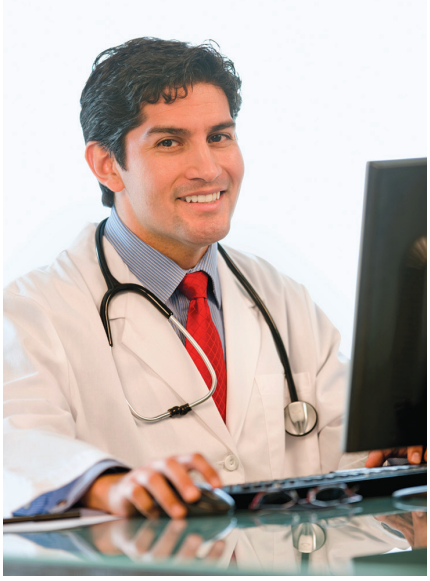
TDN Protocol Review & Data Safety Monitoring Processes



Welcome to the CFF Therapeutics Development Network

The Therapeutics Development Network (TDN) is a nationwide clinical trials network sponsored by Cystic Fibrosis Foundation for the purpose of facilitating safe, rapid and coordinated evaluation of new treatments for cystic fibrosis.

This collaborative group consists of 89 Therapeutics Development Centers (clinical sites), seven National Resource Centers (core laboratories and reading centers) and a Coordinating Center based at Seattle Children's Research Institute.

Since its inception in 1998, the TDN has conducted more than 100 clinical studies for CF in a wide range of therapeutic areas, including (Restore CFTR Function, anti-infectives, anti-inflammatories, nutritional and GI therapies and mucocilliary clearance).

As a result, network members in a variety of disciplines have developed significant expertise in the design, implementation and analysis of CF studies. One way this expertise is put to use is through participation of network members in the TDN protocol review process.

Review Expectations

All therapeutic multi-center studies to be conducted within the TDN are required to go through the network's two-step protocol review process, consisting of reviews by the TDN Protocol Review Committee and Clinical Research Executive Committee. Additionally, the Foundation expects safety oversight for all CF multicenter studies to be conducted by the Data Safety Monitoring Board (DSMB). The DSMB will also review the protocol prior to study initiation. These review processes were designed to complement and run parallel to each other.

Our goal is to help clinical trial sponsors and principal investigators:

- Optimize study design;
- Ensure efficient conduct within the CF center network;
- Protect patient safety;
- Maintain the integrity of study data and specimens; and
- See how their studies fit in with the priorities of the CF Foundation

Given that the CF patient population is a valuable and limited resource, CF clinical researchers rely on the TDN protocol review process to help ensure overall quality in CF protocols. Most sponsors find the detailed written feedback they receive to be extremely valuable.

With this brochure, we hope to provide you with the information you need to work through the protocol review and DSMB processes in an efficient and effective manner. We look forward to working together in our efforts to improve the lives of people with cystic fibrosis and move toward a cure.

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Key Points:
TDN Protocol Review

COMPOUND REVIEW

The TDN has implemented an early step in the evaluation of new potential agents that are being brought forward to the clinic. The goal of this evaluation is to independently assess the preclinical biological characteristics of a compound to better predict the likelihood of it having a strong positive clinical impact. Ideally, this review will occur prior to submission of a sponsor's first clinical trial protocol of that agent. The review is conducted by independent, therapeutic class experts and then a detailed written critique is provided to the TDN Protocol Review Committee (PRC) to aid in their review of the protocol.

PROTOCOL REVIEW COMMITTEE

The TDN Protocol Review Committee (PRC) uses a standard set of criteria to evaluate protocols for scientific merit, feasibility and study design. A detailed written critique and numerical ratings are provided in each of these categories.

One of several standing PRC review groups is assigned to each protocol. Each review group includes experienced adult and pediatric CF investigators, research coordinators, at least one biostatistician and a patient representative.

CLINICAL RESEARCH EXECUTIVE COMMITTEE

The Clinical Research Executive Committee (CREC) includes Cystic Fibrosis Foundation leadership, senior CF researchers, and members of the Therapeutics Development Network Coordinating Center (TDNCC). Following the PRC review, the CREC assesses how the protocol fits within the overall priorities of the Foundation for clinical research and assigns a qualitative rating for strategic fit.

REVIEW ADMINISTRATION

The TDN protocol review process is facilitated by the TDNCC and conducted through a secure online website for efficiency. The PRC/CREC Project Manager at the TDNCC serves as the primary contact for sponsors throughout the TDN review process.

PRC & CREC REVIEW TIMING

To allow time for contract processing and other administrative setup, sponsors/PIs should alert the PRC/CREC Project Manager *at least six weeks in advance* of any planned protocol submission. With advanced notice, the target timeline for the combined PRC and CREC reviews is 28 days once the Protocol Evaluation Agreement and any additional non-disclosure agreements have been executed and all required protocol materials have been submitted to the PRC/CREC Project Manager.

REVIEW FEEDBACK & RESPONSE

At the completion of the CREC review, the sponsor will receive compiled written critiques and ratings in four categories from the PRC and CREC reviews. After reviewing this information, the sponsor may choose to accept the ratings as is or submit a response to the PRC with a revised protocol.

If a revised protocol is submitted, PRC representatives will review the changes and determine whether they warrant a modification to the protocol ratings. (Note that the Strategic Fit rating is independent of protocol specifics and not subject to change.)

Once the protocol ratings have been finalized, a brief explanatory statement will be posted along with the ratings on a secure website for access by TDN centers.

FINAL PROTOCOL & AMENDMENTS

Most sponsors find PRC input useful and choose to incorporate many of the suggestions into their protocols even if they do not resubmit for a higher rating. After all revisions are made, a final protocol should be submitted to the PRC/CREC Project Manager before the study begins.

CONTRACTS

Due to the network's organizational structure, one agreement must be executed for protocol review by the TDN and another for DSMB services:

1) TDN reviews (PRC and CREC) are covered by a "Master Protocol Agreement" and study specific project charter between the sponsor and the Foundation. The TDN Coordinating Center (TDNCC) will facilitate execution of this agreement.

2) DSMB services are secured through a separate contract between the sponsor and the Foundation. The DSMB Program Coordinator will initate the agreement, then follow-up and execution will be handled directly by the sponsor and the Foundation.

Other TDN services such as consulting or study management require separate contractual agreements. Please contact the TDNCC for more information.

FEES

Industry sponsors are charged a flat fee for TDN protocol review. DSMB fees include a flat administrative charge plus hourly fees for reviewer time. A budget estimate for DSMB services is provided to the sponsor at the start of the contract process. Fees are waived for most investigator-initiated studies.

CONFLICT OF INTEREST

The PRC/CREC Project Manager and DSMB Program Coordinator will obtain financial disclosure statements from all assigned reviewers (PRC, CREC, and DMC) in advance of each protocol review. Individuals with a significant conflict of interest will be excluded from participating in the review process.

Please address all communications with the TDN Protocol Review Committee and Clinical Research Executive Committee to:

Kelsie Pearson
PRC/CREC Project Manager
CFF TDN Coordinating Center
(206) 884-7553
TDNCC@seattlechildrens.org

Key Points:

Data Safety Monitoring

DSMB OVERVIEW

The primary responsibility of the Data Safety Monitoring Board (DSMB) is to protect the safety and welfare of subjects participating in TDN and other Foundation-sanctioned clinical trials and to ensure the integrity of those trials.

Many of the risks for people with CF who participate in clinical trials are inherent to the disease, and thus are shared across different clinical trials. Maintaining a core of expertise specifically related to CF makes the DSMB very effective at monitoring CF clinical trials and protecting CF research participants as new drugs are developed.

Although both the TDN and DSMB are sponsored by the Foundation, the two entities are organizationally separate, allowing the DSMB to maintain independence and equipoise.

DSMB MEMBERSHIP & ADMINISTRATION

The DSMB consists of a number of experts in CF clinical care, clinical and basic science research, bioethics and biostatistics. Administrative operations are based at the University of Arizona in Tuscon. The DSMB Program Coordinator works with the DSMB Chair and Associate Chairs to facilitate the establishment of Data Monitoring Committees and coordinate reviews.

DATA MONITORING COMMITTEES

A Data Monitoring Committee (DMC) is a subcommittee of the DSMB formed for a particular clinical trial. DMCs vary in size and nature depending upon the study, but usually include three to five CF clinicians plus ad-hoc members with specific expertise as required. All DMC members sign a confidentiality agreement and are aware of the critical importance of maintaining any and all information about the given study in the strictest confidence.

DMC CHARTER

A DMC charter is developed with the sponsor and principal investigator to clearly define the function, composition and operating expectations of the study DMC. Guidelines and a standard template for DMC charter development are provided by the DSMB Program Coordinator. Statistical consultation on the charter is available from the TDNCC through a separate agreement.

DMC PROTOCOL REVIEW

To assess whether the study is designed to adequately protect patient safety and data quality, the DMC reviews the protocol, proposed safety monitoring plan, investigator brochure, and any other relevant information on the study drug prior to study initiation. The PRC critique and ratings will also be provided to the DMC to help avoid redundancy or any discrepancies.

INTERIM SAFETY MONITORING

During the study, the DMC is tasked with evaluating significant adverse events in real time and conducting interim reviews of outcome and safety data to make recommendations concerning continuation of the trial. Major study design modifications and/or protocol amendments must be reviewed by the DMC prior to implementation.

NON-DISCLOSURE AGREEMENTS

The Foundation has established standard non-disclosure agreements (NDAs) with all participants in the DSMB and TDN protocol review processes. Through these agreements, PRC, CREC and DSMB members agree to maintain confidentiality of information encountered as part of their reviews. The standard NDA templates (one for the DSMB, another for TDN protocol review) will be provided to the sponsor at the beginning of the process.

To expedite protocol review, the Foundation recommends that sponsors accept these existing NDAs as sufficient. Alternately, sponsors may choose to execute their own company-specific NDAs, but should understand that this may cause delays. If a sponsor requires separate agreements, the DSMB Program Coordinator will assist sponsors with NDA processing for DMC members. The TDNCC will provide contact information for PRC and CREC reviewers, but sponsors will be responsible for obtaining NDAs from these individuals.

STUDY SITE SOLICITATION

In conjunction with protocol review, the TDNCC can help sponsors identify possible study sites by notifying Therapeutics Development Centers of the upcoming study and providing the sponsor with a contact list for the centers who express interest. Additional support for site selection can also be arranged. Please contact the TDNCC for more information.

Study sponsors should contact the DSMB at least six weeks in advance of submitting a protocol to the TDN. All communication to the DSMB or Data Monitoring Committees from sponsors or principal investigators should be directed through:

Clara Ehrman, DSMB Program Coordinator
(520) 626-6754
csehrman@arizona.edu

Sponsor Checklist

TDN Review

- ❑ Contact PRC/CREC Project Manager (PM) at TDNCC at least six weeks prior to planned protocol submission.
- ❑ Execute Master Protocol Agreement and Project Charter with the Foundation and notify PRC/CREC PM when complete.
- ❑ Submit completed protocol, IB and PRC application to PRC/CREC PM.
- ❑ Review feedback received from PRC and CREC reviews. Notify PRC/CREC PM about intent to re-submit (response requested within 14 days of receiving committee feedback).
- ❑ (Optional) Submit revised protocol and response to PRC critiques to PRC/CREC PM for rating re-evaluation by PRC.
- ❑ Following revisions and final ratings, provide copy of final protocol to PRC/CREC PM.
- ❑ Submit any protocol amendments to PRC/CREC PM as they arise.

DSMB Review

- ❑ Contact DSMB Program Coordinator (PC) at least six weeks prior to planned protocol submission to PRC.
- ❑ Submit draft protocol to DSMB PC.
- ❑ Review DSMB NDA template and determine whether additional confidentiality agreements will be required for DMC members. If so, provide template to DSMB PC for processing.
- ❑ Review budget estimate provided by DSMB PC and respond to the Foundation with approval.
- ❑ Draft DMC charter.
- ❑ Submit final protocol, draft DMC charter and investigator brochure to DSMB PC.
- ❑ Participate in DMC call to provide clarifications.
- ❑ Approve final DMC charter.
- ❑ Execute final DSMB contract with the Foundation.
- ❑ Following revisions, submit copy of final protocol to DSMB PC.
- ❑ Submit any protocol amendments to DSMB PC for DMC review prior to implementation.

This document provides an overview of the processes for TDN protocol review and use of the Data Safety Monitoring Board. For more detailed information, please contact the PRC/CREC Project Manager and the DSMB Program Coordinator.

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