Collaborative Trial and Ancillary Study Budget Development

Purpose

This policy describes the principles, general expectations, processes and procedures underlying the development of clinical trial budgets for clinical trials conducted in the SIREN network. Budget development is a key aspect of writing NIH grant applications for SIREN trials. It is understood that budgets will always be specific to the needs and particulars of each individual trial. This document is intended to provide a common background understanding of budgeting for SIREN trials among investigators proposing trials and SIREN leadership at both the network Coordinating Centers and the NIH.

Responsible Individuals

Investigators proposing trials for SIREN
SIREN coordinating centers
SIREN enrollment sites (hubs and spokes)

Definitions

SIREN Clinical Coordinating Center (CCC) - The University of Michigan is the Clinical Coordinating Center for trials in the SIREN network.

SIREN Data Coordinating Center (DCC) - The Medical University of South Carolina is the Data Coordinating Center for the SIREN network.

Trial Scientific Coordinating Center (SCC) - is an informal designation that typically refers to a trial-specific component of the study leadership that is the grant prime recipient site and is most often the institution of the clinical contact PI.

Central Institutional Review Board (CIRB) – The single board (pursuant to NIH policy for multicenter clinical trials) serving as the IRB of record for SIREN trials and providing oversight of research (as described in 45 CFR Part 46). Advarra is contracted to serve as the CIRB for SIREN trials.

Enrollment sites - Network hubs and spokes are defined in the SIREN SOP entitled “Hub Management of Spokes”

Budgeting Principles

This policy is designed to be consistent with the following principles: .

1. **Efficiency and stewardship:** SIREN is dedicated to the good stewardship of public funds used to promote medical research and the public good. This principle incorporates both value and efficiency. We intend to conduct trials that answer important questions and produce meaningful and reliable answers using processes that are as lean and cost-effective as practical.

2. **Sufficiency:** SIREN requires investigators proposing trials to develop budgets that are sufficient to allow the successful performance and completion of a properly designed protocol appropriate to answer the question being asked and to complete the objectives of the grant application. SIREN will not pursue underfunded projects.

3. **Network Infrastructure:** Individual grant applications developed for trials to be performed in SIREN must include support for the network infrastructure as part of the individual trial budgets. The SIREN CCC and DCC grant applications are not intended to provide all the funds necessary to maintain the network infrastructure. As stated in the FOAs (RFA-NS-22-013, RFA-NS-22-014) for the SIREN coordinating centers, "Clinical trial grants will provide significant contributions to financial support of the infrastructure (i.e. CCC, DCC and Hubs), particularly during Years 2 - 5 of SIREN." "

4. **Prioritization of Site Payments:** SIREN is dedicated to ensuring the adequacy of individual enrollment site payments in clinical trials. Recognition of the importance and amount of work of a clinical trial that is done by the enrollment sites is fundamental to success. Sufficiency of reimbursements to enrollment sites is absolutely key to the successful performance and completion of SIREN trials.

Budgeting Processes

1. **Design and work scope:** SIREN trial budgets will vary depending on decisions regarding many important details of the trial design and work scope. We cannot accurately make early estimates of budget needs for trials in development until these are settled. Final budget numbers may also change if there are changes to the design or work scope, especially for items such as data collection methods, sample size or number of sites. Timelines for grant development in SIREN are described in the SIREN SOP titled "Grant Application Guidelines and Timelines"

2. **Transparency works best:** SIREN trial budgets are typically large and complex. They require coordinating budget components from several collaborating institutions. Developing trial budgets works best when all partners can see the different components of the total budget to reduce the risk of duplication, inconsistent or outdated assumptions, and other miscommunications. We recommend using a web-based shared tool, such as Google Sheets, with separate tabs for each component (subaward or companion application) Each component tab should include at least summarized or categorical budget estimates and the assumptions upon which those estimates are based. Each component tab is editable only by the partner responsible for that portion of the budget estimate. This tool is to be used only for collaborative development and communication of budget estimates, **not for submission or routing of actual budgets.**

3. **Enrollment site contracting:** As described in the SIREN SOP entitled "Financial Management" the CCC will organize hybrid subcontracts with SIREN hubs as riders to master agreements. SIREN hubs will in turn provide subcontracts to their spokes. Typically all enrolling sites are paid from the SIREN CCC budget, but exceptions may occur for enrollments at a site that is also the prime recipient, or when another trial network is collaborating in the trial.

4. **Enrolling site payments:** In SIREN trials, sites are mostly or exclusively paid through per subject payments or other milestone driven reimbursements. Start up payments are also milestone driven, and are typically modest, but may be larger when preparatory work load is substantial as in EFIC trials. Typically all ongoing site costs (investigator and staff effort, investigational pharmacy fees, participant reimbursements, etc.) are budgeted into the per subject payments. All indirect costs must be backed out of these per subject payments by the enrolling site.

5. **Funding opportunities:** Most SIREN trials submitted to NINDS will be responsive to FOA PAR-21-237 (UG3/UH3) . Most SIREN trials submitted to NHLBI will be responsive to both FOA PAR-22-192 (UG3/UH3) and FOA-22-193 (U24) . NINDS trial grants are typically a single grant application to a prime recipient with major subawards to both the CCC and the DCC. NHLBI trial grants are typically a pair of grant applications, one to the DCC, and the other to a prime recipient with a major subaward to the CCC. Typically the prime recipient organizes the Scientific Coordinating Center (SCC) and issues subawards, but alternatively, the CCC can sometimes be the prime recipient with a subaward to the SCC, or the CCC can also be the SCC.

6. **Pre-approval:** All SIREN trials and most ancillary studies are expected to have proposed budgets of a size such that the grant applications require pre-approval to submit an application from the NIH IC to which they will be proposed. The pre-approval processes are provided here for NHLBI and NINDS (see last paragraph) .

Budgeting Components

1. **Scientific Coordinating Center (SCC):** The SCC provides for overall trial leadership, scientific elements of protocol development, protocol education, recruitment and retention, and typically liaises with FDA as needed. This is most often the grant prime recipient site, typically the institution of the clinical contact PI. The SCC budget typically supports the trial PI's efforts and that of others in the trial leadership that are not at the CCC or DCC. There is often a project manager that works alongside the trial PI. Specialty cores (pharmacy, imaging, biospecimen, etc.) may be directly supported on the SCC budget or may be assigned to the CCC or DCC.

2. **Clinical Coordinating Center (CCC):** The SIREN CCC contributes to the overall trial leadership, is responsible for operational elements of protocol development, supports site management and contracting, regulatory support, CIRB support and liaison, site monitoring and source document verification, and quality improvement. The CCC budget includes effort for investigators and the administrative director at the CCC. It also supports the following staff.

    a. A site manager who wrangles enrollment site preparation and site CIRB applications, activation, regulatory compliance, recruitment, retraining for all enrollment sites. Effort depends on the number of sites, the size of study teams, and the complexity of regulatory and certifications.

    b. A site monitor or monitors who perform source document verification (both remote and on-site), support quality improvement, and are the leaderships' eyes and ears at the sites. Effort depends on the number of subjects, the percent of subjects to be monitored, the frequency of remote and on-site monitoring desired, the size of the CRF booklet and the number of data elements to be verified.

    c. Contributions from the SIREN human subjects protection specialist who supports operations related to consent and e-consent, helps with trial-level CIRB applications and issues as the operational CIRB liaison, and provides substantial additional support for EFIC trials.

    d. Contributions from the SIREN educational coordinator who supports in person training at investigator meetings, on-line training and certification platforms and documentation, virtual investigator meetings, training videos as needed, investigator and public facing websites, and internal and external newsletters and other communications.

    Other elements of the CCC budget may include financial administration support, administrative assistants, research assistants, consultants, and equipment or specialty cores not supported elsewhere.

3. **Data Coordinating Center (DCC):** The SIREN DCC contributes to the overall trial leadership and is responsible for key elements of study design and statistical methodology, statistical analyses, data management and central data monitoring, data reporting and is the primary liaison to the DSMB. The

DCC budget includes effort for investigators and the administrative leadership of the DCC. It also supports the following staff.

a. A data manager (or managers) who is responsible for the study-specific data management activities including creation of case report forms and system specifications for the study database, validation of the study database, training of all users on the SIREN clinical trials management system, point of contact for database questions and generation and follow-up of data clarification requests (DCRs) to ensure quality assurance of data entered into the study database at the clinical sites

b. A biostatistical team who will provide statistical analysis and programming support throughout the study and will create the Open and Closed DSMB reports for the trial . This team will also set up and validate the study-specific randomization algorithm, conduct internal monitoring of submitted data; ensure validation of statistical programs; participate in manuscript writing and prepare study data files for submission to the NIH data repository according to the data sharing plan.

c. A database/computer programming team who will develop and validate the necessary web-based clinical trials management system that will house the trial database and incorporate the study-related management modules, including eCRFs, site monitoring, randomization, and safety monitoring modules. They will incorporate range and logic checks into the system to minimize data entry error and facilitate the data clarification queries as well as maintain and archive the system throughout the study period.

d. Graduate Student Trainees. A Graduate Research Assistant (GRA), who is in the Biostatistics Ph.D. program at MUSC, may be added to the budget to complete necessary functions. The GRA will support any DCC study staff. The GRA will assist the PI and the co-investigators with reporting and analysis of data, and may work with the team to develop novel methodology to address potential design or randomization challenges, and participate in the presentation and preparation of manuscripts. The 100% effort for a GRA equates to approximately 20 hours of work per week (0.50 FTE).

The DCC budget supports maintenance and improvements to the CTMS that supports all aspects of trial management, external data reporting to other electronic systems (such as outcomes in clinicaltrials.gov, accrual in e-connect, or data registration in FITBIR or BioData Catalyst), development and documentation of public use data sets, and support for primary, secondary, and potentially tertiary data analyses and publications.

4. **Central IRB Costs:** Multicenter clinical trials funded by NIH are required to use a single IRB. SIREN trials use an Emergency Research Central IRB at Advarra. CIRB costs are a fee for service. Typical invoicing by the CIRB is a fee for initial master protocol application, followed by a fee for each application per site, with additional fees per site for renewals, revisions, consent form translations, and other services. CIRB services are efficient but are not inexpensive. Primary drivers of cost include the

number of enrollment sites and the number of protocol revisions over the course of the trial. Secondary drivers include the number of consent form translations and revisions, and the number of site PI changes and other reportable events and modifications. All CIRB costs are paid centrally and are included in the SIREN CCC budget. Sites do not pay CIRB costs. The CCC acts as liaison between sites and the CIRB.

5. **Travel Costs:** Clinical trial related travel costs for investigators and staff of the SCC, CCC, and DCC are included in each of the coordinating centers budgets respectively. Additional travel costs for site researchers to attend investigator meetings or for other purposes are included in the SIREN CCC budget.

6. **Data and Safety Monitoring Board Costs (DSMB)**: SIREN trials usually use a shared network DSMB administered through the NINDS but reporting to both NINDS and NHLBI. Costs for operating the SIREN shared DSMB typically do not need to be included in SIREN trial budgets. If a trial does not use the shared SIREN DSMB, individual funders may require the DCC or trial budgets to support DSMB operations. Investigator travel to in-person DSMB meetings should still be included in appropriate components of the trial budget.