Chapter 5: Ancillary Studies Policies and Procedures

5.1 POLICY

Current and previously funded PCGC site Investigators and other researchers outside of the PCGC consortium are encouraged to propose and conduct ancillary studies to advance the field of pediatric cardiac genomics. Such studies enhance the value of the PCGC and promote the continued involvement of a diverse group of investigators, which is critical to the success of the study.

A PCGC ancillary study is defined as an investigation that is supported by funding other than the PCGC and that has not been approved by PCGC working groups.

Proposed ancillary studies will be submitted to the PCGC Ancillary Study Committee (ASC) for review and consideration per the process described in section 5.2 of this document.

A study with external funding that is proposed by a PCGC investigator may be submitted to the PCGC for review and consideration by one of following options:

- A proposal that does not fit within the scope of the science of the PCGC working groups will be submitted as an ancillary study per the process described in this document.
- A proposal that fits within the scope of the science of the PCGC working groups will be submitted as a PCGC project to the PCGC Steering Committee (SC) for discussion and approval.

An ancillary study may involve:

- Use of existing PCGC data
- Use of existing PCGC specimens
- Collection of new data from participants enrolled in PCGC studies.

A currently funded PCGC PI must be included, at least, as a co-investigator in every ancillary study application.

Support for all necessary activities of the ancillary study must be obtained from sources outside the PCGC.

Ancillary studies must be reviewed and approved by the PCGC Ancillary Studies Committee (ASC), PCGC SC, Observational Study Monitoring Board (OSMB), NHLBI and possibly other regulatory bodies, including the participating facility's IRB/EC, prior to submission of a funding application. Studies requesting access to biological specimens or those involving informed consent require additional levels of review.

Maintaining the integrity of the PCGC protocols, retaining study participants, and adhering to the PCGC protocols are of paramount importance. Any PCGC protocol participant may be recruited for an approved ancillary study. Any proposed ancillary study that would interfere with PCGC protocol procedures, involve unreasonable participant burden, or possibly lead to a participant withdrawing from the study is unlikely to be approved.

Use of DNA specimens are prioritized first for core analyses described in PCGC approved protocols. Secondary consideration will be given to ancillary studies. The PCGC makes every effort to conserve valuable biospecimens, and parsimonious use of specimens is an important consideration in review of ancillary study applications.

Ancillary study investigators will coordinate activities with the PCGC Coordinating Center (CC), data and biospecimen repositories, and core facilities, as needed.

Ancillary study investigators must abide by the PCGC Research Policy (see Chapter 3, section 3.1) and must share all resulting research data with the ACC who will then make the data available to the rest of the consortium.

5.2 PROCEDURES

5.2.1. Application and Review

5.2.1.1. Application

An ancillary study application should be submitted to a currently funded PCGC PI for support and involvement, who will serve as the Sherpa for this project. Once a PCGC PI has agreed to participate in the proposed research, it should be submitted to the PCGC Ancillary Studies Committee (ASC) for consideration. This presentation can be facilitated by the participating PCGC PI.

Applications must be submitted and approved prior to submission of an application for funding. A brief application (no more than 5 pages) should be submitted to the PCGC ASC with the following information:

1. Description of the proposed research:
    - Aims and significance of the study,
    - Study design,
    - Analysis plan and power calculations to justify sample size,
    - Description of requested biospecimens, including quantity, volume, concentration, etc., with a justification for the quantity,
    - Justification for the use of PCGC biospecimens, as opposed to specimens from other sources,
    - Experience of the requesting laboratory in this or similar assays,
    - Proposed date of project completion.
2. Biographical Sketch**:** The standard two-page NIH Biosketch of the requesting principal investigator is acceptable.
3. IRB approval: This should be provided if available at time of application.
4. Supporting Documentation: Additional documentation such as a pending or awarded grant application for a similar type of work, accepted or published manuscripts or abstracts, recent supporting literature can also be included.

Applications should be submitted via email to the ASC Chair and to the CC.

5.2.1.2. Ancillary Studies Committee Review

The PCGC ASC will evaluate applications based on the following criteria:

1. Scientific Merit: scientific justification, logistics and robustness of the application;
2. Feasibility: availability of the requested biospecimens;
3. Burden on Study Participants (if applicable);
4. Study Design, Statistical Analyses and Power: appropriate study design and statistical analyses approach;
5. Preliminary Data: supporting data that will confirm the validity of the study;
6. Strength of Research Facilities: experience of the affiliated laboratory with the proposed or research tests and an indication of familiarity with the proposed methodologies; and

7. Compatibility with the active PCGC portfolio, including approved ancillary studies.

Applications are reviewed as received. If the ASC recommends to approve, the ACC will communicate this to the SC. The SC then reviews and votes to approve or not approve. If the outcome of the SC review is not favorable, the ancillary study will either be rejected, or additional information will be requested from the Lead Investigator. The SC Chair will send 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 investigators are responsible for allowing sufficient time for review before funding submission deadlines. All approved ancillary studies that require consent of subjects for additional specimen collection, testing, or data collection, must be reviewed by the OSMB prior to implementation.

5.2.1.3. NHLBI Project Office Review

The application will also be reviewed by the NHLBI Project Office to confirm that the proposed study will not compromise, complicate, or jeopardize the conduct of the PCGC protocols. Review priority will be given to studies that:

- Do not interfere with main PCGC protocol objectives,
- Have scientific merit,
- Produce the least burden on PCGC protocol participants,
- Have objectives closest to those of PCGC program, and
- Require the unique characteristics of the PCGC protocol cohorts.

As indicated, the SC and Lead Investigator will receive feedback from the NHLBI review. Studies that are not approved may be resubmitted after addressing the concerns and issues noted in the review.

5.2.1.4. Involvement of PCGC Investigators and Core Facilities

PCGC PI - To ensure continued integrity of the collected data and/or samples, a currently funded PCGC site PI must be at least a co-investigator on all proposed ancillary studies.

PCGC Coordinating Center (CC) - It is highly recommended that the Lead PI initiate discussions with the CC early in the application stage to ensure logistics and agreements are available by the planned research start date. For ancillary studies collecting additional data, coordination with the CC must be finalized prior to study start up to ensure smooth and complete transition of data from the ancillary study site to the CC. For details related to the transfer of data to the CC, refer to the PCGC MOO, Chapter 3: Consortium Policies, section 3.1.2.4.

PCGC Core Facilities - Protocols proposing use of the Core Facilities must detail the delivery of services or samples, financial support for their services and a detailed outline of the laboratory/samples use. Coordination with the involved core facilities must be completed prior to initiation of the study start date.

5.2.1.5. Post-Approval Study Modification(s)

Ancillary study modifications include changes in sample size, analysis, use of specimens, data to be collected, and any other substantive change. All proposed design changes must be reviewed by the ASC and SC prior to implementation and, where necessary, must also receive IRB approval prior to implementation. The NHLBI will determine if review by the OSMB is required. If the proposed change significantly adds to participant burden or raises new human subjects' concerns, the modification must also be approved by the NHLBI Project Office.

5.2.2. Funding

Support for all ancillary study activities must be obtained from sources other than the PCGC. Activities requiring financial support may include, but are not limited to, institutional and administrative support, scientific support, biospecimen handling, participant recruitment and consent, collection of new data, and database management, long term storage of study materials per good clinical practice (GCP), and data analysis/statistical support. (The Coordinating Center may help with some of these activities, but they will require support to do so).

Investigators must obtain PCGC SC approval before submitting funding requests for ancillary studies. NHLBI guidelines for ancillary studies require that investigators seeking funding from NIH have NHLBI approval prior to submission.

Appropriate financial support for the PCGC CC and laboratories must be included in the application's funding strategy.

5.2.3. Data Ownership

If PCGC data and/or biospecimens are requested for the ancillary study, the PCGC and the ancillary study PI must complete the appropriate agreement with terms and policies specific to what is being provided, i.e. PCGC data, materials or both. The agreement will describe the data and/or biological specimens to be released to the investigator and the relevant PCGC policies with which the investigator agrees to comply. Any participant data provided by the PCGC to the ancillary study PI may not be distributed to any other entity or individual.

The investigator must abide by the PCGC Data Sharing Policy and Plan (see Chapter 6, Section 6.1). Genotype and phenotype data will be shared through the NIH GWAS data repository (dbGaP) once the genotyping data have been cleaned; cleaning is expected to be complete approximately 2 months after genotyping is finished. From the time the dataset is made available for access through dbGaP, a 12-month period of exclusivity will exist for ancillary study investigators to submit analyses of genomic datasets for publication.

PCGC may distribute these data in the future to qualified scientific investigators requesting access through established PCGC procedures, after initial publication of findings by the ancillary study investigators (see PCGC Publication and Presentation Policy and Procedures). The PI of the ancillary study that generated the data will be offered authorship in any papers using their lab data.

5.2.4. Study Implementation

5.2.4.1. Recruitment and Consent of Participants

Upon implementation, any PCGC protocol participant may be recruited. Consenting and study conduct must conform to GCP. Communicating with and recruiting participants into an ancillary study must follow IRB approved methods outlined in the protocol.

While discussing the approved ancillary study, the PCGC protocol participant must be made aware that participation in an ancillary study is a separate activity from the PCGC studies and that any decision will not affect a subject's participation in PCGC core studies.

5.2.4.2. Biological Specimens

Ancillary studies involving biospecimens will be approved for 24 months from the date of the approval letter from the SC. If funding is not achieved within 24 months of PCGC approval, the study will need to re-apply to the ASC for approval for another 24 months approval window.

Once a protocol has SC and IRB approval and has obtained funding, the Lead PI may finalize discussions with the biospecimen and data repositories for the acquisition of the needed material. Financial burden of the movement of samples or special needs including data transfers will be the responsibility of the ancillary study.

Access to biological specimens (biospecimens) for ancillary studies is managed by the PCGC SC through an application process (see Biospecimen Sharing Policy). The standard aliquot approved for use is 1-3 µg of DNA per subject. Studies requesting more than 3 µg of specimen per subject will not receive approval unless there is SC support at the time of approval.

After receipt of ancillary study biospecimens, and upon approval of an analysis proposal by the PCGC SC (see PCGC Publication and Presentation Policy and Procedures), the ancillary study investigators can begin analyses of the data.

All unused biospecimens will be returned to the biorepository or destroyed at the discretion of the ACC by the end of the study or the 30-month agreement timeframe (unless a renewal of the agreement has extended the PCGC agreement for another 30 months).

5.2.4.3. Data Access

PCGC data required for an ancillary study will be supplied by the collaborating PCGC PI or the CC. Delivery of the protocol-defined information will be completed after coordination with the CC. A Data Use Agreement will be executed between the Lead PI and the CC.

Previously funded PCGC site PIs may maintain access to the PCGC Data Hub and will continue to have the authority to grant access to necessary students, postdocs, and junior faculty in their research group and at their institution with the understanding that the use of the PCGC Data Hub requires acceptance of the consortium's collaboration and publication rules. In particular, research projects should be presented to and approved by the respective PCGC working groups. Investigators have the option of submitting an ancillary study proposal to pursue research goals using PCGC data. It is the responsibility of the site PI to ensure that all approved users are aware of the data use rules.

All data derived from new analyses must be shared consistent with the PCGC Data Sharing Policy and Plan (see Chapter 6).

5.2.4.4. Data Management

All ancillary studies must use data collection systems which are secure, maintaining participant confidentiality, meeting HIPAA facility standards, and ensuring research data security. Additionally, every approved ancillary study will be entered and tracked in the CC PCGC study tracking database. All studies will be posted to the PCGC administrative website and progress reports are shared with the OSMB. For outside investigators, a Data Use Agreement is required.

5.2.4.5. Progress Report

From the initial approval date, annual Progress Reports will be submitted to the CC and copied to the SC and NHLBI Project Officer. 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:

- Status of study (active, pending, completed, etc.)
- Funding information
- Study activities during reporting period, including publications and presentations

- Number of participants involved
- Field centers involved and
- Findings to date.

5.2.4.6. Publications and Presentations

Publications resulting from ancillary studies must follow the policies described in the PCGC Publication and Presentation Policy and Procedures. Proposals and analysis plans for manuscripts and abstracts that will report findings from ancillary studies must be reviewed by PCGC SC before the CC and/or data repository can release the corresponding PCGC data needed for the ancillary study analysis. Ancillary Study investigators should submit a manuscript proposal(s) to the SC committee shortly after the funding period starts to ensure timely access to PCGC data.

All papers and presentation abstracts involving PCGC study data are to be submitted to the PCGC SC for approval prior to submission to the target journal or meeting organizer. The Lead Investigator should submit such documents to the CC; the CC will distribute the documents to the SC for review. Consistent with Chapter 4 Section 4.2.2., the deadline for review by the SC is 2 weeks from time of submission. Expedited approval (within 48 hours) can be requested. The SC must approve content and format prior to publication submission.

Approval requires a majority approval by the SC. Once approved, the document may be submitted.

For documents not approved:

- The SC will share specific comments with the authors.
- The Authors should edit the document based upon SC comments.
- The revised document may be resubmitted for re-review.

All papers/presentations should document the use of PCGC resources and acknowledge support of the NHLBI.