Guidelines for Clinical Studies in Tourette Syndrome

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These guidelines are provided to assist applicants in the development of competitive proposals involving human subjects. The comments are not meant to be exhaustive, but rather offer a listing of fundamental issues that need to be addressed for proposals to be successful. TAA's experience has been that clinical researchers often have good ideas and appear to have the skills to conduct the proposed study, but do not demonstrate these assets when composing their protocols. As a result, the review committee loses confidence/enthusiasm in the proposal, and it receives a less than fundable score. It is important to note that attending to these basic issues will not necessarily guarantee a successful submission, but rather it will allow for a fair review.

I. **Abstract –** The abstract should be very clear and emulate those in randomized controlled clinical trials in reputable journals.

II. **Introduction –** The introduction should be clearly presented, emphasizing the high points of the proposed intervention and its applicability to TS. A well written introduction makes it easier for the reviewer to understand the specific components of the proposal that follow.

III. **Specific Aims and Hypotheses:**

a. If your proposal is aimed at testing a hypothesis, make sure the study has sufficient power to answer the research question during the funding period.

b. If a feasibility/pilot study is the objective, then stating this up front is critical. Methods and outcomes should be tailored to this goal and give an indication of how the data will be used to estimate power for a larger trial.

c. If the proposal is an open trial, it will need to be very well justified. The published literature in TS discusses in detail the problems with open and uncontrolled trials. It is critical to understand the limitations of open trials and address them in detail in the proposal.

IV. **Background and Significance:**

a. This is the section where investigators demonstrate their knowledge of TS and its therapeutics. Use this opportunity to put forth your knowledge of the field effectively. Investigators who do not have TS experience are at some disadvantage and probably will need a consultant, or access to TS expertise, in the development of their proposals.

   i. It is very important to acknowledge the difficulties with clinical trials in TS (as in III.c) and to indicate how the proposal addresses those issues.

   ii. Comorbidity is an important issue in TS clinical trials and the implications of comorbidity in the proposal should be discussed in detail.

   iii. TS patients are often prescribed a number of medications for a variety of problems. Addressing issues of combining treatments is also important.

b. How significant and innovative is your proposal? Describe the specific role your proposal plays in the broader scheme of TS treatment.

   i. Is the treatment approach the next logical step for a particular intervention?

   ii. Is it an established treatment for another condition that may be applicable to TS?

   iii. Is it an experimental or alternative treatment that is used for TS but needs to be scientifically studied to determine whether it is effective?

c. Explain what it will mean if the intervention proves to be successful. Will it lead to another intervention study, or will it enable the intervention to be used directly in clinical treatment?

d. Investigator – Junior and senior investigators are viewed somewhat differently with respect to the expectation of a track record in TS research, but the standard of review is high for both. For junior investigators to be successful, we encourage them to identify an experienced collaborator/consultant and participate in pre-review. If a senior investigator is listed as a collaborator or consultant on the proposal of a junior investigator, the review committee would expect to see the results of the senior investigator's experience reflected in the quality of the junior investigator's proposal. In addition, a plan for supervision or consultation with the senior investigator is important.

   i. Experience with TS:

      1. For those with lots of experience in TS research please describe. This track record should also be evident in the accompanying biosketch.
      2. Applicants with little TS experience or access to TS patients need to address issues such as recruiting, evaluating, treating, and managing patients with TS, and the interpretation of outcome for both tics and comorbid conditions. Deficits in the investigative team can be addressed through consultants/collaborators, but the process of consultation must be described, and the proposal should reflect the fact that that consultation/collaboration had an impact on the development of the proposal.

e. Preliminary Studies/Pilot Data – Although it is difficult to obtain pilot data for small grant proposals it is important to demonstrate the investigator's ability to implement the critical elements of a clinical trial and show that the resources are available to bring the study to completion. This is especially true for junior investigators, senior investigators new to TS, and those who plan to study alternative or truly experimental interventions.

V. Methods – Please review CONSORT Guidelines on the reporting of clinical trials. These are the standards by which clinical trials are reviewed for publication. These standards can also be very helpful in writing a clinical trial proposal. The review committee appreciates that not all CONSORT standards can be met in small grant proposals, but addressing the key methodological issues in the proposal demonstrates the investigator's awareness of these important issues. The American Academy of Child and Adolescent Psychiatry has published standards for the publication of open trials. This document can also be helpful in developing open trial proposals in TS.

a. Subjects and sampling frame: Even for small studies, extensive detail is required. It is essential to know who will be enrolled and how the study will be done. Tell more rather than less.

   i. List age range, sex, and other demographic characteristics

   ii. Inclusion and exclusion criteria

   iii. Recruitment strategy: Indicate how and where patients will be recruited and provide evidence that the sample can be recruited within the grant funding period.

   iv. Diagnostic and symptom severity assessment: The standards used for diagnostic assessments, both in terms of rigor and comprehensiveness, are critical.

1. Diagnostic interviews (consult published trials by the *TS Study Group* or other large clinical TS trials that have been published in reputable journals for assessment strategies)
    a. Specify which interview(s) you intend to use.
    b. Indicate who will do the evaluations and present any TS background, experience or training they may or will have.
2. Clinician assessments (consult published trials)
    a. YGTSS – Probably the standard for clinician rating of tic severity.
    b. Consider whether or not to use videotaping to assess tic severity.
    c. CY-BOCS and Y-BOCS – probably the gold standard for clinician assessment of OCD.
    d. Address the standard for assessment for other comorbid conditions.
3. Parent and teacher reports
4. Self-reports
5. Assessment schedule – A figure is very helpful for reviewers.

v. Subject flow and timeline – A figure that highlights when key aspects of the study will be accomplished assures the reviewers that the study will be completed on time.

vi. Data analysis:
1. Discuss data management procedures.
2. Relating the data analysis to the specific aims or study hypotheses is often a good way to describe what statistical procedures will be used.
3. Power
    a. Are the data adequate for answering the question?
    b. Are the data adequate for determining the potential for a larger study?
4. If the proposal is for a feasibility study, describe how feasibility will be assessed.

vii. Limitations and alternative designs: This is a critical section. Describe and defend your design choices. It is also useful to anticipate the critique of potential reviewers and address these issues in your proposal. Awareness of the potential flaws of your own proposal and an indication of why you made the choices you did will demonstrated your competence to the committee and will inspire confidence in your proposal. Inadequately addressing design alternatives or limitations can be interpreted as a lack of sufficient research expertise and could adversely affect your score.

VI. Human Subjects:

a. Human Subjects issues are important for all clinical studies and need to be addressed in your proposal. Informed consent from your local IRB will be required prior to funding. It is important that human subjects concerns are addressed in your proposal.

b. TAA is interested in studies that include historically underrepresented persons, including women, minorities and people from a broad age range. Where feasible, describe strategies that will be used to maximize such inclusion.