NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

StrokeNet: Update Current Trials

Joe Broderick

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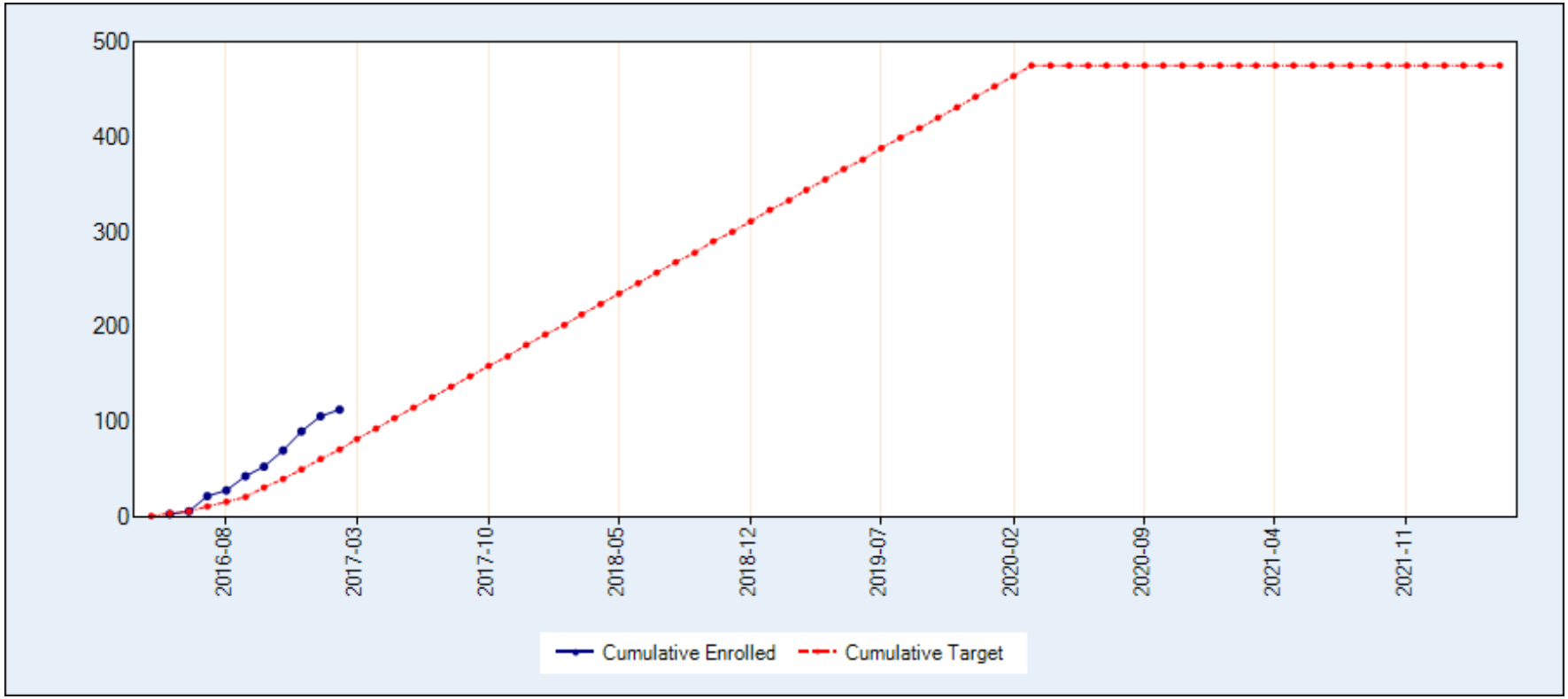
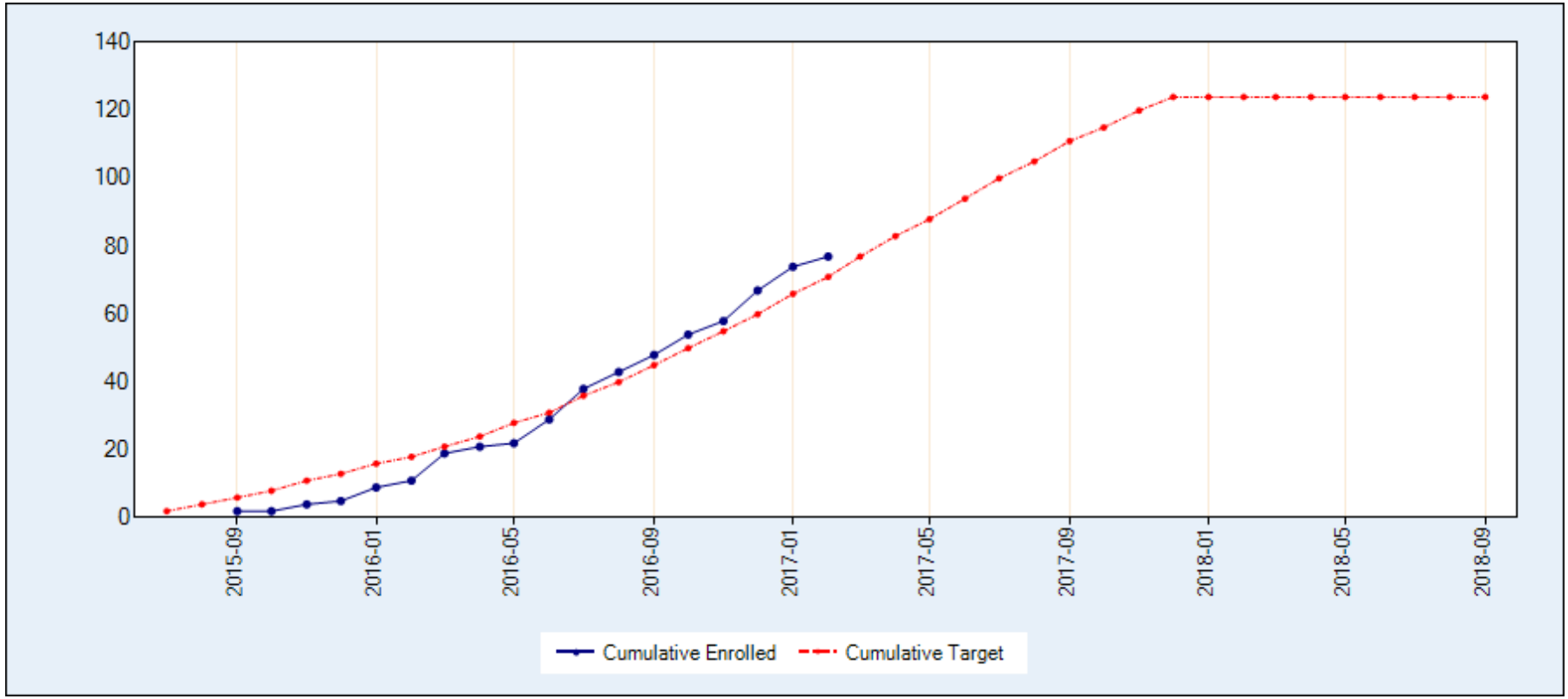
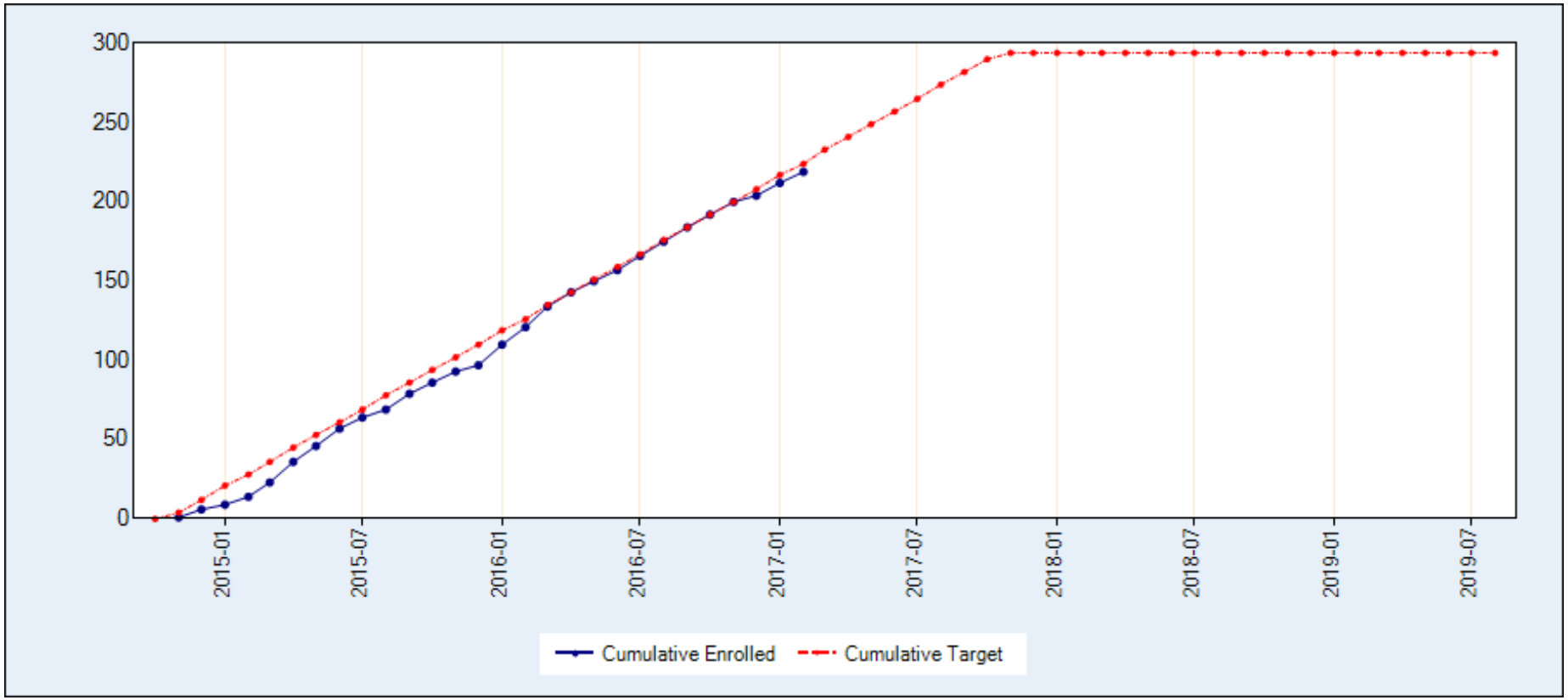
DEFUSE III – N = 114 (2-14-2017)



TELEREHAB – N = 77 (2-14-2017)

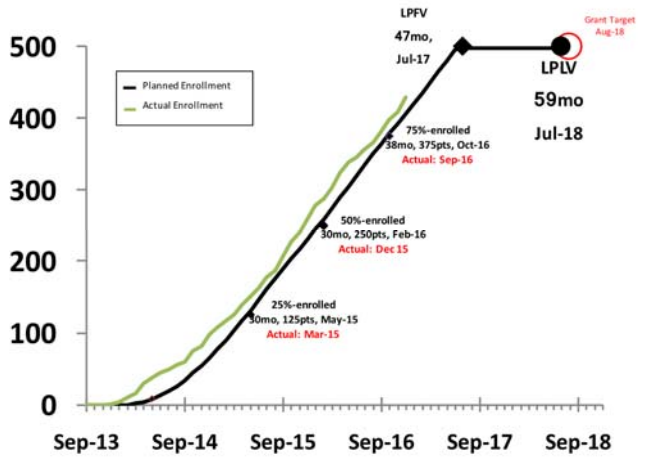


iDEF – N = 219 (2-14-2017)



Recruitment

- Total enrolled: 450/500 (90%)
- Date first subject enrolled: 12/30/2013
- Total number of sites opened to enrollment (in 9 countries): 101
- Total number of sites currently active: 72/101 (71%)
- Total number of sites enrolling: 77/101 (76%)



MISTIE III enrollment projection as of 31-Dec-2016

Comparison of Activated StrokeNet vs. All Non StrokeNet Sites

	Total Sites	% of Sites (n=101)	% of Randomizations (n=450)
StrokeNet Hub	10	10%	12%
StrokeNet Spoke	20	20%	27%
Non StrokeNet	71	70%	61%
Total	101	100%	100%

MISTIE III

*Includes sites on administrative hold and closed sites

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StrokeNet: Event Reporting

Joe Broderick

FDA Definitions of Adverse Events

- ***Adverse event*** means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- ***Life-threatening adverse event* or *life-threatening suspected adverse reaction.*** An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

FDA Definitions of Adverse Events

- ***Serious adverse event* or *serious suspected adverse reaction.*** An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- ***THESE EVENTS SHOULD BE PUT IN WebDCU WITHIN 24 HOURS*** and site investigator has primary responsibility although coordinator often enters information

FDA Definitions of Adverse Events

- ***Suspected adverse reaction*** means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

FDA Definitions of Adverse Events

- ***Unexpected adverse event* or *unexpected suspected adverse reaction.*** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
- For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

FDA Definitions of Adverse Events

- ***Serious* and *unexpected* suspected *adverse reaction*.** The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.
  - Serious, unexpected, and possibly causally related to therapy being tested.
  - Example: #1 – sICH in setting of protocol violation related to use of IA t-PA
    - #2 – anaphylactoid reaction after study medication that required hospitalization and risk not included in the informed consent
- **These are the events that FDA requires very prompt reporting.**

cIRB Reporting SOP (#ADM 12)

- **Required Report(s) – Site responsibility:** A report that must be submitted to the CIRB during the course of a trial.
  - unanticipated problems (including adverse events), injuries to subjects,
  - protocol deviations/violations
  - changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s
  - Complaints
  - non-compliance
  - cessation of research activities

cIRB Reporting SOP (#ADM 12)

- **Adverse event - OHRP**
  - "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research."
- **Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)**
  - "any incident, experience, or outcome that [is] … unexpected … related or possibly related … and that suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized."
  - A small subset of adverse events are UPIRSO.
  - Adverse events that are identified as **serious, unexpected, and related or possibly related to participation in research will meet the criteria for an UPIRSO.**

24-HOUR TABLE - Site Responsibilities To Report Through WebDCU Within 24 HOURS (CIRB Liaison must report to CIRB within 9 DAYS)

Report Type	**Adverse Event (AE)**
Description	AEs that meet the definition of a UPIRSO, as described above.
Reporting Method	WebDCU™ AE Form
Report Type	**Unanticipated Adverse Device Effect (UADE)**
Description	UADE that m meet the definition of a UPIRSO, as described above.
Reporting Method	WebDCU™ AE Form
Report Type	**Significant Protocol Deviation**
Description	Any deviation from the CIRB-approved research that has the potential to negatively impact: 1) subject safety, 2) affects subject's willingness to participate in the study, or 3) alters the integrity of study data or related analyses.
Reporting Method	WebDCU™ Unanticipated Problem Form

Unless otherwise noted, reporting timelines are stated in terms of working days. Unless otherwise noted, times are calculated from the time the trial site PI becomes aware of the event or problem.

5 DAY TABLE --- Site Responsibilities To Report Through WebDCU Within 5 DAYS (CIRB Liaison must report to CIRB within 5 DAYS)

Report Type	**Serious Noncompliance**
Description	Any failure to comply with any applicable laws or regulations or the requirements or determinations of the CIRB that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data.
Reporting Method	WebDCU™ AE Form
Report Type	**Continuing Noncompliance**
Description	Continuing noncompliance means any noncompliance that occurs repeatedly after appropriate remedial education or corrective action has been instituted.
Reporting Method	WebDCU™ AE Form
Report Type	**Major complaint**
Description	A complaint that alleges that human participants are being put at increased risk compared with risk in consent form.
Reporting Method	WebDCU™ Unanticipated Problem Form

5 DAY TABLE --- Site Responsibilities To Report Through WebDCU Within 5 DAYS (CIRB Liaison must report to CIRB within 5 DAYS)

Report Type	**Major Subject Noncompliance**
Description	Any subject non-compliance from the CIRB-approved research that has the potential to negatively impact subject safety, affects subject's willingness to participate in the study, or alters the integrity of study data or related analyses.
Reporting Method	WebDCU™ AE Form
Report Type	**Minor Unapproved Protocol Deviation**
Description	Any deviation from the CIRB-approved research that is not a significant protocol deviation (as defined above).
Reporting Method	WebDCU™ AE Form

5 DAY TABLE --- Site Responsibilities To Report Through WebDCU Within 5 DAYS (CIRB Liaison must report to CIRB within 5 DAYS)

Report Type	**Unanticipated Event or Problem**
Description	Unanticipated problem involving risks to subjects or others means any incident, experience, information, outcome, or other problem that is unexpected given the research procedures and that indicates that the research places subjects at a greater risk of physical, psychological, economic, legal, or social harm than was previously known or recognized. Unanticipated problems include, but are not limited to: -An event that may require a change to the protocol and/or informed consent -Breach of confidentiality, e.g. loss of study data or compromised computer system -Incarceration of a participant in a protocol not approved to enroll prisoners -Unapproved change to protocol made to eliminate an apparent immediate hazard to a research participant
Reporting Method	WebDCU™ Unanticipated Problem Form

Other Site investigator Responsibilities To Report Through WebDCU)

Report Type	**Cessation of Research**
Description	See Unanticipated Problems if cessation is for safety problems. If this is not for a safety problem, cessation of research may be submitted as an administrative amendment. See below for Site Administrative Changes
Reporting Method	
Report Type	**Site Administrative Changes**
Description	This includes changes in PI, staff, address of the research site, change in contact information for the research site.
Reporting Method	Within 20 days of change or cessation, site should submit Administrative Amendment.
Report Type	**Monitoring/ Audit Findings/ Enforcement Action**
Description	Any adverse findings issued to, or enforcement action taken against, the PI, e.g., FDA Form 483 or Warning Letter, change in licensure or credentialing, OHRP determination letters, other administrative actions.
Reporting Method	Within 5 days, site should submit audit report or enforcement action to CIRB Liaison.

Other Site investigator Responsibilities To Report Through WebDCU)

Report Type	**Any other problem that affects risk to subject or others**
Description	The PI may report any other problem that affects the risk to subject or others, including those that might impact the Investigator Brochure, informed consent or protocol, and the IRB will address the report accordingly.
Reporting Method	Within 5 days, the site should contact CIRB Liaison for further instruction on best way to submit.

Future Directions NIH StrokeNet

- Renewal applications in the fall
  - Our goal is for everyone be successful. Recruitment in NINDS trials will be the most important factor.
- Review process for StrokeNet applications being revised by NINDS.
- Strongly encourage new trial ideas. Discuss and engage within Working Groups.
- Goal is 6-8 trials – homegrown from StrokeNet. MISTIE III, iDEF and even Telerehab will be completing recruitment in next year.
- Global network – simple trials or trials that can be replicated and pooled.

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