

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

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45

46 **Abstract**

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

63

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

66

67 **INTRODUCTION**

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

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

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

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

104

105 **OVERVIEW OF THE ROLE OF THE DATA MONITORING COMMITTEE**

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

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

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

136 made recommendations for subsequent enrollment as well as substudies to assess heart failure
137 severity during the trial¹². DMCs can also be responsible for other functions, such as
138 recommending protocol adjustments for sample size or dose selection based on accrued data for
139 studies with adaptive designs (i.e., where the study design can be modified at planned interim
140 analyses, controlling for type I error^{13;14}) according to a valid, pre-specified plan.¹⁵

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

149

150 **IMPORTANCE OF AN INDEPENDENT DATA MONITORING COMMITTEE**

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

157

158 **Conflicts of Interest**

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

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

187

188 **Liability**

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

203 DMC member independent from the sponsor’s legal counsel to avoid legal conflicts of
204 interest.^{4;19;20}

205

206 **Communication with Steering Committee and Sponsor**

207 Processes for communication should be clearly specified in the DMC charter.

208 Opportunities for inadvertent, informal communication between the DMC and other parties
209 involved in the trial should be minimized; for instance, the DMC should avoid sponsor
210 hospitality or advisory boards. Interactions among these groups should be conducted under a
211 principle of maintaining confidentiality of interim results,²¹ since release of interim data could
212 bias investigators, study personnel, potential study enrollees, and the general public, and damage
213 the integrity of the trial (e.g., Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of
214 Glycemia in Diabetes [RECORD], Simvastatin and Ezetimibe in Aortic Stenosis [SEAS]).^{22;23}

215 The steering committee or sponsor may discuss blinded data with the DMC when appropriate to
216 inform them about the overall study progress, status of endpoint adjudication, or adverse event
217 reporting.²⁴ In the context of adaptive designs, a limited group from the sponsor may interact
218 with the DMC and have access to unblinded data, but beyond this purpose the authors strongly
219 view that unblinded data should never be shared with the study sponsor, steering committee,
220 investigators, or other study personnel that are involved with potential protocol changes or whom
221 have contact with investigators, unless the DMC is recommending premature termination, a
222 position that is in agreement with regulatory standards (Figure 1).^{2;3} Even with strict data
223 confidentiality procedures in place, release of unblinded interim data for any purpose (e.g.,
224 planning of phase 3, regulatory submissions, business purposes) can have detrimental and
225 irrecoverable effects on the integrity of an ongoing trial (e.g., naltrexone/bupropion).²⁵ While

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

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

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

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

264

265 **IMPORTANCE OF AN EXPERIENCED DATA MONITORING COMMITTEE**

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

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

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

280 The need to prepare more individuals for DMC service has been acknowledged (Table
281 2).^{4;17;30;31} Membership on a DMC involves reviewing data and making decisions that can be
282 highly nuanced, concepts which are challenging to convey in didactic type training programs.³⁰
283 Mentoring programs are one mechanism that could be implemented to provide opportunity for
284 individuals to participate as non-voting DMC members, alongside experienced DMC members,
285 to gain the skills required for independent DMC service. These programs should be extended to
286 individuals at any career stage. Targeting early career individuals will provide an opportunity to
287 realize many years of qualified service for the training investment. However, late career
288 individuals represent a valuable resource in terms of clinical and research experience, and may
289 have less competing responsibilities than early or mid-career investigators. Sharing DMC
290 experiences after a trial has concluded through publications^{7;28;32-34} or other avenues of
291 dissemination (e.g., supplementary material available with the primary publication, postings on
292 clinical trial registry database websites) is also encouraged as a means to educate current and
293 future DMC members and to achieve transparency in the DMC process. The substantial
294 contribution that DMCs often make to clinical trials deserves greater recognition, which might

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

297

298 **ROLE OF THE HEART FAILURE ASSOCIATION AND EUROPEAN HEART**
299 **AGENCY**

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

304

305 **Develop Registry of Data Monitoring Committee Members**

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

317

318 **Advisory Body for Data Monitoring Committees**

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

328

329 **Develop Training Modules and Facilitate Mentorship Programs**

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

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

342

343 **CONCLUSION**

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

355

356 **Figure Legends**

357 Figure 1. Ideal Communication Pathways for Unblinded Data

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

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

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

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

373

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

376

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Table 1. Overview of DMC Monitoring Decisions

Decision	Considerations	Examples of studies (not intended to be comprehensive)
Stopping for harm ^{11;28}	<ul style="list-style-type: none"> • 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, 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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)
	<p>patients have been enrolled or one-half of the expected events have accumulated</p>	<ul style="list-style-type: none"> • Physician’s Health Study • DCCT
<p>Stopping for futility¹¹</p>	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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)
	<p>the trial</p> <ul style="list-style-type: none"> • 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 Dronedaron 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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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)