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I. Introduction

The Clinical Antipsychotic Treatment Intervention Effectiveness (CATIE) research program is comprised by two multicenter longitudinal NIMH-sponsored clinical trials designed to evaluate the effectiveness of atypical antipsychotic medications in schizophrenia and Alzheimer's Disease. CATIE is using a public health model to study the treatment effectiveness of these medications in large samples of patients with schizophrenia or with psychosis, agitation or aggression in association with Alzheimer's Disease in a variety of clinical and geographic settings. The protocols aim to provide answers to an array of clinically important questions and better inform mental health care professionals about how to develop treatment plans for these patients. Outcomes to be evaluated include the effects of the various treatments on symptoms, function, and quality of life, as well as the overall side-effect burden of each treatment option and its cost effectiveness. The CATIE program engages a coordinated network of treatment centers to conduct these studies and will also serve as a national resource by providing a platform from which to develop independent ancillary studies. This CATIE infrastructure allows investigators to apply to NIMH and elsewhere for funding to conduct these ancillary studies. The CATIE network includes over 80 sites which will engage several thousand patients and family members in state of the art effectiveness research. Information about the CATIE research program and organization can be found on the website WWW.CATIE.UNC.EDU.

To maximize the knowledge gained from CATIE, a broad spectrum of researchers will be given the

opportunity to propose and conduct ancillary studies using CATIE patients, CATIE infrastructure and resources, and/or the CATIE network of participating sites. Drs. Robert Rosenheck and Dilip Jeste have agreed to co-chair an Ancillary Studies Committee (ASC) that will oversee the development and review proposals for ancillary studies and make recommendations about both the review process and approval of specific proposals to Dr. Jeffrey Lieberman (CATIE PI) and the CATIE Executive Committee. The goal of the ASC of CATIE is to promote innovative lines of scientific inquiry on the pathophysiology and treatment of psychosis. The ASC will review proposed ancillary studies to CATIE and consider their compatibility with CATIE objectives, their scientific merit and their impact on the CATIE infrastructure. The ASC will not function as an IRG and will not provide extensive scientific feedback to applicants.

The Ancillary Studies Committee (ASC) oversees the submission, coordination, and review of ancillary study proposals. It encourages submissions from academic and non-academic investigators. CATIE-affiliated investigators are encouraged to submit ancillary study proposals, but in order to be eligible to submit proposals, investigators need not be involved in CATIE as coordinating or site investigators. Ancillary studies involving primary data collection will need separate approval from each CATIE site that is to be involved and from the local Institutional Review Board (IRB).

It will be the responsibility of the ASC to ensure that the demands placed on the infrastructure by multiple ancillary studies do not diminish our ability to complete the parent CATIE studies. To this end, the ASC, with final review by the CATIE Executive Committee, will coordinate the approval, prioritizing and integration of ancillary studies into the CATIE program so as to minimize the burden on patients and clinicians and to maximize the efficiency of the use of infrastructure resources. Ideally, an ancillary study will lead to modest demands on the time and effort of patient participants and clinicians, obtain an answer in a relatively short time period (e.g., 6-12 months), and either open up new research areas or provide a definitive answer to a question of major public health significance. Ancillary studies will be conducted under the same policies and procedures that govern the main CATIE trials. For example, no data will be released concerning treatment assignment involving breaking the blind until after the main studies are completed. Additional demands on CATIE personnel in support of ancillary studies are likely to require payment for these additional efforts.

CATIE is a new and highly complex undertaking and it is impossible, at this time, to foresee all the contingencies that may arise. Because of the grant review process, in many cases there will be a substantial delay between the initial ASC approval and actual project initiation. As a result ASC approval may be subject to re-review at the time of project initiation. Therefore, although unlikely, it is possible that in some instances, due to changed circumstances, an approved project will not be implemented. The ASC will do everything possible to avoid this.

This memo summarizes principles concerning: (1) which projects should be reviewed by the ASC, (2) what criteria should be applied in the review process, (3) what issues should be addressed in applications, (4) how the committee will conduct its reviews, (5) how feedback and consultation will be provided to authors of ancillary proposals.

II. Definition of Ancillary Studies

A proposed study will be reviewed by the Ancillary Study Committee (ASC) if it involves: (1) patients currently participating in CATIE, (2) patients who previously participated in CATIE or (3) patients who are defined by their relationship to the CATIE study (e.g., family members or the population of patients who were approached to participate in CATIE and refused). The ASC will also review (4) requests for data collected as part of CATIE for secondary analyses (prior to release of the public access data base) and (5) studies that involve use of CATIE personnel, equipment or other resources, or that systematically draw on the network of sites participating in CATIE (e.g., provider surveys).

III. Review Criteria

Proposals will be evaluated by five criteria:

1. **Appropriateness.** First, does the proposal fit within the scope of the CATIE project? This assessment will be based on consideration of the relevance of the ancillary study's aims to those of the overall CATIE project objectives-. CATIE patient participants should not be treated as a sample of convenience for studies that do not share goals and interests in a substantive way.
2. **Compatibility.** Second, is the proposal compatible with the procedures of the CATIE project? This determination will be based upon a systematic review of the procedures and methods outlined in the proposed ancillary study. The burden on patients and investigators will be estimated in terms of time, effort, and complexity of the proposed ancillary study procedures, as well as the likelihood of a negative impact on subject enrollment and retention. Proposals that would impair the successful implementation of the parent CATIE trials will be excluded. The applicants must address these issues in their proposal (in the Human Subjects section) and explain how any additional burden will be offset, including possible remuneration for patients and clinicians involved.
3. **Benefits to CATIE.** Third, does the proposal facilitate or, at a minimum, not impede the enrollment of subjects into CATIE? This determination will be based on assessment of the "added value versus added burden" of the proposal to patients and investigators. For example, will the presence of an ancillary study that provides free screening for thyroid disease increase the chances of recruiting patients?
4. **Merit.** Fourth, does the proposal have scientific merit? This determination will be based upon a systematic review of the background and rationale, and the procedures and methods outlined in the proposed ancillary study. This review will be especially important when proposals have access to funds and are not being submitted to NIMH or other independent peer-review groups.
5. **Investigator.** Fifth and finally, is the investigator likely to successfully complete the project? This will be based on a review of the investigator's past experience, productivity, and, in the case of junior investigators, their current mentorship.

Although formal reviews will not be written, the committee will attempt to provide informal verbal feedback to applicants when appropriate.

Additional Considerations

All proposals will be rated, for committee use only, on each of these items on a five-point scale. Projects having acceptable scores on all five criteria will be certified as ancillary studies in a formal letter from the ASC. This certification can be used by the principal investigator in applications for funds from NIMH or other funding agencies, foundations, or industry as needed.

Please note that while this certification indicates ASC approval for the investigator to go forward with a request for funding, it does not guarantee that, following funding approval, the ancillary study will necessarily be implemented as part of the CATIE project. The ancillary study may incur significant time delays or design changes before it is finally funded, which could alter its feasibility. For example, if there are two proposed research projects, each of which would address the same innovative question, and one of the studies is able to obtain funding at an earlier date, the initiation of that project may reduce or obviate the need for the other study. In the unlikely event that two similar proposals (involving all sites) obtain full funding from external (non-CATIE) sources (that include the costs of offsetting the procedural burden) at the same time, the implementation of these two ancillary studies might either occur simultaneously or the number of participating sites might be divided.

Since the ASC cannot oblige all sites to serve as sites for ancillary studies that have been approved and

have obtained funding, it may be difficult to request all sites to implement two similar studies, particularly if they are both time--consuming for patients and clinicians. For these reasons, it may be advisable, whenever possible, to define which sites should be involved, if the proposal is multi-site. In some cases it will be appropriate for the investigator proposing the ancillary study to approach potential sites. In others it will be preferable for representatives of the overall CATIE project to approach the sites.

The ASC will determine whether the ancillary investigators or the CATIE staff should contact the sites to determine their interest and availability to participate. Investigators should not approach sites until the ASC has determined the best method of implementation for each project. The ASC will decide at the time of reviewing the proposal who will contact the sites and how (e. g., by direct contact, posting on the website etc.) Establishing such contact will be important in enhancing motivation to carry out the ancillary study.

CATIE particularly encourages smaller, single-site applications that may foster the career of young investigators and focus on the study of atypical antipsychotic medications. CATIE patients may participate only in ancillary studies that have received approval from the ASC and the Executive Committee. Sites must provide yearly reports listing all the studies in which CATIE patients participate. At the same time, sites will have the option of declining participation in any particular ancillary study. CATIE also provides an excellent opportunity to investigators at the sites to initiate projects by site investigators, including young investigators involved at the individual regional sites.

Ancillary studies will be subject to the same policies, reviews, and approvals as the core protocols of CATIE, described in the protocol available through the CATIE web page. Ancillary study investigators are to be viewed as collaborating investigators, with access to relevant elements in the full data set. They should state in their proposal what data from the CATIE protocol they will need, in addition to the specific data to be collected in the ancillary study.

IV. Application

The scientific proposal should be no more than five single-spaced pages and should be accompanied by the following:

1. Cover Page providing the Protocol Title, Abstract, names of all Investigators, institution and start date and stop date of the proposed ancillary study
2. Estimated budget and proposed source(s) of funds. Potential workload increment for Quintiles must be identified and budgeted.
3. Biographical Sketch for all Investigators
4. Other Support for all Investigators.
5. Scientific Proposal
 - A. Specific Aims
 - B. Background and Significance
 - C. Preliminary Studies (if applicable)
 - D. Research Design and Methods (including statistical analyses for each hypothesis)
 - E. Impact on CATIE and CATIE resources required (e.g., number of patients, proposed sites, patient time, clinician time, data management, clinical monitoring, as well as

budgeting needed to offset the procedural burden entailed in implementing the proposed research plans).

- F. Human Subjects (including subject population; sources of research material; recruitment and consent procedures; a gender and minority inclusion statement; potential risks; risk management procedures; and evaluation of risk/benefit ratio; time and effort required of patient participants)
- G. Literature Cited

If the committee has need for additional information, the PI of the proposed study will be asked to expand the proposal in areas specified by the committee. Please e-mail your proposal as a Word or PDF attachment to tiffany_harris@med.unc.edu, or mail 10 copies to the address below:

CATIE Project Office, Dept of Psychiatry
University of North Carolina at Chapel Hill
Medical School Wing B, CB#7160
Chapel Hill, NC 27599-7160

V. Review process

After an application has been received in the CATIE office, it will be forwarded to the NIMH to evaluate the study for compatibility and feasibility of incorporation into the trial. The NIMH will also determine whether expedited peer review is necessary based on the scientific goals of the project and the parent trial. The NIMH will notify the ASC of its decision and the ASC will notify the applicant.

If the NIMH accepts the application, the ASC will schedule it for review and its members will rate the proposal on each of the five criteria listed in Section II. using a 5-point scale to provide an initial assessment of its acceptability (see attached rating form). The scores will be used for internal decision-making only and will not be shared with the applicants.

All reviewers will maintain absolute confidentiality about these proposals and their reviews will be anonymous. Reviewers of the proposals will be asked to provide their initial evaluations within six weeks of receiving the proposals. The ASC will hold regular conference calls during which all ancillary study proposals received prior to that submission date and approved for Committee review will be considered. A primary reviewer and two secondary reviewers will be assigned, although all members of the committee are encouraged to read each proposal. Minutes summarizing the decision of this teleconference will be distributed to the Executive Committee, which will review and approve or disapprove the recommendations of the ASC. A letter to the investigator will be sent stating whether the proposal fits within the scope of the CATIE project and is compatible with the study and extend its scientific value. Proposals that involve human subjects may be subject to DSMB review.

Since the ASC review process may result in significant changes in the study design, the finalized ASC approved application will be submitted for final approval by the ASC to the NIMH.

The NIMH must give its consent before a proposed ancillary study can be formally accepted for implementation within CATIE regardless of the funding source. Proposed studies that do not receive approval from the NIMH or the ASC may be revised and resubmitted to the ASC.

Those ASC-approved applications seeking NIMH support and approved for expedited review by NIMH program staff, should be submitted for the monthly receipt date (the 9th of each month) and will be reviewed by a Special Emphasis Panel (SEP or special review group) in an expedited manner. A letter of

approval for expedited review should be included in the application that is submitted for NIH peer review. Those ASC-approved applications that NIMH staff determine do not require expedited review should be submitted on the standard receipt dates (<http://grants.nih.gov/grants/funding/submissionschedule.htm>) and will also follow the standard referral and review guidelines.

Special Note:

The ASC will serve as the initial point of submission for applicants however; investigators are encouraged to contact the NIMH program staff listed under INQUIRIES to discuss their proposed projects.

VI. Continuing Review

All approved ancillary studies that are ultimately implemented will be subject to periodic review. Investigators will need to submit reports on the number of subjects enrolled, retention, completion of study protocol and any adverse events. In some cases it may be necessary to discontinue an ancillary study if it appears to be interfering with the conduct of the main CATIE trials

VII. Publications

All publications resulting from ancillary studies will be considered to be part of the CATIE research program and must be reviewed by the publications committee. In some cases proposed secondary analyses of CATIE data may overlap with the main publications planned by the publications committee. In such cases the ASC will ask the publications committee to determine if the overlap represents a duplication of effort and should therefore be disapproved.

VIII. Support/Education

The ASC will play an active role in facilitating access to support and consultation for inexperienced researchers who want to pursue studies in CATIE and request assistance. Such investigators will be invited to write a brief one-page summary of an idea they wish to pursue through CATIE and their past experience doing research. The ASC will attempt to identify a CATIE investigator who would be willing to provide such support.

Robert Rosenheck MD, Co-chairman
Dilip Jeste MD, Co-chairman
April 24, 2000

IX. INQUIRIES

Direct inquiries regarding issues related to NIMH clinical trials as well as scientific issues related to programs in the Division of Services and Interventions Research to:

John K. Hsiao, M.D.
Division of Services and Intervention Research
National Institute of Mental Health
6001 Executive Boulevard, Room 7160, MSC 9635
Bethesda, MD 20892-9635
Telephone: (301) 443-1185
FAX: (301) 594-6784
Email: jhsiao@helix.nih.gov

Direct inquiries regarding scientific issues related to programs in the Division of Mental Disorders, Behavioral Research and AIDS to:

Bruce N. Cuthbert, Ph.D.
Division of Mental Disorders, Behavioral Research and AIDS
National Institute of Mental Health
6001 Executive Boulevard, Room 6184, MSC 9625
Bethesda, MD 20892-9625
Telephone: (301) 443-3728
FAX: (301) 443-4611
Email: bcuthbert@mail.nih.gov

Direct inquiries regarding scientific issues related to non-genetic programs in the Division of Neuroscience and Basic Behavioral Science to:

Steven J. Zalcman, M.D.
Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health
6001 Executive Boulevard, Room 7177, MSC 9639
Bethesda, MD 20892-9639
Telephone: (301) 443-1692
FAX: (301) 443-4822
Email: szalcman@mail.nih.gov

Direct inquiries regarding scientific issues related to genetics in the Division of Neuroscience and Basic Behavioral Science to:

Steven O. Moldin, Ph.D.
Division of Neuroscience & Basic Behavioral Science
National Institute of Mental Health
6001 Executive Boulevard, Room 7189, MSC 9643
Bethesda, MD 20892-9643
Telephone: (301) 443-2037
FAX: (301) 443-9890
Email: smoldin@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Diana S. Trunnell
Grants Management Branch
National Institute of Mental Health
6001 Executive Boulevard, Room 6115, MSC 9605
Bethesda, MD 20892-9605
Telephone: (301) 443-2805
FAX: (301) 443-6885
Email: Diana_Trunnell@nih.gov

Ancillary Studies Rating Form

Date _____

Reviewer Name _____

Primary Investigator Name _____

Proposal Title _____

Please evaluate this proposal on a 1-5 scale with 1 being the best rating and 5 the poorest rating.

- 1. Appropriateness for CATIE _____
- 2. Comptability with CATIE _____
- 3. Benefit to CATIE _____
- 4. Scientific merit _____
- 5. Investigative Team _____
- TOTAL (add 1-5) _____

1 Appropriateness. Does the proposal fit within the scope of the CATIE project? Is it relevant to the overall CATIE project and objective.

2. Compatibility. Is the proposal compatible with the procedures of the CATIE project? The burden on patients and investigators will be estimated in terms of time, effort, and complexity of the proposed ancillary study procedures, as well as the likelihood of a negative impact on subject enrollment and retention. The applicants must address these issues and explain how any additional burden will be offset, including possible remuneration for patients and clinicians involved.

3. Benefit to CATIE. Does the proposal facilitate or, at a minimum, not impede the enrollment of subject into CATIE? This review will be based on the assessment of the "added value" of the proposal to patients and investigators.

4. Merit. Does the proposal have scientific merit? This determination will be based upon a systematic review of the background and rationale, and the procedures and methods outlined in the proposed ancillary study.

5. Investigator. Is the investigator likely to successfully complete the project?