ANCILLARY STUDY PROPOSAL PROCEDURES

Ancillary Studies are investigations that are not a primary project of a CNOC committee, but use data collected by CNOC. An ancillary study may involve solely CNOC data, CNOC data with additional data collection, or merging of outside data on patients in the CNOC registry (i.e., from a clinical trial or other registry) with CNOC data. All Ancillary Studies must undergo review by the Research or QI Committee. The review is required to 1) protect the successful completion of primary CNOC projects and 2) to increase the likelihood of successful completion of the proposed ancillary project and 3) to improve chances of extramural funding of the Ancillary Study when appropriate. The review provides a thoughtful critique to address areas of the proposal that are weak, incomplete, or lack sufficient clarity in an effort to improve the application. Approval of the Ancillary Study may be accompanied by a Letter of Support from CNOC signed by the Research or QI Committee Chair and the Data Analytic Core (DAC) PI. When appropriate, ancillary studies may also undergo review by the Steering Committee and possibly other regulatory bodies, including the participating site's IRB/REC, prior to submission of a funding application.

A CNOC member with relevant area expertise must be included at least as a co-principal investigator in every Ancillary Study application. The Research Committee can be contacted for a list of CNOC members who can participate as co-principal investigators. Investigators from other CNOC centers may be included as appropriate. Ancillary Study investigators will coordinate activities with the CNOC Data Coordinating Center (DCC), DAC, and Neurodevelopmental Core (NDC) as needed. Ancillary Study investigators must abide by CNOC research and publication policies, authorship guidelines, and should make available resulting research data to other CNOC institutions and future investigators after completion of the primary ancillary project when appropriate.

1. Sources of Study Proposals

Ancillary study proposals can be submitted in multiple ways.

1) CNOC may solicit proposals from the pediatric cardiovascular and neurodevelopmental communities for applications. Requests for proposals may occur to highlight specific topics of interest and/or further engage the cardiac neurodevelopmental community in specific areas of focus, prioritized by CNOC. Formal requests for applications with CNOC funding support, will be at the discretion of the Steering Committee.

2) The Research and QI Committees may solicit or foster proposals from CNOC members and Committee members at specified intervals to augment their initiatives/mission. These may include, but are not limited to initiatives that utilize CNOC resources when available (such as DCC or DAC time) but are otherwise unfunded.

3) Investigator initiated proposals with plans for external funding can be submitted at other times outside of solicited proposals.

Additionally, the Research Committee will review unsolicited proposals for research projects intermittently as outlined below.

2. Instructions for Submission of Proposals

An Ancillary Study application should be submitted with support and involvement of a CNOC member. Ancillary Study investigators can contact the Research Committee for a list of CNOC members who can participate as co-principal investigators and for information on their specific

areas of expertise. Once a CNOC member has agreed to participate in the proposed research, the application can proceed through the submission process. The Ancillary Study application process will begin with a letter of intent (LOI). The Review Committee will be responsible for selection of LOIs for full proposal submission. All Ancillary Study applications (including letters of intent and full proposals) should be submitted to the chair of the CNOC Research or QI Committee for consideration.

If the proposed Ancillary Study is to be part of a grant application, approval from the Research or Quality Improvement Committee must be obtained before the grant is submitted. If a Letter of Support is requested for the grant application, the Ancillary Study Principal Investigator (PI) should provide a draft of the proposed letter with the application. If the study is approved, the Research or QI Committee Chair and the DAC PI will edit and sign the Letter of Support.

2.1 Proposal Formatting for Solicited Proposals

All LOIs and full proposals must adhere to the specified formatting guidelines outlined by CNOC to be considered for review.

2.1.1 Letters of Intent (LOI)

LOIs should be a one-page concept paper submitted to CNOC with the following information:

1. Title
2. Brief background
3. Aims, hypotheses, and significance of the study
4. Study design and outcomes
5. Source of funding
6. If the LOI is being submitted outside of a CNOC Request for Applications, the concept paper should also include a brief explanation about why off-cycle review is needed

2.1.2 Full Proposals

For full proposals, the application should be submitted to CNOC with the following information:

1. Title
2. Specific Aims page (one page)
3. Research Strategy (no more than 6 pages):
    a. Background/significance of the study
    b. Innovation
    c. Approach (including study design, analysis plan and power calculations to justify sample size, description of requested data, including patient cohort, data fields, proposed date of project completion)
4. Biographical Sketch: The standard NIH Biosketch of the requesting principal investigator(s) is preferred. Co-Investigator biosketches are optional but encouraged.
5. IRB approval: This should be provided if available at time of application. At the time in which an LOI is selected for full proposal, investigators should communicate with the Chair of the RC or QI Committee for recommendations on IRB approval through the DCC and/or additional institutional approval relevant to the project.
6. Budget and source of funding
7. Letters of Support (optional, but encouraged, no more than 3 letters)
8. Supporting Documentation: Additional documentation such as a planned, pending or awarded grant application for a similar type.
9. Lay Summary (no more than ½ page)

2.2 Proposal Formatting for Unsolicited Proposals

2.2.1 General research inquiries

1. Investigators are encouraged to reach out to the Research and/or Quality Improvement Committee chairs to discuss their proposal at an early stage. A web-based form requesting basic study proposal information is available at cardiacneuro.org for investigators interested in utilizing data from the CNOC registry. These inquiries will be forwarded to the Research Committee chairs and co-chairs for review. If deemed potentially feasible, the investigator will be directed to this Ancillary Study Proposal Procedures document for details regarding submission of unsolicited proposals and guidance for Letter of Intent submission.

2.2.2 Letter of Intent

Interested investigator should submit a "Letter of Intent," approximately 1 page, to the Research Committee chairs via email. LOIs should contain the following information:

1. Primary and identified co-investigators
2. Title
3. Proposed study question
4. Primary and secondary aim(s)
5. Patients to be studied (i.e., inclusion/exclusion, diagnoses/surgical cohorts, time frame, as appropriate) and approximate sample size needed
6. General description of potential variables to be utilized
7. Potential impact
8. All sources of funding obtained, requested, or to be requested
9. Anticipated need for CNOC resources including Data Coordinating Center and Data Analysis Core (tasks and anticipated #hours)
10. Timeline (if applicable)

Research Committee chairs/vice-chairs to review LOIs. If deemed potentially feasible, chairs will distribute the LOI to Research Committee members and ask the investigator to present a brief (~5-minute) overview of the project at the next available RC meeting. Depending on the maturity of the proposal, RC chairs may request the investigator meets with appropriate experts (i.e. DAC or Database Committee representative, etc) prior to the presentation.

Following the investigator presentation, RC will review the LOI to determine:

a. Feasibility of project
b. If project overlaps/duplicates other known CNOC research projects.
c. Priority of project, considering resource utilization and potential funding mechanisms.
d. Consider whether it should be a CNOC-wide project depending on the scope and content
e. If feasibility, originality, and priority warrants full proposal request, RC also to determine if additional resources (i.e. members of RC, Database Committee, Quality Committee, or other content expertise) may be required to optimize proposal creation.
    i. If full proposal requested, RC will assign an appropriate liaison to assist with proposal development
    ii. RC chair(s) to respond to investigator with written request for full proposal, including feedback from the RC
    iii. Full proposal due within 3 months of request for full proposal

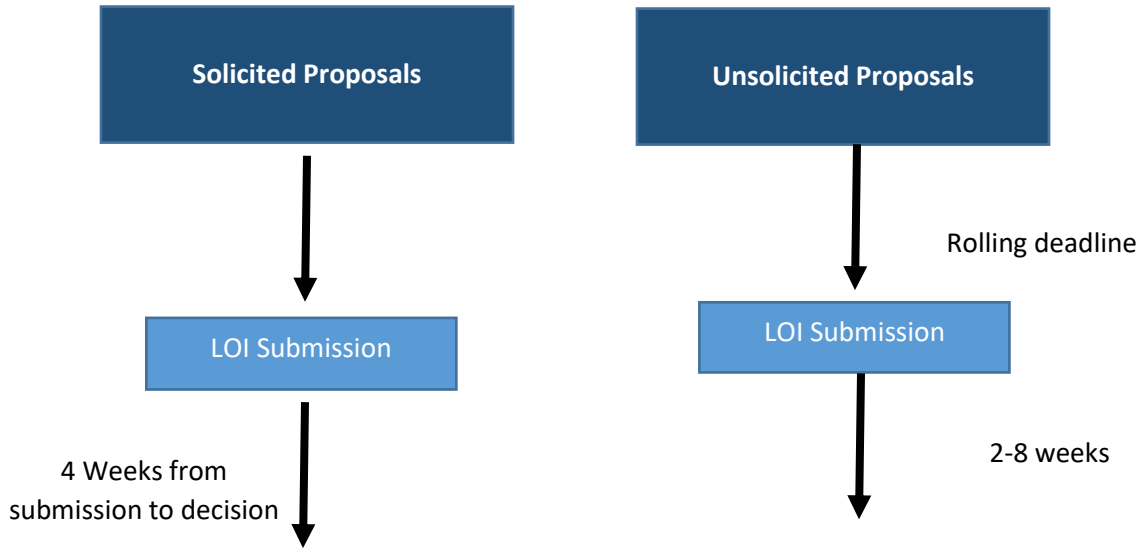
2.2.3 Full Proposal

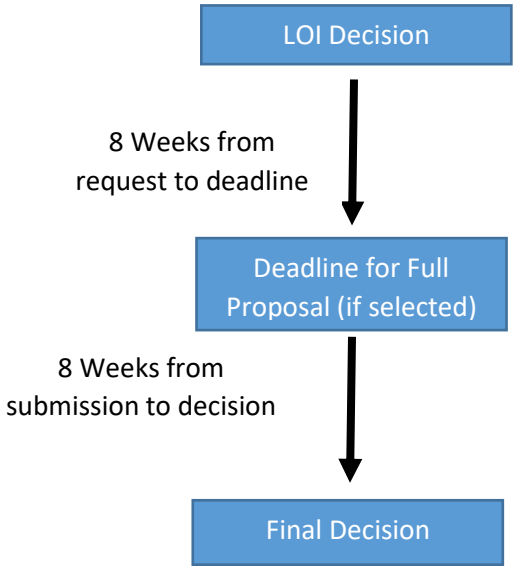
1. Format is flexible (i.e. if part of grant submission, acceptable to utilize the grant format) but should include the following information:
    a. Identified investigators and affiliations
    b. Title
    c. Specific Aim(s)
    d. Project Background
    e. Impact Statement
    f. Inclusion/Exclusion criteria and proposed timeline of subjects to be included (as well as estimate of current "n" available within CNOC database)
    g. Specific variables to be utilized (CNOC as well as other registries)
    h. Proposed analytic plan for each aim
    i. Data analysis support needs
    j. Anticipated meeting(s) for abstract presentation (and deadlines)
    k. Anticipated journal for manuscript submission
2. Once full proposal is received by the RC chairs it will be distributed to the RC for review and the investigator may be asked to return for further discussion to a subsequent RC meeting if needed
3. RC to vote if request needs revision, can be accepted as is, or will be denied
    a. If accepted RC to determine prioritization and estimated timeline for data to be provided to investigators
    b. RC to recommend potential additional co-investigators if needed (content experts, committee/SIG representation, etc.)
    c. The investigator must follow all relevant CNOC guidance with regard to authorship and publication, outlined separately within this document and the Manual of Operations

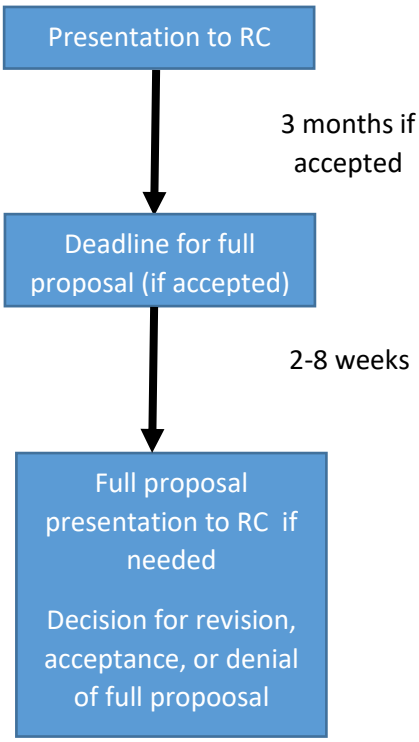
2.3 Timeline for Submission of Proposals

The anticipated timeline from submission to approval will vary for solicited and unsolicited proposals (Figure 1).

Figure 1: Timeline for Solicited and Unsolicited Proposals




LOI Decision
8 Weeks from request to deadline
Deadline for Full Proposal (if selected)
8 Weeks from submission to decision
Final Decision


Presentation to RC
3 months if accepted
Deadline for full proposal (if accepted)
2-8 weeks
Full proposal presentation to RC if needed
Decision for revision, acceptance, or denial of full propoosal

2.3.1 Timeline for solicited proposals

Requests for proposals will be solicited during a timeframe in which final review/decisions can be made prior to the CNOC Annual Scientific Sessions. Full proposals that have been accepted as CNOC Ancillary Studies will be announced during the Annual Scientific Sessions.

LOI Timeline:

- Emails soliciting an LOI will be sent, with a submission deadline of 4 weeks after the email announcement.
- Within 1 week after the LOI submission deadline, the Research or QI Committee Chairs/Co-Chairs will finalize any reviewers needed beyond their committee, will designate Primary and Secondary Reviewers, and will distribute the LOIs to the reviewers.
- LOIs will be discussed during a Research or QI Committee call. Depending on the number of proposals, these discussions may occur over several calls but will be completed within 3 weeks of proposal submission. A confidential electronic ballot will be provided and all Committee members (except those with a conflict of interest) will vote on whether the LOI should be selected for full proposal.
- Ancillary study investigators will be notified of the final decision for the LOI submission within 4 weeks of the submission deadline. Full proposals for consideration will be requested based on the submitted LOI.

Full Proposal Timeline:

- A full proposal will be due 8 weeks after the study PI has been notified that they are selected for full proposal submission based on the LOI.
- Within 1 week after the full proposal submission deadline, the Research or QI Committee Chairs/Co-Chairs will finalize any reviewers needed beyond their committee, will designate Primary and Secondary Reviewers and Patient/Family Reviewers, and will distribute the full proposals to the reviewers. Efforts will be made to maintain reviewer consistency across LOI and full proposals. All other members of the Research or QI Committee will be voting members during the review process (unless there is a conflict of interest).
- Proposals will be discussed during a Research or QI Committee Call. Depending on the number of proposals, these discussions may occur over several calls but will be completed within 4 weeks of proposal submission. All reviewers will receive a confidential electronic ballot to score the proposal. Additional discussion after scoring may occur.
- After the Research or QI Committee call, the Primary and Secondary reviewers will provide their review summary to the Committee Chairs/Co-Chairs, no later than 1 week after the call.
- The Research or QI Committee Chair will provide feedback and the review decision to the lead investigator within 8 weeks of submission.
- Studies that are not accepted may be resubmitted after addressing the concerns and issues noted in the review.
- Ancillary study investigator and CNOC RC Chair(s) may discuss a realistic timeline for review before specific funding submission deadline

2.3.2 Timeline for unsolicited proposals:

Investigators will be permitted to submit proposals outside of solicited requests. The submission of these proposals will be on a rolling basis.

Unsolicited Proposal Timeline:

- LOIs will be reviewed as received. The Research or QI Committee Chairs/Co-Chairs will determine if additional review/meeting with other CNOC parties (i.e DAC or Database

Committee representative, etc.) is needed prior to scheduling presentation. LOI will be distributed to committee prior to presentation at next available committee meeting.
- Following presentation, committee members will vote on whether a full proposal is requested for review. If full proposal requested, a committee liaison and any additional representation will be assigned
- The Research or QI Committee Chair will provide feedback and the review decision to the lead investigator within 2 weeks of presentation
- Full proposal will be due within 3 months
- Full proposals will be distributed to the committee for review and potentially presentation at a subsequent committee meeting within 2-8 weeks
- Research/QICommittee will determine need for revision, acceptance, or denial and committee chair will provide decision to the lead investigator within 2 weeks of presentation and/or receipt
- Ancillary Study investigators are responsible for allowing sufficient time for review before funding submission deadlines.

3. Review of Study Proposals

3.1. Review Committee Formation

The Research and QI Committee Chairs/Co-Chairs will be responsible for distributing proposals for review and providing a recommendation to the Steering Committee. Committee members of the relevant committee (Research or QI) will be responsible for review of the proposal. The number of committee members on the review committee will be determined by the Chairs/Co-Chairs of the committee and will be based on the topic of the proposal and breadth of expertise required for adequate review. Other CNOC members and Committees may also be asked to review proposals where appropriate (i.e. the DCC, DAC, etc). A Primary and Secondary reviewer will be designated for each proposal. The final review committee will typically consist of:

- Members of the Research or QI Committee (depending on which committee is responsible for the proposal)
- A statistician and/or quality improvement expert
- A parent or community representative
- Two of these reviewers will be designated as the Primary and Secondary reviewers

3.2. Evaluation of LOIs and Proposals

LOIs and Proposals will be discussed during a Research or QI Committee Call. The Primary and Secondary reviewers will lead these discussions and will focus on the specific criteria outlined below.

Each proposal will be assessed according to the following criteria:

- *Scientific merit:*
    - Scientific justification
    - overall design
    - meaningful, valid endpoints
    - reliable measurements
- *Relevance and importance of topic:*
    - potential impact on the neurodevelopmental care of children with CHD and their families
    - degree of controversy in the field

    - Compatibility with CNOC activity and goals portfolio, including approved ancillary studies
- *Feasibility:*
    - Ability to identify a clinically relevant and feasible primary study endpoint
    - Adequately powered to address scientific aims
    - Likelihood that patient populations of sufficient size will be available within CNOC
    - Supporting data that demonstrate feasibility and validity of proposed aims
    - Cost of proposed study and availability of adequate funds for study conduct
    - Burden/risk for study participants (if applicable)
- *Strength of Research Team:*
    - Team members have the necessary expertise to conduct the proposal
    - Early career investigators are encouraged with support from senior investigators
    - Multidisciplinary and international collaborations are encouraged

Reviewers will receive a confidential electronic ballot and will vote on whether a full proposal will be requested (if reviewing an LOI) or will score the proposal based on the above criteria (if reviewing a full proposal). If needed, presentation to, and discussion with, the SC will occur during a scheduled SC call or impromptu call.

4. Funding

Funding Support for all Ancillary Study activities must be obtained from sources other than CNOC unless a call for proposals has explicitly stated that CNOC funds or resources will be provided to support the study. Funding can be sought from a variety of sources, including NIH (or other official governmental agencies) research and career awards, grants from academic institutions, and funding from foundations, granting agencies, institutions, or other private sources. Activities requiring financial support may include, but are not limited to, institutional and administrative support, scientific support, design and collection of new data variables, data analysis, and database management, long term storage of study materials per good clinical practice (GCP), and statistical support. The budget proposed for all funding applications should include sufficient time and effort to support any relevant CNOC Cores that will be utilized as part of the proposal. This includes, but is not limited to, support for the DAC for data analysis, support for the NDC if new assessments or testing batteries are being proposed, the DCC if new modules are being created outside of the Arbormetrix platform, and support for ArborMetrix if new data variables will need to be built into the database platform. If additional data is required from CNOC centers, the additional demands on each participating center and study subject must be considered and accounted for in the budget. For example, if a study coordinator must retrieve and submit data, the Ancillary Study budget must address the hours needed to complete these tasks and include appropriate compensation. In addition to the funding needed for study execution, the budget must include funds to support the extraction of requested data from the DCC or DAC.

While the anticipated time from submission to final approval of Ancillary Proposals is 8 weeks, applicants who are also applying for funding should consider whether significant time commitments are required from a CNOC Core or from CNOC sites to determine feasibility and/or facilitate design of new data variables. In this scenario, proposals should be submitted within a timeframe that allows the Research or QI Committee to adequately review the proposal, incorporate relevant Cores, and determine feasibility within the funding application deadline.

5. Transfer and Housing of Data for Approved Projects

Requests for data by the study team for independent analysis outside of the DAC and DCC will be reviewed by the DCC. Any transfer and storage of deidentified data will be subject to terms and conditions of current data use agreements across CNOC.

6. Progress Reports

From the initial approval date, annual Progress Reports will be submitted to the Research or QI Committees and copied to the Steering Committee. The reports will be reviewed, and a memo will be sent back to the lead investigator noting its receipt and review. The Progress Report should include the following:

1. Status of study (active, pending, completed, etc.)
2. Funding information
3. Study activities during reporting period, including publications and presentations
4. Number of participants involved
5. Centers involved
6. Findings to date
7. Any protocol deviations or events reported to an institutional ethical board

7. Publications and Presentations

Publications resulting from Ancillary Studies must follow the policies of the CNOC Publications Committee. All papers and presentation abstracts involving CNOC study data are to be submitted to the CNOC Publications Committee for approval prior to submission to the target journal or meeting organizer. The lead investigator should submit such documents to the Publications Committee Chair who will distribute the documents to the Publications Committee for review. The deadline for review of manuscripts by the Publications Committee is 3 weeks from time of submission. The deadline for review of abstracts by the Publications Committee is 10 days from time of submission. The Publications Committee must approve content and format prior to publication or abstract submission, and will share specific comments with the authors. All papers/presentations should document the use of CNOC resources and acknowledge support of the Collaborative.

8. Inclusion of Contributing Centers

If the Ancillary Study utilizes CNOC data for the main outcome(s), all CNOC Centers that contributed the data may be invited to participate in writing committees for papers resulting from the study. Site author inclusion will be decided during the approval process by the Research and/or QI Committee, and may include a CNOC-wide announcement for project-specific authors and/or site authorship from each site contributing data. For inclusion in authorship, authors must meet criteria as specified by the International Committee of Medical Journal Editors (ICMJE). If a significant proportion of the data requested rely on PC^4 and PAC^3 initiatives and registry data, authorship invitation requirements may include discussion with other committees across Cardiac Networks United, as well as determination of whether the proposal should be submitted through Cardiac Networks United.

9. Scope of Work

Approval of the Ancillary Study is granted only for the specific testing and analysis detailed in the proposal. Data provided by CNOC cannot be used for other analyses or testing of additional hypotheses without prior approval from the Research or QI Committee.