UDN DUCAS Clinical Research Support Core Subawards - December 2024

Link to REDCap application: https://redcap.wustl.edu/redcap/surveys/?s=7MDDDKA4DNRP3XLJ

In collaboration with the Network Steering Committee and NIH program staff, the DMCC's Clinical Research Support Core (CRSC) at WashU will continue to use a REDCap-based Subawards' administration platform (REDCap) that permits evaluation, management, unbiased prioritization, and tracking of Subawards. **To be eligible for Subaward funding, X01 and U01 Sites must be actively recruiting UDN participants and meeting their enrollment goals.** Subawards will be funded to support:

1. *Local site coordination or data submission* (if not supported through an NIH U01 award or Administrative Supplement).
2. *Pilot research proposals investigating **undiagnosed** UDN participants* that may facilitate future, larger research studies or are needed to confirm the diagnosis of specific UDN participants (or group of participants if investigating the same candidate gene or disease mechanism) such as gene function studies in model systems or clinical genomics/metabolomics/immunologic investigations, typically not more than $50-$100K total costs.
    i. UDN participants being studied must be identified and confirmed to be undiagnosed in the Subaward application.
    ii. More advanced research proposals (e.g., characterizing a gene or genomic variant already known to cause the participant's disease) are out of scope and should be submitted to the NIH using standard grant mechanisms; projects focused on developing or improving a genomics or diagnostic assay are also out of scope.
    iii. DNA/RNA sequencing and other diagnostic investigations will not be supported if reimbursable through insurance billing or covered by an NIH U01 award, NIH administrative supplement, private/institutional sources of support, or the DMCC supported sequencing core.
    iv. Pilot data proposals about undiagnosed UDN participants may be used to facilitate future, larger research studies (e.g., by submitting an NIH grant application); **future research plans, if the project is successful, must be described in the subaward application.**
3. *Environmental exposure pilot projects* focused on development of strategies that use available databases, methods, and resources for identification of UDN participants with likely environmental causes of diagnosed and undiagnosed rare phenotypes (UDN participants being studied must be identified, including the participant's diagnostic status, in the Subaward application). See suggested projects from the Environmental Trigger Working Group (see Addendum on page 6). Note that projects that involve collaborations across multiple sites (e.g., environmental health scientists, multiple UDN Clinical Sites) are strongly encouraged and can request larger budgets if required to complete the proposed work.

All Subaward applications that include studies in model organisms or cell cultures must include a review by the UDN's Model Organism Screening Center (MOSC), which can only be secured by submission of a summary of the Subaward proposal to the MOSC no later than January 1 (MOSC review criteria and Subaward summary template available in the REDCap application).

Due Dates

Notice of funding opportunity announcements for Subawards will be posted on December 2, 2024. Applications must be submitted through the CRSC REDCap portal at WashU by February 1, 2025 at 5:00 PM CST. If the due date falls on a federal holiday or weekend, the end date will be extended to 5:00 PM CST the following business day.

Request for MOSC approval for model organisms or cell culture studies must be submitted to the MOSC by January 2, 2025.

Budget

Budgets are limited to a maximum of $100,000 total cost (includes direct and indirect costs) per Subaward (average $50,000/subaward) with the potential of larger allocations for multi-site Environmental Trigger pilot projects or if approved by the Network Steering Committee. All Subawards must be completed within the grant year (04/01/24-03/31/25), must be of 12 months' duration, and principal investigators must have all invoices submitted by 04/15 (15 days after the end of the grant year). **No carry over funding will be permitted**. The Subawards Review Committee will consider a limited number of phased applications each year with milestones that will determine funding for subsequent phases and may extend for 2 years. For example, if a Subaward proposal requires adaptation of an available model organism or cell culture platform, the applicant may apply for a second year of support contingent upon achievement of the year 1 goals. No phased applications of greater than 2 years' duration will be considered, and no carry forward funding will be permitted between years 1 and 2 of a phased Subaward.

Application and funding information

- The PIs of the Subaward **must include** the X01 or U01 site PD/PI as the contact PI and must be collaborating directly with the X01 or U01 site PD/PI.
- To be eligible for Subaward funding, X01 and U01 Sites **must** be actively recruiting UDN participants and meeting their enrollment goals.
- After evaluating the scientific/technical merit of subaward applications, additional funding considerations include distributing resources equitably across Sites and balancing research or project areas. Individual sites should consider submitting no more than 1-2 proposals/site (e.g., if studying more than one candidate gene or disease pathway/mechanism) and making proposal prioritization known to the CRSC.
- **Subawards will not support more advanced research proposals** (e.g., characterizing a gene or genomic variant already known to cause the participant's disease) since these types of proposals can be submitted to the NIH using standard grant mechanisms and will not support projects already funded through U01 or Administrative Supplements. Projects focused on developing or improving a genomics or diagnostic assay are out of scope.
- Priority will be given to those applications that follow the requirements listed.
- UDN participant ID numbers and confirmation of each UDN participant's undiagnosed status should be provided for all research proposals in a table in the Research Plan with the exception of the Environmental Trigger pilot projects.
- Categories of Subaward applications:
    - Clinical Coordination/Data Submission (if not already supported by an NIH U01 award, NIH administrative supplement or through private/institutional resources): support for X01 site operations that will improve clinical evaluation efficiency, increase recruitment of UDN participants from populations that experience health disparities, or ensure adequate UDN participant data submission via the Gateway.
    - Confirm Diagnosis: support model organism, sequencing analysis, pathogenicity prediction, or metabolomic, immunologic and/or cell culture studies needed to confirm the diagnoses of specific UDN participants (if not already supported by an NIH U01 award, NIH administrative supplement or through private/institutional resources) or obtain pilot data for future grant application (future grant mechanism must be provide in the application).
        - **All Subaward applications that include studies in model organisms or cell cultures must include a review by the UDN's Model Organism Screening Center (MOSC), which can only be secured by submission of a summary of the Subaward proposal to the MOSC no later than January 1** (MOSC review criteria and Subaward summary template available in the REDCap application).
    - Environmental exposures pilot projects focused on development of strategies that use available databases, methods, and resources for identification of UDN participants with likely environmental causes of their rare phenotypes; see suggested projects from the Environmental Trigger Working Group (see Addendum on page 6). **Collaboration with environmental health science experts and other UDN sites is strongly encouraged.**

- Scientific progress reports will include brief summaries (~1/2 page) that describe achieved vs. planned project progress and assurance that funds will be spent by the end of the grant year. They will be required at 6-month intervals for all awards; summary reports will be required at the completion of all subawards; no cost extensions will **not** be permitted. Phased Subaward applications will be required to submit scientific progress reports that will determine continuation of funding for year 2 of the Subaward.

Standing Subaward Review Committee (SRC)

- The Subaward Review process will include scientific critiques by 2-3 SRC members with expertise in the area of the application and administrative review to ensure responsiveness of the proposal to the Subaward guidelines.
- Permanent members with expertise in Clinical Site coordination/operations, clinical genetics, metabolomics, model organisms, bioinformatics, data submission to the Gateway, genomics, environmental triggers, NIH program staff, and ad hoc members with expertise required for consideration of specific subawards.
- Permanent members: Barbara B. Warner (Chair), Herman Taylor, Rachel Mahoney, Meghan Halley, Shinya Yamamoto, Matt Might, Sarah Marshall, John Mulvihill, Stephanie Tomlinson, May Malicdan, Summer Thyme, Lindsay Burrage, Julian Martinez, Jessica Swanson, Laura Mamounas (ex officio)
  - Ad hoc members invited based on topics of submitted subawards
- SRC members must complete the Confidentiality and Conflicts of Interest Agreement before each review. This agreement includes guidelines about disclosing and reviewing conflicts of interest as well as situations where members cannot be part of the review process.

UDN DUCAS Clinical Research Support Core Subaward Instructions

Instructions for Application Submission

Required for all submissions

- The UDN site PI must be listed as the Contact PI for each Subaward.
- Provide the name and email of your departmental pre- and post-grant administrator to be included on correspondence or address questions.
- Budget
  - The role of the Contact PI (UDN site PI) and her/his effort as contact PI must be included on the detailed budget and budget justification. If no effort is requested, explanation of the Contact PI role must be included on the budget justification.
  - Direct costs, indirect costs, and total cost details should be provided in both the summary section of the application (Project Budget) and on the detailed budget attachment form.
  - Budget details, summary, and budget justification must contain the same information.
  - Budgets are limited to $100,000 total costs (includes direct and indirect costs) per Subaward (average $50,000/Subaward) with the potential of larger allocations if approved by the Steering Committee. The potential of larger allocations exists for Environmental Trigger pilot projects requiring collaborations across multiple sites, or if approved by the Network Steering Committee.
  - A limited number of 2 year phased applications will be considered. Continuation of phased funding will be contingent on achieving initial milestones and can extend no longer than 2 grant years.
    - Detailed budget and budget justification pages are required for each year separately.
- NIH biosketch and other support documents are required for all key personnel (even if no effort is requested) including the Contact/UDN site PI.
- Scope of work instructions are provided in the REDCap application. Requirements include deliverables and milestones.
- IACUC approval, IRB approval, documentation of executed material transfer agreements and financial subcontracts that are required for the proposed project must be included if applicable.
- Resource and Data Sharing Plans should be included for data submission applications.
- Applications that include studies in model organisms or cell cultures must include a review by the UDN's Model Organism Screening Center (MOSC) which can only be secured by submission of a summary of the Subaward proposal to the MOSC no later than January 2, 2025 (MOSC review criteria and Subaward summary template available in the REDCap application).

Clinical Coordination/Data Submission

- Specific Aims and Research Plan (total 3 pages).
  - Specific Aims should also be provided in the REDCap application
- Overview of current plans for and progress of site-led efforts to increase efficiency of applicant evaluation, throughput, and follow up and/or to increase diversity of UDN applicants and participants.
- Include a description of how activities/personnel funding requests, as part of the Subaward proposal, will contribute to new activities that are not financially supported by other means (e.g., U01 grants, administrative supplements, institutional support).

Confirm Diagnosis/Obtain Pilot Data/Gene Function studies

- Specific Aims and Research Plan (total 6 pages).
  - Specific Aims should also be provided in the REDCap application.
- Subaward applications must include table with UDN participant ID numbers and confirmation of unsolved status as a table in the Research Plan.
- Subaward applications that propose use of model organisms or other strategies for functional confirmation should provide evidence of variant pathogenicity and include a bioinformatics review by the Model Organism Screening Core that supports the application.
- Include a description of how research/personnel funding requests, as part of the Subaward proposal, will contribute to new activities that are not financially supported by other means (e.g., U01 grants, administrative supplements, institutional support).

- For applications that propose use of other strategies for functional confirmation, availability of relevant resources (e.g., primary cells or cell lines, proposed metabolomics signature) should be provided.

Environmental trigger pilot project

- Specific Aims and Research Plan (total 6 pages)
- Subaward applications must include table with UDN participant ID numbers and confirmation of UDN participant diagnostic status as a table in the Research Plan
- Subaward applications are strongly encouraged to identify the environmental scientists who will collaborate with UDN Site PI and Site members in testing usefulness of integration of environmental triggers into the UDN's diagnostic evaluation.

ADDENDUM – Environmental Triggers Pilot Project Subaward applications
Environmental Trigger Working Group suggestions for Subaward pilot projects (note that proposals are NOT limited to these suggestions)

- Examine undiagnosed and diagnosed UDN participants for known exposure-disease associations using available databases and artificial intelligence approaches:
    - Use ROKOBOP-generated knowledge graphs (PMID: 34283031) with de-identified UDN data to discover environmental causes of rare phenotypes among undiagnosed and diagnosed UDN participants.
    - Use Adverse Outcome Pathway (AOP) (PMID: 37355733) (https://www.epa.gov/chemical-research/adverse-outcome-pathways) models to identify environmental exposures that contribute to the onset and progression of diseases in patients with undiagnosed and diagnosed conditions by mapping molecular initiating events to adverse health outcomes.
- Examine undiagnosed and diagnosed UDN participants to validate effects of candidate environmental exposures:
    - Use Zebrafish (ZFIN database, https://zfin.org/) to test for pathogenic environmental exposures among subgroups of undiagnosed and diagnosed UDN participants identified by overlap of HPO terms in the Comparative Toxicogenomics Database (https://ctdbase.org/).
    - Use the Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/) and Developmental NeuroToxicity Data Integration and Visualization Enabling Resource (https://www.niehs.nih.gov/research/atniehs/dtt/tools/dnt-diver) databases to identify environmental exposures that disrupt neurodevelopment in subgroups of undiagnosed and diagnosed UDN participants.
    - Using the Exposome Correlation and Interpretation Database (ECID) (https://www.ecidbase.org/), reprocess existing untargeted metabolomics data to annotate exposure chemicals.
- Identify objective markers of pathogenic environmental exposure beyond self-report:
    - Use targeted or untargeted metabolomics signatures of available samples from specific groups of undiagnosed and diagnosed UDN participants to identify pathogenic environmental exposures.
    - Characterize the exposome (external exposures and biological responses (e.g., adductomics, transcriptomics) in available samples from a small cohort of undiagnosed and diagnosed UDN participants to develop models for comprehensive assessment of total exposures and provide a foundation for future hypothesis generation.
- Screen undiagnosed and diagnosed UDN participants for candidate pathogenic environmental exposures:
    - Match the phenotypes of undiagnosed and diagnosed patients to known phenotypes associated with environmental exposures to generate hypotheses that lead to accurate diagnoses (*phenotype-first strategy*).
    - Use data from the UDN environmental survey and other sources (e.g., geolocation data, social deprivation index) to identify candidate exposure-related diagnoses that explain the undiagnosed and diagnosed proband's phenotypes and can potentially be validated through clinical testing (*exposure-first strategy*).