

Appendix 1
Study Progress, Data, and Safety Monitoring
STUDY MONITORING COMMITTEE (SMC) GUIDELINES

Approval Date:
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1 Note that this Appendix applies to all National Institute of Allergy and Infectious Diseases
2 (NIAID) (Division of Acquired Immunodeficiency Syndrome (DAIDS)) supported and/or
3 sponsored clinical trials with a SMC that are conducted outside of the HIV/AIDS Clinical
4 Trials networks.

5 Note: For purposes of this document, the terms data reports and summary reports are
6 defined as follows:

7 Data reports are documents containing data related to study progress, data, and safety
8 monitoring generated for the review by the designated monitor(s).

9 Summary reports are the synopsis of the observations and recommendations of the
10 designated monitor(s).

11 1. Roles and Responsibilities

12 A Study Monitoring Committee (SMC) is an independent group of experts that advises the
13 DAIDS and the study investigators. The primary responsibility of the SMC is to monitor study
14 progress and participant safety. The SMC considers study-specific data as well as relevant
15 background information about the disease, study agent, and target population under study.
16 The contents and schedule of data reports to be reviewed by the SMC will be specified in the
17 study progress, data, and safety monitoring plan (SPDSMP) with input from the SMC. A
18 member of a SMC may be designated to serve as an Independent Safety Monitor (ISM) and
19 review selected individual case adverse event reports and/or periodic cumulative adverse
20 event reports in addition to those reviewed by the entire SMC.

21 The SMC should review the protocol and the SPDSMP, and identify any major concerns prior
22 to implementation. The SMC should define its deliberative processes prior to clinical trial
23 initiation. These processes may include event triggers that would call for an unscheduled
24 review, guidelines for stopping administration of study product and accrual or unblinding
25 (unmasking), and voting procedures. The SMC must maintain the confidentiality of its
26 internal discussions and activities, as well as the contents of data reports provided.

27 During the trial the SMC should review:

- 28 • Study progress and safety data
- 29 • Adherence to the protocol
- 30 • Factors that might affect the clinical trial outcome or feasibility or compromise the
31 trial data (such as slow accrual, poor data quality or timeliness, protocol violations,

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32 losses to follow-up, etc.)

33 • Data relevant to proceeding to the next stage of the clinical trial, if applicable

34 • If appropriate, effectiveness outcomes/endpoints

35 Other relevant issues, such as endpoint evaluability, pharmacokinetics and/or
36 immunogenicity data, site performance, and factors external to the clinical trial may also
37 need to be considered, as specified in the SPDSMP.

38 The SMC should conclude each review with the committee's recommendation to DAIDS as
39 to whether the clinical trial should continue, be modified, or be terminated.
40 Recommendations regarding modification of the design and conduct of the clinical trial may
41 include corrective actions when performance is unsatisfactory, or recommendations to
42 advance to the next dose in a dose escalation clinical trial, for example, or to the next stage
43 in product testing.

44 Confidentiality must always be maintained during all phases of SMC review and
45 deliberations. Only members of the SMC and the study biostatistician should have access to
46 the emerging study data sorted by treatment group (even if the group identities are masked).
47 Exceptions may be made when the SMC deems it appropriate. Whenever blinded data are
48 presented to the SMC, the key to the group coding must be available for immediate
49 unblinding.

50 2. Membership

51 The membership of the SMC should reflect the disciplines and medical specialties necessary
52 to interpret the data from the clinical trial and to fully evaluate participant safety. The SMC
53 generally consists of at least three voting members. Membership may include an ISM with
54 expertise in the clinical aspects of the disease/patient population being studied, and
55 expertise in current clinical trials conduct and methodology. An SMC may also include one
56 or two members of a standing DAIDS Data and Safety Monitoring Board (DSMB) and this may
57 be required by DAIDS.

58 Strong consideration should be given to including an independent biostatistician if statistical
59 analysis of the data will be evaluated. A biostatistician, as well as other specialists, may be
60 invited to participate as non-voting members on an ad hoc basis at any time if additional
61 expertise is desired. SMC and ad hoc members may be from the principal investigator's
62 institution or from other participating sites but cannot be directly involved with the trial or
63 under the supervision of a trial investigator. Furthermore, the SMC members should
64 generally be in a different organizational group than the Principal Investigator (PI).

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65 DAIDS and other National Institutes of Health (NIH) staff who are not involved in the clinical
66 trial may also participate as voting members. However, members of the sponsoring DAIDS
67 Branch are discouraged from having voting privileges. Medical Officers/Medical
68 Monitors/Clinical Representatives or other NIH staff involved in the clinical trial may
69 participate as ex officio, non-voting members, in selected cases. Representatives of the
70 manufacturer (industry collaborator) of the test substance(s) or any other individual with
71 vested interests in the outcome of the clinical trial are not eligible to serve on the SMC as ad
72 hoc, ex officio or voting members.

73 2.1. Conflict of Interest

74 SMC voting members cannot have any other involvement in the conduct of the
75 clinical trial. Furthermore, no member may have financial, proprietary, professional,
76 or other interests that could affect impartial, independent decision-making by the
77 SMC. Letters of invitation to prospective SMC and ad hoc members should include
78 the following: "Acceptance of this invitation to serve on the SMC for this study
79 confirms that I do not have any financial or other interest with any of the
80 collaborating or competing pharmaceutical firms or other organizations involved in
81 the study that constitute a potential conflict of interest." In addition, all SMC voting
82 and ad hoc members will sign a Conflict of Interest certification to that effect at the
83 time they are asked to participate (see Attachment A). At the beginning of every
84 SMC meeting, DAIDS Program staff or the SMC Chair will reconfirm that no conflict
85 of interest exists for SMC members. Interests that may create a potential conflict of
86 interest must be disclosed to the SMC prior to any discussion. The SMC will
87 determine how to handle such potential conflict. The SMC can require that a
88 member with a potential conflict not vote or take other means deemed appropriate.
89 DAIDS may dismiss a member of the SMC in the event of unmanageable potential
90 conflict.

91 2.2. Selection and Invitation to Participate

92 DAIDS may retain the primary responsibility for selection of the members and
93 chairperson and for organizing the SMC, or DAIDS may delegate this responsibility to
94 the study PI. If delegated to the study PI, the proposed description, charter,
95 operating procedures (including meeting/review schedule and venues), and roster
96 (with curriculum vitae (CVs) for each member) must be submitted at least 30 days
97 before the projected date of clinical trial initiation and approved in writing by DAIDS
98 before the clinical trial may be initiated. In some cases, SMC voting members may
99 select the Chair.

100 3. Meetings or Teleconferences

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101 The structure and operating procedures for a SMC are usually less formal than that of a
102 DSMB. The initial SMC meeting or teleconference should occur before the start of the trial
103 or as soon thereafter as possible. DAIDS staff may discuss DAIDS's perspective on and
104 expectations for the clinical trial at this time. At this session, the SMC should discuss the
105 protocol and the suggested triggers for data review, define a quorum, and establish
106 guidelines for monitoring the clinical trial. The SMC should decide whether any member(s)
107 should serve as an ISM and receive individual case reports of serious adverse events (SAEs)
108 and/or cumulative adverse event (AE) reports at specified intervals between the scheduled
109 interim SMC reviews. Guidelines for stopping the clinical trial for safety concerns should be
110 established. At this meeting, the SMC should also develop procedures for conducting
111 business (e.g., data required for review, voting rules, attendance, etc.). Teleconference calls
112 are usually the most appropriate means for conducting meetings.

113 Based on initial discussions, the SMC should decide whether to have additional ad hoc
114 meetings based on the occurrence of certain types or frequencies of adverse events. Ad hoc
115 meetings may also be triggered by study progress, or data quality events, or by external data
116 that would impact the clinical trial. Scheduling of meetings should be based on the
117 magnitude of the perceived risks, decision points in the protocol (e.g., the decision to move
118 to a higher dose), rate of enrollment, or problems that occur during the progress of the
119 clinical trial. The SMC may be asked for advice at the conclusion of the clinical trial about
120 whether to proceed with the next phase of development of the study product.

121 DAIDS is responsible to convene conference calls/meetings unless this has been delegated
122 in writing to the grantee. However, for cause meetings may be requested by any member of
123 the SMC, the PI, an Institutional Review Board (IRB)/Ethics Committee (EC), an industry
124 sponsor, or DAIDS. The study statistical team preparing the SMC data reports will be
125 responsible for ensuring the distribution of materials for review to SMC members and other
126 meeting participants.

127 3.1. SMC Meeting Format

128 The recommended meeting format may consist of the following sessions: Open
129 Session, Closed Session, and Closed Executive Session (optional).

130 3.1.1. Open Session

131 Occurrences of adverse events and toxicity issues are reviewed. Issues
132 relating to the general conduct and progress of the clinical trial should also be
133 considered. Efficacy outcome results must not be discussed during this
134 session and, for comparative trials, no study group-specific data will be
135 reviewed or discussed.

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136 SMC members (voting and ex officio), DAIDS staff members, and any ad hoc
137 experts may attend and participate in this session. The PI and study
138 statistician, if applicable, should attend and participate to present results and
139 respond to questions. This session is open to study investigators, coordinating
140 center staff, representatives for industry collaborators, representatives from
141 the U.S. Food and Drug Administration (FDA), and NIH program and
142 regulatory staff.

143 3.1.2. Closed Session

144 Study group-specific data including all relevant efficacy outcome measures,
145 masked if so specified, are presented at this session. This session is normally
146 attended only by voting members, non-voting (ex officio and ad hoc)
147 members, and the study statistician. The voting members can choose as a
148 group to make decisions and formulate recommendations either during this
149 session or during a Closed Executive Session.

150 3.1.3. Closed Executive Session (optional)

151 This final session involves only voting members to ensure complete
152 independence for making decisions and formulating independent
153 recommendations. The SMC may unmask the data during this session based
154 on procedures identified in advance.

155 3.2. Voting

156 A quorum, as defined by the SMC in the initial meeting, must be present either in
157 person or by teleconference. After a thorough discussion of SMC members' opinions
158 and rationale, the final recommendations of each SMC member should be solicited
159 in either Closed Session or Closed Executive Session. The final recommendations are
160 recorded and either identified as majority or minority positions (if a general
161 consensus is achieved) or followed by a vote for recommendations without an
162 achievable consensus.

163 4. Study-related information and Data Reports for SMC Review

164 It is the responsibility of the PI to ensure that the SMC is apprised of all new safety
165 information relevant to the study product and the clinical trial. If applicable, this includes
166 providing the SMC with a copy of the Investigator's Brochure (IB) or package insert in
167 advance of the first SMC session, as well as promptly providing all IB or package insert
168 revisions and all data safety reports issued by the industry sponsor. Summary safety and
169 enrollment data must be forwarded periodically to the SMC as directed by the SPDSMP. The

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170 SMC must receive all protocol revisions and may receive other documents relating to the
171 clinical trial, such as annual data reports, manuscripts, and newsletters. Other relevant new
172 information (e.g., results from studies of the same or similar agents or important preclinical
173 testing results) must also be provided on a timely basis.

174 The SMC will review the SPDSMP and the proposed general content of the SMC monitoring
175 data reports at the initial meeting. The SMC may request changes or additions to the actual
176 data elements to be presented and to the proposed review schedule. At each meeting,
177 further additions or modifications to these data reports may be directed by the SMC on a
178 one-time or continuing basis. Distribution of written data reports must allow sufficient time
179 for review.

180 Data reports for meetings of the SMC will consist of the Open Session Data Report and, as
181 required, a Closed Session Data Report. Open Session Data Reports are distributed to all SMC
182 members, selected DAIDS staff, and other appropriate persons as directed by the SMC.
183 Closed Session Data Reports are distributed only to SMC members and others as designated
184 by the SMC. The Closed Session Data Report may contain study group-specific outcome data
185 and should be marked confidential and handled accordingly.

186 5. Summary Reports From the SMC

187 5.1. Verbal Summary Report

188 At the conclusion of a SMC meeting, the SMC should discuss its findings and
189 recommendations with DAIDS representatives and the study investigators. If DAIDS
190 is not represented at the meeting, the SMC Chair should contact the DAIDS Program
191 Officer (PO) and Medical Officer (MO) immediately after the meeting for debriefing.

192 5.2. Summary Report

193 The SMC will issue a written summary report summarizing topics discussed by the
194 SMC and describing their findings, overall safety assessment, and recommendations.
195 This generally occurs after each meeting but SMCs that meet on a very frequent
196 basis may summarize more than one meeting in a single summary report. The
197 rationale for recommendations will be included when appropriate. This summary
198 report will not include confidential information. The SMC Chair or designee is
199 responsible for preparing and distributing the summary report.

200 Unless otherwise specified, the summary report will be submitted by the SMC chair
201 to the DAIDS PO and MO. The DAIDS PO will forward the summary report to a
202 designated study team representative (usually the PI) and to other appropriate
203 DAIDS staff. The study team representative is responsible for disseminating the SMC

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204 summary report to site investigators, and any Investigational New Drug Application
205 (IND) sponsors and industry collaborators. Site investigators must, in turn, submit
206 the summary reports to their respective IRBs/ECs in accordance with the reviewing
207 IRB/EC policy. If the trial is being conducted under an IND, the IND holder will
208 forward the summary report to the FDA.

209 5.3. Closed Session Minutes (optional)

210 The SMC may also prepare confidential minutes that include details of discussions in
211 the closed session(s). Meeting minutes are to be held in strict confidence, accessible
212 only to voting members of the SMC until a) such time when the clinical trial is closed,
213 b) DAIDS accepts a SMC recommendation for early termination, or c) if the minutes
214 are requested by the FDA or DAIDS for patient safety or regulatory purposes.

215 5.4. Immediate Action Summary Report

216 The SMC Chair will notify the DAIDS PO and MO of any findings of a serious and
217 immediate nature, such as if the SMC recommends substantial clinical trial
218 modifications or that all or part of the trial be discontinued. The PO and MO will
219 immediately inform appropriate Program staff, including their Branch Chiefs and
220 others as determined by their Program. In addition to verbal communications,
221 recommendations to discontinue or substantially modify the design or conduct of a
222 clinical trial must be conveyed to DAIDS in writing within 48 hours of the SMC
223 meeting. This written, confidential briefing may contain study group-specific and/or
224 unmasked supporting data and should include the SMC members' rationale for its
225 recommendations.

226 The SMC provides recommendations concerning continuation or major changes in
227 study conduct to DAIDS. After consultation with the investigators, all final decisions
228 regarding these recommendations are made by DAIDS.