Key Points of REGARDS Ancillary Study Policies and Procedures
April 2010

- Ancillary studies are welcomed and encouraged.

- All ancillary studies must be reviewed and approved by the Executive Committee. If the study involves additional participant burden or there are new human subjects concerns, the external Observational Studies Monitoring Board (OSMB) will also need to review and approve the proposal before its inception.

- In general, ancillary studies require outside (non-REGARDS) funding.

- A written request for review of the ancillary study must be submitted on the REGARDS Ancillary Study Proposal Form to REGARDS. (**regardsadmin@uab.edu**)

- If blood samples, DNA, and/or or urine samples are requested:

    - investigators must contact the REGARDS Central Blood Laboratory to discuss considerations related to biological samples before preparing their proposals.
    - the submitted proposal will be reviewed first by an external advisory committee to the REGARDS Executive Committee, and then their review and the proposal will be considered by the Executive Committee.
    - Current NIH-GWAS policies will be followed for GWAS-based genetic studies.

- Review of the ancillary study proposal must take place before the proposal is developed into a grant application. The Ancillary Study Proposal Form should be submitted to REGARDS at least **six weeks** prior to the funding grant application deadline. Proposals requiring review by the OSMB or involving use of biological materials from the REGARDS repository must be submitted at least **eight weeks** prior to submission to the funding source.

- Proposals for industry support or collaboration will be evaluated in accordance with the same policies and procedures. As an initial step in study planning, the ancillary study PI should contact the REGARDS PI (George Howard) and the REGARDS Scientific Officer (Claudia Moy) to determine if an agreement between NINDS and industry will need to be developed.

- Ancillary study investigators must adhere to the REGARDS Publications and Presentations Policies and Procedures of REGARDS.

- Acknowledgement of funding sources in presentations and publications, grant applications, bio sketches, other support, etc. must include that this is an ancillary study to the parent study grant U01 NS041588 from NINDS.

REGARDS Ancillary Studies Policies and Procedures
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Appendices

1.0 Introduction

To enhance the value of REGARDS and involve investigators other than those from the parent study, the Executive Committee welcomes proposals from individual investigators, within and outside of REGARDS, to carry out ancillary studies. Because of the existing REGARDS infrastructure, ancillary studies provide an exceptional opportunity for investigators to conduct additional projects in an efficient and cost effective manner.

Ancillary studies generally involve the collection of new data, either directly from participants, from previously collected samples, or other sources (e.g., medical records.) An ancillary study is defined as an investigation that is based on information from REGARDS participants that was not described in the original REGARDS grant application and either:

1) requires new protocol elements and/or collection of data that were not collected as part of the REGARDS study, or
2) represents a new extensive analysis of existing data that is beyond the scope of the original application and requires additional funding (e.g., calculation and incorporation of the "glycemic index" from the nutrition data), or
3) involves analysis of stored samples that requires non-REGARDS funding. In this case, additional policies and procedures apply.

To protect the integrity of REGARDS and to assist investigators in making optimal use of the data, all ancillary studies must be reviewed and approved by the Executive Committee. If the study involves additional participant burden or there are new human subjects concerns, the external Observational Studies Monitoring Board (OSMB) will also need to review and approve the proposal. In general, ancillary studies require outside (non-REGARDS) funding. Examples include studies funded by investigator-initiated NIH research awards (R01s), grants from academic institutions, private sources (e.g., drug companies or non-profits), or those performed at no cost (generally because of the special interest of a researcher.) The processes for submission and review of ancillary studies are described in this document. [1]

2.0 Criteria for approval of an ancillary study

Before an ancillary study can be approved, it must be shown to have scientific merit and to not substantially do any of the following:

1) Interfere with the completion of the main objectives of REGARDS,
2) Adversely affect participant retention in REGARDS,
3) Create a serious diversion of study resources (personnel or study samples),
4) Jeopardize the public or participants' image of REGARDS.

[1] These policies and procedures have been developed based on the successful ancillary studies policies used in other cardiovascular epidemiologic studies such as Framingham, ARIC, MESA, and CHS.

In addition, highest priority will be given to ancillary studies that:

1) Require the unique characteristics of the REGARDS cohort,
2) Are consistent with the original purpose of REGARDS,
3) Produce the smallest burden on REGARDS participants,
4) Are characterized by innovation, novelty, and clear scientific design, likely to make a significant scientific or public health contribution
5) Have the least demand on REGARDS resources, such as blood samples.

In addition, priority for studies requesting blood and/or urine samples will be highest if they:

1) Do not make use of samples from those participants with the fewest samples remaining in the repository,
2) Use thawed samples whenever possible,
3) Use assays that can be done on more than one sample type to allow selection of the most abundant type available (e.g., serum or EDTA plasma),
4) Use the smallest sample volume possible; evidence of attempts to minimize volumes must be demonstrated, and will be reviewed by Mary Cushman, PI of the Central Laboratory for REGARDS,
5) Can be integrated with other studies to conserve sample or limit freeze-thaw cycles.

Investigators are urged to contact the REGARDS Operations Center (email regardsadmin@uab.edu or Meg Stewart at megstewart@uab.edu to discuss these considerations. If blood samples, DNA or urine are requested, please carefully review the appropriate section below. In addition, investigators are encouraged to contact the REGARDS Central Blood Laboratory (Rebekah Boyle at 802-656-8938, Rebekah.Boyle@med.uvm.edu) to discuss these considerations before preparing their proposals. Such discussions should focus on feasibility and provision of necessary resources.

3.0 Preparation of request for approval of an ancillary study

A written request for review of an ancillary study should be submitted on the REGARDS Ancillary Study Proposal Form to the Executive Committee (via regardsadmin@uab.edu and should contain the following minimum information:

1) Description of objectives,
2) Scientific merit of study,
3) Methodology for data collection,
4) Proposed statistical analyses,
5) Names of definite or possible collaborators,
6) Proposed funding sources, and
7) Discussion of impact on REGARDS operations and study participants.

The Ancillary Studies Proposal Form lists these required elements to yield a synopsis of the proposed study and its potential impact on the participants or resources of REGARDS. The form can be found in the Appendix of this document. An electronic copy can be obtained from Meg Stewart (megstewart@uab.edu)

The REGARDS investigators recognize that in order to produce the Ancillary Study Proposal, REGARDS will need to provide investigators with background information on data already being collected, planned analyses (including blood and urine analyses on stored samples), and resources within REGARDS (such as personnel percent effort) so that additional resources can be considered and budgeted.

In addition, potential ancillary study investigators need to be aware that follow-up by telephone is scheduled for every six months, and survey items may be proposed to be added to these contacts.

Data Handling: The investigators must designate the location for data analysis; either "locally" (by the ancillary study investigators) or by analysts at the REGARDS Operations Center. If analysis will be local, the PI of the proposed ancillary study should provide evidence that adequate support for carrying out data analysis is available at his/her institution; if not, the REGARDS Operations Center will conduct the analyses using resources provided by the ancillary study. (also see: "Other Requirements of an Ancillary Study" below related to integration of data into the main REGARDS database.)

For details on data distribution/use agreement, see the REGARDS Publications and Presentations Policies and Procedures, available upon request to **regardsadmin@uab.edu**

Assurances:

1. Assurance must be given that data collected as part of the ancillary study will be provided back to the main study for use by other investigators that do not overlap with the ancillary study objectives and manuscripts (see "Other Requirements of an Ancillary Study" below).
2. Assurance must be given that the Ancillary Study PI will periodically report progress of the study from status of funding through data collection and manuscript publication.
3. Confidentiality of individually identifiable REGARDS participants must be assured.
4. Assurance must be given that biological specimens will only be used for their specified purpose for REGARDS-approved assays only. If additional work is desired, addenda to the Ancillary Study must be sought.
5. Assurance must be given that DNA will not be amplified by any means once distributed to an Ancillary Study investigator without approval of the REGARDS Executive Committee.

3.1. If blood samples, DNA, and/or or urine are requested, additional information must be provided. **Investigators are encouraged to contact the REGARDS Central Blood Laboratory (call Rebekah Boyle at 802-656-8938,** Rebekah.Boyle@med.uvm.edu**) to discuss these considerations before submitting their proposals**. In addition, investigators need to be aware that their proposal will be reviewed by an external advisory committee to the REGARDS Executive Committee as an additional step in the review process.

1. Will DNA be used? Proposals for the use of REGARDS DNA will be reviewed for the amount of DNA requested based on the genotyping platform specified and the number of SNPs indicated. Additionally, in order to avoid redundancy and to conserve resources, the SNP list will be reviewed. Current NIH-GWAS policies will be followed for GWAS studies (not necessary for candidate gene or other genetic studies). The REGARDS study does not have DNA extracted on all participants and depending on availability, Ancillary Study investigators will need to include extraction costs at the Central Laboratory in their budget planning. If DNA use is planned:

a) Name the gene variant (s) or genetic analysis approach. Additional DNA analysis, beyond what is proposed here, requires approval from the REGARDS study.
b) Will genetic information be used to study a Primary REGARDS aim (stroke, vascular disease and their risk factors) or a secondary aim (other diseases)?
c) Specify amount of DNA requested. Minimization of amount is required.
d) Discuss plans for addressing any relevant clinical or other (ethical, legal, or social) implications of the findings. Should genetic results be reported to patients' physicians? Base your response on your knowledge of existing literature and current practice regarding increased risk and availability of treatment for adverse outcomes associated with the gene mutations to be studied. If reporting may be needed, how will this be accomplished?
e) Are the investigators aware of the elements of informed consent of REGARDS participants in relation to DNA use? (Copy of the REGARDS informed consent document is available upon request.)
f) Do the investigators agree to abide by the informed consent of REGARDS participants in relation to DNA consent (exclusion of non-consenting participants needs to be considered in planning at the Ancillary Study proposal stage).
g) Do investigators performing GWAS agree to abide by NIH policies for data use?
h) Will the investigators provide to UAB sufficient funds to support data management activities for the incorporation of the SNPs into the parent study database?

2. Will blood or urine be used?

    a) Sample type (e.g. serum or EDTA).
    b) Requirement for frozen vs. previously thawed samples, and if the latter, what is the maximum number of freeze-thaw cycles acceptable.
    c) Sample volumes (REGARDS has a limited repository; efforts to minimize volumes must be demonstrated.)
    d) Efforts to integrate sample needs with those of other studies to conserve sample and/or limit freeze-thaw cycles. We would be happy to do this and would approach this issue if and when the project is funded and begins. If investigators are aware of related projects that would allow this, please mention here.
    e) Are you requesting that the REGARDS lab analyze samples? If so, communicate with Dr. Cushman or Ms. Boyle at the lab before preparing your proposal.
    f) We will need your projected timeline for:
        1. pulling samples and shipping, if applicable;
        2. sample analysis, if applicable;
        3. return of samples to REGARDS lab, if applicable.
        4. data analysis files to be sent to REGARDS Statistical and Data Management Center at the University of Alabama at Birmingham (UAB)

    These aspects of workscope must be covered in the budget of the Ancillary Study, including preparation of IRB review at the REGARDS lab and UAB. The REGARDS lab cannot provide funding for sample handling.

4.0 Other requirements of an ancillary study

1. Studies that will collect new data from participants may be required to obtain a separate informed consent (verbal or written) from ancillary study participants. This consent should clearly identify the ancillary study as 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 in REGARDS. Approval from the REGARDS Executive Committee and IRB of the University of Alabama at Birmingham must be in place before implementation of the proposed ancillary study. Resources and time for the REGARDS Operations Center staff to submit and obtain IRB approval must be considered when planning the ancillary study.

2. Confidentiality of individually identifiable data about REGARDS participants must be assured. As a general rule, no personal identification of participants will be provided to ancillary studies staff. There are no assurances that participants will be able to be identified and contacted in the future for the purposes of an ancillary study, particularly after REGARDS ends.

3. If an approved ancillary study proposal involves genetic studies, sample selection will be based on the REGARDS informed consent status. Ethical, legal and social implications, as well as reporting of results, must be proactively addressed in the ancillary study.

4. The ancillary study PI must clearly delineate any findings from the new data collection that will have clinical implications (including genetic findings) and propose how these will be handled, including reporting results to the participants and providing recommendations for follow-up. These plans must be developed to be submitted for approval by the UAB IRB, and potentially included in an addendum consent form.

5. The data collected by the ancillary study are to be provided first to the REGARDS Operations Center for integration into the main REGARDS database. This must occur before the integrated file containing data from the main study will be sent to the ancillary study investigators. The ancillary study PI will be given the first and exclusive opportunity to analyze, present and publish data collected under the auspices of the ancillary study. After a reasonable time (in general, 12 months after data collection and cleaning are complete), the ancillary study data will be made available for additional uses by REGARDS investigators, in collaboration with the ancillary study investigators. It is the responsibility of the ancillary study PI to state in writing to the Executive Committee any special circumstances that would mitigate against these guidelines for data sharing. In the spirit of encouraging collaboration, reasonable and justified requests for limiting Executive Committee access to the data will be honored or some compromise will be worked out.

6. A manuscript proposal must be reviewed and approved by the REGARDS Executive Committee before data from the main study will be provided to ancillary study investigators. A data use/distribution agreement must be signed between the ancillary study PI and UAB. For information on manuscript proposals, see "Publications and Presentations Resulting from Ancillary Studies" below. All Ancillary Study papers must adhere to REGARDS publications policies.

   Details on data distribution/use agreement can also be found in the Publications and Presentations Policies and Procedures, available upon request to **regardsadmin@uab.edu**

7. No funds from the main REGARDS cooperative agreement may be used to support an ancillary study in any way. Thus, it is crucial that a subcontract to the REGARDS Operations Center be included which will cover associated costs such as administrative/IRB issues, data handling costs, survey research unit telephone contact, communications with participants by mail or telephone, hospital record abstraction, as well as data analysis, if needed. Subcontracts to

other sites may also be necessary to cover additional data collection activities and/or blood laboratory functions. Ancillary studies performed by for-profit entities or that involve patents or licenses are required to have analyses verified by the REGARDS Operations Center. The cost of the verification will be borne by the ancillary study.

8. The ancillary study PI should keep the REGARDS Operations Center (i.e., **regardsadmin@uab.edu** or Meg Stewart) appraised of major developments in the life of the application or proposal, including, but not limited to, success or failure of funding, start date, changes in the protocol. The REGARDS Operations Center will query PIs twice per year, or as needed, for a status update of their ancillary studies, the results of which will be included in the annual Progress Reports to NIH and OSMB.

9. Ancillary studies that are submitted to a funding agency and not approved become inactive. If the PI wishes to resubmit the proposal for funding, s/he must communicate this to the Executive Committee via **regardsadmin@uab.edu**. A summary of the main points of the critique, plus a summary of the PIs response to the critique should be provided. If there is any change to the participant burden, these must be stated. If the science, scope, or burden has changed, the revised proposal must be approved by the Executive Committee, or in the case of relatively minor or administrative changes, the REGARDS PI, George Howard.

10. Ancillary Study investigators must adhere to the Publications Policy and Procedures of REGARDS, which can be obtained from **regardsadmin@uab.edu** .To ensure consistency in reporting REGARDS results, no publication of data, in abstract, manuscript, or otherwise is allowed without review and approval of the REGARDS Executive Committee.

5.0 The review process for ancillary study proposals

The Executive Committee will review and approve, reject or request modification of ancillary study proposals in a timely manner. This review is primarily to determine that the ancillary study will not compromise, complicate, or jeopardize the successful conduct of REGARDS; scientific merit is also a consideration. This review must take place before the proposal is developed into a grant application. The investigator planning an ancillary study grant application must submit the Ancillary Study Proposal Form to REGARDS at least **six weeks** prior to the funding grant application deadline. Proposals requiring review by the OSMB or involving use of biological materials from the REGARDS repository must be submitted at least **eight weeks** prior to submission to the funding source , e.g., by April 1 for June 1 NIH deadline, by August 1 for October 1 deadline, and by December 1 for February 1 deadline. If approved, the application for funding will include a letter of support from the principal investigator on behalf of the Executive Committee. In the case of studies requiring development of subcontractual arrangements with a REGARDS center, it is strongly urged that investigators contact that

center at 10-12 weeks in advance of the grant deadline for assistance in preparing the Ancillary Study Proposal.

6.0 Publications and presentations resulting from ancillary studies

All the publications, presentations and abstracts from an ancillary study must be reviewed and approved by the REGARDS Executive Committee (acting as the REGARDS Publications and Presentations Subcommittee, P&P) prior to submission or presentation, in accordance with the general rules for publications and presentations. While the Executive Committee will not track these manuscripts in the detail that main study papers are tracked, it is the responsibility of the ancillary study PI to make sure that all potential manuscript proposals have been submitted for inclusion in the REGARDS P&P database, that penultimate drafts are submitted for review, and that details concerning publication status are reported back to the REGARDS Operations Center. In brief, the P&P policies include the following rules:

1. For all potential manuscripts, a formal proposal, which consists of a title, proposed Writing Group, introduction, analysis plan, conclusion, and references must be submitted to the Executive Committee. Members of the Executive Committee may nominate individuals with "special expertise" to be added to the writing group. Most manuscripts and abstracts are expected to include a REGARDS investigator / collaborator.

2. When the writing group has been finalized and the Executive Committee has reviewed the proposal, the manuscript can be started.

3. Ancillary study manuscripts are recorded and monitored for compliance with P&P Policies and Procedures but not tracked and do not need to adhere to a timeline (unlike main REGARDS manuscripts.)

4. The Executive Committee does request that the writing process involve the whole writing group, i.e., drafts circulated regularly to the writing group. All coauthors must approve submission of penultimate draft papers to REGARDS for review.

5. The Executive Committee **does** need to review the penultimate manuscript draft arising from an ancillary study.

6. Data analyses may need to be verified by the REGARDS Operations Center before submission to a journal if: (1) the analysis was not conducted at the Operations Center and (2) the REGARDS Executive Committee requests that verification of analysis is performed. If a special request is made by the Executive Committee to verify analyses, all programs must be submitted to the Executive Committee.

7. The Chairperson of the writing group for the paper is responsible for reporting to the Executive Committee on the paper's progress.

8. A copy or reprint of the final published article must be sent to the REGARDS Operations Center.

Abstracts generated from ancillary studies must follow the same guidelines for all REGARDS abstracts (see REGARDS P&P Policies). Abstracts for presentations must be based on manuscript proposals that have been approved. If an abstract is based upon an existing penultimate draft which has been reviewed and approved by the Executive Committee, the abstract can be submitted one week prior to the deadline. If it is based upon a manuscript for which there has been no prior review, it must be submitted two weeks prior to the deadline. The writing group is also responsible for getting the approval of co-authors prior to submission for approval.

While it should be a rare occurrence, if there is scientific disagreement between the ancillary study PI and the Executive Committee in the manuscript review process, and efforts at discussion are unsuccessful at resolving the issue, the ancillary study investigators can appeal to the parent study OSMB for arbitration.

7.0 Industry participation

Proposals for industry sponsorship or collaboration will be evaluated using the same procedures described above. In addition, it will be the responsibility of the PI to obtain agreement through an appropriate contractual mechanism that all data relevant to the REGARDS ancillary study will become part of the main REGARDS database. As an initial step in study planning, the PI of the ancillary study should contact the REGARDS PI, George Howard, and the NINDS Project Officer for REGARDS to determine if an agreement between NINDS and industry should be developed and implemented or to approve the agreement between industry and the ancillary study investigator's institution. Industry-sponsored ancillary studies should comply with current NINDS guidelines, which are available from the Project Officer upon request.

REGARDS Ancillary Study Policies and Procedures
Appendix A – Executive Committee and External Advisory Committees

REGARDS Executive Committee

George Howard, Chair and PI, University of Alabama at Birmingham
Mary Cushman, PI, Central Lab, University of Vermont
Virginia Howard, University of Alabama at Birmingham
Suzanne Judd, University of Alabama at Birmingham
Brett Kissela, University of Cincinnati
Dawn Kleindorfer, University of Cincinnati
Dan Lackland, Medical University of South Carolina
Leslie Ain McClure, University of Alabama at Birmingham
Claudia Moy, National Institute of Neurological Disorders and Stroke
LeaVonne Pulley, University of Arkansas for Medical Sciences
Elsayed Soliman,Wake Forest University
Monika Safford, University of Alabama at Birmingham
Fred Unverzagt, Indiana University
Virginia Wadley, University of Alabama at Birmingham

REGARDS Biorepository Research Advisory Group (for phenotyping proposals)

Michelle Albert, Harvard University
Mitchell Elkind, Columbia University
Aaron Folsom, University of Minnesota
Nancy Jenny, University of Vermont
Dariush Mozzafarian, Harvard University
David Siscovick, University of Washington
Michael Shlipak, University of California San Francisco
Russell Tracy, University of Vermont
Neil Zakai, University of Vermont

REGARDS Genetics Research Advisory Group (for genetics proposals)

Christopher O'Donnell, NHLBI
Karen Furie, Harvard University
Russell Tracy, University of Vermont
Donna Arnett, University of Alabama at Birmingham
Daniel Woo, University of Cincinnati
Nancy Jenny, University of Vermont
Jerry Rotter, Cedars Sinai
Bruce Psaty, University of Washington
Rodney Go, University of Alabama at Birmingham
Eugene Golanov, NINDS

Appendix B - REGARDS Ancillary Study Proposal Form

A. Title:

B. Investigators:

C. Date:

D. Study Goals:

1. **General Aim.**
2. **Specific Aims / Hypotheses.**
3. **Rationale and Background.**

E. Methods:

F. Ancillary Study Questions:

If a question is already answered elsewhere in the proposal, summarize the answer here and direct the reader to the appropriate section.

1. What is the expected burden to participants, and what, if any, REGARDS core data are needed for the ancillary study?
2. Describe materials to be used. If blood samples, DNA or urine is requested, please review the section 3.E of the REGARDS Ancillary Study Policies and Procedures in consideration of your description, and respond to the required questions here.
3. What collaboration with REGARDS investigators is planned? With whom? Have the collaborating investigators approved the proposal?
4. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
5. How many participants are required?
6. When will data be collected?
7. How will the ancillary study be funded? Un-reimbursed work or personnel time of REGARDS investigators or staff cannot be offered. If applying for a grant, what is the application deadline?
8. How will the confidentiality and other aspects of protection of human subjects be maintained?
9. Will the findings have clinical implications? If so, describe the plan for reporting results to participants and providing recommendations for follow-up.

10. Where will the data analyses be conducted? The ancillary study's PI should provide evidence that adequate support for carrying out data analysis is available at his/her institution; if not, the REGARDS coordinating center will conduct the analyses using resources provided by the ancillary study.
11. Does this study involve industry support or collaboration? If yes, please describe.
12. Do you anticipate using the data to file an application for a patent, to the FDA, or for other similar purposes?
13. Why will the data be collected in the REGARDS study? Why not use other populations? What is the relevance of this study to REGARDS? What is the unique advantage of using the REGARDS cohort?

Provide the following assurances (check each):

Y	**N**	
☐	☐	The Ancillary Study PI will adhere to the Ancillary Study Policy.
☐	☐	The Ancillary Study PI will report the progress of the study as requested.
☐	☐	Confidentiality of REGARDS participants will be maintained.
☐	☐	REGARDS informed consent directives will be followed.
☐	☐	Data collected by the Ancillary Study, with documentation, will be provided to the REGARDS Coordinating Center for integration into the main database.
☐	☐	Papers resulting from the Ancillary Study will follow the Publications Policies of the REGARDS Steering Committee.

For GWAS studies only:

Y	**N**	
☐	☐	NIH-GWAS policies will be followed.