Manual of Procedures
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1. OVERVIEW

Ancillary studies that utilize the D2d study are encouraged to harness the considerable potential of the parent study for obtaining new knowledge beyond its primary goals and objectives. Ancillary studies augment and promote the continued interest in the study of both participants and D2d investigators. To protect the integrity of the D2d study, ancillary study proposals must be reviewed and approved by the D2d Ancillary Studies Evaluation Subcommittee, Steering Committee and Data and Safety Monitoring Board (DSMB) prior to implementation. In addition to meeting the standard for high scientific merit, the major criterion for approval of an ancillary study is that it does not negatively impact the conduct of the parent D2d study. Ancillary analyses are *different* from ancillary studies because they do not require additional measurements or evaluations of D2d participants (see definition below). Ancillary analyses require approval by the Publications and Presentation Subcommittee and Steering Committee. This document outlines the policies and procedures that will be followed in respect to the review and evaluation of ancillary study applications and conduct of ancillary studies. Procedures followed for the review and conduct of ancillary analyses are described in the Publications and Presentations Policies and Procedures document.

2. ANCILLARY STUDY DEFINITION

A D2d ancillary study is defined as research that: (1) has not been previously described in the D2d study protocol or in ongoing ancillary study protocols; (2) derives new data through direct contact with D2d participants (via a procedure, questionnaire or observation) or through the use of stored biological specimens; (3) does not interfere with the goals and objectives of the parent study *and* (4) follows all policies and procedures of the D2d study.

3. APPLICATION PROCESS

3.1 Who can submit an ancillary study proposal

Any qualified investigator may submit an ancillary study proposal, whether the investigator is internal (a member of the D2d Study Group) or external. Ancillary studies must include a D2d investigator – defined as a member of the D2d Study Group – as the ancillary study's principal investigator, co-principal investigator or co-investigator. The member of the D2d Study Group will serve as the D2d study liaison and must be actively involved in the design, execution, data analyses and interpretation of study findings of the ancillary study. The policy of including a member of the D2d Study Group as a key investigator in the ancillary study also ensures that the conduct of the ancillary study abides by the policies and procedures of the parent D2d study.

3.2 Procedures for submitting an ancillary study proposal

Ancillary studies are administratively managed by the D2d Coordinating Center. All submissions will be by email to d2d@tuftsmedicalcenter.org. To maximize efficiency for both applicants and D2d scientific and administrative staff, a stepwise system has been established for the submission, evaluation and approval of ancillary studies proposals, as described below.

⇒ Please note that the Ancillary Studies Evaluation Subcommittee will accept applications for D2d ancillary studies for external peer review prior to the funding decision for the D2d parent study,

only if necessary to accomplish the scientific aims of the ancillary study. For example, a study that requires measurement of additional baseline variables or assessment of an outcome through a new procedure (e.g. questionnaire, imaging study) for all or a majority of the study participants would merit early submission. However, if the ancillary study only requires additional collection of data on a subset of the study participants or plans to use stored biological samples, there is no need for early submission, and investigators should wait until the funding decision for the parent study is final.

3.2.1 Ancillary Study Letter of Intent

The letter of intent includes a preliminary concept proposal and the anticipated date of submission to the funding agency (unless funding is available). The letter of intent must be signed by the ancillary study principal investigator and the co-investigator (or co-principal investigator) who is a member of the D2d Study Group (unless they are the same person) in which they agree to abide by the policies and procedures for ancillary studies herein described, including those regarding presentation or publication of results. Applicants must use the *D2d Ancillary Study Letter of Intent* fillable PDF document, which can be downloaded at www.d2dstudy.org/ancillarystudies.

3.2.2 Ancillary Study Application

After approval of the letter of intent by the Ancillary Studies Evaluation Subcommittee, applicants will be invited to submit a full application. The D2d Coordinating Center emails the *D2d Ancillary Study Application* and any applicable additional forms (e.g. specimen request or data request forms), which are fillable PDF documents, to applicants who complete and return the application to d2d@tuftsmedicalcenter.org.

1. **The D2d Ancillary Study Application** requests the following items, which follow the NIH grant application format to aid applicants in easily converting their ancillary study application into a NIH grant application.

    - Title (81 character limit)
    - Principal Investigator (with contact information and primary institutional affiliation)
    - Co-investigators (with contact information and primary institutional affiliation)
    - Identification of the member of the D2d Study Group
    - Other Key Persons
    - Part 1: Research Plan
        a) Anticipated Timeline and Enrollment (number of D2d research participants)
        b) Hypothesis and Specific Aims
        c) Significance and Brief Background
        d) Innovation and Impact
        e) Research Approach
            - Study type (e.g. interventional or observational)
            - Population and setting (inclusion/exclusion criteria)
            - Study design (e.g. study procedures, outcome assessment, confounders, bias)
            - Schedule of assessments
            - Sample size (power) calculations

        - Data analysis plan
    f) References cited (include as a separate PDF document attached to the D2d Ancillary Study Application)
- Part 2: Description of Data
    a) Required Sources of Data
        - Existing data collected as part of the D2d study [please also complete D2d Ancillary Study Data Request Form]
        - New data derived through use of stored biological specimens collected as part of the D2d study [please also complete D2d Ancillary Study Specimen Request Form]
        - New data derived through direct contact with D2d participants (via a procedure, questionnaire or observation). New proposed procedures/surveys need to be described in detail in question 2b, including the need for additional visits, or prolongation of existing visits, to obtain such data [a protocol and manual of procedures is not required to be submitted with the application but it is required prior to study initiation].
    b) New Data Acquisition (if applicable)
- Part 3: Facilities and Resources
    a) D2d Collaborating Clinical Sites [select all sites that will participate]. Please see www.d2dstudy.org/sites for a list of collaborating clinical sites. If the box is marked next to a clinical site(s), it is assumed that the ancillary study PI has secured the commitment of the site(s) to the proposed ancillary study.
    b) Description of Clinical Laboratory Facilities (if applicable). Please describe where and how bio-specimens will be handled.
- Part 4: Potential Burden of the D2d study.
    a) Participant Burden and Potential for Compromising Participant Retention
    b) Participant Safety and Confidentiality
    c) Burden on Collaborating Clinical Sites
    d) Regulatory Requirements (e.g. Informed Consent and Institutional Review Board)
- Part 5: D2d Support
    a) Description of the use of D2d resources at the Coordinating Center or Central Laboratory that will be required [mark all that apply]. Costs associated with the use of D2d resources must be included in the plans for funding the ancillary study.
- Part 6: Funding
    a) Funding Source(s)
    b) Planned Date of Submission to Funding Agency
- Part 7: NIH Biosketch [required for PI and co-investigators]
- Part 8: Acknowledgement of D2d Ancillary Studies Policies and Procedures
- Part 9: Attachments [mark all that apply]

4. REVIEW PROCESS AND TIMELINE

The Ancillary Studies Evaluation Subcommittee meets monthly and proposals for Ancillary Studies are reviewed on a first-come, first-served basis. It is the responsibility of the ancillary study investigators to allow adequate time for full review and approval by all necessary entities of the D2d study, prior to submission to a funding agency. The review of an ancillary study application (or a major

revision of a previously submitted application) may take up to 90 days to be completed; therefore, submission of ancillary study proposals as early as possible is highly recommended, since approval by many scientific and administrative components of the D2d study is necessary for investigators to get permission to apply for external funding.

4.1 Conflict of Interest (COI)

Prior to the review of a Letter of Intent or Ancillary Study application, a member of the Ancillary Studies Evaluation Subcommittee is required to excuse herself from the review if a real or apparent COI exists. The NIH peer review COI policy is applied (http://grants1.nih.gov/grants/peer/peer_coi.htm) to determine if a member needs to recuse himself from the review.

4.2 Review of Ancillary Study Letter of Intent

The letter of intent must be submitted to the Coordinating Center *at least 2 weeks* before the next scheduled Ancillary Studies Evaluation Subcommittee conference call. The Coordinating Center, after reviewing and administratively approving the submitted letter of intent, will forward it to Ancillary Studies Evaluation Subcommittee members. The Chairperson will appoint a primary and secondary reviewer, based on the reviewers' specialization, interest, and workload. These reviewers will also serve as reviewers of the application. At the next regularly scheduled meeting, the primary and secondary reviewers will present their findings. The subcommittee will discuss the LOI and approval to submit a full ancillary study application is granted by a simple majority vote.

⇒ **NOTE:** *Approval for an Ancillary Study Letter of Intent is good for up to 9 months*. Should the Principal Investigator fail to submit an Ancillary Study Application within that period, Ancillary Studies Evaluation Subcommittee may encourage LOIs in that general area from other investigators.

4.3 Review of Ancillary Study Application

The completed ancillary study application must be submitted to the Coordinating Center *at least 4 weeks* before the next scheduled Ancillary Studies Evaluation Subcommittee conference call. The Coordinating Center, after reviewing and administratively approving the ancillary study application, will distribute the proposal to the subcommittee, which is responsible for the initial review of ancillary study proposals. At its next regularly scheduled meeting the primary and secondary reviewers will present their findings and the subcommittee will discuss the application. All applications will receive a statistical review by the Coordinating Center. Additional committees (e.g. Safety and Outcomes subcommittee) may also need to review the ancillary study application. An outside reviewer may also be used if the subcommittee does not have the expertise in a specific area. The subcommittee will vote, by a simple majority vote, to (1) approve without or with only minor changes, (2) not approve or (3) reconsider with a request for revisions. The Chair of the subcommittee summarizes the committee consensus in the meeting minutes including reservations or objections and the results of the vote. The applicant investigator receives a summary of the review and recommendations (approve, not approve, or reconsider). Most frequently, the ancillary study's investigator(s) submitting the proposal will be asked to provide clarifications and/or respond to questions that arose during the review. At this point, the investigators may choose to: (1) withdraw the proposal; (2) provide clarifications and - if needed -

modify the proposal in response to the review by the Ancillary Studies Evaluation Subcommittee and resubmit the application. The Ancillary Studies Evaluation Subcommittee *will accept only a single major resubmission (A1) to the original application*. There is no time limit for the submission of the A1 resubmission application. If the subcommittee approves the application (after first submission or re-submission), a letter is sent to the ancillary study investigator stating that the Ancillary Studies Evaluation Subcommittee vote does not indicate final approval or disapproval of the proposal, but is a recommendation to be forwarded to the D2d Steering Committee, which makes the final judgment.

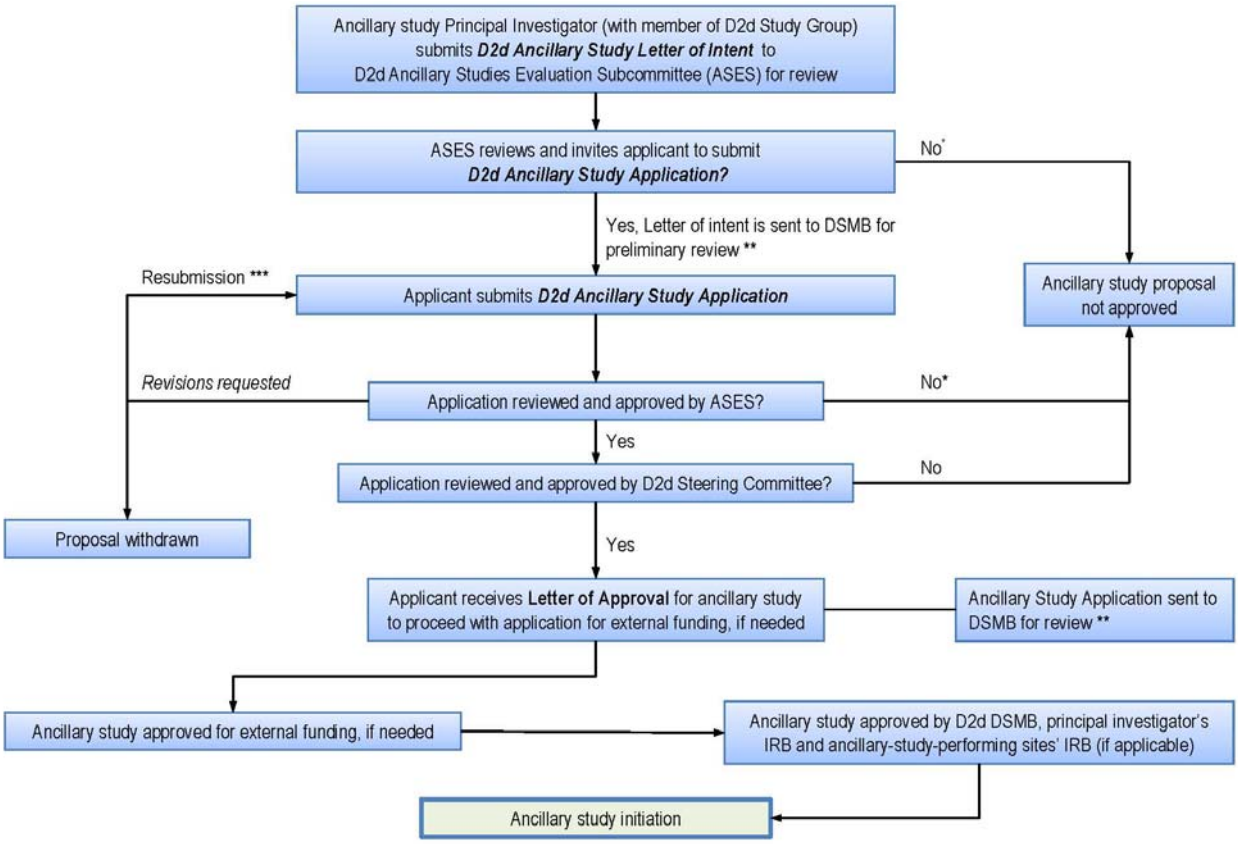
Ancillary study proposals approved by the Ancillary Studies Evaluation Subcommittee are forwarded, along with a summary of its review and recommendation and any other supporting documents, to the Steering Committee for a second level discussion and approval.

The Steering Committee will discuss the application at the next regularly scheduled meeting (held monthly) and vote (by a simple majority) to approve or not approve the ancillary study. It may do so with or without any additional comments/suggestions. Occasionally, the Steering Committee may decide to reconsider with a request for revisions. The ancillary study investigators may be invited to attend the call to provide clarification or respond to queries; the proposal's investigators will be asked to leave the call after questions are answered so that the Steering Committee can deliberate further. After the Steering Committee approves the proposal, proposals involving subject contact or use of identifiable data will be forwarded to the D2d DSMB (which meets twice yearly) for an additional review that focuses primarily on participant safety and burden. Although approval by the DSMB is required prior to study initiation, it is not required for submission of an ancillary study application for external funding. After approval by the Steering Committee, the Coordinating Center sends a preliminary (i.e. pending DSMB approval) Letter of Approval, which allows the investigator to apply for external funding, if needed.

⇒ Please note that approval of an ancillary study proposal by the D2d Ancillary Studies Evaluation Subcommittee does not guarantee approval by the D2d Steering Committee or DSMB. These multiple levels of reviews are conducted to ensure that the application receives a fair review and that the ancillary study protocol is scientifically meritorious and does not pose an undue hardship on study participants or collaborating clinical site staff.

When funding becomes available, prior to study initiation, the ancillary study principal investigator must also have the study reviewed and approved by her local IRB. If the ancillary study includes generation of new data through direct contact of participants, the study will need to be approved by the IRBs of all collaborating sites that participate in the ancillary study.

Figure. Flow diagram of the D2d ancillary study application and review process.



* Ancillary study PI may appeal decision to the D2d Steering Committee.
** Approval by D2d DSMB (meets twice yearly) is required prior to study initiation; DSMB approval is not required for investigator to proceed with application for external funding.
*** The ASES will accept only a single major resubmission to the original application.

⇒ **NOTE:** Approval for an Ancillary Study Application is good for up to 9 months or 2 cycles of NIH grant submission dates, whichever is shorter. Should the Principal Investigator fail to submit an application for a grant within that period, Ancillary Studies Evaluation Subcommittee will consider proposals on a similar topic from other investigators (within or outside the D2d Study Research Group). For example, an investigator received approval for an ancillary study on August of 2013 and the investigator missed two NIH funding cycles (October 2013 and February 2014) and has submitted no grant application to other funding agencies (e.g. ADA). Ancillary Studies Evaluation Subcommittee may encourage LOIs in that general area from other investigators.

4.4 Criteria Used for the Evaluation of Ancillary Study Applications

4.4.1 Non-interference Criteria

Proposals are first assessed to ensure that they do not interfere with the conduct of the parent D2d study. Specifically, it is essential that ancillary studies do not:

- Cause a deviation from the D2d study protocol.
- Adversely affect participant recruitment and retention.
- Adversely affect participant safety.

- Complicate the interpretation of the main results of the D2d study.
- Compromise the scientific integrity of the D2d study in any other way.
- Create a significant diversion of D2d study resources at the collaborating clinical sites, Coordinating Center, Central Laboratory or at any other level.
- In any way negatively influence the cooperative spirit of the collaborating investigators.
- Jeopardize the public image of the D2d study.
- Place undue burden on research staff and increase demand on D2d limited resources, such as use of the Coordinating Center resources or depletion of precious biological specimens.

4.4.2 Justification for Use of Bio-repository Specimens

If the ancillary study meets the criterion of non-interference with the D2d study, or if the study requests specimens only, the following criteria will be considered in evaluating the use of bio-repository specimens. The fair and useful distribution of precious specimens is consistently a challenge across studies, so the intent of the guidelines detailed below is to provide structure for the Publications and Presentations Subcommittee when evaluating the use of biorepository specimens.

% of repository volume requested from cryovials for that time point	Scientific impact required to approve
10% or less	Moderate
10-33%	Significant
33-90%	Highly significant
90-100%	Will not distribute

4.4.3 Other Important Criteria

If the ancillary study meets the criterion of non-interference with the D2d study, the following criteria will be considered in evaluating ancillary study applications:

- Scientific merit with broadest range of research questions.
- Use of the unique characteristics of the D2d population and study design.
- High ratio of potential impact to participant safety and burden.
- Qualifications of ancillary study investigator(s) and other key persons, as documented in the biosketches.

4.5 Appeal Procedure

If the Ancillary Study subcommittee does not approve the ancillary study proposal, either at the letter of intent or full application stage, the ancillary study investigator may appeal to the Steering Committee, whose majority vote can override the decision of the Ancillary Studies Evaluation Subcommittee.

5. CHANGES TO THE D2d PROTOCOL

During review of an ancillary study protocol, the Ancillary Studies Evaluation Subcommittee may determine that the proposed ancillary study requires a change in the D2d protocol. The rationale for the change and amended protocol must be submitted to the Steering Committee and the DSMB for review and approval prior to implementation. Changes to the D2d protocol will be made only after the ancillary study is funded and will be made by the Coordinating Center and ancillary study PI. The revised D2d protocol will be sent to site IRBs for review and approval prior to implementation.

6. PARTICIPATION BY COLLABORATING CLINICAL SITES

Ancillary studies may propose research that involves as many collaborating clinical sites as required based on study design and sample size calculations. No site will be required to participate in an ancillary study. If the ancillary study proposes new data through direct contact with D2d participants, the ancillary study investigator(s) and designated D2d co-investigator should consult each site principal investigator independently about participating. Clinical sites that wish to participate in the ancillary study should be given the opportunity to review the proposal (letter of intent and full application) before it is submitted to the Ancillary Studies Evaluation Subcommittee. In general, if a D2d site agrees to allow generation of data for the ancillary study through direct contact with participants, a member of that site is included as a key person. Written agreement from each participating site PI needs to be obtained by the ancillary study investigator before the ancillary study application. Funding sought for ancillary studies should include a budget appropriate for each site that has agreed to participate in the ancillary study. Ancillary studies that propose generating new data through use of stored biological specimens collected as part of the D2d study do not need to contact each site independently.

7. FUNDING

7.1 Requirement for External Funding

The D2d study does not provide funding for ancillary studies. In particular, there are no funds for Central Laboratory or any Coordinating Center activities or any other services in support of ancillary studies. Therefore, the ancillary study investigators must make provisions for securing funding for the proposed studies. Evidence of funding must be provided to the D2d Coordinating Center prior to implementation of the ancillary study. Ancillary studies are not required to have secured funding at the time of application for approval by the appropriate governing bodies of the D2d study; however, specific plans describing how the ancillary study will be funded must be provided as part of the ancillary study application. If funds are needed, the investigator must explore several avenues, including federally funded investigator-initiated research grants, non-profit organizations, pharmaceutical industry etc. Investigators are encouraged to seek funding opportunities at grants.gov where specific program announcements may be available for ancillary studies to ongoing NIH studies (e.g. PAR-09-247 Ancillary Studies to Major Ongoing Clinical Research Studies to Advance Areas of Scientific Interest within the Mission of the NIDDK and PAR-13-228). Investigators who plan to submit a NIH grant application need to provide documentation to NIH that the ancillary study proposal has been reviewed and received approval from the appropriate governing bodies of the D2d (“parent study”) to conduct the proposed ancillary study.

7.2 Funding for Statistical Analyses

The Coordinating Center will designate a data research associate to work with the ancillary study PI as soon as the proposal has been funded to help with sharing of data files and be available for questions. The Coordinating Center does not provide a statistician for ancillary studies. However, depending on availability of statisticians and agreed-upon arrangements between the ancillary study principal investigator and the Coordinating Center, the ancillary study may contract a D2d statistician at the Coordinating Center to conduct the analyses proposed in the ancillary study.

7.3 Funding for Data and Laboratory Coordination Services

Ancillary studies that require data and/or specimen retrieval or other coordination services by the Coordinating Center must make adequate provisions for defraying the costs of such services. These costs will be determined by the Coordinating Center and communicated to the applicants so they are included in the ancillary study budget.

8. REGULATORY

When funding becomes available, prior to study initiation, ancillary studies must submit the following regulatory documents to the Coordinating Center:

- Current version of the ancillary study protocol and manual of procedures, if applicable.
- Evidence of IRB approval by the ancillary study's principal investigator's institution.
- Evidence of Human Subject Protection Training for key persons.
- If the ancillary study involves generation of new data that requires contact with participants, each collaborating clinical site that is included in the ancillary study must submit:
    - Approval letter by IRB that oversees the parent D2d study at the site.
    - Approved consent form(s) and other required forms (e.g. HIPAA)

9. PRESENTATION AND PUBLICATION OF ANCILLARY STUDY RESULTS

The ancillary study application must include a publication and presentation plan. The Publications and Presentations subcommittee must review ***all*** abstracts, manuscripts, presentations (e.g. posters, electronic media) resulting from the ancillary study, prior to submission to scientific meetings or journals, in compliance with the D2d publications and presentations policies and procedures. Ancillary study investigators should be familiar with these policies. Abstracts, manuscripts and presentations resulting from the ancillary study are expected to include a D2d investigator as co-author, except under circumstances that should be stated and justified as part of the original ancillary study application.

⇒ Abstracts, manuscripts and presentations utilizing any D2d study data *cannot be submitted for peer review (e.g. scientific journals, society meetings) until after the manuscript describing the primary outcome in the D2d study* has been published.

10. USE OF ANCILLARY STUDY RESULTS IN GRANT APPLICATIONS

Occasionally, ancillary study investigators may wish to use data available to them through their respective ancillary studies in grant applications as preliminary data. The inclusion of such data in a grant application needs to be consistent with the user agreement documents signed, which stipulates that the investigator can use the data *only for the purposes described in their ancillary study application, namely to conduct specific analyses to test specific hypotheses*. Ancillary Studies investigators may have access to data that the D2d study group may not have seen and to which they may not have access. Using data that have been provided through their Ancillary Study in *unapproved* analyses (i.e. new analyses not consistent with the user agreement documents signed) to support a grant application gives the Ancillary Study investigators an unfair advantage in grant applications compared with other D2d investigators who do not have access to such data. In the spirit of fairness, such use of unapproved analyses in grant applications is not allowed. However, the Ancillary Studies Evaluation Subcommittee will consider requests to use data in a grant application on a case-by-case basis. For example, if an Ancillary Study is approved to examine the effects of vitamin D supplementation on asthma, the investigators can use the results of their approved analyses, as described in the user agreement documents, to support a grant application for a new study on vitamin D and asthma. However, the investigators cannot use the ancillary study data in a grant application for a new study on vitamin D and multiple sclerosis.

11. MONITORING OF PROGRESS

The Coordinating Center will monitor the progress of approved ancillary studies to ensure that the aims of the ancillary studies are being met. The ancillary study principal investigator is required to submit a brief annual progress report to the D2d Coordinating Center using the D2d Ancillary Study Progress Report fillable PDF document. The report will include the following information:

- Date of initiation
- Study status (not yet submitted for funding, submitted for funding, active, completed)
- Funding source (if funded)
- Progress to Date / Results
    - Number of participants enrolled, if applicable
    - Success of data collection / measurements, if applicable
    - Results of data analyses
    - Future plans
- Publications and Presentations
    - List all abstracts, manuscripts or presentations derived from the ancillary study

Approval for an ancillary study shall lapse if the study has not been initiated after one year from the date of approval to submit for funding, in the absence of extenuating circumstances. Significant deviation from the research plan or scientific, ethical or procedural infringements will be grounds for termination of an ancillary study.

12. DATA SHARING

Ancillary studies are required to share their data with the parent D2d study by providing an electronic dataset of the newly generated data for integration into the D2d database. The timeline for such integration will be finalized during the planning process and will be consistent with the NIH policy of data sharing. *Ancillary studies investigators cannot share data that have been provided through their Ancillary Study with investigators that are not included in the Ancillary Study application and cannot use these data to conduct research that is not included in the original Ancillary Study protocol and user agreement documents.*

13. ROLE OF THE D2d COORDINATING CENTER

13.1 Coordination

Ancillary studies are administratively managed and coordinated by the D2d Coordinating Center. All communications with participating clinical sites should be conducted via the Coordinating Center. To avoid replication of work and use resources efficiently, the Coordinating Center will provide coordination, site management and data management services to the ancillary study. These services must be negotiated during the planning and budget process.

13.2 Funding

Ancillary studies that require D2d Coordinating Center services, including for retrieval and shipment of laboratory specimens, must provide the Coordinating Center with funds to cover the cost of the Coordinating Center's personnel time and effort. The fee for these services is negotiated during the planning phase and needs to be included in the ancillary study budget.

13.3 Regulatory

The Coordinating Center will maintain a copy of all required regulatory documents, as described earlier.