Independent Academic Data Monitoring Committees for Clinical Trials in Cardiovascular and Cardiometabolic Diseases

Gerasimos S. Filippatos;[1] Pieter de Graeff;[2,3] Jeroen J. Bax;[4] John-Joseph Borg;[5] John G. F. Cleland;[6] Henry J. Dargie;[8] Marcus Flather;[9] Ian Ford;[10] Tim Friede;[11, 12] Barry Greenberg;[13] Cécile Henon-Goburdhun;[14] Richard Holcomb;[15] Bradley Horst;[16] John Lekakis;[1] Guenther Mueller-Velten;[17] Athanasios G. Papavassiliou;[18,19] Krishna Prasad;[20, 21] Giuseppe M. C. Rosano;[22,23] Thomas Severin;[17] Warren Sherman;[24] Wendy Gattis Stough;[25] Karl Swedberg;[26,27] Luigi Tavazzi;[28] Dimitris Tousoulis;[29] Panagiotis Vardas;[30] Frank Ruschitzka;[31] Stefan D. Anker[32]

[1]National and Kapodistrian University of Athens, School of Medicine, Athens University Hospital Attikon, Athens, Greece; [2]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [3]Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands; [4]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [5]Medicines Authority, Malta, [6]National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, United Kingdom; [7]Merck Research Laboratories, New Jersey, United States; [8]Cardiology Department, Western Infirmary, Glasgow, Scotland, United Kingdom; [9]Norfolk and Norwich University Hospitals NHS Foundation Trust and Norwich Medical School, University of East Anglia, Norfolk, United Kingdom; [10]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom; [11]Department of Medical Statistics, University Medical Center Göttingen, Germany; [12]DZHK (German Centre for Cardiovascular Research), partner site Göttingen, Göttingen, Germany; [13]University of California at San Diego, California, United

States; [14]Servier, Suresnes, France; [15]Independent Biostatistician, Minneapolis, Minnesota, United States; [16]Boston Scientific, St. Paul, Minnesota, United States; [17]Novartis Pharma AG, Basel, Switzerland; [18]Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [19]Chair, National Ethics Committee for Clinical Trials, Athens, Greece; [20]United Kingdom Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [21]Consultant Cardiologist, St. Thomas' Hospital, London, United Kingdom; [22]IRCCS San Raffaele Hospital Roma, Rome, Italy; [23]Cardiovascular and Cell Sciences Institute, St. George's University of London, London, United Kingdom; [24]Celyad, Mont Saint Guibert, Belgium; [25]Campbell University College of Pharmacy and Health Sciences, North Carolina, United States; [26]Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [27]National Heart and Lung Institute, Imperial College, London, United Kingdom; [28]GVM Care and Research, E.S. Health Science Foundation, Maria Cecilia Hospital, Cotignola, Italy; [29]1st Department of Cardiology, Hippokration Hospital, University of Athens, Athens, Greece; [30]Department of Cardiology, Heraklion University Hospital, Crete, Greece; [31]Department of Cardiology, Heart Failure Clinic and Transplantation, University Heart Center Zurich, Zurich, Switzerland; [32]Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany

Corresponding Author: Stefan D. Anker, MD PhD; Division of Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG); Robert-Koch-Str. 40; D-37075 Göttingen, Germany; Email: s.anker@cachexia.de

Abstract

Data monitoring committees (DMCs) play a crucial role in the conduct of clinical trials to ensure the safety of study participants and to maintain a trial's scientific integrity. Generally accepted standards exist for DMC composition and operational conduct. However, some relevant issues are not specifically addressed in current guidance documents, resulting in uncertainties regarding optimal approaches for communication between the DMC, steering committee, and sponsors, release of information, and liability protection for DMC members. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC), in collaboration with the Clinical Trials Unit of the European Heart Agency (EHA) of the ESC convened a meeting of international experts in DMCs for cardiovascular and cardiometabolic clinical trials to identify specific issues and develop steps to resolve challenges faced by DMCs. The main recommendations from the meeting relate to methodological consistency, independence, managing conflicts of interest, liability protection, and training of future DMC members. This paper summarizes the key outcomes from this expert meeting, and describes the core set of activities that might be further developed and ultimately implemented by the ESC, HFA, and other interested ESC constituent bodies. The HFA will continue to work with stakeholders in cardiovascular and cardiometabolic clinical research to promote these goals.

Keywords: clinical trials; data monitoring committees; data safety monitoring board; clinical trials as topic; cardiovascular diseases

INTRODUCTION

Data monitoring committees (DMCs) play a key role in the conduct of clinical trials. Their primary obligation is to ensure the safety of study participants while maintaining trial integrity.[1] DMCs achieve these functions primarily through reviewing interim safety and efficacy data, which assess the likelihood of harm, efficacy, or futility and the balance of risk versus benefit, supplemented by existing knowledge and evidence external to the trial. Pre-defined statistical guidelines serve as a construct for decision-making, but DMCs may legitimately take action outside of these guidelines if the data are sufficiently compelling to do so.

DMCs are required by regulatory authorities for some, but not all studies. Studies requiring a DMC are typically large, later phase (usually phase 3), randomized, multi-center trials that evaluate mortality or major morbidity outcomes. Early phase or feasibility trials may also warrant a DMC if there is a potential for significant risks to subjects, or for complex, novel therapies where little may be known about the array of potential responses to the study agent.[2;3] DMCs assembled for earlier phase studies may be responsible for multiple studies and often continue through phase 3, or DMCs may be set up program-wide for more than one study in parallel, to achieve continuity and maximize the DMC's experience with the therapy, which may be particularly important for novel regimens.

Generally accepted standards exist for DMC composition and operational conduct.[2-5] Often, some relevant issues are not specifically addressed in current guidance documents or DMC charters, such as the communication structure between the DMC, steering committee, and sponsors (specifically when DMC recommendations are not followed), release of information, and liability protection for DMC members.

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC), in collaboration with the Clinical Trials Unit of the European Heart Agency (EHA) within ESC recognized that independent, qualified, and experienced DMCs are an important vehicle for protecting the integrity of cardiovascular clinical trials, and these areas of uncertainty warranted discussion in an open forum. A meeting of international experts in DMCs for cardiovascular and cardiometabolic clinical trials was organized in 2015 and supported by the HFA to identify specific issues and advise steps to resolve challenges faced by DMCs. These societies acknowledge that identifying experienced individuals without significant conflicts of interest (i.e. potential for themselves or close personal connections to substantially benefit financially, professionally, or intellectually from the trial results) who are willing to participate on a DMC can be challenging. Finally, formal approaches are lacking to cultivate a greater number of appropriately experienced individuals to serve on DMCs, and the participants sought to use this forum to explore training approaches for future DMC leaders and members. This paper summarizes the key outcomes from this expert meeting.

OVERVIEW OF THE ROLE OF THE DATA MONITORING COMMITTEE

DMCs are primarily in place to ensure that patient safety is not compromised in an ongoing trial, and these committees consider safety from several perspectives. The most straightforward aspect is monitoring for emergence of serious or unexpected adverse events or toxicities and stopping a trial for evidence of harm. For less severe safety signals, the DMC may convey relevant information to the steering committee or study sponsor that triggers a protocol amendment, increased surveillance, or additional training in studies that involve devices or procedures. More complex considerations include stopping a trial early when there is

overwhelming evidence (i.e., beyond a reasonable doubt and statistically supported) of a mortality benefit, such that the trial can be brought to rapid completion to expedite the availability of an effective therapy to the broader patient population, and to protect placebo/control group and future patients from the risk of delayed access to treatment. However, stopping early for benefit must be balanced against the risk of stopping too early on a "random high" such that the results, once released, are misleading, uninterpretable, or insufficiently convincing to obtain regulatory approval/marketing authorization, change clinical practice, or satisfy payers.[6-11] A trial stopped inappropriately early also faces the ethical problem of wasting the contributions of study participants if the data are ultimately not informative. DMCs are also charged with protecting subjects from assuming unnecessary risks of clinical trial participation when a study appears to be futile (i.e., no chance for participating patients to benefit). Both industry and publicly funded trials may consider futility analysis to avoid wasting limited resources. However, declaring futility also assumes risks, such as the potential for missing a delayed treatment effect, an effect on important secondary endpoints, or definitive evidence of neutrality which is important information especially for marketed products (Table 1).

DMCs may also provide recommendations for clinical trial operations to the extent that it impacts the DMCs ability to effectively monitor safety (e.g., timeliness of adjudication and obtaining source documentation, interim data, or event reporting) or if study integrity is at risk (e.g., minimizing missing data or dropouts, avoiding excessive regional variation in application of guideline-directed medical therapy). DMCs are becoming more pro-active in recognizing problems that may impact study integrity as they are occurring in real-time. For example, the DMC in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial [TOPCAT] reviewed characteristics and event rates of enrolled patients and

made recommendations for subsequent enrollment as well as substudies to assess heart failure severity during the trial[12]. DMCs can also be responsible for other functions, such as recommending protocol adjustments for sample size or dose selection based on accrued data for studies with adaptive designs (i.e., where the study design can be modified at planned interim analyses, controlling for type I error[13;14]) according to a valid, pre-specified plan.[15]

The DMC charter should include the responsibilities of the DMC, its structure, format for reports, statistical guidelines for recommending trial termination, contractual and indemnification information, processes for conducting open meetings (may include sponsor, steering committee, study personnel to facilitate sharing information relevant to study progress but interim data are not discussed) and closed sessions (limited to DMC members and the data center statistician since interim data are discussed), procedures to ensure confidentiality, and communication pathways.[4;16;17] Although charter templates have been proposed,[16] none have been uniformly adopted.

IMPORTANCE OF AN INDEPENDENT DATA MONITORING COMMITTEE

Independence is an attribute that is necessary for the DMC to perform its intended function. The DMC must be free to evaluate the data, request analyses, and make recommendations without influence (or the perception of influence) from the sponsor, steering committee, investigators, or other parties involved in the trial. DMC members should have no other involvement with the trial and maintain strict confidentiality with regards to interim data. Relevant financial or intellectual conflicts of interest should be avoided or mitigated.

Conflicts of Interest

Independence as it relates to a DMC can be complex. Steering committee members may propose potential candidates to serve on a DMC to the study sponsor or at a minimum, provide advice to the sponsor regarding the proposed DMC membership. Sponsors may have sole responsibility for choosing DMC members for trials without a steering committee (e.g., some phase 2 trials). It is pertinent to note that the term "sponsor" is a single term but it can describe different entities or roles, depending on the study. The sponsor generally maintains final responsibility for the study, and may be the "owner" of the data and results, but the sponsor is not necessarily the funding source, and the funding source is not necessarily a commercial company. It is important to note that DMCs are in place to protect patient safety and the overall integrity of the trial, which is in the interest of all stakeholders (i.e., patients, investigators, sponsors, clinicians). However, remuneration for DMC services could be perceived as a conflict. Serving on a DMC requires considerable expertise and time commitment; thus, reasonable compensation commensurate with the time commitment and work involved is justified and in accordance with regulatory guidance,[3] although no compensation standards are available. Involving highly knowledgeable individuals on a DMC is desirable, but these individuals may be more likely than non-experts to have conflicts that need to be managed.[18] Although some conflicts may exist, DMC members should not have relationships that would result in significant financial, academic, intellectual, career, professional advancement, or other gains for themselves, their family members, or other close personal relationships based on the trial outcome.[17] Potential conflicts should be initially disclosed, and comprehensive reporting at routine intervals (i.e. every 6 to 12 months) should occur throughout the study. Using contract or academic research organizations, professional organizations such as the HFA, or other third parties

independent of the sponsor to recommend or select DMC members and handle contracts and payments to DMC members has been proposed as a method to manage conflicts. The structure of the contractual relationship should be transparently provided in legal documents and the "independence" of the third party should also be clearly described. This approach has not yet been systematically implemented,[4;17] and whether it would promote more efficient management of potential conflicts or create reporting inefficiencies remains to be determined.

Liability

The issue of liability has been raised as a theoretical concern among DMC members.[17-20] The lay public and legal personnel are unlikely to appreciate the nuances of interpreting fluctuations in interim data, and they may fail to understand how early data may be misleading.[19] In the context of a litigious society, DMC members may be appropriately concerned that uninformed misinterpretations of safety data could expose them to legal action.[20] Although actual cases have not yet been reported, many DMC members are concerned about potential legal action taken by patients who feel they have been harmed by participation in a study (and not adequately protected by the DMC), patients enrolled in placebo or standard therapy arms when the therapy tested is ultimately shown to be advantageous (i.e. holding DMC members liable for recommending that a study continue), or investors (e.g., either for allowing a study that was negative to continue or for not stopping a positive study earlier). Sponsors may not provide indemnification of DMC members, a factor which may be a disincentive to DMC participation or unduly influence DMC decision-making.[20] Several authors have called for indemnification of DMC members by the study sponsor, which should include support to cover legal counsel for the

DMC member independent from the sponsor's legal counsel to avoid legal conflicts of interest.[4;19;20]

Communication with Steering Committee and Sponsor

Processes for communication should be clearly specified in the DMC charter. Opportunities for inadvertent, informal communication between the DMC and other parties involved in the trial should be minimized; for instance, the DMC should avoid sponsor hospitality or advisory boards. Interactions among these groups should be conducted under a principle of maintaining confidentiality of interim results,[21] since release of interim data could bias investigators, study personnel, potential study enrollees, and the general public, and damage the integrity of the trial (e.g., Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes [RECORD], Simvastatin and Ezetimibe in Aortic Stenosis [SEAS]).[22;23] The steering committee or sponsor may discuss blinded data with the DMC when appropriate to inform them about the overall study progress, status of endpoint adjudication, or adverse event reporting.[24] In the context of adaptive designs, a limited group from the sponsor may interact with the DMC and have access to unblinded data, but beyond this purpose the authors strongly view that unblinded data should never be shared with the study sponsor, steering committee, investigators, or other study personnel that are involved with potential protocol changes or whom have contact with investigators, unless the DMC is recommending premature termination, a position that is in agreement with regulatory standards (Figure 1).[2;3] Even with strict data confidentiality procedures in place, release of unblinded interim data for any purpose (e.g., planning of phase 3, regulatory submissions, business purposes) can have detrimental and irrecoverable effects on the integrity of an ongoing trial (e.g., naltrexone/buproprion).[25] While

representation of government sponsors, including project officers and other administrative staff, during DMC meetings sometimes occurs,[24] the authors of this paper discourage such involvement since the government sponsor's role is to select centers, monitor progress, and financially support a clinical trial. Minimally, unblinded staff should not participate in discussions or decisions to modify the protocol or be in a position to directly or indirectly, knowingly or unknowingly, convey information about interim data to others involved in the study.

In special circumstances, regulatory agencies may request information from the sponsor on interim, unblinded data when adverse events of concern have been observed in other studies of the same drug, drug class, or device. The DMC may provide this information to regulatory agencies if the sponsor agrees with the request. However, regulatory actions taken in response to the interim data may have major implications on the ability of the study to continue to completion. Thus, before undertaking this approach, regulatory agencies should give careful consideration to all factors, including the strength of the safety signal, quantity of the data, potential for exposure of the general public (e.g., if the study involves a commercially available drug), potential for the action to result in premature cessation of the study, and loss of the ability to achieve a precise answer to the research question of interest. Rather than request access to unblinded data, it may be preferable for regulatory agencies to communicate with the sponsor and request that the DMC undertake closer monitoring for a specific adverse event and allow the DMC to review the data and make appropriate recommendations regarding study continuation or termination. However, this may lead to problems in practice, and regulatory authorities may decide to take their own, independent, responsibility (e.g., Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure [ATMOSPHERE]).[26;27] Clear communication between the

regulators, sponsor, steering committee, and DMC can help to ensure optimal decisions are made that both protect patient safety and trial integrity. These groups should jointly develop processes to streamline interactions (e.g., sharing statistical analysis plans rather than unblinded data in certain circumstances), which might help resolve difficult situations without compromising the role and responsibilities of either group.[26;27]

The DMC acts in an advisory capacity to the executive leadership of the trial and the study sponsor. They make recommendations, which the steering committee and/or sponsor must decide whether or not to follow. Cases have arisen where steering committees or sponsors chose not to follow the recommendation of the DMC.[28] Likewise, cases have arisen where sponsors have chosen to release information without involving the DMC (e.g., RECORD, SEAS, naltrexone/buproprion).[22;23;25;29] The DMC charter should describe the course of action that will be taken in the case of such disagreements (e.g., clear reporting structure to delineate which party has final decision-making capabilities, processes that will be implemented to resolve disagreements and achieve consensus such as use of a third-party expert panel to act as arbitrator).

IMPORTANCE OF AN EXPERIENCED DATA MONITORING COMMITTEE

The need for an experienced DMC, particularly the committee chair, has been underscored by other authors[4;17] and regulatory guidance documents.[2;3] DMCs should ideally comprise 3-5 members, including ideally a specialized statistician with experience in cardiovascular clinical trials and physicians who have clinical training and experience in the field relevant to the specific study, which might extend beyond the immediate disease state of interest to other fields (e.g., hepatology, nephrology, neurology, oncology) if there is pre-existing

concern about specific adverse events or toxicities. The data center statistician is a non-voting contributor who should have pertinent experience to construct reports, may maintain minutes, and will ensure confidentiality of interim data and DMC proceedings.[17]

Prior participation in steering committees is desirable preparation for individuals interesting in serving on a DMC. Important knowledge is generated through this experience regarding clinical trial protocol design, study execution and operations, and DMC interactions that cannot be obtained through seminars, training modules, or reading textbooks or journal articles on the topic.[30]

The need to prepare more individuals for DMC service has been acknowledged (Table 2).[4;17;30;31] Membership on a DMC involves reviewing data and making decisions that can be highly nuanced, concepts which are challenging to convey in didactic type training programs.[30] Mentoring programs are one mechanism that could be implemented to provide opportunity for individuals to participate as non-voting DMC members, alongside experienced DMC members, to gain the skills required for independent DMC service. These programs should be extended to individuals at any career stage. Targeting early career individuals will provide an opportunity to realize many years of qualified service for the training investment. However, late career individuals represent a valuable resource in terms of clinical and research experience, and may have less competing responsibilities than early or mid-career investigators. Sharing DMC experiences after a trial has concluded through publications[7;28;32-34] or other avenues of dissemination (e.g., supplementary material available with the primary publication, postings on clinical trial registry database websites) is also encouraged as a means to educate current and future DMC members and to achieve transparency in the DMC process. The substantial contribution that DMCs often make to clinical trials deserves greater recognition, which might

include being a co-author on papers of study design or primary results, although the potential for introduction of academic or intellectual bias should be considered.

ROLE OF THE HEART FAILURE ASSOCIATION AND EUROPEAN HEART AGENCY

A key objective of the HFA workshop was to identify areas where HFA, ESC constituent bodies, and the EHA could contribute to strengthening the utilization of DMCs in cardiovascular and metabolic clinical trials. Several areas of potential involvement were identified and will be further explored and developed by the leadership of these organizations.

Develop Registry of Data Monitoring Committee Members

The importance of access to experienced DMC members was a recurring theme raised during the workshop. DMC members may be selected on the basis of recommendations from the steering committee or industry sponsor, but smaller companies or newcomers to the field may have less knowledge about suitable individuals for DMC service or may lack access to them. The HFA in collaboration with other ESC constituent bodies (i.e., the Clinical Trials Unit of the ESC) could create a registry of potential DMC members, including information on past steering or DMC committee experience and unique expertise they may have in specific disease states or novel therapeutics. This would be a valuable resource for Steering Committees and Sponsors, while also serving to enhance the independence of the DMC since potential members would be first identified by querying the HFA DMC registry rather than by direct nomination from the sponsor or steering committee.

Advisory Body for Data Monitoring Committees

Managing conflicts of interest was also emphasized during the workshop as a concern for modern DMCs. Conflict of interest information would also be maintained in the registry, and individuals with conflicts that could not be adequately managed (according to clearly pre-defined criteria) would be excluded from selection. For individuals where potential, but manageable, conflicts were present, the HFA or other relevant ESC constituent bodies could advise steps to further mitigate the conflict (e.g., discontinue consultant or advisory activities during the course of the trial). Finally, HFA or other relevant ESC constituent bodies could lobby sponsors to provide indemnification with language that protects DMC members from liability and ensures individual legal counsel will be provided in the event it is needed.

Develop Training Modules and Facilitate Mentorship Programs

The suggested DMC registry would also provide infrastructure to match investigators interested in gaining DMC experience with seasoned DMC members willing to provide mentorship opportunities. The mentorship program would combine web-based training modules with real-life, hands-on experience within a DMC (Table 2). Trainees would be non-voting members of the DMC and would gain exposure to all aspects of the DMC process, including developing a charter, regulatory requirements and expectations for DMCs, reviewing DMC reports, participating in open and closed DMC sessions, and exposure to communication pathways between the DMC, sponsor, steering committee, investigators, and regulatory bodies. The HFA encourages publication of DMC proceedings after completion of those trials where "lessons learned" would be of value for future DMCs. HFA, and more broadly ESC, may be

positioned to facilitate the transparent reporting and public dissemination of this information through its journal, website, and annual meeting.

CONCLUSION

Data monitoring committees play a vital role in protecting human subjects enrolled in clinical trials, and they instill confidence that the integrity of the trial is intact and the data are reliable. The increasingly widespread use of DMCs is accompanied by concerns related to their independence, conflicts of interest, liability protection, and a lack of qualified individuals for DMC service. The topic of DMCs is often discussed in the literature and academic circles, but few efforts have been adopted to address these challenges. During the workshop, the HFA suggested a core set of activities that might be further developed and ultimately implemented to impact these areas. The HFA will continue to advise stakeholders in cardiovascular and cardiometabolic clinical research to promote the integration of independent DMCs in clinical trials where needed, protect the interests of those serving as DMC members, and cultivate highly skilled individuals for DMC service.

Figure Legends

Figure 1. Ideal Communication Pathways for Unblinded Data

Figure represents a "firewall" around the DMC (denoted by thicker border), where one-way input to the DMC can be provided by regulatory authorities or external DMCs, usually with the knowledge or approval of the steering committee or sponsor. One-way output of unblinded data to the steering committee or sponsor only occurs when premature termination is recommended, although partial flow of unblinded information may occur between a small group of people within the steering committee or sponsor in an adaptive design. The only two-way communication of blinded data occurs between the DMC and the data center statistician.

*Regulatory bodies may request (with the knowledge/approval of the steering committee or sponsor) that the DMC monitor specific events if concerns emerge from external trials or data.

†Other DMCs may suggest specific events for monitoring if concerns emerge from ongoing external trials (with the knowledge/approval of the steering committee or sponsor).

‡Blinded data may be communicated between the DMC and steering committee and/or sponsor when the DMC has concerns about issues that affect the quality of the study (e.g., concerns about data integrity, timeliness of reporting adverse events, concerns about the nature of the patients enrolled)

ARO, academic research organization; CRO, contract research organization; DMC, data monitoring committee; EC, ethics committee; IRB, institutional review board

Acknowledgements

The authors acknowledge the Heart Failure Association of the European Society of Cardiology for organizing the meeting during which this topic was discussed.

The authors acknowledge Robert J. Cody for his contributions and participation during the workshop on which this paper was based.

Conflicts of Interest

Gerasimos S. Filippatos: Participated in Committees of trials and Registries sponsored by Bayer, Cardiorentis, Medtronic, Novartis, Servier, Vifor.

Pieter de Graeff: None declared

Jeroen J. Bax: None declared

John-Joseph Borg: None declared

John G. F. Cleland: Research grants from Amgen, Novartis, Stealth BioTherapeutics; personal fees from Novartis, Stealth BioTherapeutics, and Servier

Henry J. Dargie: Personal fees for DMC membership from Novartis, TEVA, Amgen, Janssen, Boston Scientific, and Servier

Marcus Flather: Personal fees from AstraZeneca (speaker fees, advisory boards); Research grant from Novartis (steering committee member)

Ian Ford: Research grants from Vifor (FAIR-HF trial), Servier (SHIFT trial), Biotronik (EchoCRT trial); personal fees from ResMed (DMC membership), Servier, Biotronik

Tim Friede: Personal fees for consultancies (including DMC membership) outside the submitted work from Novartis, Bayer, Biogen, AstraZeneca, Grünenthal, Janssen, SGS, and Pharmalog

Barry Greenberg: Personal fees from Actelion, St. Jude, CardioCell, Amgen, Trevena, Viking, Celladon, Teva, J&J, Zensun, Novartis, Relypsa, Otsuka

Cécile Henon-Goburdhun: Employee of Servier

Richard Holcomb: Travel support to attend DMC workshop from Heart Failure Association of the European Society of Cardiology

Bradley Horst: Employee of Boston Scientific

John Lekakis: Personal fees from MSD, Actelion, Bayer

Guenther Mueller-Velten: Employee of Novartis

Athanasios G. Papavassiliou: None declared

Krishna Prasad: None declared

Giuseppe Rosano: None declared

Thomas Severin: Employee of Novartis

Warren Sherman: Employee of Celyad S.A.

Wendy Gattis Stough: Personal fees for consulting to European Society of Cardiology, Heart Failure Association of the European Society of Cardiology, European Drug Development Hub, Relypsa, CHU Nancy, Heart Failure Society of America, Overcome, Stealth BioTherapeutics, University of Gottingen, University of North Carolina, Respicardia, and Celyad

Karl Swedberg: Personal fees (consulting) from Amgen, AstraZeneca, Novartis, Servier, Vifor Pharma; research grants from Servier

Luigi Tavazzi: Personal fees from Servier (trial committee member, speaker's bureau), SJM (trial committee member), Cardiorentis (trial committee member), CVIE Therapeutics (trial committee member), Boston Scientific (trial committee member ending 2015), Medtronic (trial committee member ending 2015),

Dimitris Tousoulis: None declared

Panagiotis Vardas: None declared

Frank Ruschitzka: Research grant from St. Jude Medical; Personal fees from St. Jude Medical, Servier, Zoll, AstraZeneca, HeartWare, Sanofi, Cardiorentis, Novartis

Stefan D. Anker: Research grants from Vifor, Abbott Vascular; personal fees from Vifor, Abbott Vascular, Bayer Pharma, Novartis, Lonestar Heart, Respicardia, ZS Pharma, Relypsa, Biotronik, Cardiorentis, Servier

References

1. Slutsky AS, Lavery JV. Data safety and monitoring boards. *N Engl J Med* 2004;**350**:1143-1147.
2. European Medicines Agency. Guideline on data monitoring committees. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf (5 Jan 2016)
3. US Department of Health and Human Services and Food and Drug Administration. Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring committees. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf (5 Jan 2016)
4. Hess CN, Roe MT, Gibson CM, Temple RJ, Pencina MJ, Zarin DA, Anstrom KJ, Alexander JH, Sherman RE, Fiedorek FT, Mahaffey KW, Lee KL, Chow SC, Armstrong PW, Califf RM. Independent data monitoring committees: preparing a path for the future. *Am Heart J* 2014;**168**:135-141.
5. Hicks LK, Laupacis A, Slutsky AS. A primer on data safety monitoring boards: mission, methods, and controversies. *Intensive Care Med* 2007;**33**:1815-1818.
6. Pocock S, White I. Trials stopped early: too good to be true? *Lancet* 1999;**353**:943-944.
7. Pocock S, Wang D, Wilhelmsen L, Hennekens CH. The data monitoring experience in the Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2005;**149**:939-943.
8. Pocock SJ. When (not) to stop a clinical trial for benefit. *JAMA* 2005;**294**:2228-2230.

9. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, Heels-Ansdell D, Walter SD, Guyatt GH, Flynn DN, Elamin MB, Murad MH, Abu Elnour NO, Lampropulos JF, Sood A, Mullan RJ, Erwin PJ, Bankhead CR, Perera R, Ruiz CC, You JJ, Mulla SM, Kaur J, Nerenberg KA, Schunemann H, Cook DJ, Lutz K, Ribic CM, Vale N, Malaga G, Akl EA, Ferreira-Gonzalez I, Alonso-Coello P, Urrutia G, Kunz R, Bucher HC, Nordmann AJ, Raatz H, da Silva SA, Tuche F, Strahm B, Djulbegovic B, Adhikari NK, Mills EJ, Gwadry-Sridhar F, Kirpalani H, Soares HP, Karanicolas PJ, Burns KE, Vandvik PO, Coto-Yglesias F, Chrispim PP, Ramsay T. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010;**303**:1180-1187.

10. Zannad F, Gattis SW, McMurray JJ, Remme WJ, Pitt B, Borer JS, Geller NL, Pocock SJ. When to stop a clinical trial early for benefit: lessons learned and future approaches. *Circ Heart Fail* 2012;**5**:294-302.

11. Pocock SJ, Clayton TC, Stone GW. Challenging Issues in Clinical Trial Design: Part 4 of a 4-Part Series on Statistics for Clinical Trials. *J Am Coll Cardiol* 2015;**66**:2886-2898.

12. Bristow M, Enciso J, Gersh B, Grady C, Rice M, Singh S, Sopko G, Boineau R, Rosenberg Y, Greenberg B. Detection and management of geographic disparities in the TOPCAT trial: lessons learned and derivative recommendations. *J Am Coll Cardiol Basic Trans Sci* 2016;**1**:180-189.

13. European Medicines Agency. Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf

14. Food and Drug Administration. Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

15. Sanchez-Kam M, Gallo P, Loewy J, Menon S, Antonijevic Z, Christensen J, Chuang-Stein C, Laage T. A practical guide to data monitoring committees in adaptive trials. *Therapeutic Innovation & Regulatory Science* 2014;**48**:316-326.

16. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005;**365**:711-722.

17. Fleming TR, Hennekens CH, Pfeffer MA, DeMets DL. Enhancing trial integrity by protecting the independence of data monitoring committees in clinical trials. *J Biopharm Stat* 2014;**24**:968-975.

18. Ellenberg SS. Protecting clinical trial participants and protecting data integrity: are we meeting the challenges? *PLoS Med* 2012;**9**:e1001234.

19. DeMets DL, Fleming TR, Rockhold F, Massie B, Merchant T, Meisel A, Mishkin B, Wittes J, Stump D, Califf R. Liability issues for data monitoring committee members. *Clin Trials* 2004;**1**:525-531.

20. Tereskerz PM. Data safety monitoring boards: legal and ethical considerations for research accountability. *Account Res* 2010;**17**:30-50.

21. Fleming TR. Protecting the confidentiality of interim data: addressing current challenges. *Clin Trials* 2015;**12**:5-11.

22. Califf RM, Harrington RA, Blazing MA. Premature release of data from clinical trials of ezetimibe. *N Engl J Med* 2009;**361**:712-717.

23. Drazen JM, Wood AJ. Don't mess with the DSMB. *N Engl J Med* 2010;**363**:477-478.
24. Borer JS, Gordon DJ, Geller NL. When should data and safety monitoring committees share interim results in cardiovascular trials? *JAMA* 2008;**299**:1710-1712.
25. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, Perez A, Smith SR. Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients With Cardiovascular Risk Factors: A Randomized Clinical Trial. *JAMA* 2016;**315**:990-1004.
26. Swedberg K, Borer JS, Pitt B, Pocock S, Rouleau J. Challenges to Data Monitoring Committees When Regulatory Authorities Intervene. *N Engl J Med* 2016;**374**:1584.
27. Salmonson T, Janssen H, Sudhop T, Stahl E. Regulatory Reply to the ATMOSPHERE Data Monitoring Committee. *N Engl J Med* 2016;**374**:1585-1586.
28. DeMets DL, Furberg CD, Friedman LM. *Data monitoring in clinical trials: a case studies approach*. New York: Springer Science+Business Media, Inc., 2006.
29. Cleveland Clinic. Clinical trial testing safety of obesity drug Contrave halted; 50 percent interim data released by the study's executive committee [press release]. (10 Jun 2015)
30. Zuckerman J, van der Schalie B, Cahill K. Developing training for Data Safety Monitoring Board members: A National Institute of Allergy and Infectious Diseases case study. *Clin Trials* 2015;**12**:688-691.
31. Armstrong PW, Califf RM. Data and safety monitoring boards: academic credit where credit is due? *JAMA* 2013;**310**:1563-1564.
32. Hillman DW, Louis TA. DSMB case study: decision making when a similar clinical trial is stopped early. *Control Clin Trials* 2003;**24**:85-91.

33. Pocock S, Wilhelmsen L, Dickstein K, Francis G, Wittes J. The data monitoring experience in the MOXCON trial. *Eur Heart J* 2004;**25**:1974-1978.

34. Wittes J, Barrett-Connor E, Braunwald E, Chesney M, Cohen HJ, DeMets D, Dunn L, Dwyer J, Heaney RP, Vogel V, Walters L, Yusuf S. Monitoring the randomized trials of the Women's Health Initiative: the experience of the Data and Safety Monitoring Board. *Clin Trials* 2007;**4**:218-234.

Table 1. Overview of DMC Monitoring Decisions

Decision	Considerations	Examples of studies (not intended to be comprehensive)
Stopping for harm[11;28]	• Evidence of harm that creates an unfavorable balance between risks and potential benefits • Review interim data more frequently • For known or suspected safety issues, stopping boundaries may be defined; often less stringent than applied when stopping for benefit or futility • Safety is multi-factorial and less amenable to statistical planning. Unexpected safety signals need to be interpreted in the context of multiplicity, biologic plausibility,	• ILLUMINATE • PALLUS • MOXCON • CAST • PROMISE • HERS • ALLHAT • TRACER

Table 1. Overview of DMC Monitoring Decisions (continued)

Decision	Considerations	Examples of studies (not intended to be comprehensive)
	external data, and the anticipated benefit.	
Stopping for benefit[6-11]	• Should be based on proof beyond a reasonable doubt that a treatment effect is adequately robust to allow a benefit:risk assessment sufficient to impact clinical practice and regulatory decision-making for pivotal trials • Pre-specified statistical stopping guidelines should be more stringent early in the trial when the number of events is likely to be small • Stopping for benefit should not be considered until at least one-half of the	• ASCOT • CIBIS-II • MERIT-HF • COPERNICUS • RALES • A-HeFT • EMPHASIS • MADIT • MADIT II • MADIT-CRT • COMPANION • PARADIGM-HF

Table 1. Overview of DMC Monitoring Decisions (continued)

Decision	Considerations	Examples of studies (not intended to be comprehensive)
	patients have been enrolled or one-half of the expected events have accumulated	• Physician's Health Study • DCCT
Stopping for futility[11]	• Stopping for futility should not be considered until at least one-half of the patients have been enrolled or one-half of the expected events have accumulated • Should consider potential for loss of information on clinically relevant secondary endpoints, safety, a delayed treatment effect, definitive evidence of neutrality, or other important knowledge that may be generated by	• PERFORM • CONSENSUS II (stopped for futility + harm in other endpoints) • ALTITUDE (stopped for futility + harm in other endpoints) • EchoCRT

Table 1. Overview of DMC Monitoring Decisions (continued)

Decision	Considerations	Examples of studies (not intended to be comprehensive)
	the trial • Predictive and conditional power are useful concepts when considering futility	

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints; CAST = Cardiac Arrhythmia Suppression Trial; DCCT = Diabetes Control and Complication Trial; EchoCRT = Echocardiography Guided Cardiac Resynchronization Therapy; HERS = Heart and Estrogen/Progestin Replacement Trial; ILLUMINATE = Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure; MOXCON = Moxonidine Congestive Heart Failure Trial; PALLUS = Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy); PERFORM = Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack; PROMISE = Prospective Randomized Milrinone Survival Evaluation; RALES = Randomized Aldactone Evaluation Study; TRACER = Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome

Table 2. Methods of Training Future DMC Members

	Type of Training		
	Web-based Didactic Training Modules	Training Workshops (1-2 day)	Hands-on Training
Content	• Review of regulatory guidance involving DMCs • Discussion of charter and what should be included • Introduction to contractual agreements and indemnification considerations • Introduction to viewing and interpreting sample interim data reports • Methods and processes to maintain appropriate firewalls between DMC and other study personnel • Presentation of case examples	• Presentation of case studies from past real-life DMC experiences and interactive discussion about possible actions, DMC decision making and implications • Basic training on statistical issues including stopping rules and analysis of safety data • Interpretation of data reports • Sample exercises for writing a DMC charter	• Assign trainee to a DMC as non-voting DMC member • Partner trainee with experienced DMC member, provide mentorship • Participate in all aspects of DMC (e.g., drafting charter, reviewing contracts, negotiating indemnification, review of protocol and analysis plan, review of draft data report, review of actual data reports, participation in all meetings, including sponsor or steering committee interactions)