

Ethics and Bias of Enrolling in Competing Trials: a StrokeNet Survey & Status Update

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For the Committee:

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Brief summary of the issues:

- StrokeNet provides lots of trials
 - Patients are/will be eligible for >1 trial
 - Patients are typically not allowed to participate in > 1 clinical trial
- How do we determine what trials to disclose and offer to patients, particularly when time is limited?
- It is typically considered most ethical (least paternalistic, promotes autonomy) to disclose, discuss, and offer *all* available trials to a patient.
 - In tight time windows, does this create confusion and undue distress?
 - Is it even possible?
 - Will there be distrust, anger if study participants find out after-the-fact that there was an alternative they were not aware of? Particularly if their participation in the chosen study did not go as hoped?
- This gets even more complicated with triple priorities: acute, recovery, and prevention

Brief summary of the issues:

- Possible ways to address this:
 1. Full disclosure: all trials are fully discussed
 2. Paternalistic: we choose which trial is offered based on our own factors
 3. Random: we choose one trial to offer based on random factors
- Possible factors – all with possible scientific biases
 - Trial specific factors:
 - Time windows
 - Trial complexity
 - Quota urgency
 - Remuneration
 - Sponsoring trial agency
 - Patient clinical factors relevant to trial (HTN, DM, etc)
 - Site-specific factors:
 - Clinical coordinator availability
 - Site characteristics
 - Investigator belief in efficacy
 - Internal needs

Committee Charter / Purpose

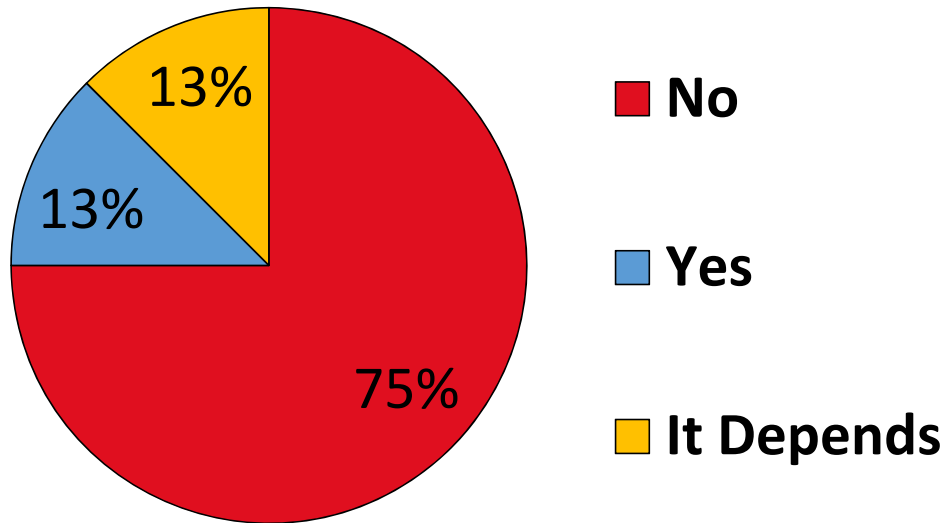
Provide guidance to the Network on how to approach discussing and offering enrollment to patients eligible for multiple trials

- StrokeNet Goals:
 - Minimize selection bias in StrokeNet trials
 - Maintain appropriate ethical principles of research: balancing research value, scientific validity, and respect for persons
 - Maximize patient enrollment
 - Respect autonomy of RCCs: unique structures, finances, and internal goals

Background: Data collection

- Dept of Health & Human Services (HHS)/ Office for Human Research Protections (OHRP): no guidance at this time
- FDA DRAFT Guidance for Informed Consent
- NIH Clinical Center, Department of Bioethics - Informal discussion
- Sampled University IRB policies, discussed with cIRB
- StrokeNet RCC SOPs (only 1 mentions this issue specifically)
- Published literature
 - *Coping with an Embarrassment of Riches: How Stroke Centers may Participate in Multiple, Concurrent Clinical Stroke Trials* (Saver, 1995)
 - *An Ethical Hierarchy for Decision-Making during Medical Emergencies* (Lyden, 2010)
 - *Competing for patients: an ethical framework for recruiting patients with brain tumors into clinical trials* (Ibrahim, 2011)
- Survey of current practices by StrokeNet RCCs: Response rate: 24/25 sites

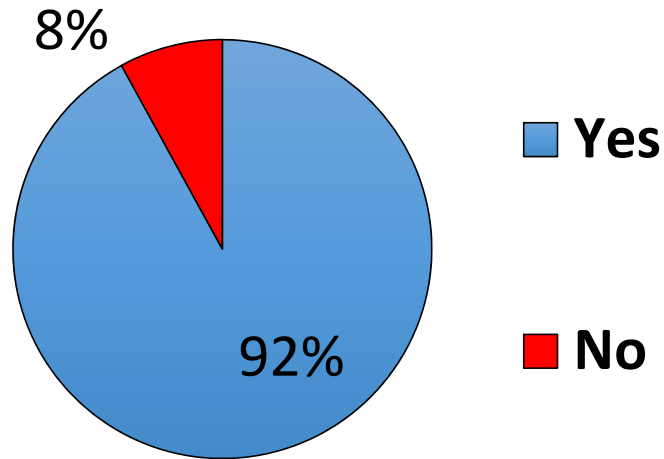
If a patient is eligible for more than one stroke trial, do you currently inform them of all available trial options?



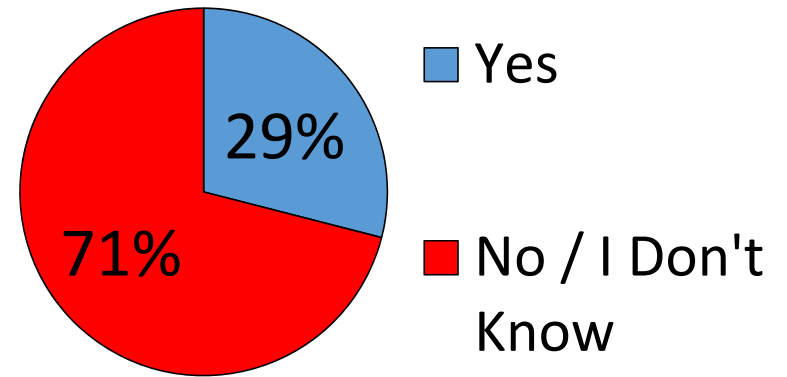
It Depends On:

- Acuity of trial (2)
- One site only informs of 1 main trial but their IRB requires all eligible trials to be disclosed (1)

Do you have a policy in place detailing which trial a stroke patient should be offered in the event he/she is eligible for multiple trials?

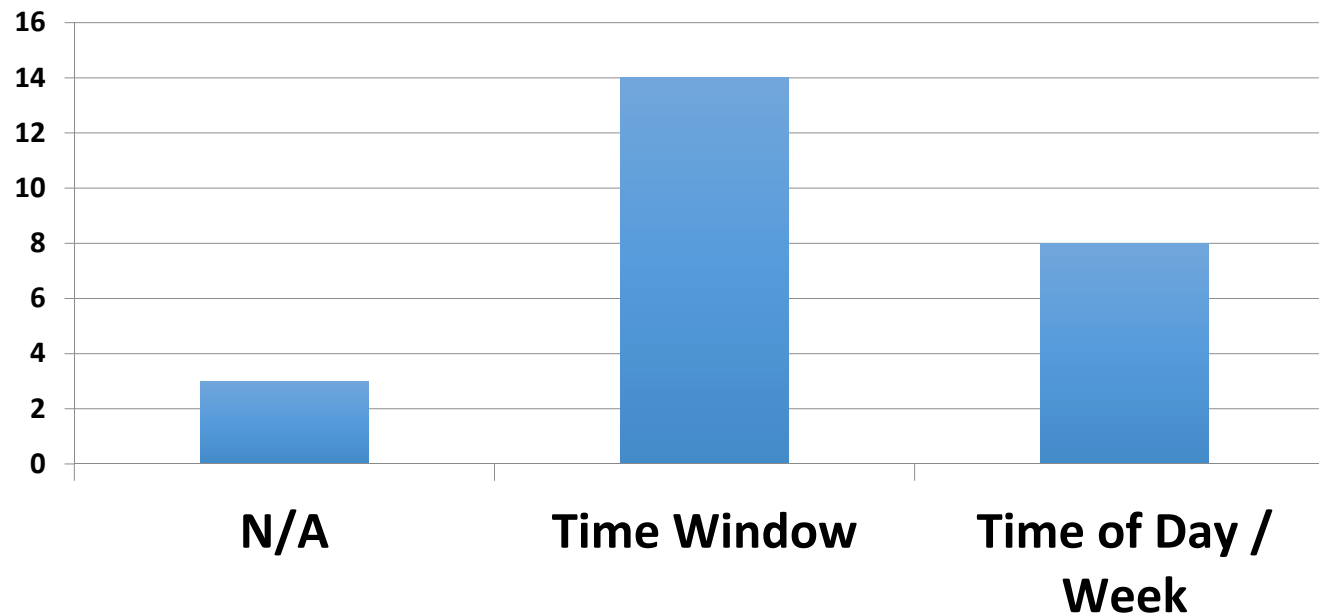


RCC



CPS's

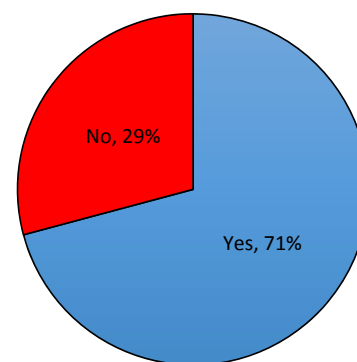
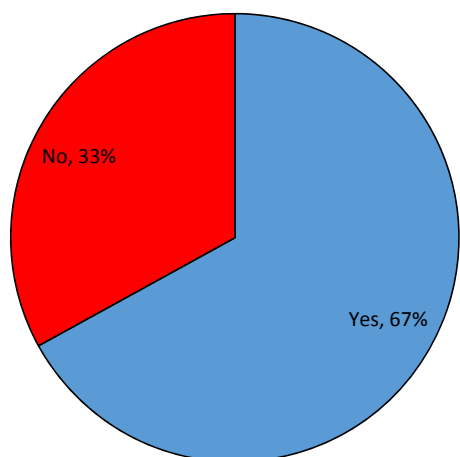
What factors affect *whether* you inform patients of their eligibility in multiple trials?



Study Allocation Methods from the Survey – common methods

- **Random Methods** (can be equal chance or biased coin):
 - Priority set for odd / even days or every other month
 - Random “hat” draw
- **Pre-Specified Allocation Grid Methods**
 - Priority set ahead of time. Does not have to be equal chance.
 - Sample factors:
 - Stratification by certain factors (e.g., time window)
 - “Importance to the field”
 - Funding source
 - PI (internal vs external)
 - Current enrollment success (quotas)
 - Time of day / week

Are you interested in a central option (e.g. WebDCU™) to assist in randomizing to individual trials by using screening criteria?

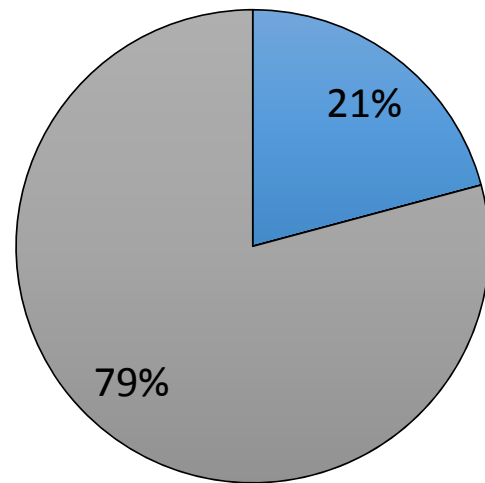


Would your interest in the central option increase if the system were operationalized to include non-StrokeNet trials?

(Only 1 additional yes)

Specific Competing Trial Scenarios

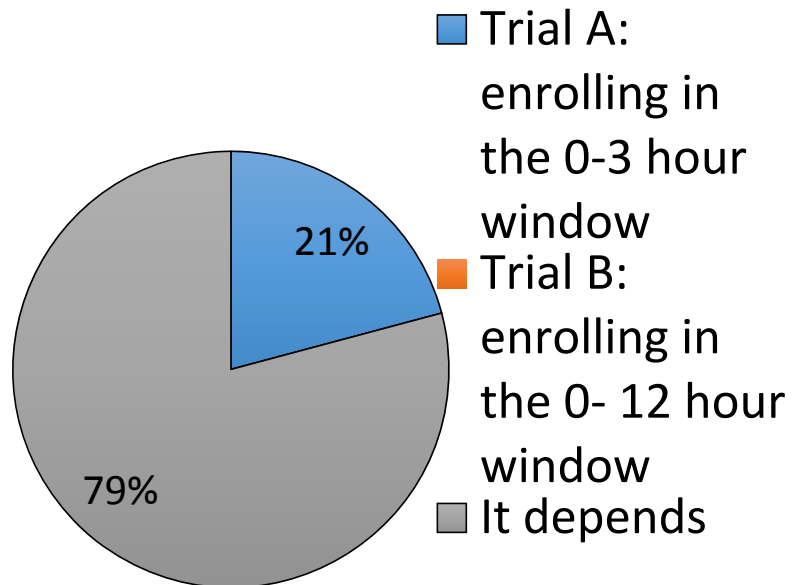
Which trial would you offer to a patient presenting at 90 minutes after stroke onset if eligible for both trials?



- Trial A: enrolling in the 0-3 hour window
- Trial B: enrolling in the 0-12 hour window
- It depends

Specific Competing Trial Scenarios

Which trial would you offer to a patient presenting at 90 minutes after stroke onset if eligible for both trials?

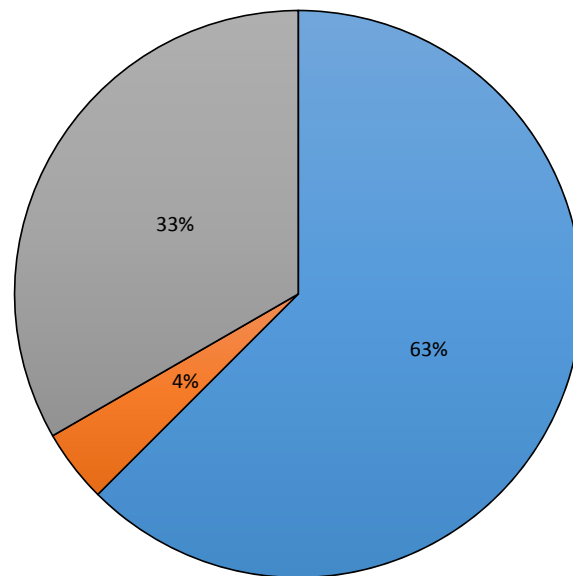


It Depends On (19):

- **Allocation Grid / randomization scheme (11)**
- **Best for patient (2)**
- **Trial intervention (reperfusion vs other) (2)**
- **Funding source (1)**
- **Previous enrollments, other factors (3)**

Specific Competing Trial Scenarios

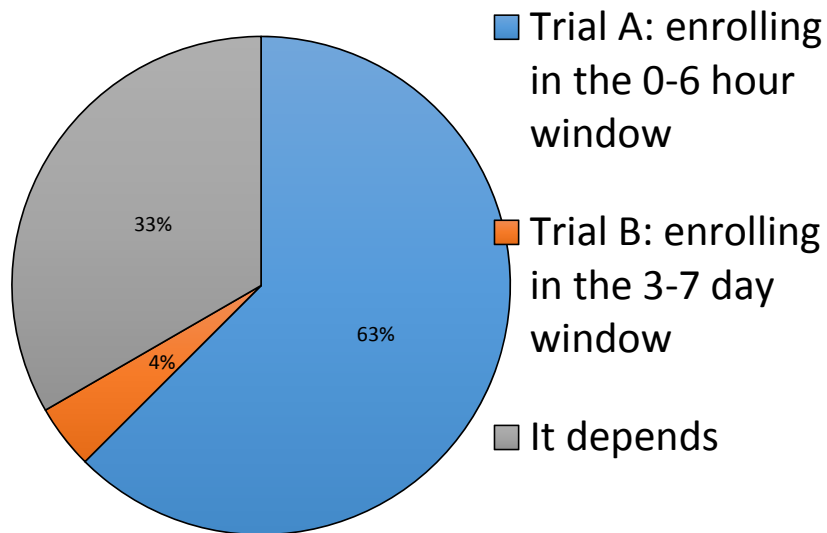
Which trial would you offer to a patient presenting at 2 hours after stroke onset if eligible for both trials?



- Trial A: enrolling in the 0-6 hour window
- Trial B: enrolling in the 3-7 day window
- It depends

Specific Competing Trial Scenarios

Which trial would you offer to a patient presenting at 2 hours after stroke onset if eligible for both trials?

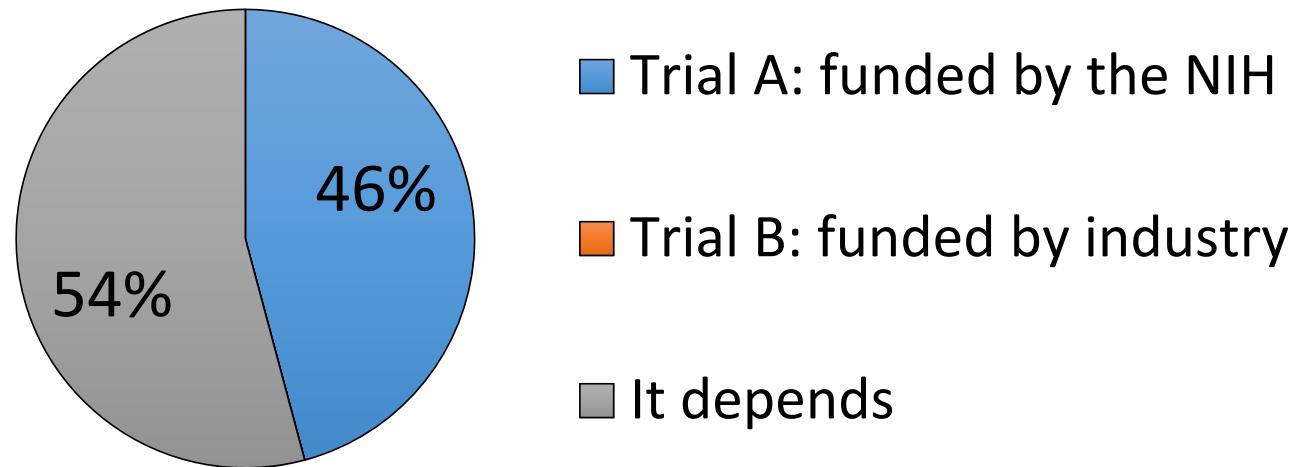


It Depends On:

- **Allocation / randomization scheme (4)**
- **Not actually competing (2)**
- **Best for patient (2)**
- **Other (funding, nursing) (2)**
- **“A” first but “B” if: under-enrolling, patient says “no” to A**
- **Hyperacute patients are more rare so choose A**

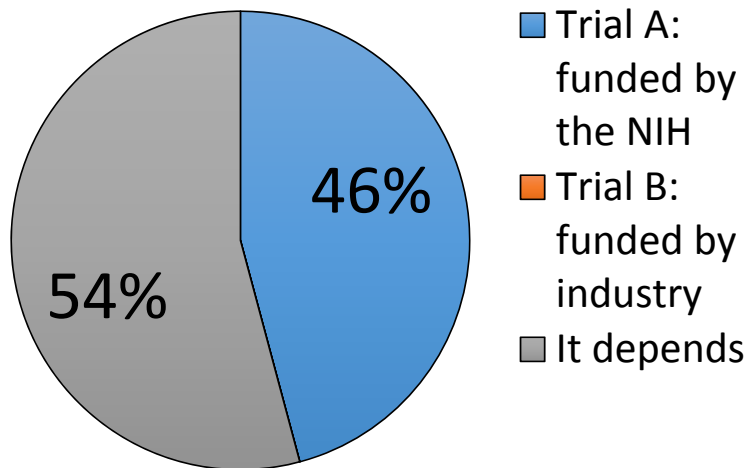
Specific Competing Trial Scenarios

Which trial would you offer to a stroke patient that met enrollment criteria for two trials in the same, hyperacute (0-6 hours) time period?



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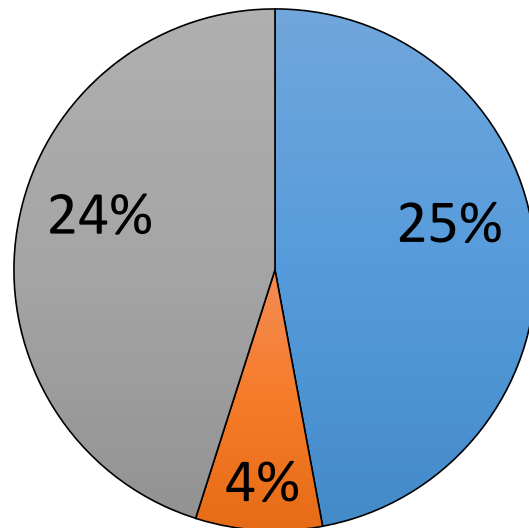


It Depends On:

- **Allocation / randomization scheme (8)**
- **Best for patient (2)**
- **Trial intervention (reperfusion vs other) (1)**

Specific Competing Trial Scenarios

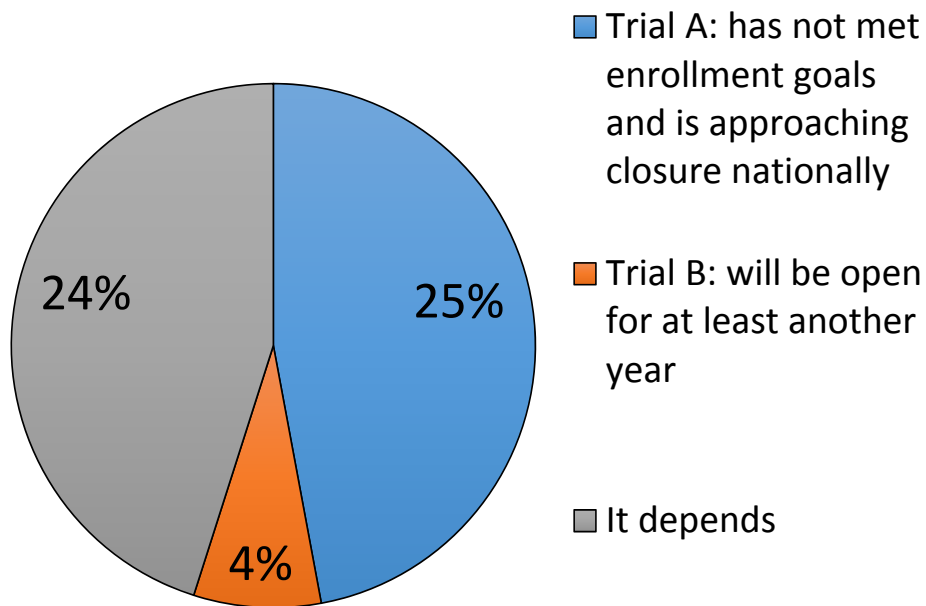
Which trial would you offer to a stroke patient that met enrollment criteria for both trials?



- Trial A: has not met enrollment goals and is approaching closure nationally
- Trial B: will be open for at least another year
- It depends

Specific Competing Trial Scenarios

Which trial would you offer to a stroke patient that met enrollment criteria for both trials?

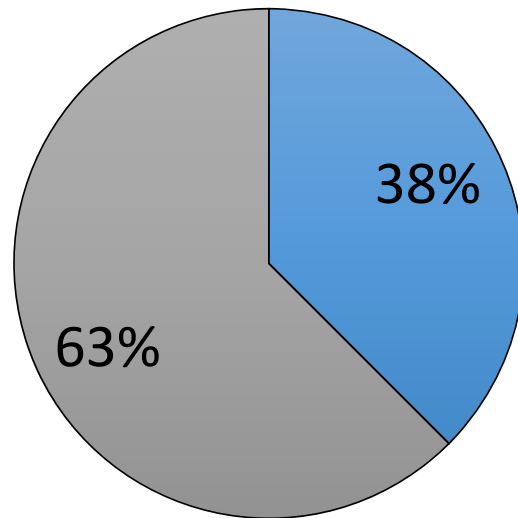


It Depends On:

- **Allocation / randomization scheme (10)**
- **Best for patient (4)**
- **Other (funding, nursing) (3)**

Specific Competing Trial Scenarios

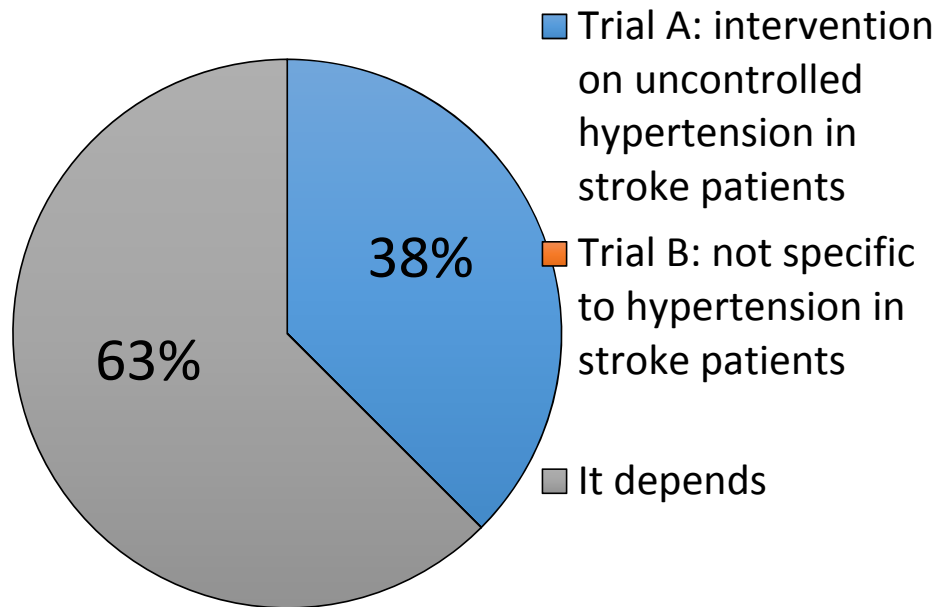
Which trial would you offer to an acute stroke patient with uncontrolled hypertension if eligible for both trials?



- Trial A: intervention on uncontrolled hypertension in stroke patients
- Trial B: not specific to hypertension in stroke patients
- It depends

Specific Competing Trial Scenarios

Which trial would you offer to an acute stroke patient with uncontrolled hypertension if eligible for both trials?



It Depends On:

- **Allocation / randomization scheme (8)**
- **Best for patient (1)**
- **Other (funding) (1)**

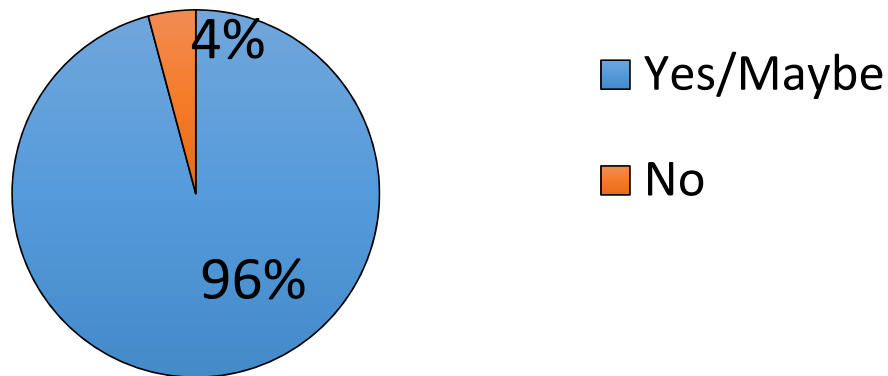
Additional Comments of Experience

- Create a local leadership team to provide consensus on how to determine prioritization
- Those that use allocation schemes often change them based upon enrollment goals / recruitment success
 - “If a trial has not met enrollment goals and is approaching closure nationally, then we may prioritize the trial in the rotation schedule. This would not be a decision made at the time of enrollment.”
- When possible, using a research enrollment team separate from the clinical care team can reduce conflict
- Non-trial studies: Determine how staff should approach patients enrolled in clinical trials for observational studies (blood draws, imaging studies)

Do These Trials Compete?

Could patients be enrolled in both of these trials
(non-concurrently)?

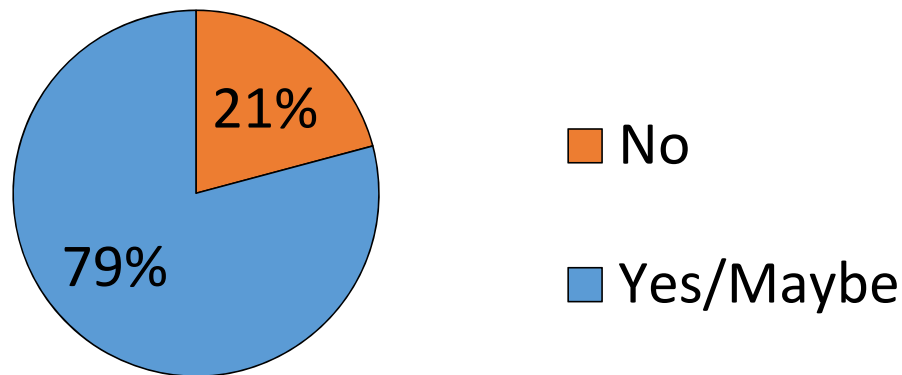
- Trial A: an acute stroke study of an investigational drug with a primary 90 day outcome measure
- Trial B: a rehabilitation trial with enrollment beginning after 90 days



Do these Trials Compete?

Could patients be enrolled in both of these trials (concurrently)?

- Trial A: a study with non-investigational, FDA-approved medications (e.g. clopidogrel vs placebo)
- Trial B: a study that is not affected by either of those medications (e.g. a rehab study of foot drop)



Comments on Competing Trials Definition

- Categories
 - Policy and Procedure
 - “Our institution does not allow enrollment into two interventional trials” (many responses)
 - “Trials A and B would both have to approve co-enrollment.”
 - IRB asks: Is patient risk increased?
 - Patient Burden
 - “We try not to dual enroll in therapeutic trials to minimize study fatigue.”
 - Scientific data integrity
 - Difficulty in assigning any AE/SAE to correct trial
 - Outcomes may be affected by both trials
- In StrokeNet: opportunity to define what constitutes “competing” trial-by-trial

Summary of Survey

Areas of Agreement

- Vast majority do not offer all trials to acute patients
- Recovery trials: different story
- Most RCC's claim to have a policy in place (not SOPs though?)
- Most view acute patients as more "valuable" than sub-acute because they are rarer

Areas of Divergence

- Most CPS's do not have policies
- How studies are prioritized varies by site; some are doing at time of enrollment
- Use of centralized WebDCU for randomization of trial choice
- Definitions of competing trials

Draft Guideline Elements

1. When timeframes permit, all trials for which a patient is eligible should be discussed with the patient / family. This is expected to be the case for prevention and recovery trials.

Draft Guideline Elements

2. For acute trials, where investigators have only minutes to hours to treat a patient with standard of care therapies and to enroll in studies, practical considerations may outweigh the most ethical considerations. In these time windows, only one trial should be offered to a patient at a time.
 - Open: whether or not to disclose other trials exist
 - Open: whether or not a second trial should be offered if the first is refused is left to the sites but patient fatigue may mount as more trials are offered.

Draft Guideline Elements

3. Each StrokeNet RCC & CPS should specify in their management SOP a formalized method to determine how they approach the patient who is eligible for multiple trials.
 - Such protocols should consider how/whether to incorporate the following elements:
 - Day / time of presentation (weekday / weeknight / weekend)
 - Time frame of presentation (hyperacute, acute, subacute)
 - Time frame of trial closure and/or not meeting recruitment goals (quota urgency)
 - Trial sponsor: NIH/StrokeNet trials vs. vs other funders vs internally-sponsored
 - Trial finances (it is acceptable to close trials that are not financially viable)
 - Clinical criteria of trial (stroke severity, presence of co-morbidities)
 - Phase of trial (II vs III)

Draft Guideline Elements

4. We affirm the importance of enrolling in all 3 domains – prevention, treatment, recovery. Unique challenge.
 - We do not expect sites to keep patients from a hyper-acute trial in favor of the possibility of later enrollment in a subacute or recovery trial.
 - Though shunting patients to hyperacute trials when eligible may indeed create an enrollment bias for later trials, we are willing to accept that bias in an effort to allow enrollment into the hyperacute study. Otherwise such trials will fail and we will never learn what we set out to learn.

Draft Guideline Elements

5. We understand that StrokeNet sites are enrolling in studies not NIH-funded. We affirm the value of those studies both to the individual sites and to stroke research as a whole.
 - It is expected that StrokeNet resources will be used for NIH-funded trials.
6. Education of inexperienced CPS's is critical. RCC leaders are to work with them to create site-specific allocation protocols.

Work that is to be continued...

1. Work with the cIRB, Steering Committee, NDMC to develop guidelines about what constitutes a competing trial within StrokeNet.
2. Receive feedback on guideline, finalize guideline
3. Each RCC to ensure their and their CPS's Management SOP addresses the issues.

Thank you