StrokeNET Webinar
Grant Writing

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NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Grant Writing

1. Overview of Patient-Based Research
2. A Reviewer's Thought Process
3. Considerations for NIH StrokeNet

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1. Overview of Patient-Based Research
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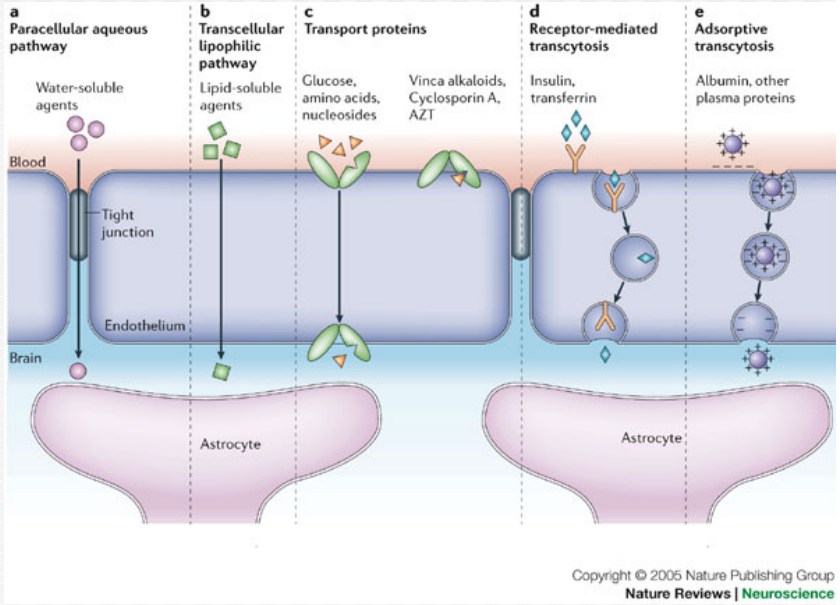
Why would anyone study human disease in humans?

- In vitro systems are flexible and elegant
- Wide range of available pharmacologic or genetic manipulations
- A lot easier to order a vial of cells or a colony of mice than a cohort of patients

…especially neurologic disease?

- Difficulty acquiring CNS tissue
- Blood-brain barrier to both influx and efflux



Strengths of Patient-Based Research

- Studying humans means studying the disease, not the disease model
- New findings increasingly flow not just bench to bedside, but also bedside to bench

> "Scientists are increasingly aware that [the] bench-to-bedside approach to translational research is really a two-way street…."
>
> -NIH Roadmap for Medical Research "Re-engineering the Clinical Research Enterprise"

Biologically

Clinically

Crafting Proposals to Study Mechanisms of Disease

1. Define compelling biological questions
   - No unimportant question is worth answering
   - What unknowns stand between where we are and where we need to be?
   - Which are accessible to current technology?
   - One eye on clinical translation, other on underlying pathogenesis

Crafting Proposals to Study Mechanisms of Disease

1. Define compelling biological questions
2. Identify potential bedside-to-bench methodologies
   - Neuroimaging (structural, functional, molecular)
   - Biomarkers (beware of cause vs effect issue)

Crafting Proposals to Study Mechanisms of Disease

1. Define compelling biological questions
2. Identify potential bedside-to-bench methodologies
3. Collaborate widely and generously
   - Impossible to "go it alone" in clinical research
   - Durable collaboration meets everyone's needs ($'s, publication credit, shared personnel, training, samples, friendship)

Crafting Proposals to Study Mechanisms of Disease

1. Define compelling biological questions
2. Identify potential bedside-to-bench methodologies
3. Collaborate widely and generously
4. Get your own patients
   - Sample size projection is inherently shaky, but…
   - No study is worth doing or funding if not powered to detect *something*

   i.e. No one loves your study as much as you

Interest of other site = Interest of your site / (distance between sites)^2

Crafting Proposals to Study Mechanisms of Disease

1. Define compelling biological questions
2. Identify potential bedside-to-bench methodologies
3. Collaborate widely and generously
4. Get your own patients
5. Don't lose hope
   - NIH funding is cyclical
   - Special paylines for NI/ESI

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Classes of NIH Grants

1. R Series Awards
   - R01 “research project”
   - R03 “small project” ($100K /2 yrs)
   - R21 “exploratory/developmental” ($275K /2 yrs)

Review Clusters

- Cluster A = R01 from established investigators
- Cluster B = R01 from New or Early Stage PI
  - **New Investigator** = not previously competed successfully as PD/PI for a substantial NIH independent research award
  - **Early Stage Investigator** = New Investigator within 10 years of last degree or residency
- Cluster C/D = R03 and R21

R Series Awards

- Significance
- Investigator
- Innovation
- Approach
- Environment

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Overall Impact

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
2. Can this applicant answer it?
3. Are the studies feasible?

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
   - Scored as *Significance*
   - Not sufficient to state that disease X is common, devastating, and untreatable. Your specific question needs to have impact.
   - Established largely by Specific Aims, reinforced by Significance

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
2. Can this applicant answer it?

<u>Productivity of investigative team</u>

- Scored as *Investigator*
- Publications (number, quality, relevance)
- Record of similar projects
- Co-Investigators can inoculate from some critiques…but ultimately rests on PI

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
2. Can this applicant answer it?

Power and Elegance of Proposed Techniques

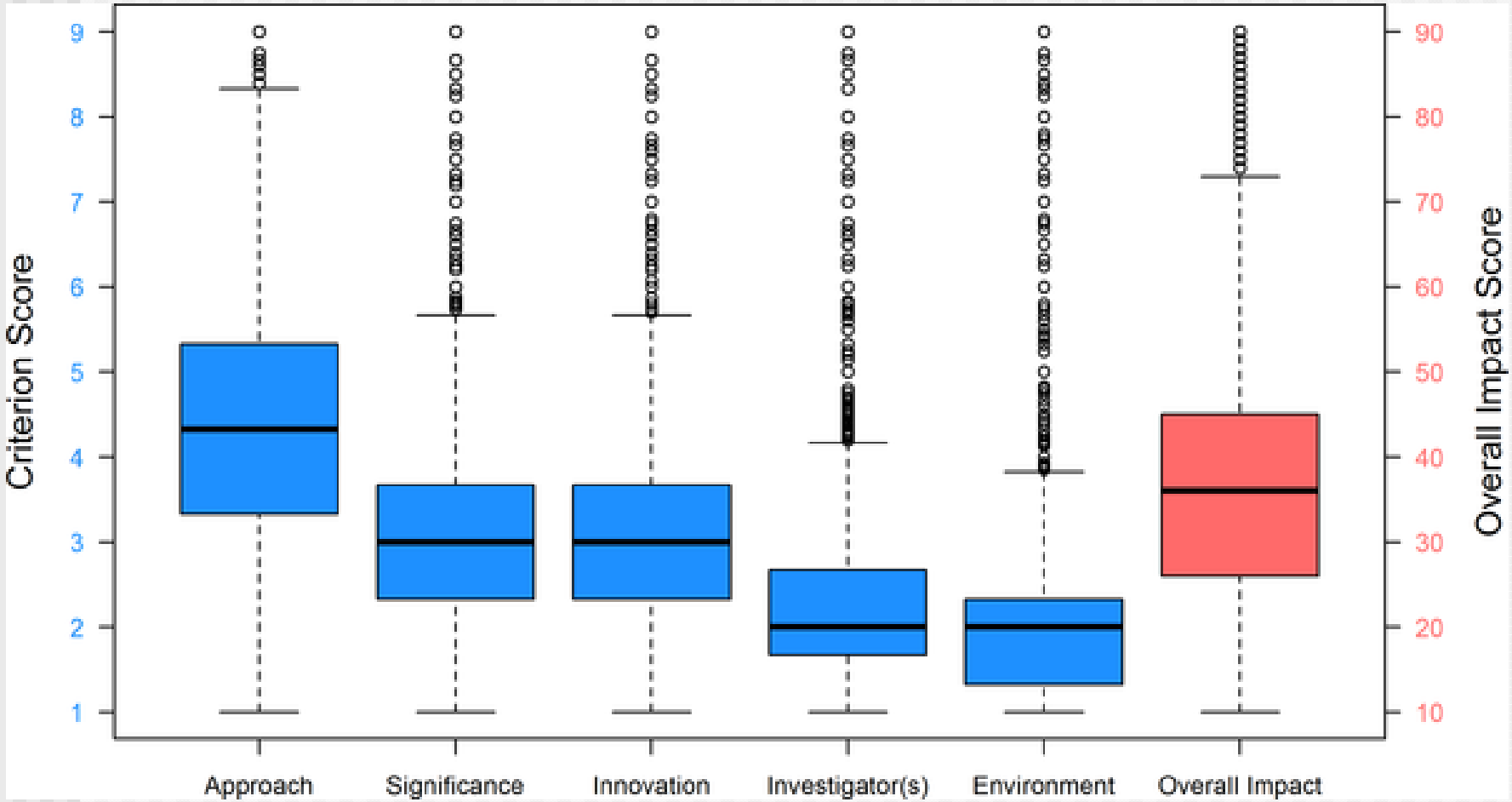
- Straightforward appropriateness (*Approach*)
- Elegance, novelty, "sparkle" (*Innovation*)
- Reviewer's impression largely driven by preliminary data (not required for R03/R21)

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
2. Can this applicant answer it?
3. Are the studies feasible?

- Ability to meet targeted recruitment (*Approach, Environment*)
- Soundness of sample size estimate (*Approach*)
- Inclusion of women, minorities, children, especially for phase 3 (*Approach, Environment)*
- Hard to gain points in *Approach*, easy to lose

Variability of R criterion scores



Eblen *PLoS ONE* 2016

R01 Overall Impact
A Reviewer's Thought Process

1. Does the question need to be answered?
2. Can this applicant answer it?
3. Are the studies feasible?

- Every sentence in your proposal should help reviewer answer "Yes!"
- Reviewer begins to form impression at the Abstract, certainly at the Biosketch and Specific Aims.

Phrases in a R01 review

- Ones you want to hear
  - compelling, exciting
  - nationally/internationally recognized team
  - state-of-the-art techniques
- Ones you don't
  - incremental, descriptive
  - speculative, overly ambitious
  - contingent (if SA1 fails, whole grant fails)
- Range from solid SA1 to exciting SA3

New emphasis areas (2016-)
Rigor and reproducibilility

- Scientific premise (*Significance*)
- Scientific rigor (*Approach*)
- Biological variables (*Approach*)
  - e.g. sex, age, weight, comorbidities
- Authentication (*other*)

grants.nih.gov/reproducibility/index.htm

A Reviewer's Thought Process
Personal reflections

- Writing clarity/style matter
- Small factual or conceptual errors matter (unfortunately)
- Reputation matters (unfortunately)
- Who reviews your grant matters…but unpredictably
- NEVER attempt to tamper with review

Classes of NIH Grants

1. R Series Awards
2. K08/K23 Awards
   - Typically 75% effort
   - Modest additional funds, e.g. coursework, part of a research assistant

R Series

- Significance
- Investigator
- Innovation
- Approach
- Environment

K Series

- Candidate
- Career Development Plan
- Research Plan
- Mentor
- Environment/Institutional Commitment

K Overall Impact
A Reviewer's Thought Process

1. Is the applicant a winner?
2. Can the mentor move the applicant to independence?
3. Will the research move the applicant to independence?

K Overall Impact
A Reviewer's Thought Process

1. Is the applicant a winner?
   - Obviously subjective
   - Publications, national/international presentations, applicant-generated preliminary data
   - Letters of support (mentor, referees, institution)
   - Quality of research plan

K Overall Impact
A Reviewer's Thought Process

1. Is the applicant a winner?
2. Can the mentor move the applicant to independence?

Ideal mentor

- Productive
- Senior enough to expose applicant nationally
- Nurturing
- Established by track record of previous trainees, level of commitment in letter

K Overall Impact
A Reviewer's Thought Process

1. Is the applicant a winner?
2. Can the mentor move the applicant to independence?
3. Will the research move the applicant to independence?

- Intrinsic impact of plan less important than capacity for moving applicant to his/her R01
- An unfeasible plan (lack of resources, expertise, subjects) is a poor training vehicle

K Overall Impact
Other Elements

Handle comprehensively and methodically

- Didactic training (e.g. biostatistics)
- Training in responsible conduct of research
- Institutional support
- Unconditional guarantee of protected time
- Like *Approach* in R01: Hard to gain points, easy to lose.

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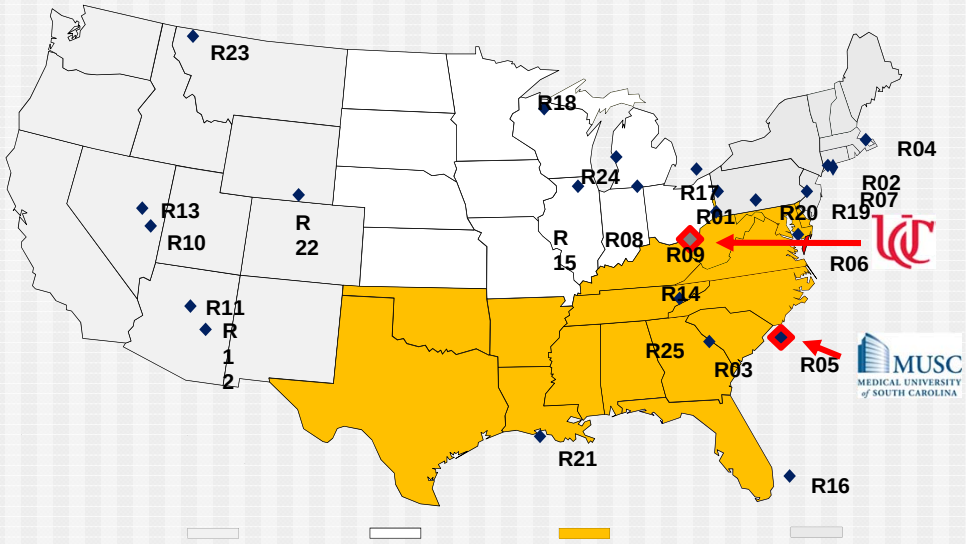


NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NIH StrokeNet

- “The primary goal of this network is to maximize efficiencies to develop, promote, and conduct high-quality trials focused on key interventions in stroke prevention, treatment and recovery.”
- Funding mechanisms
  - U01
  - X01 (Infrastructure access for industry)
  - U44 (Funding for small business)

StrokeNet
Types of trials

- Multicenter only (≥5 sites)
- Stroke patients, not healthy volunteers
- Primary/secondary prevention, acute treatment, or recovery/rehabilitation
- Exploratory phase 1/2 (dose finding, safety, target engagement, technique), phase 2/3 transition, phase 3 confirmatory
- Biomarker/PK/outcome validation (if immediately preparatory to trial)

NIH StrokeNet
Process for proposals

- Concept synopsis reviewed for completeness/appropriateness (NINDS staff), alignment with mission/priorities (ESC)
- Executive/working committees review feasibility
  - Availability of patients (GCNKSS)
  - Willingness/ability of sites to participate
  - Availability of drug, etc
- If approved, PI writes proposal with input/letters from StrokeNet

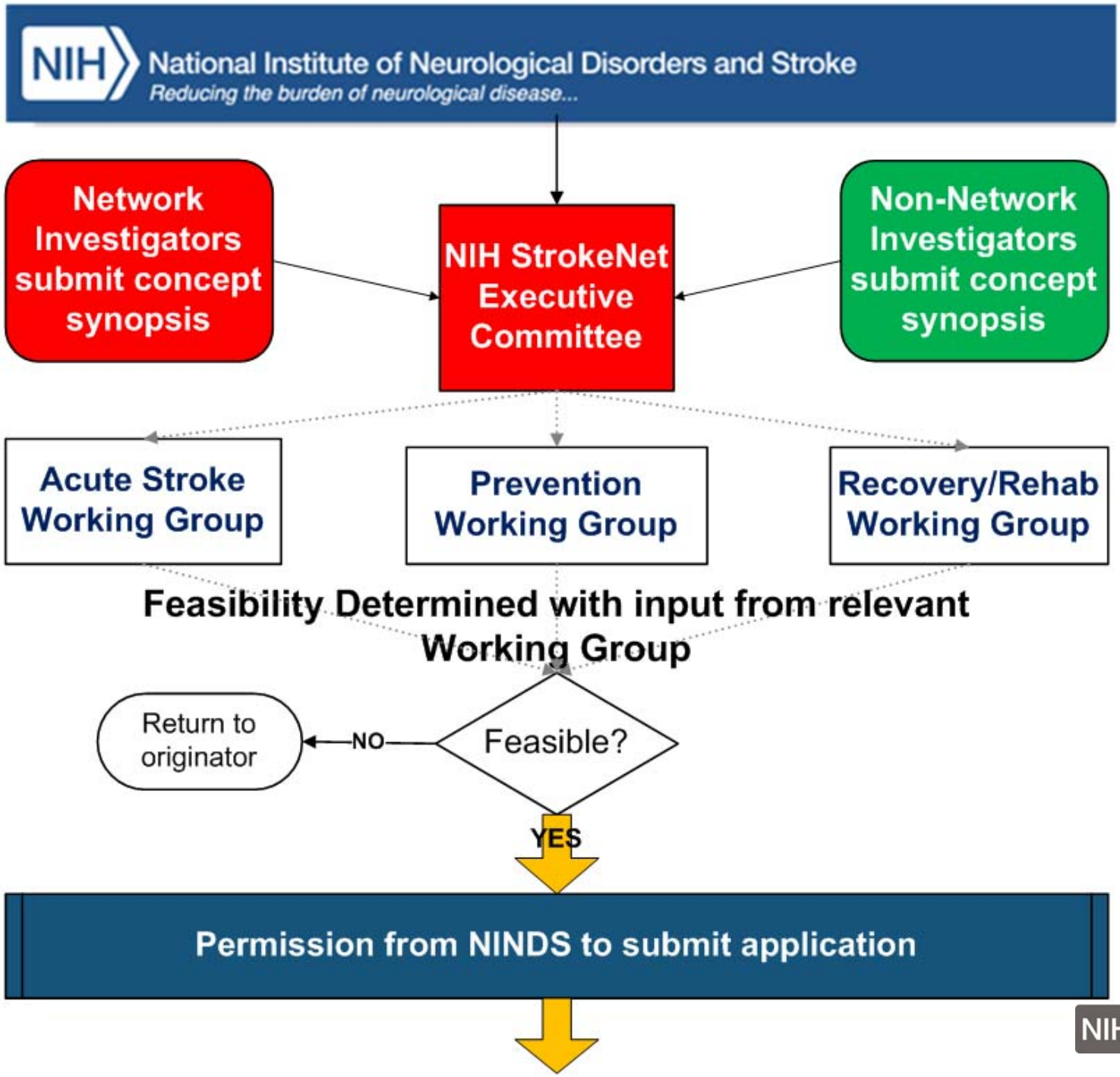
StrokeNet
Dispelling misconceptions

- StrokeNet doesn't fund your trial
  - The network delivers the sites, the local support (dedicated site PI, fellow, coordinator), the cIRB and MCTA structures, and the imprimatur
- StrokeNet doesn't fund your grant
  - U01 proposals peer reviewed by NINDS special emphasis panel
- StrokeNet doesn't write your grant
  - But working groups may help you develop your concept for your U01

A Reviewer's Thought Process
Considerations for StrokeNet

1. Does the question need to be answered?
   - Address unmet need
   - Unravel biological mechanism
   - Provide crucial information for phase 3 study
2. Can this applicant answer it?
   - StrokeNet brand very helpful here
3. Are the studies feasible?
   - Stroke trials have history of underrecruitment, too many exclusions, too intricate protocol
   - Safety, analytic plan also key

"Mr. Osborne, may I be excused? My brain is full."



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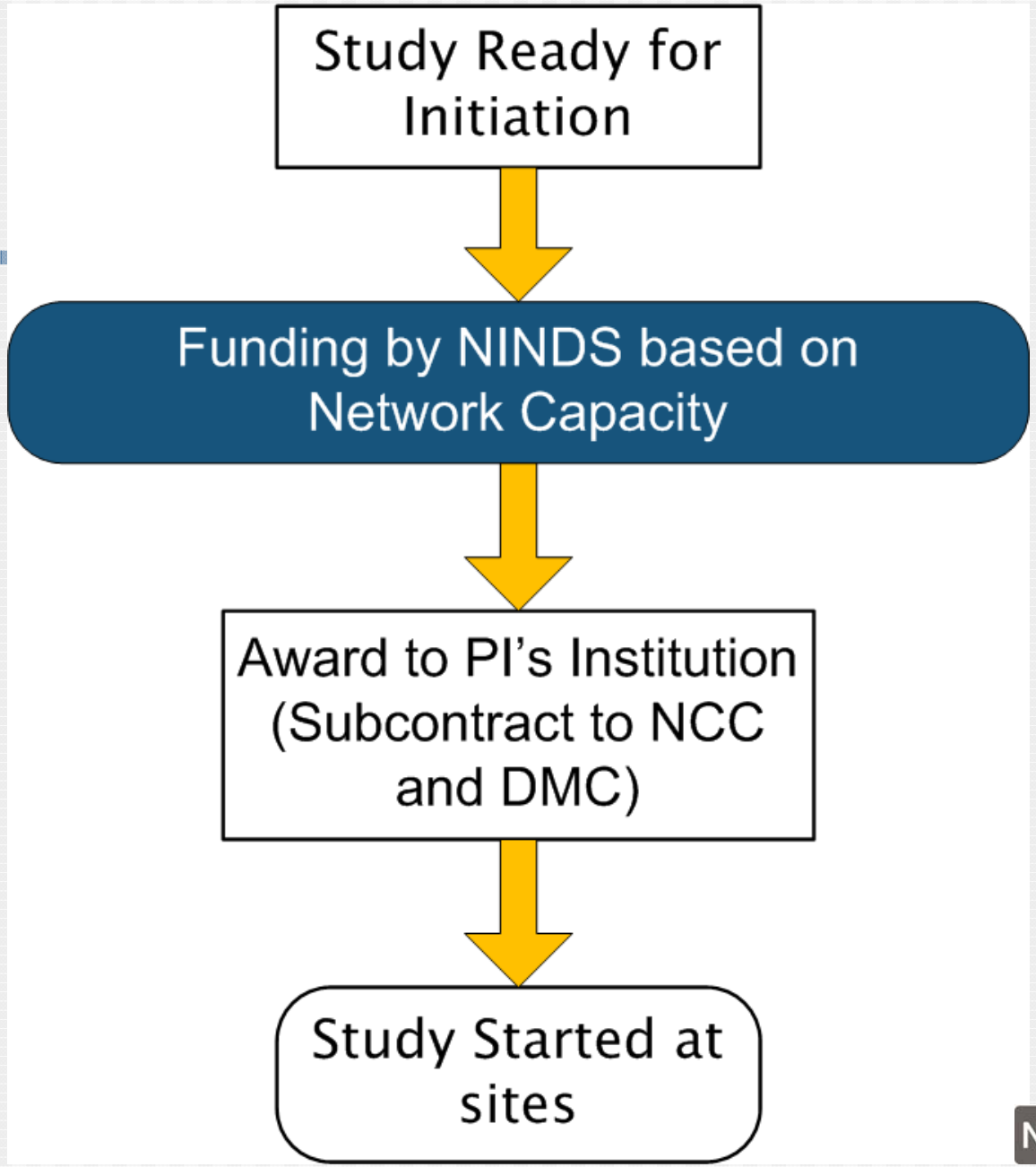

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