TINSAL-T2D Study Group
ANCILLARY STUDIES POLICY

Sponsored by
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

Maintained and distributed by
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CONFIDENTIAL

1. Overall Principles

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the TINSAL-T2D clinical trial. Investigators and participants are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

- cause a deviation from the protocol,
- confound interpretation of the TINSAL-T2D study results (e.g., request unmasking of study data prior to TINSAL-T2D study-wide unmasking),
- adversely affect participant cooperation,
- jeopardize the public image of the TINSAL-T2D study,
- create a significant diversion of the TINSAL-T2D resources at the clinical centers, at the coordinating center, or at any other level,
- in any way negatively influence the cooperative spirit of the collaborating investigators, or
- otherwise compromise the scientific integrity of the TINSAL-T2D study.

Ancillary 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 major TINSAL-T2D study, a proposal to conduct an ancillary study must be reviewed and approved by the Ancillary Studies Committee, the TINSAL-T2D Steering Committee, and the TINSAL-T2D Data Safety Monitoring Board before its initiation. A major review criterion is the impact on the TINSAL-T2D protocol. No clinical center will be required to participate in an ancillary study.

2. Definition of an Ancillary Study

An ancillary study is defined as research using TINSAL-T2D study participants (including their laboratory specimens or tests) to collect or derive *supplemental* data for purposes above and beyond those set forth in the TINSAL-T2D protocol. This includes a technique, therapy, procedure, questionnaire, or observation that results in the acquisition of additional data. In addition, ongoing as well as future observational studies involving TINSAL-T2D study participants require approval according to the Ancillary Studies Policies and Procedures.

The investigator responsible for the conduct of an ancillary study must be a member of the TINSAL-T2D study group or work in close collaboration with a TINSAL-T2D investigator. If a research request is made by an individual external to the TINSAL-T2D study group, a member of the study group must be a co-PI of the ancillary study.

3. Overview of Procedures

The Ancillary Studies Committee has established a stepwise system of proposal, 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:

1. Investigators submit a preliminary concept proposal (3-5 pages) to the Ancillary Studies Committee through the coordinating center, along with 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 proposal is reviewed by all members of the Ancillary Studies Committee, which votes to approve (by majority vote) at its monthly conference call.
3. The Ancillary Studies Committee submits the proposal to the TINSAL-T2D Steering Committee along with a summary of its review and recommendation to approve or not. The proposal investigators also receive the summary and vote results.

4. The TINSAL-T2D Steering Committee reviews and votes to approve (by majority vote) at its monthly conference call.
5. The proposal passed by the Ancillary Studies Committee and the Steering Committee is submitted for review by the TINSAL-T2D Data Safety Monitoring Board, which acts as an external review board.
6. Approved proposals are returned to the investigators who write a complete proposal to the applicable funding agency.
7. The investigators have a maximum of 6 months from Steering Committee approval to prepare the final complete proposal for review by the Ancillary Studies Committee. After 6 months, procedures start again at step 1.
8. The final proposal is resubmitted to the Ancillary Studies Committee for review and approval and to the coordinating center to ensure adequate funding for coordinating center activities.
9. Final proposals that are approved by the Ancillary Studies Committee may be submitted to the designated funding agency.
10. Ongoing observational studies that involve potential TINSAL-T2D study participants undergo a modification of the above procedures. As such studies have already received funding and approval, the Ancillary Studies Committee requires copies of the observational study protocol and IRB approvals to be kept on file at the coordinating center.

4. Funding

The TINSAL-T2D study will not provide funds for ancillary studies. In particular, no funds are provided for central laboratory, central reading center, 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., a foundation, drug company, etc.). The anticipated source of funds must always be identified.

5. Publication and Presentation of Results

All manuscripts, abstracts, or presentations for scientific meetings based on ancillary study data must follow the policies and procedures of the TINSAL-T2D Publications and Presentations Committee.

6. Participation by Clinical Centers

In general, each clinical center principal investigator determines whether or not his/her center will participate in a proposed ancillary study. Prior to submitting the ancillary study proposal, the ancillary study PI and/or the designated TINSAL-T2D co-PI should consult each clinical center PI 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, however, also consider ancillary study submissions proposing participation of only one or a few 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.

A TINSAL-T2D clinical center investigator must be included as a co-PI in every ancillary study proposal. In general, if a TINSAL-T2D clinical center agrees to provide participant data for the ancillary study, a member of that clinical center is included as a co-investigator. In order to avoid misunderstandings, all communication with the TINSAL-T2D coordinating center, participating clinical centers, and the TINSAL-T2D study group must be conducted with the ancillary study PI and/or the

TINSAL-T2D co-PI. Following approval of an ancillary study by the TINSAL-T2D 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.

7. Proposal Procedures

The preliminary concept proposal should be 3-5 pages and contain:

1. Investigators and collaborators name, role, and institutional affiliation. 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.
    - Sample size and justification (including power calculation).
    - Data needed (a) from the TINSAL-T2D study central database and (b) from additional tests, surveys, etc.
    - Description of additional methods and procedures to be carried out on a study participant.
    - Plans for analysis.
    - Burden on participants.
    - Impact on TINSAL-T2D study.
    - Measures to be taken to ensure participant safety and confidentiality.
    - Payment or incentives to participants.
5. Coordinating center and other study resources requested.

8. Review Process

It is the responsibility of the investigators to allow adequate time for full review and approval by the TINSAL-T2D study prior to a funding agency submission deadline according to the following review process:

- The preliminary concept proposal must be submitted to the coordinating center at least 2 weeks before the next scheduled Ancillary Studies Committee conference call. The coordinating center reviews the proposal for completeness and distributes a copy to each member of the committee. Each member of the committee completes the Ancillary Studies Evaluation Form (see last pages of policy). The committee votes to approve or disapprove.

  The Ancillary Studies Committee may elect to use both e-mail exchange and conference call in their review. Approval or disapproval is based on a simple majority vote of the Ancillary Studies Committee. Highest priority will be given to studies that:
    - have the highest scientific merit,
    - produce the least burden on TINSAL-T2D participants,
    - have objectives closest to those of the TINSAL-T2D study, and
    - require the unique characteristics of the TINSAL-T2D cohort.

- The Ancillary Studies Committee chair summarizes the committee consensus on the 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 that the Ancillary Studies Committee vote does not

indicate approval or disapproval of the proposal, but is a recommendation to the TINSAL-T2D Steering Committee which makes the final judgment. 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 Ancillary Studies Committee, or
- provide written clarification in response to the summary Ancillary Studies Evaluation Form to the Ancillary Studies Committee and to the TINSAL-T2D Steering Committee prior to its deliberations. This documents is submitted to the coordinating center for distribution.

- Members of the TINSAL-T2D Steering Committee receive both the preliminary concept proposal and the summary evaluation form, as well as written clarification if applicable.

  The TINSAL-T2D Steering Committee will need 1 months for review and vote on the preliminary concept proposal. During that period the committee will hold its weekly conference call. The investigators may attend the call to provide clarification or response to queries; however, the proposal investigators will be asked to leave the call so that the steering committee can deliberate further.

  The Steering Committee may elect to use either or both e-mail exchange and conference call in their review.

  A majority of the voting members must approve the proposal. Vote results are acknowledged in a letter to the proposal PI from the coordinating center PI.

- With approval of the preliminary concept proposal, the investigators may proceed to prepare a full proposal to the designated funding agency. At least 2-4 weeks in advance of the funding agency deadline, the investigators submit the complete protocol (formatted as required by the funding agency) to the coordinating center to distribute for review and approval by:
  - the Ancillary Studies Committee (the Ancillary Studies Committee has been designated by the TINSAL-T2D Steering Committee to act on their behalf regarding the final proposal; however, the Ancillary Studies Committee may request a review of the full proposal by the Steering Committee and/or DSMB), and
  - the coordinating center (for adequacy of external funds to cover coordinating center resource requests and for validity of study design and other statistical issues).

  If the full proposal has been significantly changed from the preliminary proposal, the Ancillary Studies Committee may request revisions and a full review by the Steering Committee and/or DSMB. In such cases, it would be advisable for the investigators to submit their revised proposals at least 6-8 weeks in advance of the deadline.

- With committee approval, the investigators may proceed with the proposal submission. The funded ancillary study begins according to the proposed timetable.

9. Appeal Procedures

In the event that the Ancillary Studies Committee disapproves a proposed ancillary study, the investigator(s) may appeal to the Steering Committee, whose decision may override that of the Ancillary Studies Committee. If the Steering Committee also disapproves of the ancillary study, the proposal will not be undertaken.

10. Protocol Changes

If the Ancillary Studies Committee feels that the proposed ancillary study requires a change in the TINSAL-T2D protocol, this must be reviewed by the Steering Committee for benefit to the TINSAL-T2D study and final vote of approval according to protocol amendment procedures (consensus of Steering Committee required to change or amend the TINSAL-T2D protocol).

11. 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 TINSAL-T2D staff, as well as the use of irreplaceable TINSAL-T2D 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 study (i.e., the progress report should follow the same format as that for annual funding requests). All presentations and publications must follow the TINSAL-T2D study Publications and Presentations Policy.

12. Analysis

All TINSAL-T2D approved ancillary studies include plans for data analysis, who will perform the analysis, and what their credentials are. Data analysis must be financed by the investigators submitting the proposal.

13. Informed Consent

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 TINSAL-T2D 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 consent/assent forms before a clinical center may participate in the ancillary study.

14. Incorporation of Additional Data Collection to TINSAL-T2D 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 TINSAL-T2D study. The proposal should address the potential impact of additional data collection on participation in the TINSAL-T2D study.

15. TINSAL-T2D Participants and Local Studies

TINSAL-T2D study participants are encouraged to participate only in approved ancillary studies. If a TINSAL-T2D participant wishes to participate in another local study, he or she must notify the clinical center PI who will bring the request to the attention of the Steering Committee to determine whether the participant will be allowed to continue active participation in the TINSAL-T2D study.

16. Changes to Ancillary Studies Policies and Procedures

Any changes in the policies and procedures described in this document require a majority vote of the TINSAL-T2D study Steering Committee.

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 will…

a.	cause a deviation from the protocol.	☐ Yes*	☐ No
b.	confound intepretation of TINSAL-T2D study results.	☐ Yes*	☐ No
c.	adversely affect subject/family participation in the TINSAL-T2D study.	☐ Yes*	☐ No
d.	jeopardize the public image of the TINSAL-T2D study.	☐ Yes*	☐ No
e.	negatively influence the cooperative spirit among TINSAL-T2D clinical centers.	☐ Yes*	☐ No
f.	compromise the scientific integrity of the TINSAL-T2D study.	☐ Yes*	☐ No
g.	raise concerns with the TINSAL-T2D DSMB.	☐ Yes*	☐ No

*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. ☐ Yes ☐ No*

   *Explanation:

   b. The study will create a significant diversion of TINSAL-T2D resources. ☐ Yes* ☐ No

   *Explanation:

7. Critique of strengths and weaknesses:

8. Recommendation ☐ Approve

   ☐ Disapprove

9. Additional comments: