Cure Glomerulonephropathy Network
Ancillary Studies Policy

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1 INTRODUCTION

Cure Glomerulonephropathy (CureGN) is a multi-center consortium that is working collaboratively to recruit and follow a large, ethnically diverse cohort of patients with one of the following diagnoses: Minimal Change Disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), Membranous Nephropathy (MN), or IgA Nephropathy (IgAN). The study will establish an infrastructure that enables the following questions to be addressed:

- What is this disease?
- Why do I have this disease?
- What will happen to me?
- What effective treatments can you offer me?

To make the best possible use of this valuable resource, CureGN encourages investigators to submit ancillary study proposals (ASPs) to CureGN. An ancillary study uses data and/or biospecimens from CureGN participants, and/or uses CureGN infrastructure, in an investigation or analysis which is relevant to CureGN goals but is not described explicitly in the CureGN protocol.

To maintain scientific integrity of CureGN, prioritize use of its resources, ensure regulatory compliance, and monitor burden to participants, ASPs must be reviewed by the CureGN Ancillary Studies Committee (ASC), approved by the CureGN Principal Investigator Group (PI Group) voting body, and fully funded before inception of activities. Annual review of ancillary studies by CureGN is also required.

2 GENERAL PRINCIPLES

2.1 Definition of Ancillary Studies

Ancillary studies typically propose new use of biospecimens or other study resources that have already been collected (or planned to be collected), collection of additional data/biomaterials, or an interventional study using the CureGN cohort as a basis for recruitment. A study based on an analysis of existing CureGN data, and with goals that are not within scope of the core CureGN study aims, is considered an ancillary study (i.e., is subject to approval via the CureGN Publications and Presentations Policy but not the ASP).

2.2 Who Can Apply

ASPs may be submitted by CureGN Consortium investigators (i.e., study investigators at a CureGN Participating Clinical Center [PCC], PCC sub-site, or the Data Coordinating Center [DCC]) or investigators outside of the CureGN Consortium (“external investigators”).

External investigators submitting an ASP are required to identify a CureGN investigator to sponsor their study. There are 25 eligible sponsors nominated by each PCC and DCC (5 sponsors per site). Their names and contact information are listed on the CureGN website. Sponsors are CureGN co-investigators or committee members that are familiar with the core study and can provide insight and guidance to interested ancillary study investigators (ASI). The sponsor will advise the ASI on how to align the study with the overall objectives of the CureGN project, and how to minimize the burden to clinical sites and study participants.

If the CureGN sponsors listed on the website do not have sufficient expertise to sponsor a certain study, investigators may contact a PCC or DCC PI for referral to another CureGN investigator to serve this role. It is not required that the sponsor be listed as an investigator on submissions for funding or as co-author on eventual manuscript(s), unless her/his role while the project is carried out warrants this inclusion.

2.3 Funding

All ancillary studies must have sufficient external (non-CureGN) funding to support the goals of the ancillary study, including costs for all required study personnel, labs, administration, shipping, obtaining biosamples from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) repository, data extraction, preparation of data files, statistical analyses, and integration of new data/biomaterials/analyses into the CureGN infrastructure. Examples of potential sources of funding are: investigator-initiated awards from the National Institutes of Health (NIH, e.g., R01 or non-US sources), academic institutions, private foundations, and pharmaceutical companies.

The investigator applying for an ancillary study must supply all additional funds required to conduct the study. The ASC and PI Group will be concerned with both the obvious and the hidden costs to CureGN entailed by an ancillary study, such as costs to PCCs and sub-sites related to new data collection, costs for retrieving samples, and costs to the DCC. DCC activities may include, for example, providing support for data collection, data management including quality control and integration of ancillary data with CureGN data, data analysis, study coordination and communications, and other functions. Prospective ASIs are welcome to consult with the CureGN DCC prior to submission of the ASP to CureGN to determine what level of DCC involvement may be needed.

2.4 Site of Analytic Activities

To assure integrity of CureGN research output and thereby maximize overall scientific impact, the CureGN Consortium has agreed that the DCC would have the opportunity for oversight over the design and quality of analyses performed with CureGN data. This may be approached in one of three ways:

(1) The DCC helps design the study, conducts the full analysis, and is responsible for producing methods, tables, and figures for manuscripts or abstracts. Prioritization among approved projects will be brought to the PI Group as needed.

(2) The ancillary study investigator (ASI) team designs the study and conducts the analysis. In this case, the ASI team assumes responsibility for the integrity of their results. Upon review by the Publications and Presentations Committee (PPC), the results may undergo additional quality review by the DCC or other methodological experts. This may include review of the statistical code and re-analysis if recommended. The PI Group may also request review or re-analysis by the DCC. (See also CureGN Publications and Presentations Policy.)

In the event the PPC or PI Group requests validation of selected statistical analyses, the ancillary study team will make relevant statistical code and analysis results available to the DCC for review before publication.

(3) A hybrid approach, e.g., with some aims analyzed by the ASI team and others by the DCC.

The proposed location of the analyses should be specified in the ASP and agreed upon at time of AS approval. For ASI-led analyses, qualifications of the analytical team should be included. For analyses of

clinical data, it is expected in most cases that work be performed, at a minimum, by a masters-level biostatistician or epidemiologist under the supervision of a PhD level biostatistician or epidemiologist. ASIs may provide a justification in the proposal if this standard is not met.

2.5 Data Sharing

Data (e.g. bioassays, PRO data, etc.) generated from ancillary studies are to be provided, in an agreed upon format, as soon as reasonably feasible and no longer than 6 months after data generation to the CureGN DCC for integration into the CureGN dataset. For analyses conducted by the ASI, after integration of ancillary study data into the CureGN dataset, the DCC will develop an analysis file to share with the ASI. Exceptions to this policy may be considered by the CureGN PI Group on a case-by-case basis.

After a reasonable time (in general, 6 months after data generation including quality control), the ancillary data will be made available for use by other CureGN investigators. Data will also be transferred to the NIDDK data repository at the end of the study. It is the responsibility of the ASI to state in writing to the ASC any special circumstance that would hinder adherence to these guidelines for data sharing.

3 ANCILLARY STUDIES COMMITTEE

3.1 Charge

The ASC: (1) works with the ASI to develop the protocol, and (2) recommends approval or non-approval to the CureGN PI Group voting body.

3.2 Membership and Chairs

The ASC consists of two members from each of the four PCCs and the DCC, and at least one member from the NIH-NIDDK. Please refer to the CureGN Committee Membership and Chairs policy for further details.

Non-voting members (e.g. Biostatistical and Pathology) may serve on the ASC at the discretion of the ASC and are dependent on the workload and needs. The ASC Co-Chairs may request input from outside peer reviewers with expertise on the proposed topic. They would serve on an ad hoc basis and be considered non-voting. This scenario is especially encouraged for ASPs that will not be subjected to peer scientific review, e.g., a proposal that already has an established funding mechanism.

3.3 Voting

The ASC voting body consists of two members from each of the four PCCs, DCC, and NIDDK, with one vote allotted per site. Each site may designate an alternate to participate if ASC members are not available. A quorum consists of one representative from 5 of the 6 voting sites, i.e. the NIDDK, DCC, and the four PCCs. Decisions are based on a majority vote of a quorum. Biostatistical and pathology experts and invited outside reviewers on the ASC are non-voting members.

If an Ancillary Studies Committee member proposes an ancillary study, collaborates on an ancillary study, or has a perceived or real conflict of interest in the outcome of a vote, he/she will be excused from reviewing and voting on that ancillary study proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest. In the event that such conflicts result in a quorum

not being reached, the definition of a quorum will be modified such that a only those without a conflict can participate in the vote, and a majority vote of the present members is necessary to reach consensus.

3.4 Meetings

ASC conference calls will be scheduled as needed.

3.5 Duties

Review all ASPs to:

- Provide feedback to the proposing ASI regarding the suitability of the ancillary study protocol.
- Evaluate the proposed study's impact on CureGN resources.
- Make recommendations for approval or rejection to CureGN PI Group voting body.
- Work with the DCC to maintain lists of:
    - All ASPs, including dates of submission, review, approval/disapproval decision, date of study start, enrollment, samples used, and progress reports.
    - Samples tissues, slides, and other CureGN materials available and used for ancillary studies.

4 PROPOSAL SUBMISSION AND REVIEW

4.1 Submission and Review Process

All proposed ancillary studies must be submitted to the CureGN DCC for circulation and review as per procedures below. Each step will include interaction with the ASI as necessary. Studies must be submitted at least 12 weeks prior to a funding application. Studies submitted after this deadline may not receive review and approval in time for the intended funding cycle. In addition, studies that involve a subcontract to the DCC and/or PCCs must have the subcontract budget approved for institutional review at the subcontracting site no later than 4 weeks prior to submission for funding.

1. Pre-submission
    a. The ASI will contact a CureGN sponsor for guidance, and possible collaboration, before submission to the ASC. An up-to-date list of sponsors is available posted on the CureGN website.
    b. The ASI is encouraged to contact the DCC to discuss feasibility or other relevant issues prior to ASP submission.
2. Submission
    a. The ASI will submit the ASP using the CureGN ASP Form (available on the CureGN website). The form will be submitted to: CureGN-Admin@arborresearch.org.
    b. The CureGN DCC Project Manager will review the proposal for completeness and to determine need for involvement of other CureGN Committees or Workgroups, e.g. Biospecimens Workgroup.
    c. The proposal will be shared with the PI group principally for informational purposes. Members will have one week to provide comments if desired.
    d. The ASC Co-chairs will evaluate the AS proposal for overlap (e.g. of scientific aims or bioassays) with funded core or ancillary CureGN studies. Proposals or components of proposals that substantially overlap with studies already funded will not be approved

unless there is a sound scientific rationale (e.g., to test reproducibility).The ASC Co-Chairs will also identify appropriate committee members to review completed proposals.

3. Initial assessment (2 weeks)
    a. If the proposal avoids substantial overlap and is generally feasible (per the initial assessment), the ASC Co-chairs will assign 2 reviewers to each draft a brief summary and provide a preliminary recommendation, with rationale, to the ASC.
        i. The ASC assigned reviewers in collaboration with the ASC co-Chairs can determine that e-mail review of a proposal is appropriate and does not require a formal teleconference.
    b. Burden and Feasibility: The DCC will conduct a burden and feasibility assessment and provide to the ASC reviewers.
    c. The DCC analytic and biostatistical review occurs at the first research meeting following receipt of a complete proposal.
    d. Communication with ASI: The ASC/DCC will provide the ASI with a brief summary of the initial assessment activities.
4. ASC e-mail review and recommendation (Studies involving ONLY Data or by ASC determination) (4 weeks)
    a. The ASC will review by e-mail the proposal and summary review and will vote regarding recommendation for approval or rejection, or alternatively ask the ASI for revisions.
    b. The ASC will provide a recommendation letter to the CureGN SC, along with the ASC summary reviews and draft burden and feasibility assessment. The ASI will also be notified of the ASC recommendation.
    c. Revision and resubmission, if needed (4 weeks)
        i. Proposal revisions should be completed within two weeks.
        ii. ASC re-vote will occur within two weeks of resubmission.
5. ASC review of studies not qualifying for e-mail review and recommendation (4-8 weeks)
    a. The ASC will hold a teleconference to review the proposal and summary reviews, and will vote regarding recommendation for approval or rejection, or alternatively ask the ASI for revisions. The ASC will provide a recommendation letter to the CureGN SC, along with the ASC summary reviews and draft burden and feasibility assessment. The ASI will also be notified of the ASC recommendation.
    b. Revision and resubmission, if needed (4 weeks)
        i. Proposal revisions should be completed within two weeks.
        ii. ASC re-vote will occur within two weeks of resubmission.
6. PI Group vote (1 weeks)
    a. The CureGN PI Group voting body will review the ASP by e-mail and make a final determination on approval.
        i. A Letter of Support (LOS) will be provided to the ASI if the CureGN PI Group voting body approves the proposal.
        ii. A notice of final decision will be provided to the ASI if the CureGN PI Group voting body does not approve the proposal.
7. Post-approval (4 weeks before submission for external funding)
    a. A budget (or budgets) that accounts for costs related to involvement in the ancillary study will be provided to the ASI by each PCC and/or DCC involved with the ancillary study.

b. In case of submissions for external funding, the CureGN LOS and all DCC/PCC budgets are required for submission of the ASP to the funding body.
c. The final aims page submitted to the funding body will be sent to the DCC.
d. If funded, the final (accepted) proposal will be sent to the DCC.
e. The DCC will post approved proposals on the secure CureGN website. Information will include title, authors (with email of corresponding author), abstract, and date of approval.

4.2 Ancillary Study Review Criteria

The proposed study must:

1. Not interfere with the completion of the main objectives of CureGN or with continued participation and adherence to the CureGN protocol.
2. Have adequate resources to effectively carry out the project, including sufficient budget and staff with requisite expertise.
3. Be of sufficient scientific merit with respect to significance and strength of approach to justify use of CureGN resources (e.g., personnel effort, equipment, or biosamples) and potential additional burden on participants and study sites.

If the ancillary study will reduce the number of available biosamples below the standards approved by the CureGN PI Group, the proposal will be subject to scrutiny to determine if its scientific merit outweighs the loss of this resource for future studies.

Beyond evaluation of scientific merit sufficient to justify use of CureGN resources, ASC members may provide additional scientific input or critique on a courtesy basis. Note that a response from investigators is not required.

4.3 Scientific Overlap

Overlap (e.g. of bioassays or experimental strategy) will be identified during the ASC burden and feasibility assessment. Overlap with funded CureGN studies will not be approved unless there is scientific rationale to do so (e.g., reproducibility). Overlap amongst ASPs not yet funded is permissible, but will be brought to the attention of the ASIs for their consideration.

4.4 Ongoing Review of Approved Ancillary Studies

The ASC reviews approved ancillary studies annually. The ASI must submit annual study updates on a timely basis to the ASC. These updates should include number of samples/patients analyzed, deviations from timeline and other problems, preliminary results, published abstracts and manuscripts, etc. In the interest of efficiency, reports submitted for other purposes (e.g. reports to the funding body, OSMB, etc.) may be used for this purpose, if the ASI has received prior approval by the ASC to use this documentation instead of submitting a separate annual report. At the annual review, the ASC will approve, terminate, or request modifications/clarifications to the ancillary study.

4.5 Modifications to an Approved Ancillary Study

After an ancillary study is approved by the CureGN PI Group, any meaningful changes, such as a change to study aims or substantial change to data elements or analysis plan, must be submitted to the DCC for routing to the PI Group for approval before submission to a funding agency or implementation of any protocol updates.

4.6 Submission and Timelines for External Funding

An ASP should be submitted to the CureGN ASC at least 3 months prior to the anticipated date of submission for funding. After approval and LOS receipt, the ASP must be submitted to the funding body within 6 months. Proposals submitted for funding must include the CureGN LOS and budgets from all involved CureGN sites and the DCC. The ASI must notify the ASC of the funding body's decision within 2 weeks of its receipt.

4.7 Approval Expiration

Ancillary studies are expected to start within 18 months after CureGN PI Group approval. In the event that an approved study is not funded, the CureGN AS approval will remain in effect for re-application for funding or for application to an alternative funding source. Re-submission of the ASP to CureGN is necessary if there is a change in resources required from CureGN or if 18 months has elapsed since initial approval, for studies that have not yet started. This proposal must include justification for prior delays and the expected timeline for study initiation. The 18 month requirement is not intended to be obstructive, but is instead in place to foster open opportunity amongst a wide range of interested investigators.

The ASI and the CureGN sponsor will receive written notice 2 months before an ancillary study's approval is due to expire.

AS's that receive funding and begin within 18 months of CureGN approval are subject to the annual review detailed below.

5 TRAINING/CAREER DEVELOPMENT PROPOSALS

CureGN recognizes the need to provide for research training of junior investigators, and encourages the submission of training grants. Ancillary studies that are training grants must include a CureGN investigator as part of the mentoring committee or project consultant. The mentor(s) for the trainee will abstain from the CureGN PI Group vote.

When a training proposal is submitted, a paragraph from the mentor(s) indicating relevant experience, as well as commitment to the trainee, is required. The CV of the mentor(s) may be submitted, but is not mandatory.

6 PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS FROM AN ANCILLARY STUDY

All publications and presentations resulting from ancillary studies must adhere to the requirements of the CureGN Publications and Presentations Policy.

7 HUMAN SUBJECTS AND DATA CONFIDENTIALITY

7.1 Consent and Institutional Review Board (IRB) Issues

Each ancillary study must follow federal human subjects research regulatory requirements and have its own IRB approval. Where new subject interventions or interactions are included in the AS, participating site IRB approval and consent forms will also be required. The ASI must submit a copy of the IRB

approval for the project before project initiation. Copies of notices of renewals of IRB approval must also be provided to the ASC on an annual basis. The DCC will maintain records of IRB approvals and IRB-approved consents. For ancillary studies that are deemed exempt from oversight, the ASI will send the local IRB's determination of exempt status to the DCC.

7.2 Confidentiality

Confidentiality of a study participant's identifiable health data must be assured. CureGN provides no assurances that ASIs will be able to identify and contact CureGN participants in the future, particularly after the CureGN study ends.

8 BIOSPECIMENS

Access to and handling of biospecimens will be in accordance with NIDDK Central Repository polices (https://www.niddkrepository.org).

9 INTERACTION WITH PRIVATE ENTITIES

Several considerations should be made when the ASP requires interaction with private entities (e.g., private foundations, non-profit organizations, or for-profit corporations) including:

1. The number of clinical sites involved;
2. If the private entity is providing funding, or supplying a product;
3. Familiarity of the clinical site PI or counsel with federal terms and restrictions related to sponsored research and interaction with private entities.

Following ancillary study approval by the CureGN PI Group, if the ASP involves more than one clinical site, the ASI will contact NIDDK to establish consistency across multiple agreements and to explore the need for a CRADA (Cooperative Agreement and Development Process) with the NIDDK. If the ASP involves one clinical site, the ASI may contact the PCC PI(s) directly regarding interaction with private entities.

Acknowledgement: This policy was developed with the use of the Nephrotic Syndrome Study Network (NEPTUNE), Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL), and Chronic Renal Insufficiency Cohort Study (CRIC) Ancillary Studies Policies as reference. NEPTUNE is supported by the NIDDK, the NIH Office of Rare Diseases Research (ORDR), and NephCure Kidney International. A2ALL and CRIC are supported by the NIDDK.

ASC = Ancillary Studies Committee
ASI = Ancillary Study Investigator
SC = Steering Committee