**SCT DMC Training Initiative: Closing the Gap**

The increase in the number and complexity of Phase 3 randomized clinical trials (RCTs) over the past decade has led to a growing need for more and more Data Monitoring Committees (DMCs). We, the Society for Clinical Trials (SCT), should recognize the shortage of clinical trialists with expertise and experience in DMCs by inaugurating an initiative to close the gap between supply and demand. We should encourage the training of the current and next generation of clinical trialists involved in medical research so they may serve effectively as members of independent DMCs sponsored by government, industry, and not-for-profit organizations.

While the DMC process had largely gone unnoticed by the general public, this is changing with the recent launching of numerous COVID-19 treatment and vaccine trials. The public not only is asking about whether they can trust the results of these clinical trials, but also is seeking a better understanding about the role and functioning of the “secret committee”, i.e., the trial’s DMC, that has sole access to emerging data during trial conduct. Having a well-functioning DMC is critical to safeguarding interests of study participants, to protecting trial integrity and to maintaining public trust in a clinical trial process that medical science has relied on for decades.

The SCT DMC Initiative Committee (henceforth, the Committee) has developed a three-component initiative: 1) a **formal training program** that will offer didactic material on the function and structure of DMCs; 2) a **mentorship model** that will allow colleagues new to DMCs to gain experience as members of a DMC; and 3) a **SCT DMC Registry** that will provide sponsors with a list of potential DMC members, all of whom will either have had experience participating on DMCs or will have had some training in DMCs.

This document describes the Committee’s proposal and urges the SCT Executive Committee to provide intellectual and financial support for the activities.

**Brief Background**

Over the past five decades as the randomized clinical trial has evolved to become the gold standard for evaluation of new pharmaceuticals, devices, procedures and behavioral interventions, so has the role of DMCs. In response to recommendations promulgated in the Greenberg Report (ref), the National Heart, Lung, and Blood Institute (NHLBI) implemented DMCs in the Institute’s early primary and secondary prevention trials. In that report, the DMC went by the name Data and Safety Monitoring Board (DSMB). Accompanying the growth of the use of DMCs has been the increased use of an independent reporting group that provides interim reports for the DMC. These reports allow the DMC to fulfill its role in insuring patient safety by monitoring the progress of the trial as well as by reviewing interim unblinded safety and efficacy data to assess whether it is appropriate for the trial to continue. After reviewing the totality of the evidence, including the emerging unblinded data, the DMC may recommend changes in the trial conduct or perhaps early termination of the trial if the data show evidence of harm, overwhelming evidence of benefit, or evidence that the trial will never reach a definitive and/or reliable result. Many papers (ref) and several recent meetings (ref) have described and discuss these activities.

At the current time, hundreds, or perhaps thousands, of DMCs are in operation (ref Califf et al). Despite this enormous growth in use of DMCs, the number of clinical and statistical scientists trained to be members of DMCs and statistical groups with expertise and experience in reports to DMCs is seriously inadequate. The Clinical Trial Transformation Initiative (CTTI) surveyed the state of activity and training by contacting current DMC members, sponsors or randomized controlled trials, reporting groups, and regulatory agencies regarding the level of participation in DMCs and reporting groups. While the survey found variations in practice, it reported many commonalities (ref Calis, Bain et al). One outstanding result of the survey is that few current DMC members had any formal training for their role. Even many with DMC experience expressed the belief that they would have benefited from some formal training. The literature and forums mentioned above have called for an organized training program to fill this growing gap.

The SCT is the ideal organization to take the leading role in this activity.

**I. DMC TRAINING**.

**The primary contribution to DMC training is a series of recorded lectures, commentaries and discussions.**

**SCT Video Presentation Library**

Over the past several years, individuals with extensive expertise and experience in DMC service have presented short courses or workshops that have been video recorded. Selected lecture recordings are being made available as listed below.

Currently available DMC Videos

* **Neaton-DeMets DMC Presentation**

 <http://media.biostat.wisc.edu/demetsfiles/DeMets-Neaton_DMC_Lectures/index.html>

 The Neaton-DeMets presentation was recorded for the benefit of the NIH-funded Clinical Translational Science Award (CTSA) network of academic clinical research centers as well as other training opportunities. The presentation contains three 90- minute lectures covering the fundamentals of DMCs, several DMC case studies, and statistical principles with tools for data monitoring.

 James Neaton, PhD Professor of Biostatistics, University of Minnesota School of Public Health. Dr Neaton has 50 years of experience in the design, conduct, and analyses of clinical trials including DMC interim analyses.

 David L DeMets, PhD, Max Halperin Emeritus Professor of Biostatistics, University of Wisonsin-Madison School of Medicine and Public Health. He has been involved for 50 years in the design, conduct and analyses of clinical trials with special interests in statistical methods for interim analyses for DMCs.

* **University of Washington Summer Institute in Biostatistics**

 Video recording has been retrieved and soon should be available for access

This video is a recording of a short course, held in 2020, entitled, ‘Data Monitoring Committees and Statistical Data Analysis Centers: Guiding Principles and Best Practices’. The three half day sessions were presented, using Zoom, by Susan Ellenberg, Tom Fleming, and Janet Wittes. The topics were DMC rationale and overview, the role of the reporting statistician, and DMC best practices, with case studies used throughout.

Susan Ellenberg, PhD, Professor of Biostatistics, University of Pennsylvania School of Medicine. Dr Ellenberg has the unique experience of a career that has spanned the National Institutes of Health in both cancer and AIDS, the CBER at the FDA and currently in academia.

Thomas Fleming, PhD, Professor of Biostatistics, University of Washington. Dr Fleming has been involved in cancer trials and many other diseases including AIDS and Covid trials with special interests in statistical methods for both interim and final analyses of these trials.

Janet Wittes, PhD, President and CEO, Statistics Collaborative Dr Wittes had a distinguished career at the National Heart Lung and Blood Institute before forming and leading a major consulting group with a focus on clinical trials and interim analyses for DMCs in particular.

* **FDA CDER DMC Workshop**

 The FDA CDER DMC video is a record of a one-day workshop held at the FDA CDER in 2018. The faculty were Dave DeMets, Susan Ellenberg, Tom Fleming, and Janet Wittes. The statistical methods for interim analyses for DMCs is provided. The FDA lectures by Elllenberg, Fleming and Wittes are similar to those presented in the Seattle Biostatistics Symposium,

* **Clinicians’ View of a DMC**:

The lectures on DMC structure and function, best practices, statistical methods and DMC Reports via the independent statistician were presented by four PhD statistical experts. The SCT DMC Training Committee sought clinicians with DMC expertise, either as a member or as a chair to share their experiences in either a half hour recorded commentary or in a recorded discussion.

**Barry Davis**, MD/PhD, University of Texas-Houston School of Public Health. Dr Davis has been involved leading a statistical coordinating center supporting clinical trials in cardiology, ophthalmology and other disease areas. He has served on numerous DMCs and FDA panels.

**Chris Granger**, MD Duke University Clinical Research Institute and Duke University Medical School, Dr Granger is a very experienced cardiologist and clinical trialist who has been involved in numerous trials, as study chair, DMC member and DMC chair.

**Charles Hennekens**, MD/DPH, Professor at Charles Schmidt College of Medicine at Florida Atlantic University, formerly professor at the Harvard University Medical School Dr Hennekens in a leading researcher in preventive cardiology, has led many trials as study chair and is a very frequent chair of DMCs in a variety of diseases.

**William Kelly**, MD Professor of Oncology at the Thomas Jefferson School of Medicine and a member of the Sidney Kimmel Cancer Center. Dr Kelly has been involved in all stages of cancer trials, Phase I, II & III, facing the challenges of monitoring each phase and a member DMCs for cancer cooperative trial networks

**Marc Pfeffer**, MD/PhD, Professor of Cardiology, Harvard University Medical School, Dr Pfeffer is a leading researcher in advancing treatments for heart failure & diabetes, has led many heart failure trials as study chair, served on numerous trials as a DMC member or chair.

**Jean Rouleau**, MD, Professor of Cardiology and former Dean, Montreal Heart Institute. Dr Rouleau is a cardiologist who has been involved in numerous cardiovascular trials, has served on numerous DMCs and chaired many of them.

**Peter Sandercock**, MD Professor of Neurology, University of Edinburgh. Dr Sandercock is an experienced clinical trialist in neurology and related diseases who has served on numerous DMCs and chaired many, including a recent Oxford University based covid platform network DMC

**Lew Smith**, MD Professor of Pulmonology, Northwestern University School of Medicine. Dr Smith has served as a researcher in numerous pulmonary clinical trials, and has been involved in many such trials as a member and chair of the corresponding DMC.

**Richard Whitley,** MD, Professor of Infectious Disease, University of Alabama School of Medicine. Dr Whitley is an experienced researcher in infectious diseases, has chaired the DMC for the NIAID/ NIH sponsored AIDS Clinical Trial Group (ACTG) and the more recent NIAID/NIH network for Covid vaccine trials, each of which led to important methodology for DMC structure and function.

**Video Menu of Presentations**

* **1 DeMets Introduction: DMC Training Zoom Video**
* **2 Neaton DeMets DMC Video**
* **2.1 Lecture I: DMC Structure & Function**
* **2.2 Lecture II: DMC Statistical Tools**
* **2.3 Lecture III: DMC Case Studies**
* **3 Seattle Symposium on DMCs**
* **3.1 Lecture I: Susan Ellenberg, PhD – DMC Structure & Function**
* **3.2 Lecture II: Tom Fleming, PhD - DMC Best Practices**
* **3.3 Lecture III: Janet Wittes, PhD – Independent Statistician & DMC Reports**
* **4 FDA CDER DMC Workshop**
* **4.1 Lecture IV: Dave DeMets, PhD – Statistical Methods for DMCs**
* **5 DMC Clinician Experiences (30 minute videos each)**
* **DMC COMMENTARIES**
* **5.1 Barry Davis, MD/PhD Univ of Texas SPH**
* **5.2 Chris Granger, MD Duke University**
* **5.3 Charles Hennekens, MD/DPH Florida Atlantic University**
* **5.4 Jean Rouleau, MD Montreal Heart Institute**
* **5.5 Peter Sandercock, MD University of Edinburgh**
* **5.6 Lew Smith, MD Northwestern University**
* **5.7 Richard Whitley, MD University of Alabama**
* **DMC CONVERSATIONS with Dave DeMets**
* **5.8 William Kelly, MD Thomas Jefferson University**
* **5.9 Marc Pfeffer, MD/PhD Harvard University**
* **5.10 Peter Sandercock, MD University of Edinburgh**
* **5.11 Richard Whitley, MD University of Alabama**

**Live Internet or Onsite Presentations**

For a particular short course, three of four members of a small pool of faculty with DMC and reporting expertise are available to provide a short course with relevant topics in keeping with the CTTI IDMC and other publications such as the FDA guidance document on DMCs and the text by Ellenberg, Fleming, and DeMets.

Onsite or Live Internet Sessions can be tailored to the interests of the audience. They can range from a 1-2 hour seminar to a half day or full day workshop, or sessions divided up over a series of days.

The faculty listed on the web site have agreed to engage in these training sessions with no honorarium or compensation other than to have their travel expenses paid.

**II. MENTORSHIP MODEL**

The Society for Clinical Trials (SCT) Data Monitoring Committee (DMC) Initiative has the goal of identifying and training the next generation of DMC members as well as offering some practical experience to people interested in serving on DMCs. While formal training through courses or workshops are important first steps, having some experience is essential to complement formal training.

The SCT DMC Apprenticeship subcommittee discussed several options to provide this type of experience. The consensus was that an experienced clinical trialists with little to no DMC experience appointed to a DMC should be paired with a member with DMC experience as their mentor. This discussion led to the Mentorship Model. For clinicians, if the DMC Chair is a clinician, the logical mentor would be the Chair. If the DMC Chair is not a clinician, most DMCs have a Safety Officer; that person would be the obvious mentor. For statisticians, the most appropriate mentor would be a statistician on the DMC who had prior DMC experience. For DMCs that have an ethicist, a patient representative, or someone with another field of expertise, the usual mentor would be the Chair.

The Mentorship Model is intended to help train experienced clinical trialists, either clinical or statistical professionals, by affording them some “on-the-job” training. Under this model, the mentee would be a full member of the DMC. The mentee should be encouraged to take advantage of the expertise and experience of the other DMC members as well as the appointed mentor.

The mentee will serve as a full member of the DMC, attending all meetings either in person or by virtual software support and participating in review and discussion of interim data.

For this approach to be effective, sponsors must agree to participate in this Mentorship Model. The model is advantageous to trial sponsors because it trains the next generation of DMC members and expands the pool of qualified DMC candidates. Most sponsors have learned through experience the importance of a well-functioning DMC with highly qualified members.

.

**III SCT DMC REGISTRY**

**The Registry Concept**

With the increase in the number of Data Monitoring Committees (DMCs) over the past decade, the number of clinicians and statisticians with experience and expertise in DMC activities has lagged. In addition, sponsors who organize DMCs often return to a same cadre of DMC members with whom they have worked with in the past. Word of mouth is currently the major way currently for sponsors become aware of DMC members with expertise and experience. The Committee proposed that SCT create a DMC Registry: as resource to assist sponsors in identifying DMC members, both those who have experience and those who have little experience but would like to join a DMC under the Mentorship model.

This SCT DMC Registry allows sponsors of clinical trials, especially Phase 3 trials, to have access to information about potential DMC members, their contact information, their affiliations and professional credentials, their areas of expertise, their experience in clinical trials, and their experience in DMCs The Committee does not consider the registry a DMC credentialing process, but rather a source of information for sponsors to search for potential DMC members meeting needs of their clinical trials.

The Committee encourages individuals with interest in DMC participation should be able to log into the SCT DMC Registry and build their profile and keep their profile up to date. The Registry should serve clinicians, statisticians, medical ethicists, epidemiologists and other related professions by increasing their visibility to sponsors. Someone with little to no experience can register but express interest in training programs.

Interested clinical trialist will be able to enter their information into this registry at no cost. SCT should require sponsors, as users of the registry, to pay a modest charge for the use of this registry, using the revenue to support the registries maintenance.

**SCT DMC Registry Access**

The Committee suggests that SCT create a structure in which sponsors who wish to use this registry establish an account with the SCT in order to log in. Potential users need not be SCT members but availability of this registry this might encourage them to join. A user fee may be necessary to ensure adequate funding for maintenance once the Registry is well established, a user fee might be necessary to cover costs.

Registration by potential DMC members will be at no cost to the members but they will be responsible for keeping their own profile up to date. A login password will be necessary to insure data quality and accuracy for each registrant.

**IV References**

Buhr KA, Downs M, Rhorer J, Bechhofer R, Wittes J. "Reports to Independent Data

Monitoring Committees: An Appeal for Clarity, Completeness, and Comprehensibility." Therapeutic Innovation & Regulatory Science. 2017 Nov 13. <https://doi.org/10.1177/2168479017739268>.

Calis K, Archdeacon P, Bain R, DeMets D, Donohue M, Elzarrad MK, Forest A, McEachern J, Pencina M, Perlmutter J,, Lewis R, Recommendations for Data Monitoring Committees from the Clinical Trials Transformation Initiative, Clinical Trials, 2017 Vol 14, 342-348.

Calis K, Archdeacon P, Bain R, Forrest A, Perlmutter J, DeMets D, Understanding the Functions and Operations of Data Monitoring Committees: Survey and Focus Group Findings" to Clinical Trials: Journal of the Society for Clinical Trials, 2017, Vol 14: 59-66.

DeMets DL & Ellenberg S, Data monitoring committees: expect the unexpected, NEJM, 2016;375:1365-71.

DeMets DL, Friedman L, Furberg CD. *Data Monitoring in Clinical Trials: A Case Studies*

 *Approach.* Springer Science+Business Media, New York, NY, 2005.

Ellenberg S, Fleming T and DeMets D:  *Data Monitoring Committees in Clinical Trials: A*

 *Practical Perspective*. John Wiley & Sons, Ltd., West Sussex, England, 2002.

Evans S, Ting N; Fundamental Concepts for New Clinical Trialists, Chapman and Hall, CRC Press, Sept 25, 2015.

Fleming T, DeMets D et al, Data Monitoring Committees: Promoting Best Practices to Address Emerging Challenges, Journal of the Society for Clinical Trials, 2017, p1-9.

# Sartor O, Halabi S. Independent data monitoring committees: an update and overview. Urol Oncol. 2015 33(3):143-8. doi: 10.1016/j.urolonc.2014.12.013.

Herson J. Data monitoring boards in the pharmaceutical industry. *Statist Med* 1993; 12:555-561.

Herson J, Data and Safety Monitoring Committees in Clinical Trials, Second Edition (Chapman & Hall/CRC Biostatistics Series) 2nd Edition.

Lewis R, Calis K & DeMets DL, Enhancing the Scientific Integrity and Safety of Clinical Trials: Recommendations for Data Monitoring Committees from the Clinical Trials Transformation Initiative, JAMA, Dec 13 2016.

Pitt, Bertram; Julian, Desmond Gareth; Pocock, Stuart J., eds. (1997). Clinical Trials in Cardiology. W. B. Saunders. [ISBN](https://en.wikipedia.org/wiki/International_Standard_Book_Number) [978-0-7020-2156](https://en.wikipedia.org/wiki/Special%3ABookSources/978-0-7020-2156-5).

Pocock, S (1983). Clinical Trials: A Practical Approach. [Wiley-Blackwell](https://en.wikipedia.org/wiki/Wiley-Blackwell). [ISBN](https://en.wikipedia.org/wiki/International_Standard_Book_Number) [978-0-471-90155-6](https://en.wikipedia.org/wiki/Special%3ABookSources/978-0-471-90155-6).

Pocock S & Furberg C, Procedures of Data and Safety Monitoring Committees

[American Heart Journal](https://www.researchgate.net/journal/0002-8703_American_Heart_Journal) 141(2):289-94 · March 2001 DOI: 10.1067/mhj.2001.113082.

Pocock S, Wilhelmsen L, Dickstein K, Francis G, Wittes J, The data monitoring

experience in the MOXCON trial European Heart Journal, Volume 25, Issue 22, 1 November 2004, Pages 1974–1978, <https://doi.org/10.1016/j.ehj.2004.09.015>.

Pocock S, McMurray J & Collier T, Making sense of statistics in clinical trial reports Part

1 of a 4 part series, J American College of Cardiology, Vol 66, No 22, 2015.

Wittes J. Behind closed doors: the data monitoring board in randomized clinical trials. *Statist Med* 1993; 12:419-424.

CTSA Collaborative DSMB Workgroup. DSMB Training Manual. Medford, MA: Tufts Digital Library; 2018 May [cited YYYY Month DD]. Available from: https://www.tuftsctsi.org/research-services/regulatory/ data-and-safety-monitoring-board-training-manual-for-investigator-initiated-studies/