ANCILLARY STUDIES POLICIES AND PROCEDURES: Publications, Presentations, and Ancillary Studies Committee of the Dietary Biomarker Development Consortium (DBDC)

1. Background

The Dietary Biomarker Development Consortium (DBDC) encourages investigators to develop ancillary studies. Interested investigators must identify a DBDC investigator who is willing to oversee the ancillary study and serve as a liaison between the proposer and the DBDC Steering Committee (SC).

2. Definition of an ancillary study

An ancillary study is defined as a study that uses any DBDC data or biological specimens for a new research question, including data generated by the site proposing the new research

3. Ancillary studies policy and procedures

The ancillary studies policy includes the following:

- The maintenance of a list of proposed, in progress, and completed ancillary studies, including the investigators, DBDC sponsor, and applicant institutions. For approved studies, the list will indicate the consortium approval date and the DBDC centers participating in the ancillary study. The list of all approved ancillary studies will be available on the DBDC website.

The Data Coordinating Center (DCC) will support ancillary studies operations by monitoring progress, arranging conference calls, receiving submitted applications for ancillary studies, administering the process for review of submitted applications, writing correspondence on behalf of the SC, and maintaining the lists of ancillary studies and correspondence files relating the Publications, Presentations and Ancillary Studies Committee (PPAC) activities. The DCC will also help the DBDC to manage tracking of ancillary studies' publications, progress reports, and disposition of biospecimens, datasets, and consortium data sharing plans.

4. Proposing an ancillary study

Investigators wishing to conduct an ancillary study must complete a DBDC Ancillary Study Proposal/Concept Application form (Form A). Completed forms are submitted to the PPAC in care of the DCC to the email address provided on the form. Deadlines for receipt of ancillary study proposals for initial review will be set by the DBDC PPAC.

An ancillary study that is proposed by an investigator outside of the DBDC must have a DBDC sponsor. This sponsor must be a DBDC investigator (i.e., PI, Co-I). The sponsor serves as a facilitator and the communications link between the PPAC, the DBDC SC, and the ancillary study team. For example, the sponsor would provide status reports for review on the ancillary study as needed at PPAC or DBDC SC meetings and would assist the DCC as needed in communicating with the ancillary study PI and investigators. The Sponsor may be a collaborator or active investigator on the project, but this is not a requirement. Each ancillary study must have the approval of the Principal Investigator(s) at the relevant DBDC clinical center(s) that will participate in the study.

Investigators who wish to perform a DBDC ancillary study as part of applying for funding to NIH or other funding agencies must gain DBDC SC approval for the ancillary study **before** submitting their application to the funding organization.

Completion of the Ancillary Studies Proposal requires the following information:

- Name of the principal investigator for the ancillary study, institutional affiliation, and contact information.
- Name of the DBDC sponsor, institutional affiliation, and contact information.
- Names of other key personnel for the ancillary study and their institutional affiliations.
- Assurance that all study investigators have reviewed the proposal and agreed to participate **prior** to submission of the proposal to the PPAC.
- The study title, objective, and estimated start and end dates.
- DBDC Ancillary Study Proposal/Concept Application form (Form A) describing the specific aims, research design and methods for achieving the study objectives, and the need for the DBDC resources. The DCC will provide a template for the proposal to include Aims, Brief Background and Premise, Significance and Innovation, and Brief Approach.
- A Statistical Analysis Plan (SAP) (Form D) describing the primary outcome variable, and sample size justification.
- Specification of the DBDC resources which the ancillary study wishes to use and rationale for use of DBDC resources.
- The proposed funding source, funding amount, status of funding and proposed submission date for the ancillary study should be specified.
- A statement regarding the funding, if any, to be requested for DCC or DBDC investigator-personnel time or other costs must be specified. DCC and other DBDC central resources including the NIH-NIDDK central repository may be contracted by the ancillary study PI to provide services for the proposed ancillary study.
- The status of IRB approval, if a separate IRB approval is required, and plans and procedures to protect participant confidentiality.
- An acknowledgment that the DBDC Ancillary Studies Policy and the policy on presentations and publications arising from ancillary studies have been read and will be abided by the study principal investigator and personnel.
- A signed statement attesting that the proposed study has no conflict or overlap with existing DBDC studies.
- Considering the time it will take for the PPAC to review applications and make recommendations to the SC for approval, ancillary studies applications should be submitted no less than **12 weeks** prior to the funding agency due date.

Ancillary study activities may not proceed until the DBDC SC has approved the ancillary study and proof of funding has been received by the DBDC SC.

5. Review process for proposed ancillary studies

The DCC will circulate the submitted DBDC Ancillary Studies Proposal/Concept Application (Form A) to the members of the PPAC with instructions that they are to send their comments to the DCC by a specified date, typically one week before the PPAC meeting at which it will be discussed.

The DCC will assist the PPAC Chair and Co-Chair to collate the comments and prepare a written memo to the SC specifying the recommendation for "approval, disapproval, or resubmit with additional information or revision." The SC will review that recommendation and make a decision. The principal investigator of the ancillary study and the DBDC sponsor will each receive notice of the date of the SC review of the ancillary study application, in a letter indicating the SC decision, and contextual information related to the decision (see below).

PPAC members (and, as needed, other reviewers) will be asked to assess the following:

- Scientific merit
- Investigator expertise and resources needed to deliver on the project
- Participant burden
- Statistical power and adequacy of statistical analysis plan
- Overlap redundancy, or conflict with ongoing DBDC studies
- Justification of biospecimen request (volume of request, appropriateness of proposed assays) and impact on the biorepository
- Justification of dataset request
- Funding plan for the use of DBDC or non-DBDC resources for the study aims
- For studies involving biospecimens, the proposed plan and timeline for destruction or other disposition of biospecimens remaining at the completion of the ancillary study

6. Ancillary Studies Funding

Ancillary studies must be supported with independent funding from non-DBDC resources. The DBDC SC will provide a letter of support for an approved ancillary study, to use in the funding application to be submitted by the ancillary study investigator(s). If funding is not approved, the letter of support and ancillary study approval may not be used for other applications without permission. For example, a revised ancillary study proposal or amendment should be submitted to the DCC and the PPAC will review and make recommendations to the SC.

Note that any requested DBDC data, specimens, and other resources will not be provided until a Notice of Grant Award is issued from the sponsor. IRB approval and relevant material transfer agreements must also be in place.

7. IRB compliance and Approval

The DBDC sponsor to the ancillary study and the site(s) Principal Investigator(s) who have signed the ancillary study proposal document are responsible for ensuring that all uses of any DBDC biospecimens or clinical data provided to the ancillary study are in accordance with the informed consent statements signed by the DBDC study participants. It is possible that some ancillary studies will require separate IRB approvals. The DBDC sponsor to the ancillary study is responsible for informing the DBDC SC and PPAC (via the DCC) of IRB submissions, amendments, and annual renewals.

8. DBDC general guidelines for access to and use of participant data

Access by ancillary studies teams to DBDC participant data will be governed by the DBDC SC and administered by the DCC. Associated data and information about treatment assignment in a DBDC clinical trial are unlikely to be available until after the DBDC trials have ended and the primary papers from the DBDC trials have been accepted for publication, regardless of the timing of the submission of the ancillary study. Ancillary study investigators should be aware that there may be delays before the requested DBDC data are approved for release. DBDC data will be provided to the ancillary study investigator only if the following conditions are agreed to in writing by the ancillary study institution:

1) The necessary funding support and availability of staff and equipment to conduct the ancillary study are secured and ready to start the ancillary study.

2) The new data derived from the ancillary study must be generated within 24 months of receipt of the participant data.

3) The ancillary study's principal investigator must review the NIH Data Sharing Policies, as well as the Data Sharing requirements designated in the DBDC Ancillary Studies Policy and Site-Specific Data Use Agreement and provide assurance to abide by these requirements.

DBDC data sets use the DBDC participant ID number to link records. Ancillary study investigators should request data on the DBDC participants in their study by providing the relevant DBDC ID numbers. The DCC will accept SAS, Excel, Access, ASCII, and other data files of records of DBDC ID numbers (word processing files are not acceptable, other identifiers are not acceptable).

All data collected using DBDC central resources belong to the NIH-NIDDK. The DBDC data are provided to the ancillary study investigators with the understanding that all new data (e.g., biomarker and genomic data) generated through the ancillary study will be shared with DBDC investigators once the primary paper(s) for the primary aims of the ancillary studies are accepted for publication. All publications and presentations stemming from ancillary studies requires approval by the PPAC in accordance with the DBDC Publications and Presentations Policy.

9. DBDC Biospecimens

9.1. Access to DBDC Biospecimens

DBDC biospecimens will be provided to the ancillary study investigator only if the following conditions are agreed to in writing by the ancillary study institution:

1) The necessary funding support and availability of staff and equipment to generate the new data are secured and ready to start the ancillary study.

2) The new data generated from the ancillary study must be obtained within 24 months of receipt of the specimens.

4) The ancillary study's principal investigator must review the NIH Data Sharing Policies, as well as the Data Sharing requirements designated in the DBDC Ancillary Studies Policy and Site-Specific Data Use Agreement and provide assurance to abide by these requirements.

5) The ancillary study's principal investigator must share a plan for biospecimen disposal upon completion of the ancillary study as stipulated by the following section.

9.2. Disposal of biospecimens remaining at the end of the ancillary study or at the end of DBDC funding

It is the responsibility of the ancillary study PI to arrange for proper disposal or return of any remaining DBDC biospecimens after completion of all of the ancillary study aims. Documentation confirming the disposal in accordance with the previously approved plan must be submitted to the DCC within one month of disposal.

If the primary results of each of the aims of the ancillary study have not been published within 3 years of receipt of the biospecimens, then the investigator may request permission from the DBDC sponsor(s) and originating DBDC PI(s) or Co-I(s), to extend retention of the specimens to enable that all the aims of the ancillary study have been published. If, for some reason, the specimens have not been used or are not depleted at the end of the ancillary study, and residuals are sufficient to perform additional studies, it is desirable and responsible to make them available for additional research. When possible, samples should be returned to the DBDC sponsor(s) and originating DBDC PI(s). All chain of handling, storage temperatures, volume of residuals, and specimen handling details should be logged and such information should accompany any returned specimens.

Specimens and participant data provided by the DBDC for an ancillary study must only be used for the approved aims specified in the ancillary study proposal. Any new aims will require either an ancillary study amendment or a new ancillary study proposal to be considered for approval. Additional information concerning amendments is provided in section 13.2. Misuse of the biological specimens or participant data provided by the DBDC is a serious breach of academic trust and may violate NIH-NIDDK policies.

12. Progress reports

A written progress report must be provided to the DBDC SC every six months, which outlines funding status, data analysis results and other relevant activities. A final report outlining study results and publications must be sent to the DBDC SC at the completion of the project. Additionally, the ancillary study PI is responsible for the applicable timely deposits of the ancillary study data to the appropriate public use data repository.

13. Miscellaneous issues

13.1. Failure to initiate the ancillary study

In general, approved ancillary studies should be funded within one year of being approved. If an ancillary study is not funded within one year of DBDC approval, additional time may be requested. This request will be reviewed by the PPAC but the review does not guarantee approval.

13.2. Amendments to an approved ancillary study research plan

If a major change occurs to an approved ancillary study's research plan, the ancillary study PI must submit an amendment that explains the change: i.e., the need for additional biospecimen samples, adding additional ancillary study aims in alignment with the overall objective of the originally-approved ancillary study, a change to the method of ascertaining the new data, or a substantive change in the analysis plan. Approval of amendments will be provided by the DBDC SC and in consideration of PPAC recommendations.

13.3. DSMB Oversight

During the active phase of the Consortium, the Data Safety Monitoring Board (DSMB) requires a listing and progress update on each ancillary study during DSMB meetings. The DCC will prepare a summary of the active ancillary studies for DSMB review and acknowledgment as well as their assessment on how the ancillary studies may impact the DBDC.

Appendix A: DBDC Ancillary Study Proposal/Concept Application Form (Form A)
For reference purposes only. Submission will be made via email through a separate downloadable form

Notes to the Applicant on application process and flow:
Following the completion of this form, the applicant must submit an electronically signed version of this application, along with all required attachments, to the Data Coordinating Center (DCC) via email at will.simmons@duke.edu.
The DCC will circulate the submitted ancillary studies proposal/concept application to the members of the Publications, Presentations, and Ancillary Studies Committee (PPAC) with instructions that they are to send their comments to the DCC by a specified date, typically one week before the PPAC meeting at which it will be discussed.

The DCC will assist the PPAC Chair and Co-Chair to collate the comments and prepare a written memo to the Steering Committee specifying the recommendation for "approval, disapproval, or resubmit with additional information or revision." The Steering Committee will review that recommendation and make a decision. The principal investigator of the ancillary study and the DBDC sponsor will each receive notice of the date of the Steering Committee review of the study application, in a letter indicating the Steering Committee decision, and contextual information related to the decision (see below).

PPAC members (and, as needed, other reviewers) will be asked to assess the following:

- Scientific merit
- Investigator expertise and resources needed to deliver on the project
- Participant burden
- Statistical power and adequacy of statistical analysis plan
- Overlap redundancy, or conflict with ongoing DBDC studies
- Justification of biospecimen request (volume of request, appropriateness of proposed assays) and impact on the biorepository
- Justification of dataset request
- Funding plan for the use of DBDC or non-DBDC resources for the study aims
- For studies involving biospecimens, the proposed plan and timeline for destruction or other disposition of biospecimens remaining at the completion of the ancillary study

Date:	
Proposed Study Title:	
Principal Investigator:	

Principal Investigator Contact Information:
Site/Institution:
Email:
Phone:

Collaborating Investigators or Key Personnel (Names/Institutions):

Attestation (required): The submitting investigator attests that all study investigators have reviewed the proposal and agreed to participate **prior** to submission of the proposal to the PPAC.

Yes☐
No☐

DBDC sponsor (if applicable) where proposing investigators are outside of the DBDC:
Site/Institution:
Email:
Phone:

Study Objectives:

Estimated Start Date:

Estimated End Date:

Statistical Analysis Plan (Goals/Objectives/ Research Question, Hypothesis(es), Background/Rationale, Primary and Secondary Outcomes/Endpoints, Statistical Analysis Methods, and include sample figures and table shells if available**) Attached (Form D):**
☐ **Yes** ☐ **No**

Specify the DBDC resources which the ancillary study wishes to use and rationale for use of DBDC resources*:

*DBDC data sets use the DBDC participant ID number to link records. Ancillary study investigators should request data on the DBDC participants in their study by providing the relevant DBDC ID numbers. The DCC will accept SAS, Excel, Access, ASCII, and other data files of records of DBDC ID numbers (word processing files are not acceptable, other identifiers are not acceptable).

Financial Considerations

1. Specify the proposed funding source:
2. Funding amount:
3. Status of funding (i.e., awarded, submitted, etc.):
4. If not submitted, include the proposed submission date:
5. Specify if any funding is to be requested for DCC or DBDC investigator-personnel time or other costs. DCC and other DBDC central resources including the NIH-NIDDK central repository may be contacted by the ancillary study PI to provide services for the proposed ancillary study:

6. If the funding is being provided through a collaboration with industry or a federal funding agency (designated as the ancillary study's Collaboration Partner), then the DBDC sponsor must have a Collaborative Partner Agreement in place with relevant institutions.

Status of IRB Approval and Approval Date (unless the IRB application is still pending, attach IRB Approval Letter to this application):

Required Attachments:

1. Statistical Analysis Plan (Form D)
2. IRB Approval Documentation (unless the IRB application is still pending)

Attestations (required)

1. The submitting investigator attests that all study investigators have reviewed the proposal and agreed to participate **prior** to submission of the proposal to the PPAC.
   Yes ☐
   No ☐

2. The DBDC Ancillary Studies Policy and the policy on presentations and publications arising from ancillary studies have been read and will be abided by the study principal investigator and personnel.
   Yes ☐
   No ☐

3. The submitting investigator understands that they are responsible for ensuring that all uses of any DBDC biospecimens or clinical data provided to the ancillary study are in accordance with the informed consent statements signed by the DBDC study participants.
   Yes ☐
   No ☐

4. The proposed study has no conflict or overlap with existing DBDC studies.
   Yes ☐
   No ☐

5. The submitting investigator understands that the ancillary study activities may not proceed until the DBDC Steering Committee has approved the ancillary study and proof of funding has been received by the Steering Committee*.
   Yes ☐
   No ☐

6. The submitting investigator attests that this form has been completed to the best of their ability using the information and knowledge available to them at the time of this submission. Any changes to the content of the form should be submitted as a revised application making note of the amendments.

Yes☐
No☐

* Ancillary studies must be supported with independent funding from non-DBDC resources. The DBDC Steering Committee will provide a letter of support for an approved ancillary study, to use in the funding application to be submitted by the ancillary study investigator(s). If funding is not approved, the letter of support and ancillary study approval may not be used for other applications without permission. For example, a revised ancillary study proposal or amendment should be submitted to the DCC and the PPAC will review and make recommendations to the Steering Committee.

Appendix B: NIDDK Central Repositories Data and Resources Use Agreement (Form B)

For reference purposes only. Submission will be made via email through a separate downloadable form

SAMPLE DOCUMENT – FOR INFORMATIONAL PURPOSES ONLY
DO NOT USE THIS SAMPLE.
THE CUSTOMIZED AGREEMENT FOR EXECUTION WILL BE GENERATED DURING THE REQUEST PROCESS
ITALICIZED AND HIGHLIGHTED TEXT APPLIES ONLY TO BIOSPECIMEN REQUESTS

NIDDK Central Repository
DATA and RESOURCES USE AGREEMENT
Contact: NIDDK-CRsupport@niddk.nih.gov

This Data and Resources Use Agreement ("**DUA**") is made and entered into as of the last date of signature by the Parties ("**Effective Date**"), by and between the National Institute of Diabetes and Digestive and Kidney Diseases ("**NIDDK**"), and the Requesting Institution identified below. This DUA sets all terms and conditions to transfer Resources from, and Materials to NIDDK Central Repository for the specified approved Research Project in "**Appendix A.**"

Requestor:

E-mail Address:

Requesting Institution:

Requested Data:

If Requestor is funded by NIH for this Research Project, the grant number is:

If Research Project is associated with the X01 access mechanism, the grant number is:

Introduction

NIDDK has supported the collection of phenotypic data and specimens from participants in numerous studies. The Data and Resources are held by NIDDK Central Repository (hereinafter referred to as the "**Repository**"). In order to maximize the benefits of data and specimens collected with public funds and maximize their research value, it is important that these be made available, with appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner.

Transfer of Resources from, and Materials to the Repository is governed by NIH and NIDDK sharing policies and applicable federal regulations.

The Repository receives only data and specimens that do not include direct personal identifiers or codes linking to the identifiable information and distributes these Resources via controlled access.

In the event that investigators from more than one institution will be collaborating on a Research Project using the Resources transferred under this DUA, an investigator from each Requesting Institution is required to complete a separate DUA.

It is the intent of NIDDK that Requestors must follow the limitations imposed by the contributing study's informed consent agreements.

NIDDK has established policies and processes to make Data and Resources available through appropriate terms and conditions to qualified Requestors. The Repository requires the Requestor and Requesting Institution to read, understand, and sign this DUA and to agree to abide by the terms and conditions of this DUA, and sign as a condition of access. A Requestor who is granted access to Resources must adhere to the specifications of this DUA as executed in its final form. Failure to do so may result in denial of further access by the Requestor's Institution to Resources available through the Repository.

Terms of Access

1. Definitions:

"**Access Renewal**": Renewal of controlled access for continued research use of previously approved Resources.

"**Authorized Organization Representative (AOR)**": Individual, named by the Requesting Institution, who is authorized to act for the Requestor and to assume the obligations imposed by the federal laws, regulations, and requirements.

"**Contributing Study Investigators**": Research investigators who provided the phenotypic data and specimens to the Repository.

"**Data**": Controlled access data provided by NIH/NIDDK in limited data set format (do not contain direct identifiers, are sensitive, and must be protected), that may also be available from repositories other than the Repository (for example, dbGaP).

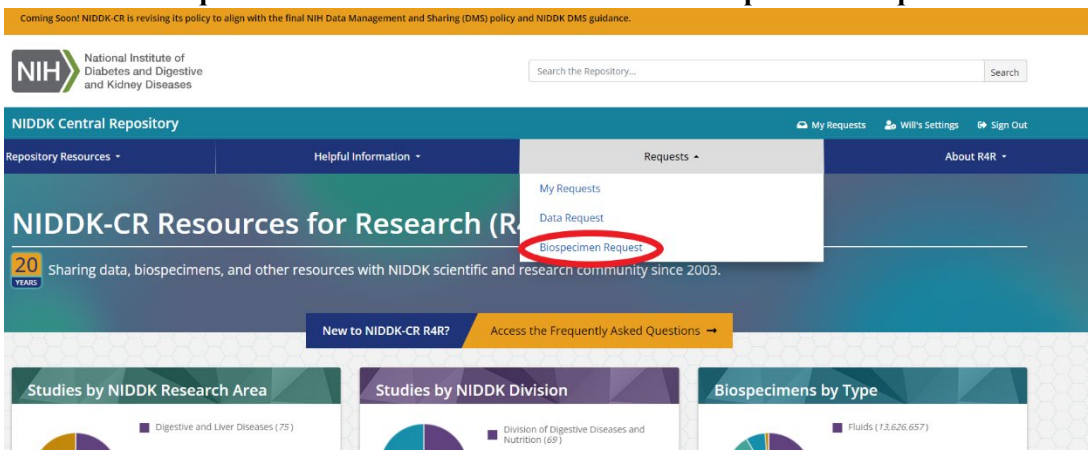
"**Materials**": Include but are not limited to all data, specimens, products, analytes, metadata,

Appendix C: Process to obtain samples from the NIDDK Biorepository (Form C)

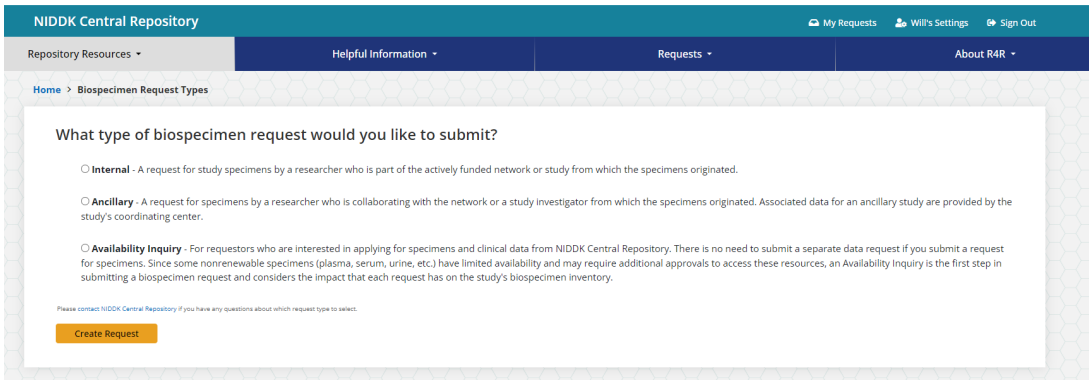
For reference purposes only. Submission will be made via email through a separate downloadable form

1. **Log into the NIDDK Central Repository website:** https://repository.niddk.nih.gov/home/

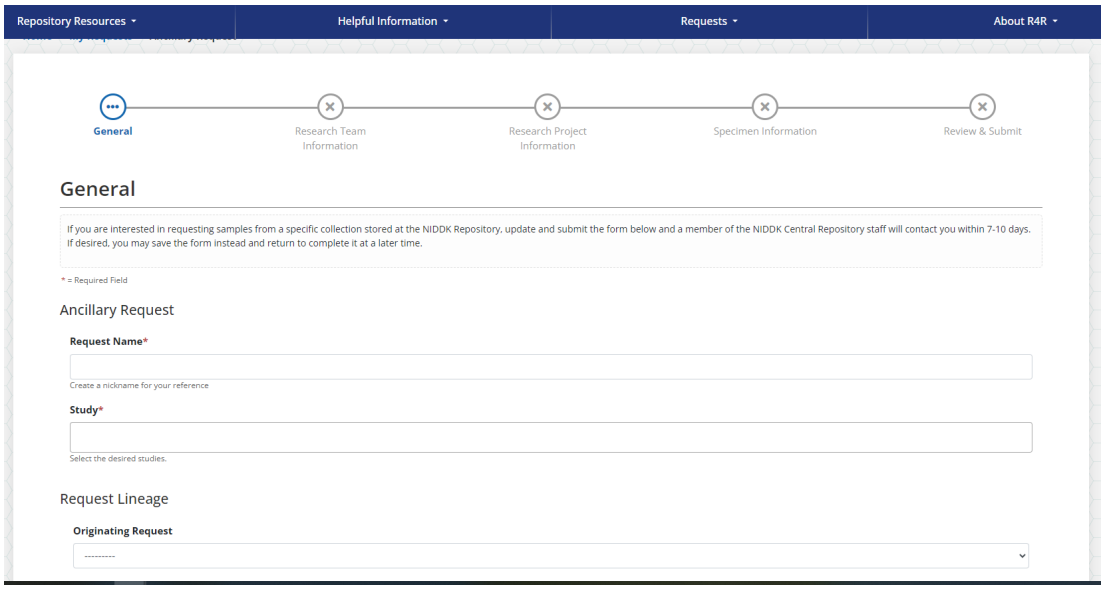
2. **Access the "Requests" menu on the tool bar and select Biospecimen Request:**



3. **Select the appropriate choice for your biospecimen request, and click "Create Request":**



4. **Complete the form that is generated based on your request selection above, and submit your request to the NIDDK Central Repository:**



5. **Additional resources are also available here:**
   https://repository.niddk.nih.gov/pages/instructional_materials/

Appendix D: DBDC Statistical Analysis Plan Template (Form D)

For reference purposes only. Submission will be made via email through a separate downloadable form

Project: Project Title

First Author(s):
Appointment(s) of First Author(s): List only those relevant to the current study.
Lead Statistician:
Co-authors (follow the PPAC guidelines):

Deadlines:

NOTE:

- All comments pertaining to writing the SAP are colored **in red**. Prior to circulating the SAP, these comments should be deleted.
- **This is a living document.** This document can be changed/updated based on data availability and or primary analysis outcomes. The purpose of this document is for DCC Stats personnel to review the data requests for the proposed ancillary studies and to provide guidance to the DBDC investigators.

Background

This section should be provided by the primary author and should give sufficient context to the research question.

Suggested information:

- Description of the study
- Motivation for the current study
- Previous studies/state of the field in question
- Primary objective

Analytic Goals:

All analytical goals and corresponding hypotheses should be described here. These are determined by the primary author(s). The goals should clearly define the outcome and information to be used, and the hypotheses should clearly define the expected results. Make sure that descriptive aims are clearly marked as such.

- **Aim 1:** Write aim here.
  - **Hypothesis:** Write hypothesis / hypothesis generating question here
- **Aim 2:** Write aim here.
  - **Hypothesis:** Write hypothesis / hypothesis generating question here

Population:
Suggested information (can be bulleted) for main analysis and sensitivity analyses.
Analysis population A

- Inclusion criteria
- Exclusion criteria
- Timepoints

Outcomes and Variables of Interest: Please list all of variables required for the analyses.
Outcomes should be clearly defined and include units of measure when necessary. If outcomes are time-dependent, be sure to include the timepoints. These can be bulleted.

Data Sources:
If the investigator(s) have some variables of interest, it will be helpful to know where they will get the data. Will all of the data needed for analyses are from the site datasets transferred to the DCC? Or will they use some data from their own sources? If they use their own data sources, it will be important to know the data sources are in good quality and approved by the PPAC.

Adjustment Variables
This should be a list (preferably bulleted) of variables that are associated or prognostic of the primary /secondary endpoints

Handling of Missing Data
Plan for handling all missing data, e.g. exclude incomplete observations, impute missing data, etc.

Quality Assurance Procedure
The statement below is typically sufficient to address quality assurance concerns, but other information/proposed steps may be added if appropriate.

Modification History:

Date	**Modification**
dd/mm/yyyy	Initial draft completed
dd/mm/yyyy	