The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness Study

(GRADE Study)

GRADE ANCILLARY AND SUB-STUDIES

POLICIES AND PROCEDURES

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This document describes the policy and procedures for Ancillary Studies (and Sub-studies) for the GRADE Study.

1. Overall Principles

Ancillary studies (and sub-studies) that complement the objectives and thereby enhance the value of the study are encouraged. Such studies should augment and promote the continued interest of both participants and investigators. To protect the integrity of the GRADE study, a proposal to conduct an ancillary or sub-study must be reviewed and approved by the Ancillary Studies Committee and the GRADE Executive Committee, the GRADE Steering Committee, and the Data and Safety Monitoring Board before its initiation. In addition to scientific merit, a major review criterion is the impact on the GRADE protocol.

Ancillary studies and sub-studies will be evaluated with careful consideration of their relevance to and potential impact on the objectives and performance of the GRADE clinical trial. All ancillary studies and sub-studies must be of high scientific merit and quality, must add to the scientific merit of GRADE, ideally take advantage of the GRADE design and cohort, and must not interfere with achieving the aims of the GRADE Study. All ancillary studies should be developed in a spirit of collaboration with the GRADE Research Group and their proponents should be receptive to criticisms and revisions by the GRADE review committees and Research Group. Study Centers will be offered the opportunity to participate, recognizing that only a limited number may be selected to participate depending upon availability of participants, study resources, and expertise needed to conduct the study. No study will:

- cause a serious deviation from the protocol or a change in the study question,
- confound interpretation of the GRADE study results or jeopardize the results of the primary study,
- adversely affect participant cooperation,
- create a diversion of the GRADE resources at the clinical centers, at the coordinating center, central laboratory or at any other level, or
- in any way negatively influence the cooperative spirit of the collaborating investigators, or otherwise compromise the scientific integrity of the GRADE study.

2. Definition of a Sub-study, Ancillary Study and Ancillary Analysis

A ***sub-study*** is defined as research using GRADE study participants (including their data, laboratory specimens or tests) to collect or generate data *to address additional scientific objectives that are consistent with and augment the hypotheses/study aims in the GRADE protocol*. The sub-study can involve all or a subset of clinical centers and/or study participants as required to meet the sub-study objectives. Regardless, each sub-study will be a research initiative of the full GRADE Research Group and will be developed and conducted under the auspices of the full Research Group. Sub-study funding will be provided by sources beyond the core funding of the study, although in some cases supplemental funding may be added to the core funding to support a sub-study. A sub-study may arise from deliberations within the Research Group or be initiated by individual members of the Research Group or by collaborators.

An ***ancillary study*** is defined as research using GRADE study participants (including their laboratory specimens or tests) to collect or derive *supplemental* data *for purposes above and beyond*

those set forth in the GRADE protocol. This includes use of new data from questionnaires, biologic samples or from new procedures to answer questions that are not directly related to the overall scientific objectives of GRADE. An ancillary study can involve all or a subset of study participants. Funding support is provided by sources outside the primary study. An ancillary study may be initiated by individual members of the Research Group or by collaborators.

An ***ancillary analysis*** is defined as an analysis of pre-existing GRADE study data that *addresses questions not addressed by the planned analyses* of the GRADE Study and is funded independently of the core GRADE funding. Proposals for such analyses would require approval of the Ancillary Studies Committee, the Publications and Presentation Committee and Steering Committee. The plans for such analyses should also be approved by the GRADE biostatisticians at the Coordinating Center. The dissemination of the research would comply with the policies stated herein. An ancillary analysis may be initiated by individual members of the Research Group or by collaborators.

Studies involving GRADE study participants require approval according to the Ancillary and Sub-studies Policies and Procedures set forth herein, specifically approval by the Ancillary Studies Committee, GRADE Steering Committee and the GRADE Data and Safety Monitoring Board (DSMB).

The investigator responsible for the conduct of a sub- or ancillary study must be a member of the GRADE Research Group or work in close collaboration with a GRADE investigator. If a research request is made by an individual external to the GRADE Research Group, a clinical site PI must be a co-investigator of the sub-study or ancillary study.

3. GRADE Support, Funding and Sharing of Data

The processes of funding and support of ancillary studies and sub-studies differ substantially.

3.1 Ancillary Studies

The GRADE study will not provide funds for ancillary studies. In particular, no funds are provided for clinical centers, central laboratory or Coordinating Center activities or services in support of ancillary studies. If funds are needed, the investigator must explore other avenues such as submission of a research grant application or use of other sources of funds (i.e., federal agency, a non-profit foundation, pharmaceutical company, etc.). The anticipated source of funds must always be identified.

Ancillary studies are responsible for obtaining funding to support data management and statistical analysis required for the study. The GRADE Coordinating Center will not provide such support for ancillary studies. All ancillary studies must include a description of plans for data management and analysis, identify the resources to provide this support and provide information on their credentials. Data analysis for ancillary studies must be financed by the investigators submitting the proposal.

Since ancillary studies will not be supported by the Coordinating Center, there is no need for The George Washington University (GWU) Biostatistics Center to be party to the ancillary study proposal or the application for funding. Each Ancillary Study will identify a prime site, usually the institution of the ancillary study chair or PI, and the prime site will then submit the application for funding. If funded, the prime site would then execute sub-agreements with all the other participants including the clinical

centers and any other resources or collaborators. The ancillary study funding would be completely independent of the core project funding that comes through the Coordinating Center. Further, since the Coordinating Center would not be providing direct support, there would be no sub-agreement with GWU.

If the ancillary study requires some of the GRADE study data to support analyses of the ancillary study, then that data will be provided by the Coordinating Center as part of the core support for GRADE. However, if the requirements for the Coordinating Center are extensive, additional funding support for these activities may be requested by the Coordinating Center.

Since ancillary studies are funded separately, the data so generated from an independent mechanism, belongs to the investigator. However, as a condition of approval to conduct the study through GRADE, the investigators must agree that all data generated by the study will be forwarded to the GRADE Coordinating Center and that the GRADE Research Group may use that data to conduct other analyses. With the permission of the ancillary study investigators, the Coordinating Center may also share that data with the GRADE Research Group. The ancillary study investigators may, if required by the funding agency or of their own volition, contribute the data to a public repository, such as the NIDDK data repository. However, the Coordinating Center will not do so on behalf of an ancillary study.

3.2 Sub-studies

A sub-study may be developed as an extension of the core study by the GRADE Research Group. The Principal Investigator for the sub-study will then work closely with the Coordinating Center to develop the preliminary proposal and subsequently, if approved, the funding application. Sub-study planning is a core responsibility of the Coordinating Center and funding is provided for this activity.

The sub-study funding application budget would include additional Coordinating Center support staff above and beyond that funded by the core project. To facilitate funding it is preferred that the sub-study application be submitted with GWU as the prime site, i.e. the Coordinating Center Director as the sub-study PI, and the sub-study scientific leader (PI) as the Co-PI on the grant. The application would include funding for the Coordinating Center, clinical centers, labs, etc., all supplemental to the funding from the core project award.

All sub-studies will be considered part of the whole GRADE project. In most cases, sub-study data will be collected, managed, and analyzed by the GRADE Coordinating Center. In sub-studies where that is not the case, all data generated by the sub-study will be forwarded to the GRADE Coordinating Center. While a sub-study will be funded via an independent mechanism, as a condition of GRADE authorization to conduct the study, the named investigators must agree that ownership of the data will vest with the GRADE Research Group. The GRADE Coordinating Center may then use the data to conduct other analyses and may also share that data with the GRADE Research Group.

If required by the funding agency, the Coordinating Center may contribute biological specimens and data from the sub-study to a public repository, such as the NIDDK data repository. Appropriate wording to permit this sharing of study materials with the repository should be included in the sub-study consent documents.

4. Publication and Presentation of Results

All manuscripts, abstracts, or presentations for scientific meetings based on ancillary or sub-study data must follow the policies and procedures of the GRADE Publications and Presentations Policy.

In particular, the policy, Section 2, describes the duties and responsibilities of the Publications and Presentations Committee and states

> In addition to the issues cited in the editorial policy above, proposed publications/presentations of ancillary studies will be scrutinized to ensure that their presentation will not threaten the integrity or conduct of GRADE.

Thus, the ancillary or sub-study investigators may not be allowed to publish the study results, prior to the publication of the main study results, tentatively scheduled for 2021. Likewise, the investigators may not be provided with the main study data necessary to conduct analyses of the ancillary study results until after the main study has been completed. All ancillary and sub-studies should be prepared to accept a recommendation from the Publications and Presentations Committee that no publication of that study results be published or presented prior to the close of the main study.

5. Participation by Clinical Centers

In general, each clinical center PI determines whether or not his/her center will participate in a proposed ancillary study. No clinical center will be required to participate in a given ancillary study. However, where appropriate, all clinical centers may be expected to participate in a sub-study of the whole cohort.

Ideally, every ancillary study should include a variety of clinical centers with the goal of studying a representative sample of GRADE subjects and distributing the work over the study group, while minimizing the overall cost of the study. Further, all clinical centers should have the opportunity to express interest in participating. Thus, when planning the ancillary study proposal, the ancillary study PI should notify all GRADE clinical center PIs, and other components (e.g. the CBL), of the proposed study to allow sites to express an interest in participating. The ancillary study PI should then consult a variety of clinical center PIs independently about participating. Clinical center PIs who wish to participate in the ancillary study should be given the opportunity to review and critique the proposal before it is submitted to the Ancillary Studies Committee.

The Ancillary Studies Committee will also consider ancillary study submissions proposing participation of only one or a few clinical centers if they can be shown to have adequate power (and potentially lower costs). In such cases, consultation only with participating center PIs will be required prior to submission. The Ancillary Studies Committee retains the prerogative to request broader participation.

Any funding sought for ancillary studies should include a budget appropriate for each of the centers that have agreed to participate in the study and for data analysis. If a center has opted out of a proposed ancillary study, that center's information and data may not be included in the proposal.

All GRADE ancillary studies must have the PI from a clinical center as a co-investigator. In general, if a

GRADE clinical center agrees to provide participant data for the ancillary study, a member of that clinical center has the opportunity to be included as an author on a paper per the GRADE Publications and Presentations Policy. In order to avoid misunderstandings, all communication with the GRADE Coordinating Center, participating clinical centers, and the GRADE Research Group must be conducted with the ancillary study PI and/or the GRADE co-PI. Following approval of an ancillary study by the GRADE Steering Committee, there can be no substantial changes in the type or amount of data requested from the Coordinating Center. If major changes are made, the Steering Committee must reconsider both the data request and the priority of the ancillary study.

6. The Proposal

The preliminary concept proposal should be **3 pages** and contain:

1. Investigators, and collaborators, names, roles, and institutional affiliations. Include NIH biosketches for investigators and key personnel.
2. Planned start and end dates.
3. Estimated costs and plans for funding, including the anticipated source of funding.
4. Design and methods:
    - Statement of primary and secondary goals and objectives.
    - Brief background, significance, and rationale.
    - Description of additional methods and procedures to be carried out on a study participant.
    - Data needed (a) from the GRADE study central database and (b) from additional tests, surveys, etc.
    - Plans for analysis.
    - Sample size and justification (including power calculation).
    - Burden on participants.
    - Impact on GRADE study (clinical centers and central units).
    - Measures to be taken to ensure participant safety and confidentiality.
    - Payment or incentives to participants.
5. Declare whether the application is for an ancillary study or a sub-study (see the Policy for explanations). If a sub-study, describe the Coordinating Center and other study resources to be requested. If an ancillary study, describe the source of the statistical support to be provided, and whether additional support is needed from the Coordinating Center (see the Policy).

In addition to the 3 page proposal, the collaborating investigators should each provide a statement that they have reviewed and approved the application, are committed to participate and that they approve the funding arrangements and level of funding proposed.

7. Submission and Review Process

The ASC has established a stepwise system of proposal submission, review and approval. The system is designed to avoid a lot of up-front effort by investigators for proposals that are rejected. The steps are also displayed in the attached figure. A member of the Coordinating Center staff will be designated to support the review activities of the committee.

It is the responsibility of the investigator(s) to allow adequate time for full review and approval by the GRADE study prior to a funding agency submission deadline according to the following review process. In the best case scenario for a perfect application, the entire review and approval process is anticipated to take a minimum of 14 weeks (see the attached flow chart). If any revisions are required during the review and approval process, more time will be needed.

It is recommended that preliminary proposals be submitted at least 6 months prior to the funding source deadline. However, even if so submitted there is no guarantee that a final decision will be made before the projected proposal date of submission for funding. The steps in the review are as follows.

1. The dates of future meetings of the ASC will be posted to the GRADE study website at least 4 weeks in advance. The ancillary study preliminary concept proposal (3 pages) must be submitted to the Coordinating Center at least 2 weeks before the next scheduled ASC conference call in order to be reviewed at that meeting. The proposal should be accompanied by a letter signed by the principal and all collaborating investigators in which they agree to abide by the policies for ancillary studies herein described, including those regarding publication or presentation of results.

2. The Coordinating Center forwards the preliminary concept proposal to the ASC Chair who assigns it to an ASC member to act as liaison between the submitting investigator(s) and the committee. The liaison is selected from among the ASC members who are eligible to vote on that ancillary study (see item 3 below). The liaison then reviews the proposal for completeness, confers with the submitting investigator(s) as necessary to point out omissions or suggested improvements, and obtains a revised preliminary concept proposal if applicable. If complete, the liaison notifies the Coordinating Center to distribute a copy to each member of the committee. If, by this time, less than 2 weeks remains before the scheduled committee meeting, the proposal is deferred for review at the subsequent meeting of the committee.

3. At least one additional member of the ASC from among those eligible to vote is assigned to be a reviewer. The liaison and reviewer(s) prepare a review of the proposal using the Ancillary Studies Evaluation Form (copy attached hereto). All members of the ASC are also expected to read the proposal and provide comment where appropriate to the full committee. During the ASC meeting, the liaison presents the proposal and the designated reviewer(s) provide a synopsis of their evaluations. At the end of the discussion, the eligible members vote to approve or disapprove. The ASC may elect to use both e-mail exchange and conference calls in their review.

   Highest priority will be given to studies that:
   - have the highest scientific merit,
   - produce the least burden on GRADE (clinics, laboratories, Coordinating Center),
   - produce the least burden on GRADE study participants,
   - have objectives closest to those of the GRADE study, and
   - require the unique characteristics of the GRADE cohort.

   Approval or disapproval is based on a simple majority vote among all eligible members of the ASC. Abstension or failure to cast a vote will be counted as a vote to disapprove. Eligible ASC

members are those voting members who are free of a duality or conflict of interest with respect to the proposal at hand. Ineligible members would include collaborators or investigators on a proposed ancillary or sub study, or those who have declared a significant financial interest with an entity that could be affected by the outcome of the study, or otherwise as declared by the Chair.

4. The liaison summarizes the committee consensus on the GRADE Ancillary Studies Evaluation Form, including reservations or objections and the results of the vote. A copy is sent to the submitting investigator(s) with a letter stating the results of the committee vote. Approved studies will be reviewed by the Steering Committee (see next step). If the study is not approved, at this point, the investigators may choose to:

   - withdraw the proposal,
   - modify the proposal based upon the summary Ancillary Studies Evaluation Form and re-submit to the ASC, or
   - provide written clarification in response to the summary Ancillary Studies Evaluation Form to the ASC and to the GRADE Steering Committee with a request that the Steering Committee proceed with a review and vote.
   - In cases where there is disagreement, the proposal's PI may appeal to the Steering Committee.

5. Whether approved or disapproved by the ASC, the preliminary concept proposal and the summary evaluation form, as well as written clarification, if applicable, will be provided to the Executive Committee. Within 2 weeks, the Executive Committee will communicate to the chair of the ASC whether they concur with the evaluation and recommendation of the ASC.

6. If the Executive Committee concurs that the proposal merits further consideration, then the proposal materials and ASC review are provided to the members of the GRADE Steering Committee. The GRADE Steering Committee will be provided 2 weeks for review and vote on the preliminary concept proposal. During that period, the investigators may provide clarification or response to queries that arise in the review.

   The Steering Committee will conduct the vote at an in-person meeting or on the study website. The Steering Committee is allowed 2 weeks to review and vote to approve or reject the ancillary study. A 2/3 majority vote among all eligible members is required for approval. Abstension or failure to cast a vote will be counted as a vote to disapprove. Eligible Steering Committee members are those voting members who have not declared a significant financial interest with an entity that could be affected by the outcome of the study, or otherwise as declared by the Chair. Collaborators or investigators on a proposed ancillary or sub-study who are members of the Steering Committee would otherwise be eligible to vote. Proposal approval or disapproval will be communicated to the proposal PI from the Coordinating Center PI or Project Director.

7. If approved by the Steering Committee, the proposal materials will be forwarded to the DSMB for review using the same approach employed by the Steering Committee. The DSMB will be provided up to 4 weeks to review and vote on the preliminary concept proposal.

8. If approved by the DSMB, the investigators may then prepare a full application in keeping with the requirements of the proposed funding agency that will include a synopsis of the scientific protocol (formatted as required by the funding agency), the list of participating investigators, and the budget. The investigators have a maximum of 6 months from Steering Committee approval to prepare the full proposal for review by the ASC. After 6 months, procedures start again at step 1.

9. The full proposal is then submitted to the Coordinating Center that in turn provides it to the ASC for evaluation. The proposal is also placed on the secure GRADE Research Group website and a notice is distributed to the Steering Committee that the full application is now open for review and comment over a 4-week period. No formal vote is taken by the Steering Committee.

10. The Ancillary Studies Committee has been designated by the GRADE Steering Committee to act on their behalf regarding the final proposal. The appointed liaison and committee chair (or designee) will perform a review on behalf of the ASC of the full application.

    - If review determines that there are *no substantial differences* between the final proposal and the preliminary proposal, and if no substantive critical comments are received from the Steering Committee, then approval on behalf of the Steering Committee is granted. In this case, the full proposal does not need to be reviewed by the DSMB.
    - If *substantive changes* have been made to the final proposal, or substantive critical comments are received, the proposal is reviewed by the full ASC. The committee may then approve the proposal as revised or forward the proposal back to the applicants with recommendations for revisions. If the ASC determines that the changes fundamentally constitute a new application, then the committee may request that a new proposal be initiated with step 1 above. In this case, the revised proposal, if approved by the Steering Committee, would also be reviewed by the DSMB.
    - The ASC and the Coordinating Center will review the budget to ensure that adequate funding is provided for biostatistical support, and where appropriate, support for the Coordinating Center and other GRADE units.

    The ASC review will include an evaluation by the Coordinating Center of the adequacy of the requested funds to meet the needs of the study, and the validity of the statistical components of the application (design, analysis, etc.).

11. Proposals that are approved by the ASC may be submitted to the designated funding agency. The application should be submitted within 4 months, preferably in the next eligible review cycle. If funded the ancillary study is initiated according to the proposed timetable.

12. If the initial submission is not funded, the investigators should immediately determine whether they intend to revise and resubmit and so inform the ASC liaison and chair. If the intention is to resubmit, the investigators have 6 months from the time of notification of the initial review decision to prepare a resubmission or revised application that must be submitted to the ASC along with a description of the changes to the prior approved proposal. Both the liaison and ASC Chair (or designee) will perform an initial review on behalf of the committee. If *substantive*

changes have been made to the revised proposal, it should be distributed to the ASC for further consideration as in step 10 above. The ASC can at that time recommend that the study be disapproved for implementation in GRADE.

The ASC will provide reports at Research Group meetings on the status of all proposals received and reviewed, and the progress of approved proposals.

8. GRADE Protocol Changes

It is possible that the Ancillary Studies Committee may conclude that a proposed ancillary or sub-study would require a change in the GRADE study protocol. In this case, on behalf of the ancillary or sub-study investigators, the Ancillary Studies Committee may recommend the protocol change to the Steering Committee. The Steering Committee would then evaluate the merits of the change for the GRADE study and vote on the protocol change according to protocol amendment procedures that require a 2/3 majority of Steering Committee in favor of the change in order to amend the GRADE protocol.

9. Monitoring

The Ancillary Studies Committee will track and record the progress of approved ancillary studies. Central monitoring is needed to ensure that the composite impact of the total number of active studies does not have unforeseen consequences. Monitoring will include evaluating the burden on participants and GRADE staff, as well as the use of irreplaceable GRADE resources such as stored blood samples.

Investigators with approved ancillary studies will submit an annual progress report to the Ancillary Studies Committee regarding the status of study funding, initiation and termination dates, success of data collection, and any presentations or publications derived from the ancillary or sub-study (i.e., the progress report should follow the same format as that for annual funding requests). All presentations and publications must follow the GRADE study Publications and Presentations Policy.

10. Analysis

All GRADE approved ancillary studies must include plans for data analysis, the group responsible for performing the analysis, and information on their credentials. Data analysis for ancillary studies must be financed by the investigators submitting the proposal.

11. Informed Consent and Institutional Review Board Approval

When required by federal regulation, separate informed consent must be obtained from all ancillary study participants for participation in the ancillary study. Any consent documents and associated communication with the participants should clearly identify the ancillary study as one being performed *in addition to* the main study and inform subjects that their participation in the ancillary study is not necessary for them to continue to be enrolled and involved in the GRADE study.

All ancillary study protocols must be submitted to the relevant local Institutional Review Boards. The Coordinating Center must receive copies of the IRB letter of approval and the stamped approved consent forms before a clinical center may participate in the ancillary study.

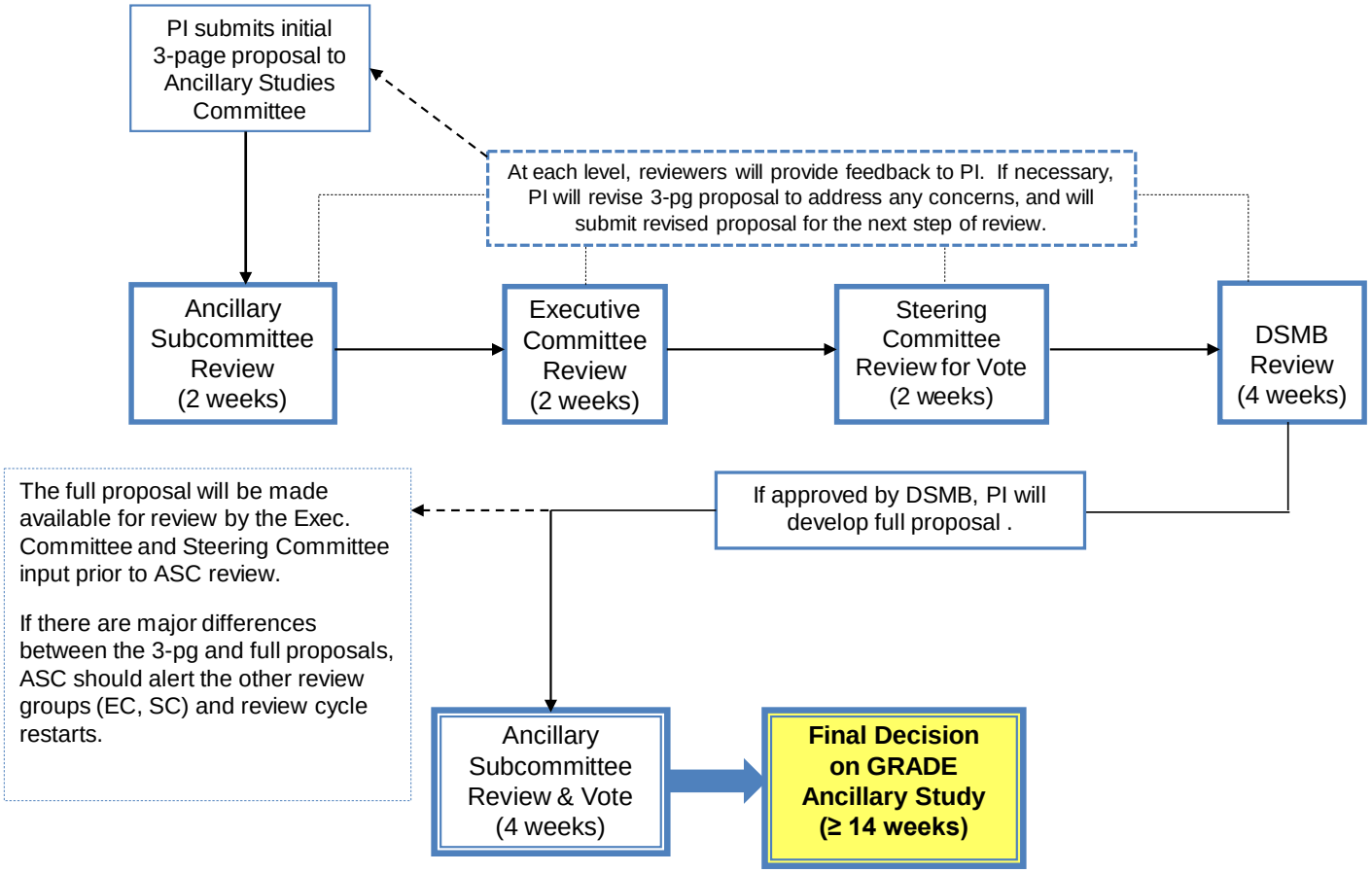
12. Incorporation of Additional Data Collection to GRADE Study Visit

If investigators propose to collect additional data from the participant—whether during a study visit or at another contact—they need to consider the impact of the burden of additional tests or survey questions on participation in the GRADE study. The proposal should address the potential impact of additional data collection on participation in the GRADE study.

13. Changes to Ancillary Studies Policies and Procedures

Any changes in the policies and procedures described in this document require a majority vote of the GRADE Steering Committee.

GRADE Ancillary Study Proposal Review Process



Ancillary Study Evaluation Form: Reviewer: _____

1. Title:

2. Principal Investigator(s):

3. Summary of ancillary study:

4. It is the consensus of the Ancillary Studies Committee that this study

a.	may cause a deviation from the protocol.	☐ Yes*	☐ No
b.	may confound interpretation of GRADE study results.	☐ Yes*	☐ No
c.	may adversely affect subject/family participation in the GRADE study.	☐ Yes*	☐ No
d.	may negatively influence the cooperative spirit among GRADE clinical centers.	☐ Yes*	☐ No
e.	may compromise the scientific integrity of the GRADE study.	☐ Yes*	☐ No
f.	may raise concerns with the DSMB.	☐ Yes*	☐ No
g.	could be conducted on its own or in other settings, i.e. does not require GRADE for its conduct.		

*Explanation:

5. Scientific merit score (standard NIH system)

☐ Outstanding (100-150) ☐ Excellent (151-200) ☐ Very good (201-250)

☐ Good (251-300) ☐ Fair (301-350) ☐ Poor (> 350)

6. Funding source and resource utilization

a.	Sufficient funds are available to complete the study at the sites.	☐ Yes	☐ No*

b.	Sufficient funds are available to provide data management and statistical support	☐ Yes	☐ No*
c.	Sufficient funds available for other collaborating unit(s) (e.g. central lab) to complete the study.	☐ Yes or NA	☐ No*
d.	Specify collaborating units (e.g. clinical centers, central laboratory, etc. or none if N/A):		
e.	Have all clinical centers been afforded to option to participate and has the process for selection of sites been described.	☐ Yes or NA	☐ No*
f.	Has the PI of each collaborating unit provided a statement that they approve the protocol and the funding.	☐ Yes or NA	☐ No*

*Explanation:

d.	The study will create a significant diversion of GRADE resources.	☐ Yes*	☐ No

*Explanation:

7. Critique of strengths and weaknesses:

8. Recommendation ☐ Approve ☐ Disapprove

9. Additional comments: