

DAIDS
Bethesda, MD USA
Appendix 2
Study Progress, Data, and Safety Monitoring
INDEPENDENT SAFETY MONITOR (ISM) GUIDELINES

Approval Date:

No.: DWD-POL-SR-01.00A6

Effective Date:

1 Note that this Appendix applies to all National Institute of Allergy and Infectious Diseases
2 (NIAID) Division of AIDS (DAIDS) supported and/or sponsored clinical trials with an
3 Independent Safety Monitor (ISM) that are conducted outside of the HIV/AIDS Clinical Trials
4 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 An ISM is a physician or other health-care professional with relevant expertise whose
12 primary responsibility is to provide independent safety monitoring in a timely fashion.
13 There are two common circumstances in which an ISM functions, [A\) as the sole
14 independent reviewer](#) for a clinical trial or B) as a [member of a Data and Safety
15 Monitoring Board \(DSMB\) or Safety Monitoring Committee \(SMC\)](#), designated to
16 perform interim safety reviews between DSMB and SMC meetings.

17 A. ISM as Sole Independent Reviewer

18 1. Role and Responsibilities

19 An ISM is appropriate as the sole independent reviewer for small, early phase studies,
20 such as some pharmacokinetics, proof-of-concept, or immunogenicity studies, or other
21 studies of short duration. The ISM will work with the study team and the DAIDS Medical
22 Officer/Medical Monitor/Clinical Representative in review of safety data/reports,
23 including both individual case adverse event (AE) data and periodic cumulative AE
24 reports. Based on review of this safety data, the ISM will make recommendations
25 regarding the safe continuation of the clinical trial.

26 DAIDS may retain the responsibility to identify the ISM and define his/her role. The ISM
27 will be selected based on relevant study-related expertise. Participation will usually be
28 for the duration of the clinical trial. In some cases, DAIDS may delegate nomination of
29 the ISM to the study Principal Investigator (PI). If delegated, the study PI must submit to
30 DAIDS the CV of the person(s) proposed to serve as the ISM and a detailed description of
31 his/her role at least 30 days before the projected date of clinical trial initiation. DAIDS
32 must provide written approval for the ISM(s) recommended by the study PI and his/her
33 role, before the clinical trial is initiated.

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34 2. Conflict of Interest

35 An ISM cannot have any other involvement in the conduct of the study. He/she may be
36 a member of a participating institution's staff, but cannot be under the direct supervision
37 of an investigator and should preferably be from a different organizational group.
38 Furthermore, no ISM may have financial, proprietary, professional, or other interests
39 that could affect impartial, independent decision-making. Letters of invitation to
40 prospective ISMs should include the following: "Acceptance of this invitation to serve as
41 the ISM for this study confirms that I do not have any financial or other interest with any
42 of the collaborating or competing pharmaceutical firms or other organizations involved
43 in the study that constitute a potential conflict of interest." In addition, all ISMs will sign
44 a Conflict of Interest certification to that effect at the time they are asked to participate
45 (see Attachment A).

46 The DAIDS Program/Project Officer (PO) will reconfirm at least annually that no conflict
47 of interest exists. Interests that may create a potential conflict of interest must be
48 disclosed to the DAIDS PO prior to any review of data. The DAIDS PO, in consultation with
49 their Branch Chief, Program Director, or other appropriate staff, will determine if the
50 relationship is in conflict or gives the appearance of a conflict such that the individual
51 should not serve as the ISM. DAIDS may replace an ISM in the event of unresolvable
52 potential conflict.

53 3. Study Materials for ISM Review

54 The primary focus of the ISM is to independently review selected safety data as
55 determined by the Study Progress, Data, and Safety Monitoring Plan (SPDSMP). This will
56 include thorough evaluation of some or all individual SAEs and/or review of periodic
57 cumulative AE reports. Clinical and laboratory data, clinical records, and other study-
58 related records should be made available for ISM review. If necessary, special data
59 reports are prepared by the investigator or study statistician.

60 It is the responsibility of the PI to ensure that the ISM is informed of all new safety
61 information relevant to the study product. This includes providing the ISM with a copy
62 of the current Investigator's Brochure (IB) or the study product's Package Insert before
63 clinical trial initiation as well as promptly providing all IB revisions and all safety data
64 reports issued by the sponsor. Summary safety and enrollment data should be forwarded
65 periodically to the ISM. The ISM should receive all protocol revisions and may receive
66 other documents relating to the clinical trial.

67 4. Summary Reports From the ISM

68 The following summary reports are submitted by the ISM.

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69 4.1. Summary Report

70 According to pre-specified criteria delineated in the SPDSMP, and as needed in
71 response to study developments, the ISM will communicate in writing a summary of
72 his/her findings, any concerns, and recommendations. The SPDSMP will include a
73 communication pathway. Unless otherwise specified, the ISM will submit the
74 summary report to the DAIDS PO and MO. The DAIDS PO will forward the summary
75 report to a designated study team representative (usually the PI), and to other
76 designated DAIDS staff. The study team representative is responsible for
77 disseminating the ISM summary report to any other study investigators, and
78 relevant staff and each investigator must, in turn, submit the summary report as per
79 the reviewing Institutional Review Board (IRB)/Ethics Committee (EC) policy. If under
80 an Investigational New Drug Application (IND), the sponsor is responsible for
81 submitting the summary report to the Food and Drug Administration (FDA) and to
82 any industry collaborators as appropriate.

83 4.2. Immediate Action Summary Report

84 The ISM will immediately notify the DAIDS PO and MO of any findings of a serious
85 nature including any recommendations to significantly modify or discontinue all or
86 part of the clinical trial. The SPDSMP should state whether the PI will be informed
87 simultaneously or after DAIDS has had an opportunity to discuss and formulate a
88 plan. In addition to verbal communications, recommendations to discontinue or
89 substantially modify the design or conduct of a clinical trial must be conveyed to
90 DAIDS in writing within one day of the ISM review. This written, confidential
91 summary report may contain unblinded supporting data and include the ISM's
92 rationale for the recommendations. The summary report will be submitted to the
93 DAIDS PO and MO, who will determine further distribution. If under an
94 Investigational New Drug Application (IND), the sponsor is responsible for
95 submitting the summary report to the Food and Drug Administration (FDA) and to
96 any industry collaborators as appropriate.

97 4.3. Recommendations and Actions

98 ISM recommendations concerning continuation or major changes in study conduct
99 will be made directly to the DAIDS PO and MO. Final decisions regarding these
100 recommendations will be made by DAIDS.

101
102 B. ISM as Member of a DSMB or SMC

103 1. Role and Responsibilities

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104 DSMBs and SMCs may consider designating one or more members as ISM(s) to
105 review serious adverse events (SAE) reports and/or review periodic cumulative
106 adverse event reports between scheduled interim full committee reviews. Based on
107 this review, the ISM may make recommendations for an *ad hoc* or urgent full
108 committee review. The contents and schedule of data reports to be reviewed by the
109 ISM will be specified in the SPDSMP with additional input from the DSMB or SMC.

110 2. Conflict of Interest

111 See [Appendix 1, SMC Guidelines](#), section 2.1 for COI information on SMC members.

112 The ISM will confirm that he/she has no conflict of interest prior to performing the
113 independent review. Interests that may create a potential conflict of interest must
114 be disclosed to the DSMB or SMC Chair prior to the review. The DSMB or SMC will
115 determine how to handle such potential conflict. The DSMB or SMC can require that
116 an ISM with a potential conflict be replaced or take other means deemed
117 appropriate.

118 3. Study Materials for ISM Review

119 The primary focus of the ISM is to independently review selected safety data as
120 guided by the DSMB or SMC. This may include thorough evaluation of some or all
121 individual SAEs and/or review of periodic cumulative AE reports. Clinical and
122 laboratory data, clinical records, and other study-related records should be made
123 available for ISM review. If necessary, special data reports are prepared by the
124 investigator or study statistician.

125 4. Summary Reports From the ISM

126 The ISM operates under the guidelines of the DSMB or SMC

127 4.1. Summary Report

128 According to pre-specified criteria delineated by the DSMB or SMC, and as needed in
129 response to study developments, the ISM will communicate in writing a summary of
130 his/her findings, any concerns, and recommendations. The ISM will submit the
131 summary report to the DSMB or SMC and additional parties as specified in the
132 SPDSMP. When appropriate, the ISM will recommend an urgent or ad hoc, for cause
133 DSMB/SMC meeting.

134 4.2. Recommendations and Actions

135 The ISM will bring his/her concerns to the DSMB or SMC. The DSMB or SMC will be
136 the body to make recommendations to DAIDS. See the [DSMB Charter](#) and [Appendix](#)

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137 [1, SMC Guidelines](#) for information on the DSMB and SMC processes to communicate
138 recommendations to DAIDS. Final decisions regarding these recommendations will
139 be made by DAIDS.

140

141 For additional information on the DSMB, see the [NIAID Policy on Data and Safety](#)
142 [Monitoring Board \(DSMB\) Operations](#). For additional information on the SMC, see
143 the [Appendix 1, SMC Guidelines](#).