



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

Lessons Learned



Tracy Glauser, M.D.
Cincinnati Children's Hospital
Medical Center

Overview

1. Lessons Learned
 - a. NeuroNEXT Executive Committee
 - b. NINDS clinical trials (NSD-K) study section
 - c. PI on NeuroNEXT clinical trial (Fox)
 - d. PI on NINDS clinical trial (Glauser)
2. Epilepsy advisory team

NeuroNEXT Executive Committee



Christopher S.
Coffey, Ph.D.



Karen
Marder, M.D.



E. Clarke
Haley, Jr., M.D.



Tracy
Glauser, M.D.



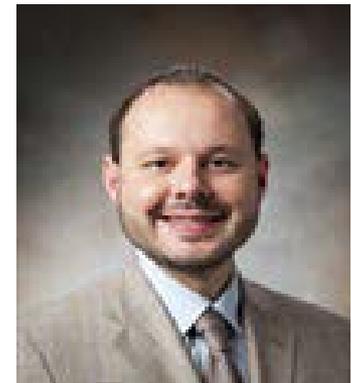
Merit
Cudkowicz, M.D.



Stephen J.
Kolb, M.D.



Robert
Fox, M.D.



Richard
Nowak, M.D.

NEC on Feasibility assessment

■ Key concepts

- NeuroNEXT is more than just the DCC and CCC
- Proposed trials must be multi-center clinical trials to be conducted in at least 4 network sites in addition to the proposer's site.

■ Common design mistakes

- Conflating Phase II and III goals
- Needing for special equipment that might not be widely available.
- Grossly underestimating true sample size needs (multifactorial reasons for this)

NEC on Feasibility assessment

- Budget miscues
 - Budget estimates often grossly wrong
 - Mistakes cause problems
 1. Proposal may not go to ESC early in process because PPI tells them less than 500K/year
 2. If does go to ESC- then PPI still sets too low a limit and ends up having to squeeze the per subject fee.
- Preclinical data may not be sufficient to pass ESC or review

NEC on Preparing the submission

- Surround yourself with experience
 - Consult with national disease experts
 - Consult with an experienced clinical trial statistician prior to protocol synopsis submission
 - Consult with an experienced clinical trials mentor (someone with experience in design and conduct of clinical trials and can think like a reviewer!).
- Avoid incorrect expectations
 - Feasibility \neq Scientific Merit
 - NeuroNEXT feasibility and support \neq funding

NEC on Preparing the submission

- Give yourself plenty of time
 - A lot of effort is required during the preparation and application phase
 - Get buy-in from your chair/supervisor to spend this time on this project.
- Do not to bite off more than you can chew
 - A medium-sized Phase II trial that is sure to answer a couple important questions is probably better than a large Phase II trial that tries to answer all the questions, but becomes too wieldy to actually conduct

NEC on Preparing the submission

- Secure your drug supply (and placebo) from the company
 - Source of delay if drug is delayed
 - Buying drug can bust a budget
- Reach out to a national disease advocacy foundation for support.
 - Often very interested
 - Can provide a lot of support (logistics/money)
 - Start with a phone call to one of the foundation grant officers

NINDS clinical trials study section



David
Wright, M.D



Gail
Anderson, Ph.D.



Tracy
Glauser, M.D



Rema
Raman, Ph.D.



Greg
Samsa, Ph.D.



Alex
Valadka, M.D.

Study section – Pick the right project

- Think 7-10 years ahead
- **Significant** study question
- Apply a sound **approach** to answering the question.
- **Innovation** - lesser importance (icing on the cake)

Study section – Get your own reviewers

- Create an elevator speech about significance
- Try out that speech on some internal reviewers, including some both inside and outside your discipline, who can be counted upon to give honest feedback
- Ask your reviewers to echo or otherwise restate what they understand your argument about significance to be
- Directly ask them whether the question is significant enough to fund.

Study section – Build your team

- If you are not the expert in an area – get one
 - For example - If proposing a PK study as a specific aim, include a co-investigator that has demonstrated that they can perform a PK analysis.
- Foster a collaborative and mutually advantageous partnership with your research team
- Communicate frequently with the program officer as you prepare your application.

Study section - Connect the dots

- Be faithful to the preclinical/Phase I data. Inadequate, inconsistent, or inappropriate supporting data will be noticed. You can't ignore data just because it's inconvenient.
- For Human trials, animal data that includes multiple species (including gyrencephalic, multiple different labs, and models that realistically reflect the human condition) and/or human pilot trials showing proof of concept (connect the dots) must be provided/described. (is there a clear basis for proceeding to human Phase II or III trial?)

Study section - Connect the dots

- Include in the proposal what is known regarding the pharmacology and pharmacokinetics of the proposed drug, including metabolic pathways and possible drug interactions. Drug interactions are often not included in inclusion/exclusion criteria.
 - Provide justification for all inclusion and exclusion criteria
- Design
 - Don't design an underpowered phase III trial instead of a phase II trial.
 - Sample Size and enrollment ability matters.

Study Section – attention to detail

- Approach is biggest weakness in most grants.
- Carefully articulate the recruitment, enrollment process, allocation and blinding, protocol compliance, follow up and how missing data will be handled.
- Invest as much time in planning the administrative parts of the grant as the scientific side.
- Make sure the grant is vetted (read multiple times) by experienced clinical trialist
- Proof read the application and do a spell check - protocol must match the grant
- Avoid including large numbers of individuals with low % effort. You need time to conduct studies.

Study Section – attention to detail

- Include following statistical sections
 - Randomization (who does it and how will it be protected)
 - Power analysis with justification of final sample size used
 - Analysis plan for each aim and sub-aim
 - Discussion on confounders, dropout, impact of missing data
 - Safety plan (internal/external DSMB)
 - Plan for next steps – what is the next study?
- Show that you are capable of enrolling the appropriate numbers – ideally with proof from a pilot trial or another trial that your team has done. Over estimation is one of the most common errors (if you think you can enroll 10, predict 1).

Study section

- Plan ahead
 - Think of the reviewers - cramming tons of information into long paragraphs is not as effective as short paragraphs with frequent subject headings.
- Dealing with reviews
 - Reviewers were selected because of their expertise AND their ability to identify the best science
 - If your original proposal is criticized for inadequate or unsatisfactory preliminary data, **don't argue with the reviewers** and resubmit the exact same data in your revised application!
 - Respond to reviewer's critiques in a re-submission even if you disagree with what was said.

NeuroNEXT PI (Steve Kolb's top 10)

10. You don't know what you don't know.
9. Site selection is hard.
8. Your proposed study will evolve... Don't Fight It
7. Understand the critical relationship with your site
Research Coordinator
6. The DCC is your friend
5. The CCC is your friend
4. Your % effort will be bigger than you think
3. Feasibility does not mean it is well designed
2. Recalibrate your definition of doable
1. You will be part of something bigger than your disease-related community

[NINDS PI (My top 6)

- 6 Your idea needs to be creative, exciting, worth funding, filling a gap in the existing literature, important and testable and resonate with your mentors and colleagues.
5. Know the NIH mission (increase our understanding of biologic processes, diseases, treatments, or prevention) and the Epilepsy benchmarks
4. Build the team that the study needs
3. Address a clearly defined research problem; each specific aim is focused on addressing some aspect of the problem.
2. Each specific aim should be concise, concrete, clear and goal-oriented (emphasize “product” over “process”).

[NINDS PI (My top 6)

1. Follow the following fundamental principles:

Read the RFA!

Keep it simple – KISS principle

Clearly articulate the HYPOTHESIS

Avoid the “over-ambitious” label

Connect the aims thematically

Avoid contingent aims

Do not procrastinate

Submit your best work

NeuroNEXT epilepsy team

■ Goal

- Advisory - to serve as experienced trialists advisors for epilepsy investigators interested in submitting their project to NeuroNEXT
- Scientific - To help develop studies we feel would be good candidates for NeuroNEXT –

NeuroNEXT epilepsy team

■ Members

- Tracy Glauser
- Shlomo Shinnar
- Dale Hesdorffer
- Page Pennell
- Gary Mathern
- David Loring