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Original Article

A model for oversight of rare disease studies: The 25-year experience of the cystic fibrosis foundation data safety monitoring board

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ABSTRACT

This manuscript addresses the development and operating procedures of the Cystic Fibrosis Foundation Data Safety Monitoring Board (CFF-DSMB) and its role in the development and approval of new therapies through complex clinical trials with an emphasis on ensuring patient safety and study integrity. The authors describe the processes that have been developed over the last 25 years including the development of educational curricula for DSMB members and patient representation on DSMBs. The experience and success of the CFF-DSMB can serve as a model for providing high quality oversight of clinical trials for other groups who are dedicated to developing treatments for rare and complex diseases.

1. Introduction

Cystic Fibrosis (CF) is the most common life-threatening monogenetic disease affecting an estimated 100,000 people worldwide [1]. The disease affects multiple organs but most significantly it leads to chronic, progressive lung disease and malnutrition from pancreatic insufficiency. CF was described as a distinct entity in the 1930′s with the first large case series published in 1938 by Dorothy Andersen, a pathologist who recognized on autopsy a pattern of bronchiectasis and pancreatic disease in children [2].

In 1955, the Cystic Fibrosis Foundation (CFF) was formed by a group of parents in the hope of improving care for their dying children [3]. Over the ensuing seven decades, the CFF has evolved to become one the most successful rare disease organizations by developing effective programs to advance research, patient care, education, and advocacy. Therapeutic approaches fifty years ago were limited with a median predicted survival of approximately only 20 years in 1970 [4]. Over the intervening five decades the development of dedicated care centers and effective therapies have increased the predicted survival to 56 years of age for a baby born between 2018 and 2022 [5].

The 1980′s ushered in a new era for people with CF; research was starting to unravel the mystery of the basic defect on a genetic, molecular, and cellular level with the potential to develop targeted therapies [6]. As basic science research discoveries offered opportunities for drug development, the CFF recognized the need for designated clinical research centers that would be able to conduct clinical trials efficiently. With these goals in mind, in 1998 the CFF launched its Therapeutics Development Network (CFF-TDN) to centralize, standardize, and promote clinical research [7]. Over the years, the network has grown to more than 90 sites in the US located at CFF-accredited clinical care centers. The CFF-TDN provides training and financial support creating a research environment that can efficiently carry out rigorous clinical research. To receive its support, the CFF-TDN requires that trials be sanctioned based on review of study design, feasibility, and strategic fit for the CF community.

A top priority of the CFF-TDN is to protect the safety of patients participating in clinical trials and to ensure the scientific integrity of the studies. In 1999, the CFF and CFF-TDN developed a CF specific data safety monitoring board (CFF-DSMB). The initial design of the CFF-DSMB was based upon seminal work by Ellenberg, Fleming, DeMets and others [8]. CF is a complex multi-system disease making clinical trial subjects susceptible not only to adverse events from the study drug, but also co-morbidities of the disease. The CFF-DSMB ensures not only efficiency but study oversight by professionals familiar with the unique aspects of CF. Since its formation, the number of studies per year that are overseen by the CFF-DSMB has steadily increased with over 66 clinical trials monitored in 2019. (There was an expected decline in the number of studies since the pandemic with an uptick anticipated in 2024.) This

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paper describes the processes of developing and maintaining a disease specific DSMB over the past 25 years during which time we have seen data from approximately 34,000 participant entries (personal communication) and approximately 250 trials.

2. DSMB membership

The leadership of the CFF-DSMB consists of three pulmonologists-two pediatric and one adult, who have extensive experience with clinical trial oversight, CF clinical research and patient care. The CFF-DSMB has grown to approximately 100 members who are selected by the CFF-DSMB leadership. DSMB members are chosen based on their clinical or research expertise, experience, and limited potential for conflicts of interest (see below). The CFF-DSMB consists of adult and pediatric pulmonologists, medical ethicists, endocrinologists, gastroenterologists, infectious disease specialists, and clinical trial biostatisticians. Within the greater CFF-DSMB, each study is assigned a study specific Data Monitoring Committee (DMC). *Ad hoc* specialists are recruited to join a DMC if needed to advise on topics outside the expertise of the other DMC members. A critical component of the CFF-DSMB membership are community representatives who are either people with CF (PWCF) or parents of children with CF.

The CFF-DSMB has an administrative staff that manages the generation and execution of contracts, schedules meetings, records meeting minutes, and maintains a secure electronic data storage site that houses CFF-DSMB related documents and data. The CFF provides funds and supports the CFF-DSMB infrastructure, which helps to offset monitoring costs to sponsors. All CFF-DSMB members are indemnified by the CFF and compensated for their time based on fair market rates.

Although the CFF-DSMB has a cooperative relationship with the CFF and TDN, it remains organizationally and functionally independent in its oversight duties. Decisions and recommendations of DMC's are not shared with the CFF and TDN. The official line of communication between the CFF-DSMB and the CFF and TDN for general DSMB topics is through the Vice President of Clinical Research of the Cystic Fibrosis Foundation (see Appendix 1).

Initially, all studies were based in the US but over time many studies included international sites. In addition, some sponsors have utilized the services of the CFF-DSMB for studies exclusively performed outside the US. Accordingly, international members have been added to the CFF-DSMB to ensure regional representation. International members of the DSMB are suggested by their respective associations and meet the same criteria as those from the US. The Board leadership collaborates closely with its non-U.S. counterparts including the CF Canada Accelerating Clinical Trials Network (CF CanACT) and the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN). Regulatory agencies outside the U.S. such as the European Medicines Agency (EMA), the United Kingdom Medicines & Healthcare Products Regulatory Agency (MHRA) and Health Products and Food Branch (HPFB) of Health Canada have permitted CFF-DSMB DMCs to oversee clinical trials that are under their jurisdiction. Recognizing that safety monitoring is a learned skill that improves with experience, we have not imposed term limits for DSMB membership. CFF-DSMB members with more experience may serve as DMC chairs. Each CFF-DSMB member serves on 1–3 DMCs at any given time and great effort is placed on ensuring that there is no conflict of interest between the studies they are overseeing. CFF-DSMB members are compensated for their time at fair market rates.

DMC members are required to be free of significant financial, intellectual, and professional conflicts of interest (COI). In a community where patient care, research and clinical trials are closely interconnected, this posed a challenge. Had the CFF-DSMB decided to preclude anyone affiliated with a study site, this would have prevented the development of a CFF-DSMB board with the needed expertise, especially for large multicenter trials. Unless prohibited by a sponsor, a clinical trial may be conducted at a DMC member's care center. However, neither the DMC member nor the member's program may benefit directly from the conduct or outcome of the clinical trial. Furthermore, a trial can be run at a DMC member's center providing the sponsor agrees, and the DMC member is not the local principal investigator or directly involved in performance of the clinical trial. These stipulations create a firewall between any accrued benefits to the center and the DMC member's personal gain. COI is reviewed when a DMC is constituted and confirmed at all DMC meetings. CFF-DSMB members are regularly surveyed to detect potential conflicts. Any new issues are resolved with adjudication by the CFF-DSMB leadership.

In 2016 the CFF-DSMB recognized the potential benefit of having the patient voice as an integral part of clinical trial oversight. Incorporating PWCF into DMCs is supported by FDA guidance [9] and by the Clinical Trials Transformation Initiative (CTTI) [10]. Since 2016, community representatives have been appointed to DMCs as full voting members. This effort began as a pilot program with 2 adult PWCF and has subsequently become the norm; the CFF-DSMB now includes 17 community representatives of whom 11 are adults with CF and 6 are parents of children with CF. Community representatives apply to become members of the CFF-DSMB through the CFF patient advocacy program Community Voice. Applicants are screened by Community Voice and interviewed by the CFF-DSMB leadership. Community Voice is committed to diversity and inclusion and the applications for CFF-DSMB membership are targeted to reflect the diversity of the CF patient community. Community members are not required or expected to have a science background but should have personal experience with participation in a clinical trial. They complete the same educational training as the other members (see below) and receive the same level of financial compensation. This program has been very well received by the participating community representatives, the other CFF-DSMB members and sponsors as confirmed by quality improvement surveys.

3. Training of DSMB members

From the inception of the CFF-DSMB, the leadership recognized that new members of the DSMB might have different levels of knowledge and experience regarding clinical trial oversight. All members are expected to complete formal training on HIPPA, human subject research and security. New members complete an onboarding curriculum developed by the CFF-DSMB leadership. The course content includes introduction to DSMB processes and procedures with special emphasis on the importance of adhering to non-disclosure agreements, avoiding conflicts of interest, and the basic tenets of human subject protections. Training emphasizes the importance of timely reviews to avoid impairing study progress. Every two years the CFF-DSMB convenes a two-day symposium with discussions about processes and program development. Small group sessions are used for anonymized case presentations. Topics have included stopping rules, oversight of early phase studies, and managing DMC-sponsor relationships. Presentations are streamed, recorded, and archived. The in-person meetings and archived presentations ensure ongoing education for DSMB members. Unexpected challenges that arise during study monitoring often provide opportunities for ad hoc education of CFF-DSMB members.

4. Operating procedures

A policy manual (PM) and standard operating procedures (SOPs) were developed by the core CFF-DSMB team and are updated every two years. The PM delineates the CFF-DSMB organizational structure, membership, responsibilities, confidentiality, and conflict of interest guidelines. SOPs are updated and reviewed every two years. Data management is centralized on a secure cloud-based server compliant with EU General Data Protection Regulations and FDA CFR 21 Part 11. This single website facilitates CFF-DSMB member access to policies, training materials and study documents. Security oversight is done by monitoring when and by whom files have been opened and access is terminated when a member leaves the CFF-DSMB. The site is partitioned

so that each clinical trial has its own folder and access is limited to DMC members assigned to that specific study.

While a study is being reviewed for sanctioning by the CFF-TDN, a parallel process is initiated between the sponsor and the CFF-DSMB. During this early period the sponsor is provided with a charter template appropriate to the type of study (available upon request) and check list to facilitate their future contractual relationship. The diagram in Appendix 2 demonstrates the complexity of the process needed for compound and protocol review including CFF-TDN sanctioning, contract execution with the CFF-DSMB and charter development. The DMC charter outlines the responsibilities of the study specific DMC and is approved by the DMC prior to screening the first participant. The sponsor's study team in collaboration with the DMC develops the charter. Sponsors of CF clinical trials overseen by the CFF- DSMB have included industry leaders to smaller startup companies, academic investigators. Early involvement of the CFF-DSMB, particularly with less experienced sponsors and investigators, has avoided costly delays.

5. DMC composition

Each DMC typically comprises a Chair, a biostatistician, a variable number of clinicians depending on the size and scope of the study, and a community representative. A CFF-DSMB coordinator is assigned to each DMC for administrative support. The DMC Chair is always a CFF-DSMB member with extensive DMC experience. DMC members are selected based on the specific needs of a study; for example, a clinical trial for a new compound targeting liver disease or with a high risk of hepatic toxicity would include a hepatologist. Each DMC has consultative support from the CFF-DSMB leadership group should the DMC feel they need additional guidance when faced with unanticipated complex challenges. The structure of the CFF-DSMB allows us to maintain the same DMC throughout the phases of a drug's development which facilitates efficient and effective review of protocols and charters. Historical knowledge also reduces the number of potential delays due to adverse events that have been fully evaluated during previous studies. This has been especially beneficial in the development and approval of CFTR modulators.

Although independent DMCs are usually considered unnecessary for phase 1 and early phase 2 studies, FDA guidance recommends that sponsors consider using a DMC when the study is being performed in a potentially fragile population such as children or other vulnerable populations [8]. We consider people with CF to be a vulnerable population in part because of their dependence on their care center team who are often involved not only in clinical care but also recruitment and execution of clinical trials. Further, to reassure the CF community that clinical trials are run safely, the CFF has made public commitments that all CFF sanctioned clinical research will be monitored. Early phase studies require a different approach to monitoring especially when they are done in CF patients without prior experience in healthy volunteers. Early studies typically have an internal scientific review committee (ISRC) managed directly by the sponsor. We have developed a hybrid model that allows the ISRC to function with input from the CFF-DSMB. This is accomplished by the creation of a full DMC that reviews the protocol and safety monitoring plans. The chair of the DMC is then assigned to serve on the ISRC. If situations arise where broader input is needed, the full DMC can be called upon to review and make recommendations. In addition, if the study proceeds with drug development, this same DMC can assume monitoring of subsequent studies thus providing continuity.

6. CFF-DSMB biostatiscal participation

Since the formation of the CFF-DSMB a core group of biostatisticians has played an integral role of the evolution of the CFF-DSMB. They have not only participated in DMCs, but they have served as educators of the non-statistical CFF-DSMB members and participated in the developed SOPs. Biostatistical approaches are discussed at the in-person meetings and sessions are recorded and archived for CFF-DSMB members.

DMCs are frequently challenged by receiving data sets that are voluminous and poorly displayed making it difficult to detect potentially significant safety issues. Consequently, in 2019 the CFF-DSMB convened a biostatistical working group to develop DMC statistical analysis plan templates including shells to generate the data tables, figures, and listings. This revised model is given to sponsors when they submit their protocol for review to the TDN with encouragement that it be used for DMC reviews (available upon request).

7. Quality improvement

The CFF has a long-standing commitment to quality assurance. The CFF-DSMB internally reviews its PM and SOPs every two years. Over the last decade, the CFF-DSMB has undergone several external audits by industry sponsors that have been used as quality improvement (QI) opportunities. We have also surveyed sponsors to determine how well their needs are being met and surveyed DSMB members and sponsors about their experience with DSMB community representatives.

8. Outreach to the CF community

In a survey of 760 adults with CF and parents of children with CF conducted in 2015 by the CFF, 32 % of respondents expressed concerns over possible adverse effects and safety as a reason they would choose not to participate in a CF clinical trial (*Retsch-Bogart G. Opening doors to CF clinical research: Change is coming. 29th Annual North American Cystic Fibrosis Conference; Phoenix, AZ; 2015.*) This led to increased resources being directed to educate people with CF and their families on how safety is protected during a clinical trial through a series of webinars, web pages on the CFF website (www.CFF.org), and handouts. Information explaining the role of the CFF-DSMB has been presented periodically to site investigators and research coordinators during the biannual meetings of the TDN. As the CF community embarks on gene-based therapies, the value of outreach to the community is increasingly important.

8.1. Synopsis of DSMB activity over 25 years

Tables 1 and 2 provide a record of CFF-DSMB activities over the past 25 years. Of the 247 studies, 137 of them had international enrollment and most were completed as planned. Approximately 66 studies did not progress either because of futility, efficacy, or a decision by the sponsor not to proceed or to change to another lead product. When a study has either not progressed or been stopped, by and large this has been a joint decision between the DMC and the sponsor or principal investigator. Likewise, it is not uncommon for the DMC to work with a sponsor to stop one study and embark on an offshoot study based on early results.

To date the DSMB has been directly involved with decisions to prematurely stop all or parts of seven studies. Two were for safety, one for efficacy, and four for futility. In particular, a phase 2 randomized trial was stopped for safety after an interim analysis found an excessive rate

Table 1
Distribution of studies by phase.

	Industry sponsored studies	CFF sponsored studies*
Phase 1	27	5
Phase 1/2	10	1
Phase 2	60	13
Phase 3	94	4
Phase IV	8	6
Observational	2	10
Other	2	5
TOTAL	203	44

* 12 studies were also supported by NIH/ FDA/NHLBI sponsored.

Table 2
Study categories.

Intervention	Number
Airway clearance	25
Anti-infective	57
Anti-inflammatory	22
Behavioral	4
Endocrine	3
Gene Therapy	3
Nutritional- GI	27
Restore CFTR function	102
Other	4
TOTAL	247

of pulmonary exacerbations in the groups receiving study drug compared with placebo [11]. In another phase 2 clinical trial in which participants were randomized to switching to an investigational drug or remain on an active comparator, the two lower dose groups on study drug were discontinued because of reductions in FEV_1 [12]. One study was stopped early for efficacy after an interim analysis found an overwhelmingly significant beneficial effect of treatment [13]. Of the trials stopped for futility, two were halted due to irreparably slow recruitment making it highly unlikely that a sufficient number of participants would enroll to provide informative results. One of these studies was further impaired by a high dropout rate. Two subgroups in an open label extension of a randomized placebo controlled trial were stopped after the parent studies were finalized, and no treatment benefits were observed [14]. Finally, a trial was stopped for futility when an interim analysis found that the predetermined futility boundary had been crossed for the primary endpoint and there were no counterbalancing benefits seen in the secondary endpoints. Of note, crossing a predetermined futility boundary does not always lead to early trial termination. In particular, one of the DMCs decided to allow a study to complete despite the futility boundary being crossed at a late interim analysis because there were not safety concerns, the study was near completion, and other potentially important results were being observed. It is noteworthy that the community representative advocated strongly that collecting a complete set of data would yield important data concerning the secondary endpoints. This case highlights two important issues; the value of the community representative and the fact that although stopping rules are in place, they are in fact guidelines and not rules. The value of a unblinded DMC is their ability to gauge the risks and benefits of completing a study.

9. Summary

The CFF-DSMB has grown from a small group of CF clinician scientists that started in 1999 to a large, well-integrated organization that provides high quality oversight to the majority of CF clinical trials conducted both in the US and internationally. The CFF-DSMB's involvement in the CF research process has supported a high volume of therapeutics to move rapidly yet safely through the CF drug discovery pipeline. By so doing, the CFF-DSMB has been an important contributor to the marked improvement in survival and quality of life enjoyed by people with CF today due to improved therapeutics. Over time we have evolved to continually address the changing clinical research landscape while at the same time meeting the needs of the greater community. The success of the CFF-DSMB can serve as a model for providing high quality oversight of clinical trials for other groups who are dedicated to developing treatments for rare diseases.

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Lynne M. Quittell: Conceptualization, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Richard H. Simon:** Conceptualization, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Wayne Morgan:** Conceptualization, Validation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Supplementary materials

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References

[1] Grasemann H, Ratjen F. Cystic fibrosis. N Engl J Med 2023;389:1693–707. https://doi.org/10.1056/NEJMra2216474.
[2] Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. Am J Dis Child 1938;2:344–99.
[3] Doershuk CF. Cystic fibrosis in the 20th century, people, events and progress. AM Publishing Ltd; 2001.
[4] Warwick WJ, Pogue RE. The prognosis for children with cystic fibrosis based on reasoned approaches to therapy: past, present, and future. J Asthma Res 1968;5:277–84. https://doi.org/10.3109/02770906809100345.
[5] Cystic Fibrosis Foundation Patient Registry 2022 Annual Data Report. Cystic Fibrosis Foundation. Bethesda, Maryland, 2023.
[6] Ramsey BW, Welsh MJ, AJRCCM: 100-year anniversary. Progress along the pathway of discovery leading to treatment and cure of cystic fibrosis. Am J Respir Crit Care Med 2017;195:1092–9. https://doi.org/10.1164/rccm.201702-0266ED.
[7] Goss CH, Mayer-Hamblett N, Kronmal RA, Ramsey BW. The cystic fibrosis therapeutics development network (CF TDN): a paradigm of a clinical trials network for genetic and orphan diseases. Adv Drug Deliv Rev 2002;54:1505–28. https://doi.org/10.1016/s0169-409x(02)00163-1.
[8] Ellenberg SS, Fleming TR, Demets DL. Data monitoring committees in clinical trials. John Wiley and Sons; 2019.
[9] Guidance for Clinical Trial Sponsors; Establishment and Operation of Clinical Trial Data Monitoring Committees, U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (CBER) Center for Drug Evaluation and Research (CDER) Center for Devices and Radiological Health (CDRH), 2006.
[10] Calis KA, Archdeacon P, Bain R, DeMets D, Donohue M, Elzarrad MK, Forrest A, McEachern J, Pencina MJ, Perlmutter J, Lewis RJ. Recommendations for data monitoring committees from the clinical trials transformation initiative. Clin Trials 2017;14:342–8. https://doi.org/10.1177/1740774517707743.
[11] Konstan MW, Doring G, Heltshe SL, Lands LC, Hilliard KA, Koker P, Bhattacharya S, Staab A, Hamilton A, Investigators, Coordinators of BIT. A randomized double blind, placebo controlled phase 2 trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of lung disease in children and adults with cystic fibrosis. J Cyst Fibros 2014;13:148–55. https://doi.org/10.1016/j.jcf.2013.12.009.
[12] Uluer AZ, MacGregor G, Azevedo P, Indihar V, Keating C, Mall MA, McKone EF, Ramsey BW, Rowe SM, Rubenstein RC, Taylor-Cousar JL, Tullis E, Yonker LM, Chu C, Lam AP, Nair N, Sosnay PR, Tian S, Van Goor F, Viswanathan L, Waltz D, Wang LT, Xi Y, Billings J, Horsley A, Vx, Groups VXS. Safety and efficacy of vanzacaftor-tezacaftor-deutivacaftor in adults with cystic fibrosis: randomised, double-blind, controlled, phase 2 trials. Lancet Respir Med 2023;11:550–62. https://doi.org/10.1016/S2213-2600(22)00504-5.
[13] Gibson RL, Emerson J, McNamara S, Burns JL, Rosenfeld M, Yunker A, Hamblett N, Accurso F, Dovey M, Hiatt P, Konstan MW, Moss R, Retsch-Bogart G, Wagener J, Waltz D, Wilmott R, Zeitlin PL, Ramsey B, Cystic Fibrosis Therapeutics Development Network Study G. Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. Am J Respir Crit Care Med 2003;167:841–9. https://doi.org/10.1164/rccm.200208-855OC.
[14] Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, De Boeck K, Sawicki GS, Chang P, Paz-Diaz H, Rubin JL, Yang Y, Hu X, Pasta DJ, Millar SJ, Campbell D, Wang X, Ahluwalia N, Owen CA, Wainwright CE, VX18-121-101; VX18-561-101 Study Groups. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or

heterozygous for phe508del CFTR (EXTEND): an open-label extension study. Lancet Respir Med 2021;9:733–46. https://doi.org/10.1016/S2213-2600(20)30510-5.