD	19%	32%	74%	31%
4: Dose 2 MTD	8%	42%	88%	30%
5: Dose 1 MTD	9%	53%	88%	26%
6: No Dose Safe	6%	60%	94%	40%

# NeuroNEXT NN104 Study

- Also found that CRM design provided adequate power to detect differences in bleeding of interest, under reasonable assumptions
- Choosing final design required many discussions with a diverse group of investigators across multiple organizations
- Existence of NeuroNEXT infrastructure made this much more feasible, and provide support to conduct a thorough simulation study to assess the properties of various options

# [Phase II Studies

After one or more successful phase I studies have been completed, phase II studies may be initiated.

- Larger sample sizes: 50-200 subjects
- May or may not contain concurrent control group
- May be more important to control type II error rates – WHY?
- Selection of design & endpoint critical to shorten study duration compared to phase III trials
- May have strict eligibility criteria

# [Phase II Studies

## Main Goals:

- Provide assessment of preliminary efficacy
  - Screen out ineffective treatments
  - Determine if new treatment is sufficiently promising to justify inclusion in large-scale randomized trials
- Further characterize the safety profile

# [Phase II Studies

Avoid early phase designs that look to simply be an underpowered phase III study.

- “Treatment Effects” estimated in pilot studies often tend to be over-estimates of true effect

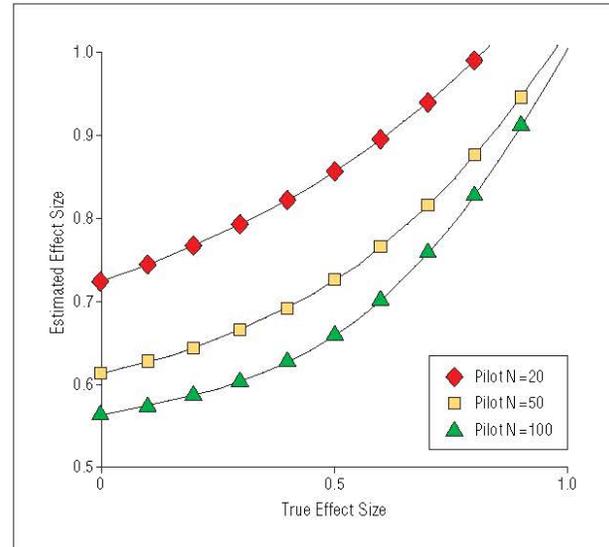


Figure 3. The estimated effect size if the study is not aborted, relative to the true effect size using pilot studies with sample sizes of 20, 50, and 100.

# [Phase II Studies

Due to concerns about missing an important effect, researchers may be tempted to include a large number of endpoints.

- When this occurs, study design often calls for “going forward” if any endpoint shows hint of an effect
- However, this type of design will almost always “go forward” – even if treatment does not work

# [Phase II Studies

Due to budgetary constraints, researchers may insist on sample size limitations, regardless of whether there is scientific justification.

- Study may not be able to adequately answer question of interest
- Results become somewhat subjective
  - A researcher who views treatment favorably will likely see positive trends
  - A researcher who views treatment unfavorably will likely see negative trends

# [Phase II Studies

Due to business implications, early phase studies with positive findings are more likely to be highlighted.

- Early reports of positive findings may be real, or due mostly to 'chance'
  - Could suggest intervention works
  - Could suggest intervention does not work, and results were solely due to chance
- If researchers looked at large number of endpoints, may be tempted to emphasize those that give positive results while de-emphasizing those that give negative results

# [ Surrogate Endpoint Design

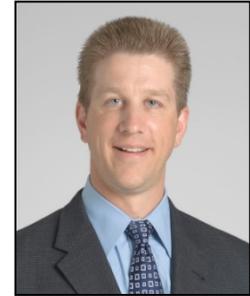
As previously discussed, a surrogate endpoint (biomarker) can be measured earlier, easier, and more frequently than many standard clinical endpoints.

A surrogate endpoint design allows using surrogate for 'go' / 'no go' decision making.

This often leads to reduced sample size or length of study – allowing screening process to move more efficiently.

Subsequent confirmatory studies can still be powered on the gold standard clinical endpoint.

# NeuroNEXT NN102 Study



## NN-102 SPRINT-MS Study:

- A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Activity of Ibudilast (MN-166) in Subjects with Progressive Multiple Sclerosis

- PI: Robert Fox (Cleveland Clinic)
- Primary Objective:

Evaluate activity, safety, and tolerability of ibudilast (MN-166 – 100 mg/day) versus placebo administered orally in subjects with primary progressive and secondary progressive multiple sclerosis

# NeuroNEXT NN102 Study

## Primary Activity Endpoint:

- Covariate-adjusted mean rate of change in brain atrophy over 96 weeks, as measured by brain parenchymal fraction (BPF)

## Secondary Clinical Endpoints:

- Disability – As measured by:
  - Expanded Disability Status Scale (EDSS)
  - Multiple Sclerosis Functional Composite (MSFC)
- If positive results obtained on BPF endpoint, one of these secondary clinical endpoints is likely primary outcome in subsequent trials

# [ Futility Design

A futility (non-superiority) design is a screening tool to identify whether agents should be candidates for phase III trials while minimizing costs/sample size.

- If “futility” is declared, results would imply not cost effective to conduct a future phase III trial
- If “futility” is not declared, suggests that there could be a clinically meaningful effect which should be explored in a larger, phase III trial

# Futility Design

Statistical Properties:

	<b>Null Hypothesis (H<sub>0</sub>)</b>	<b>Alternative Hypothesis (H<sub>A</sub>)</b>	<b>Rejecting H<sub>0</sub></b>	<b>Type I Error (α)</b>	<b>Type II Error (β)</b>
<b>Usual Design</b>	$\mu_T = \mu_P$	$\mu_T \neq \mu_P$	<b>New Treatment is Effective (Harmful)</b>	<b>Ineffective Therapy is Effective</b>	<b>Effective Therapy is Ineffective</b>
<b>Futility Design</b>	$\mu_T - \mu_P \geq 0$	$\mu_T - \mu_P < 0$	<b>New Treatment is Futile</b>	<b>Effective Therapy is Ineffective</b>	<b>Ineffective Therapy is Effective</b>

# [ Futility Design

- High negative predictive values:  
If “futility” declared, treatment likely not effective
- Low positive predictive values:  
Lack of “futility” does not imply treatment is effective

Thus, futility designs are good at identifying ineffective treatments, but not very good at identifying effective treatments.

However, improvement over running underpowered efficacy trials in phase II or conducting phase III trials as first rigorous test of efficacy for a new treatment.

# NeuroNEXT NN103 Study



## ➤ NN-103 - BeatMG

- **PI:** Richard Nowak (Yale)
- A previous study at Yale demonstrated that ~80% of subjects treated with rituximab achieved at least a 75% reduction in their prednisone dose at 52 weeks
- **Primary Objective:** Determine whether large benefit observed in prior Yale study can be refuted in a multi-site trial, or looks promising enough to justify a future phase III trial (“go”)

# NeuroNEXT NN103 Study

Suppose a 30% increase in favorable response rates (achieving a 75% reduction in prednisone dose) with rituximab over placebo is clinically meaningful.

This futility design tests the following hypothesis:

$H_0$ : Rituximab improves outcome by at least 30% compared to placebo  
( $p_R - p_P \geq 0.30$  – not futile)

versus

$H_A$ : Rituximab does not improve outcome by at least 30% compared to placebo  
( $p_R - p_P < 0.30$  – futile)

# NeuroNEXT NN103 Study

Power to declare “futility” for range of true response rates for rituximab (assumes placebo rate of 40%):

Rituximab Rate ( $p_R$ )	30%	35%	40%	45%	50%	60%	70%	80%	90%
Pr (Futility)	92%	84%	74%	63%	50%	25%	10%	2%	<1%

Table demonstrates benefits of using futility design, if true rituximab success rate:

- Near/below placebo rate, declare “futility” with high probability
- Well above placebo rate, low probability of declaring “futility”
- In between, uncertainty to address in subsequent trial

# NeuroNEXT NN103 Study

- Futility design was an attractive option that met the competing needs of this study
- Because of unfamiliarity of researchers with design, required a lot of discussion and explanation during design phase
- Again, feasibility of achieving this with investigators across multiple institutions would have been very difficult without existing NeuroNEXT infrastructure



# Network Summary Metrics

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# [ Increased Efficiency

Network Coordinator at each site ensures efficient study start up and quality data collection in funded studies:

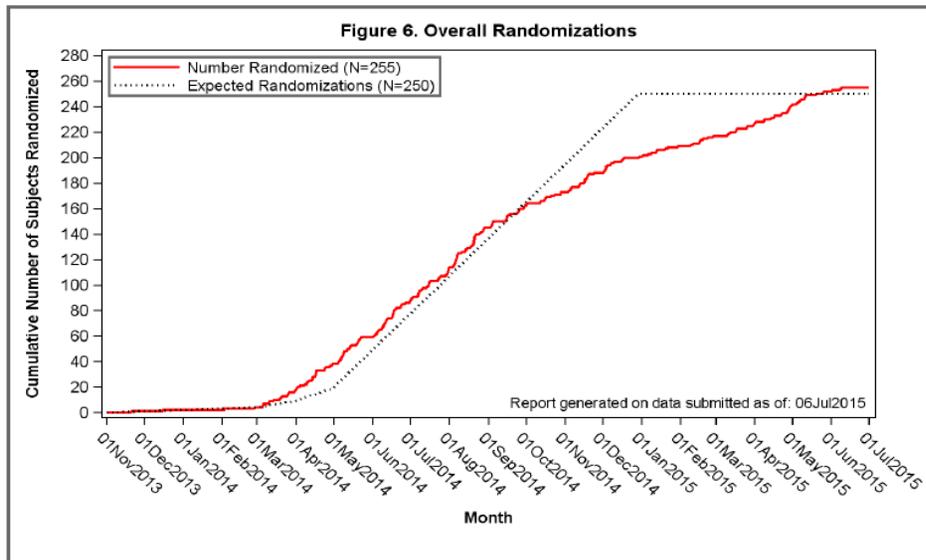
- Reduced time for contract execution
- Reduced time for CIRB protocol approval
- Reduced time from Notice of Award to:
  - Database Ready
  - 1<sup>st</sup> Site Activated
  - 1<sup>st</sup> Subject Enrolled

# [ Network Efficiency

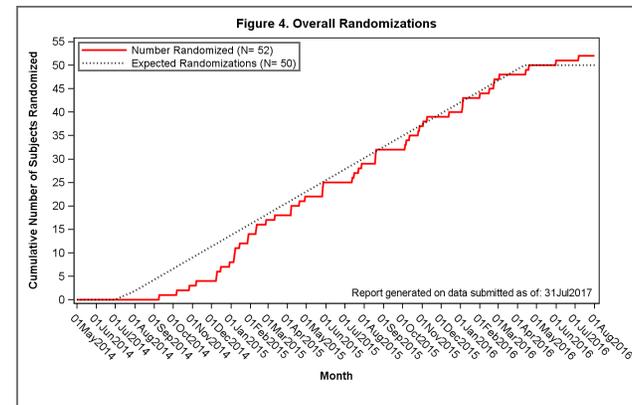
- Startup
  - Time from NoGA to 1<sup>st</sup> subject enrolled – median of 90 days shorter than non-NN studies
- Recruitment examples
  - NN102/SPRINT – MS – Recruitment rate > 2 x comparable studies (savings of 21.8 months)
  - NN103/Beat-MG – Recruitment rate 2x comparable studies (savings of 20 months)
- Data cleaning/closeout

# Network Enrollment

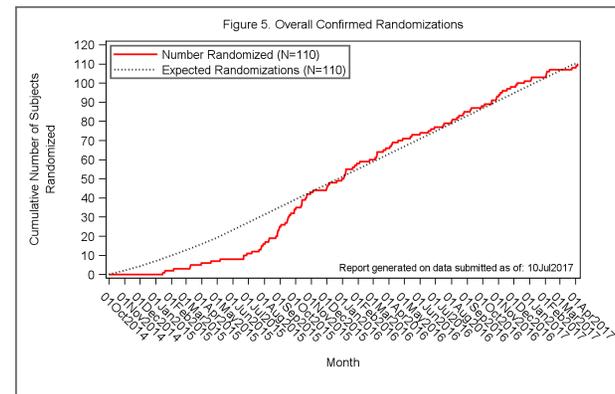
## NN102 Enrollment:



## NN103 Enrollment:



## NN104 Enrollment:



# Network Accomplishments

- ✓ **Test promising (new) agents in Phase 2 clinical trials**
  - NN102, NN104, NN105, NN107, NN108
- ✓ **Establish efficient clinical trials infrastructure**
  - Central IRB (first for NINDS)
  - Master clinical trial agreements
  - Optimal use of NINDS CDEs
- ✓ **Coordinate public/private sector efforts**
- ✓ **Conduct clinical trials/biomarker studies with**
  - Academics – NN101, NN102, NN103, NN104, NN106, NN107, NN108
  - Small business – NN105
  - Industry partnerships – NN102 and NN104
- ✓ **All studies enrolling on time and sites providing high quality data!**



Questions?