



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

Peer Review Considerations



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NINDS

Review: Where & How

- **In a Special Emphasis Panel (SEP)**
 - Core group of experts in clinical pharmacology, statistics, industry experts in early clinical development.
 - Ad hoc disease specific expertise: both basic/preclinical & clinical.
 - 6-8 reviewers/application.
- **A telephone-assisted “reverse site visit”**
 - Investigators available on standby for questions during the time window their proposals get discussed.

Review Discussions: Part 1

Applications selected for discussion by the review panel are evaluated from two separate perspectives:

- Part 1: *greater* focus on scientific premise
 - a. an unmet medical need
 - b. a plausible biological mechanism
 - c. non-clinical (in vitro and/or in vivo) data; &/or
 - d. early clinical data

Landis SC., et. al: “A call for transparent reporting to optimize the predictive value of preclinical research” Nature 2012 Oct 11;490(7419):187-91.

http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf

Review Discussions: Part 2

- Part 2: focus on the clinical & statistical aspects of the study including experimental design and the review criteria listed in the PAR.
 - 1) Significance
 - 2) Investigators
 - 3) Innovation
 - 4) Approach
 - 5) Environment

Overall Impact \neq Significance

& . . .if the study were conducted as currently designed.

Common Issues in Review. . .(1)

- **Dose/Frequency/Duration/Route of Administration:** adequate justification? is the drug reaching the intended 'target' at the 'right' concentration? PK/PD: is there adequate exposure time?
- **Biological Mechanism:** is there a measure of target engagement? Is the intervention 'appropriately' timed?
- **Study Population:** homogeneity vs. generalizability.
- **Controls:** concurrent vs. historic
- **Inclusion/Exclusion Criteria:** well-justified? overly restrictive vs. too broad.
- **Endpoints:** (*where applicable*) intervention effects in opposite directions.

Common Issues in Review. . . (2)

- **Randomization:** imbalance, bias
- **Blinding:** effectiveness
- **Effect Size:** adequately justified?
- **Sample Size:** basis of calculation? Loss to follow-up accounted for?
- **Feasibility/Recruitment:** realistic estimates/timeline
- **Analysis Plans:** Do they match the aims proposed? Confounders addressed? Power for secondary endpoints addressed?
- **Safety Study:** are there adequate stopping rules? is there a truly independent safety monitor?

Common Issues in Review. . . (3)

- **Imaging Outcomes:** standardized equipment across sites?
- **Fluid Biomarkers:** attention to standardized sample collection/handling?
- **Collaborators/Consultants:** hands-on involvement in /commitment to the study?
- **Further Clinical Development:** Clear Go/No Go?
Consider Thoughtful Milestones.
- **Human Subject Protections:** consent forms.
- **Inclusion Policies:** concrete plans.

Questions from Applicants

- How do I address ~30 pages of critiques in a 1 page introduction?
 - Use the Research Strategy Section and the Protocol Synopsis (Appendix 1) effectively.
- Can I send supplemental information?
 - Std. NIH Policies apply [NOT-OD-10-115](#)
 - Regulatory Requirements [NOT-NS-11-018](#)
 - **Contact the SRO**

When in Doubt (& even otherwise). . .ask



- **Contact your PD & SRO: pre-Submission and post-Review**
 - Even if your budget is < 500K/year.
 - Especially if unclear regarding how best to address reviewer critiques: “*Were they just asking for more justification or do they really want me to change this part?*”

Contact Information:

- Questions? Call or email:

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