

Ancillary Studies Policy
Biliary Atresia Research Consortium (BARC)
(Revised 05/10/2006)

GENERAL CONSIDERATIONS

The Biliary Atresia Research Consortium (BARC) is a NIDDK-funded network of ten clinical sites and a data coordinating center (DCC) whose goal is to study the etiology, pathogenesis, diagnosis and treatment of biliary atresia and other infant liver diseases. BARC has implemented three primary (index) studies: (1) a prospective observational database of all infants with cholestasis who are diagnosed by six months of age; (2) a prospective clinical trial of the use of adjuvant therapy in the immediate post-portoenterostomy period; and (3) a prospective observational database of infants, children and adults with biliary atresia, both pre- and post-transplant.

Ancillary studies are studies that are not part of the BARC index studies, but that propose questions and test hypotheses that are relevant to, and congruent with, the goals and purposes of the BARC. Such studies may require additional tests or data that are not routinely obtained in the main BARC protocols. Ancillary studies may involve all BARC subjects and clinical sites, or subsets of either, depending on the eligibility criteria of the study, sample size needed, and interest of BARC investigators in participating. Ideally, an ancillary study will require modest demands on the time and effort of participants, clinicians, and clinical center study coordinators. These studies may include the use of stored specimens (serum or plasma, DNA or cell lines, urine, bile and hepatobiliary tissues) and data already obtained from BARC subjects.

Ancillary studies must be independently funded by the investigator or by resources obtained by the investigator. Investigators proposing ancillary studies must seek funding from outside sources to conduct their research. Examples include funding obtained through investigator-initiated NIH research grant awards (R01's, R21's, R03.s, etc.), grants from academic institutions or foundations, or private funds. The BARC Steering Committee can provide a letter of support to funding agencies for proposals that have been approved by the Steering Committee.

Investigators who are not a part of BARC must have a BARC investigator as a sponsor and collaborator. Investigators who are not part of BARC may contact any member of the BARC Steering Committee or its Chair who will help the investigator identify a potential appropriate collaborator.

When the study involves additional primary data collection by BARC, data management must be performed by the BARC Data Coordinating Center in coordination with the investigator, and the data from the ancillary study will become part of the BARC archive. Raw and "processed" data will be archived. Any additional data or sample collection will become part of the BARC study.

When the study involves only the analysis of samples from the BARC repository, data management may be performed by the investigator. However, the investigator must provide a dataset of the raw and processed data to be archived with the BARC database, which will be arranged with the DCC.

In both situations, all analyses of data must be confirmed by the BARC Data Coordinating Center and resources must be provided by the investigator to the BARC Data Coordinating Center for these efforts. Publications must follow the BARC guidelines.

SUBMISSION AND APPROVAL OF PROPOSAL FOR ANCILLARY STUDIES

Concept Proposal

Concept proposals should be a brief overview of a proposed topic of research, about 2-3 pages in length. The written concept proposal should include sections comparable to the following:

- **Abstract:** a brief summary of the proposed research that includes the primary research question, specific aims and hypotheses.
- **Background and significance:** a brief summary of supporting research and preliminary studies.
- **Study design:** a preliminary description of how the study will be executed including the study population, inclusion and exclusion criteria, primary outcome measures, randomized groups (if applicable), and research methods. An estimate of and justification for the sample size must be included.
- **Impact on BARC:** A description of the BARC data and specimens that are required and of any additional primary data collection. Specific size and amounts of samples requested must be included.
- **Budget:** a rough estimate of research costs (excluding clinical costs that can be charged to third parties) must be included. The budget should also include the incremental costs of the central resources of BARC, such as the DCC and the repository that will be used and will need to be provided. It should indicate the source of funding and/or the plans to obtain external funding and the deadline for application for the funding, if appropriate.
- **References.** These are not included in the page limits.

All concept proposals should be submitted electronically to the BARC Executive Committee (via the DCC who will assign a number to it) at least 3 weeks before a Steering Committee (SC) meeting conference call or face-to-face meeting. The BARC Executive Committee will ascertain that the concept proposal contains sufficient details (see above) to be presented. If the concept proposal is approved by the BARC Executive Committee for presentation, it will be added to the agenda and the investigator will present the proposal at the next Steering Committee meeting or conference call. Two primary reviewers will be chosen among the members of the BARC SC, who will summarize the strengths and weaknesses of the proposal on the conference call or at the meeting. The

concept proposal will be distributed to the BARC Steering Committee members as part of the agenda before the next Steering Committee meeting for review and consideration. After presentation and discussion, the investigator may withdraw the concept proposal from immediate voting if substantial revisions have been suggested by the Steering Committee. (One possible type of revision is a recommendation that two or more proposals be merged or that a concept proposal be merged with a study already under development.) If so, the revised concept proposal would then be presented at a subsequent Steering Committee meeting or conference call.

If the investigator decides to submit the concept proposal to a vote, the Steering Committee will decide whether to advance the concept proposal to a protocol. Voting is by secret ballots that are counted immediately after they are cast. (If by teleconference, the DCC principal investigator will conduct an e-mail poll.) A concept proposal is approved to advance to a protocol with a simple majority vote of the SC. If a concept is proposed and not approved by the SC, the investigator may develop the proposal independently with no obligation to the BARC.

Once approved, the investigator is responsible for expanding the concept and developing it into a protocol within 6 months (unless an extension is authorized by the BARC Executive Committee) and submitting the full protocol to BARC for approval.

Protocol Committee

When the concept proposal is approved, a Protocol Committee is set up:

- The lead investigator designates a Protocol Committee chair (almost always himself or herself). In an unusual circumstance, co-chairs may be appointed.
- The lead investigator should consider including investigators from other clinical sites, the DCC and NIDDK on the Protocol Committee depending on the involvement of those individuals in the conduct of the study.
- Lack of participation in protocol development does not preclude participation in the protocol when it is ready to be implemented with subject enrollment or sample collection; neither does it preclude authorship as long as all other criteria for authorship are met.
- The Protocol Committee, once established, is responsible for protocol development under the leadership of the Protocol Committee chair.

Once a Protocol Committee has been formed for a protocol, the names of all members and their institutional affiliation and email addresses are listed under the name of the committee chair.

The BARC DCC will assign a number to approved protocol; please put the study number at the top of the first page of the proposal and refer to it as the study number in the subject line of all e-mail communications regarding the proposal.

Protocol

The protocol is an expanded version of the concept proposal, about 20-30 pages in length for index studies and 5-10 pages for ancillary studies, which should incorporate comments and recommendations made by the Steering Committee at the initial presentation. The concept proposal should be expanded to a protocol as follows:

- Study Design: should now include specific details of study implementation.
- The sample size calculation should be provided with detailed justification. Investigators should work with the DCC for assistance with sample size calculation.
- Budget: a detailed estimate of research costs should be included.
- The protocol must also include a description of the proposed method of funding.

The protocol should also include:

- A list of clinical sites that have expressed intent to participate.
- BARC and other resources (including data, samples, etc.) required.
- Source of funding of project.
- Timeline.
- Relevance to BARC hypotheses and interpretation of results.
- Impact on BARC recruitment and conduct of study (details of the time and effort for subjects and work requirements for clinical center coordinators must be given).
- Risks and safety concerns.
- Impact on the Data Coordinating Center for data management and analysis.

If the protocol is to be funded by funds available to the investigator that do not require the study to undergo external peer review (i.e., discretionary funds, grant funds already available to the investigator, industry, etc.), the BARC Steering Committee will develop either an internal or external peer review process for the proposal.

APPROVAL PROCESS

Protocols should be submitted to the BARC Executive Committee electronically for review and approval at least 3 weeks before the next Steering Committee meeting or teleconference. The BARC Executive Committee will ensure that the protocol contains sufficient details for presentation and it will then be added to the agenda and the investigator will present the protocol to the Steering Committee. The protocol will be distributed to members of the BARC as part of the agenda before the Steering Committee meeting for review and consideration. Two primary reviewers will be chosen from the BARC SC members before the meeting and they will present a summary of strengths and weaknesses of the protocol at the meeting, and ask questions of the protocol PI. Following presentation of the protocol, one of three decisions will be made:

1. The Steering Committee will recommend that the protocol be revised and re-presented to the BARC at a subsequent Steering Committee teleconference or meeting; or
2. The Steering Committee decides not to approve the protocol; or
3. The Steering Committee decides to approve the protocol.

Voting is by secret ballots that are counted immediately after they are cast. Approval of a protocol requires a majority of the Steering Committee.

Approved BARC ancillary and index studies are submitted to the DSMB for evaluation and critique if necessary. The investigator may be invited to attend the DSMB meeting or that portion that relates to the protocol. The NIDDK Program Director will apprise the investigator of the DSMB's comments and suggestions.

The initial approval for an ancillary study that would significantly impact the BARC serum, DNA or tissue repository is for a period of 270 days (nine months). If the investigator submitted a grant proposal for external funding which was not successful and informs the BARC Executive Committee that he/she intends to resubmit an amended proposal in the next cycle or following cycle, the approval will be extended for up to an additional 365 days (one year). Otherwise the authorization to use the specimens will be withdrawn and the Steering Committee will consider other proposals to use the specimens. Within 5 working days of receiving a decision from the funding source (e.g. NIH), the investigator is required to inform the BARC Executive Committee of the decision; and if unsuccessful, whether a revised application is planned. Within 3 working days of being notified that the specimens are no longer committed to the investigator, the BARC Executive Committee will inform Steering Committee members of the availability of the stored specimens for other ancillary studies. All proposals (re-submission and new proposals) must be sent to the Data Coordinating Center for distribution to the BARC Executive Committee for review.

Individual sites wishing to join in an ancillary study may do so at any point during its submission, by notifying the BARC Data Coordinating Center and the principal investigator of the ancillary study.

TIMING AND PROCEDURES FOR SUBMISSION

Concept proposals and protocols should be sent to the BARC Data Coordinating Center at least **three weeks before the scheduled meeting of the BARC Steering Committee** (via the address below).

A full protocol must be submitted no less than 8 weeks prior to a funding source submission date or starting date if funding is available. This allows

at least 4 weeks for Steering Committee review of the revised protocol and a mail ballot.

An electronic copy on disk or via e-mail of the proposal should be sent to:

John Magee
BARC Data Coordinating Center
The University of Michigan Medical School
Department of Surgery
Room 2926G Taubman Center
1500 East Medical Center Drive
Ann Arbor, MI 48109-0331
Phone: 734 936-9623
FAX: 734 763-3187
Email: mageej@umich.edu

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