

Study
Data and Safety Monitoring Board

1.0 INTRODUCTION

The *Data and Safety Monitoring Board (DSMB)* is the primary data and safety advisory group for the *Sponsor* (Sponsor) study entitled "*Title*." The *DSMB* periodically reviews study results, evaluates the treatments for excess adverse effects, determines whether the basic trial assumptions remain valid, judges whether the overall integrity and conduct of the trial remain acceptable, and makes recommendations to the *Study Steering Committee*. The *Steering Committee* has the responsibility to accept, reject, or to modify *DSMB* recommendations.

2.0 ORGANIZATION

2.1 Composition of the *DSMB*

The Committee consists of *number* individuals. The membership includes clinicians, *laboratory scientists, surgeons*, and at least one member is a statistician. All members shall have experience and expertise in clinical trials. Committee members may not participate in the study as principal or co-investigators, or as study patient care physicians.

2.2 Selection of *DSMB* Members

The *DSMB* Chair and members are selected by the *Steering Committee* Chair, after consultation with the Sponsor.

In the event that a member is unable to continue participation on the *DSMB*, the *DSMB* chair recommends a replacement to the *Steering Committee* Chair.

3.0 RESPONSIBILITIES AND FUNCTIONS

The *DSMB* is responsible to the *Steering Committee* for oversight of the study data and safety considerations. Initially, the *DSMB*:

- Reviews the study protocol and any protocol amendments, makes recommendations to the *Steering Committee* and Sponsors with regard to changes, and gives approval.

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- Reviews overall data collection methods and safety monitoring procedures and makes recommendations for additions or adjustments.
- Defines safety and related parameters to be monitored, frequency of committee monitoring reviews, methods for review, and establishes criteria for making recommendations to the *Steering Committee*.

The *DSMB* reviews data generated by the study and study safety events on a periodic basis and recommends one of the following actions to the study *Steering Committee*:

- Discontinue the study (with provisions for orderly discontinuation in accord with good medical practice).
- Discontinue one treatment arm of the study (with provision for orderly discontinuation).
- Modify the study protocol. Modifications may include, but are not limited to, changes in inclusion/exclusion criteria, frequency of visits or safety monitoring, alterations in study procedures, adjustments in sample size, changes in duration of observation and follow up.
- Continue the study according to the protocol and any related amendments.

4.0 RESPONSIBILITIES OF THE SPONSOR

The Sponsor is responsible to the *DSMB* for the following:

- Making resources available to the *DSMB* as required to carry out its designated functions.
- Creating and maintaining an independent Statistical Data Analysis Center to receive data from the Data Management Center. The Statistical Data Analysis Center prepares reports for the *DSMB*.
- Communication of all pertinent regulatory information to the Federal Food and Drug Administration (FDA).

5.0 RESPONSIBILITIES OF THE DATA MANAGEMENT CENTER

The Data Management Center will be responsible for the following:

- Collection and on-site monitoring of case report forms (CRF).
- Ensuring the completeness and accuracy of all data collected to the extent required by the *DSMB* and the Sponsor; this includes CRF data, *central-laboratory data and data from central endpoint review committees*.
- Providing analysis data sets to the Statistical Data Analysis Center containing all CRF data necessary for creating *DSMB* reports.

6.0 RESPONSIBILITIES OF THE STATISTICAL DATA ANALYSIS CENTER

The Statistical Data Analysis Center (SDAC) is responsible for the overall data analysis preparation for review by the *DSMB*.

The Statistical Data Analysis Center prepares reports for review by the Committee based on data generated by the Sponsor and the Data Management Center. It also prepares reports based on supporting documentation for events and may receive copies of case report forms directly from study patient care physicians for these events.

The SDAC will prepare interim reports on recruitment, baseline comparisons of risk factors, compliance, primary and secondary outcomes, safety and adverse effects, and a limited number of sub-group analyses. *The SDAC will repeat these analyses for the final analysis of the trial.*

7.0 CONDUCT OF *DSMB* MEETINGS

7.1 Scheduled Meetings

The *DSMB* physically convenes prior to initiation of the study. Thereafter, the frequency of scheduled meetings depends on patient enrollment and safety event rates. However, a scheduled meeting convenes in a single location at a minimum of once yearly. *If necessary, additional meetings may be held by conference calls if the DSMB so decides.*

7.2 Quorum

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A quorum of Committee members are required at either scheduled meetings, phone conferences, or unscheduled meetings. *Three quarters* of the Committee members must be present for voting on recommendations to the *Steering Committee*.

7.3 Voting

The *DSMB* members vote on all recommendations to be submitted to the *Steering Committee*. To vote, a Committee member must be present at convened scheduled meetings or be a participant through conference calls. A simple majority of members present passes a proposal, motion, or recommendation to the *Steering Committee*.

7.4 Procedures for Recommendations to the Steering Committee

Duly voted and passed *DSMB* recommendations to the *Steering Committee* are transmitted in writing to the *Steering Committee* chairman within seven working days of the meeting at which the recommendation was formulated and passed. *The Steering Committee* has the responsibility to communicate recommendations to the Sponsor.

7.5 Summary Notes

Summary notes are prepared by *SDAC* for each *DSMB* meeting, distributed in a timely manner after each meeting, and reviewed and approved at the subsequent meeting.

With the expectation that the *Steering Committee* and its chairman are masked to study treatments, and that the summary notes will contain some data by treatment groups (even with treatments designated by code), the summary notes will not be forwarded to the *Steering Committee* chairman or the Sponsor. At the end of the study and after treatment is unblinded, a copy of the summary notes are forwarded to the Sponsor and the *Steering Committee*.

7.6 Meeting Format

Meetings will consist of open and closed portions. During the initial open portion of a meeting, the Sponsor and Study Chair may be invited to make brief presentations and be available for questions from the *DSMB* members. The open session will only discuss aggregate data. The closed session will be restricted to the *DSMB* and the staff from the Statistical Data Analysis Center. The closed session will discuss accumulating data by assigned treatment group.

7.7 Confidentiality

All members will treat as confidential the reports, meeting discussions, and minutes.

7.8 Conflict of Interest Guidelines

Members of the *DSMB* will not buy, sell, or hold stock options in the Sponsor for the following periods: from the first meeting of the *DSMB* until the last meeting and the study results are made public; or from the first meeting until the member's active personal involvement in the *DSMB* ends.

Each member agrees not to serve as a paid consultant to the Sponsor during these same periods unless exempted by the *DSMB* chair. The guidelines will also apply to the member's spouse and dependents and to the Statistical Data Analysis Center and Data Management Center.

Certain other activities are not viewed as constituting conflicts of interest but must be reported annually to the *DSMB chair*. These include: the participation of a member in educational activities supported by the Sponsor, the participation of members in other research projects supported by the Sponsor, and occasional scientific consulting to the Sponsor on issues not related to the product in the trial and for which there is no financial payment or other compensation.

APPENDIX I - STATISTICAL GUIDELINES

A. General Considerations for Repeated Tests

Interim data safety reports pose well recognized statistical problems related to the multiplicity of statistical tests to be conducted on the accumulating set of data. The basic problem is well known and is referred to as “sampling to a foregone conclusion” (Cornfield)¹ or the problem of repeated significance tests (Armitage, McPherson, and Rowe²; McPherson³). Armitage et al² have shown that, with successive repeated significance tests at the usual 0.05 significance level using the corresponding critical value of 1.96, the likelihood of a Type I (false positive) error increases from $\forall = 0.05$ for the first test to $\forall = 0.14$ after five tests, 0.19 after 10 tests, 0.32 after 50 tests, and eventually to $\forall = 1.0$.

1. Adjustment for Repeated Significance Tests

An obvious solution to the problem of repeated tests would be to require a smaller p-value or a correspondingly larger critical value for statistical significance at each successive test so that the realized overall Type I error level would still be within the desired limits. For example, if up to five data analyses were to be conducted for a single primary question, based on the work of Armitage et al² and Pocock^{4,5}, each of these five reports should employ an alpha level of 0.016 for significance (or critical Z value of 2.413 rather than 1.96) in order to ensure an overall (two-sided) Type I error level of $\forall = 0.05$. Procedures such as this one are referred to as “group sequential” procedures. Among the group sequential procedures, the group sequential boundary proposed by O’Brien and Fleming⁶ will be adopted as a guide in interpreting interim analyses. The boundary requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final scheduled analysis is near the “nominal” critical value. For example, for four interim analyses with a two-sided \forall of 0.05, the critical value at the scheduled termination is 2.01, close to the “nominal” value of 1.96. An example of these boundaries is shown below. The result of this procedure is that sample size does not need to be increased over the fixed sample size estimate and the power is decreased only slightly; usually less than 1%. Group sequential procedures, however, require that the total number of tests (i.e., analysis or “looks” at the data) be specified beforehand, as well as the exact increments between each look. For example, the validity of four interim analyses with the above critical values is based on four tests each with an equal increment in study experience.

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A more general approach to sequential testing has been presented by Lan and DeMets⁷, for which neither the number of analyses nor the increments between analyses must be pre-specified. Rather, Lan and DeMets only require specification of the rate at which the Type I error, say total $\alpha = 0.05$, will be “spent.” This procedure allows “spending” a little at each interim analyses in such a way that, at the end of the study, the total Type I error does not exceed, for example, 0.05. A spending function can be defined which provides an O’Brien-Fleming type boundary while allowing more flexibility. A spending function is defined in terms of information time, which in the case of this protocol will be *the fraction of total expected events observed* (Lan and DeMets⁸).

| Information Fraction (% of placebo events) | Critical Value | Nominal P-value (two-sided) |
|---|--------------------|--------------------------------|
| .25 | $\alpha \leq 3.5$ | .0004 |
| .50 | $\alpha \leq 2.99$ | .0028 |
| .75 | $\alpha \leq 2.36$ | .018 |
| 1.00 | $\alpha \leq 2.01$ | .044 |

2. *STUDY* Group Sequential Plan

In *STUDY*, we have the following primary comparisons:

If the *DSMB* should meet at different information fractions, the Lan-DeMets procedure will adjust the critical values in order to guarantee an overall α level. Changing frequency, even if data-dependent, affects the alpha level very slightly and thus no further formal adjustments are necessary.

The boundaries used in this study will be two-sided (α %), symmetric O’Brien-Fleming type boundaries. Since this O’Brien-Fleming procedure is quite conservative, critical values obtained early in the trial can be quite large, in fact, larger than say ± 3.5 . Results which exceed this early in the trial might cause the *DSMB* a great deal of discomfort. A slight modification which never allows the critical value to exceed ± 3.5 can be superimposed on the “O’Brien-Fleming” type boundary as implemented by Lan and DeMets.

The Lan and DeMets procedure will be formally applied to the primary outcome comparisons expressed as Cochran-Mantel-Haenszel Statistics. These will entail

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an analysis of time to event using the log-rank tests. Using the log-rank test in the group sequential format has been established by Tsiatis⁹, Gail, DeMets and Slud¹⁰, and DeMets and Gail¹¹.

Repeated confidence intervals such as those proposed by Jennison and Turnbull¹² can be obtained for this procedure. The confidence interval for the parameter is $\pm Z*SE$, where Z is the critical value produced by the alpha spending function. Following study termination, confidence intervals can be obtained for spending functions as indicated by Kim and DeMets¹³ following work of Tsiatis, Mehta, and Rosner¹⁴.

The assessment of side effects and other secondary outcomes will also use the O'Brien-Fleming boundaries generated by the Lan-DeMets procedure as working guidelines. For these interim analyses, the critical Z value and the corresponding p-value required for significance can be assessed precisely.

There are a wide variety of other statistical methods that could be applied to the problem of early termination of a clinical trial when a significant difference emerges. The above procedures, however, are widely accepted in use in the interim analysis of clinical trials and quite appropriate to most trials.

B. Multiplicity of Analyses

Another consideration when interpreting p-values is the multiplicity of analyses for individual secondary and safety variables conducted for a given report. If K variables are analyzed at true significance level, then the probability that at least one could be “significant” by chance could be as high as $1 - (1 - \forall)^K$, (e.g., if $K = 50$ and $\forall = 0.05$, this probability could be as high as 0.92.) The improved (“Sidak”) Bonferroni inequality (Miller¹⁵) provides a conservative adjustment for this requiring that each analysis reach $\forall_K = 1 - (1 - \forall)^{1/K}$ to ensure that the Type I error for the total study does not exceed alpha. Again for $\forall = 0.05$ and $k = 50$, $\forall_K = 0.001$ would be required for significance in any one of the 50 analyses to ensure the probability of one or more chance findings does not exceed 0.05. Less conservative improved Bonferroni critical values have been proposed (Holm¹⁶ and Hochberg¹⁷), since each requires the traditional Bonferroni adjustment only for the most extreme difference observed.

Clearly, to attempt to adjust for the effects of repeated significance test and the multiplicity of analyses would require absurdly small significance levels. Instead, we shall be conservative in the interpretation of the multiple analyses, looking for consistency across variables. The primary outcome variable and a few selected secondary outcomes should be declared *a priori* to help guard against the multiple variable testing problem and are listed under Section *XX.X* of the main protocol.

APPENDIX I - REFERENCES

1. Cornfield J. Sequential trials, sequential analysis, and the likelihood principle. *American Statistician*. 20:18-23, 1966a.
2. Armitage P, McPherson CK, Rowe BC. Repeated significance tests on accumulating data. *Journal of the Royal Statistical Society, Series A*. 132:235-244, 1969.
3. McPherson K. Statistics: The problem of examining accumulating data more than once. *New England Journal of Medicine*. 290:501-502, 1975.
4. Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*. 64:191-199, 1977.
5. Pocock SJ. Interim analyses for randomized clinical trials: The group sequential approach. *Biometrics*. 38:153-162, 1982.
6. O'Brien PC and Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 35:549-556, 1979.
7. Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 70:659-663, 1983.
8. Lan KKG and DeMets DL. Changing frequency of interim analysis in sequential monitoring. *Biometrics*. 45:1017-1020, 1989.
9. Tsiatis, A. A. The asymptotic joint distribution of the efficient scores tests for the proportional hazards model calculated over time. *Biometrika*. 1981; 68:311-315.
10. Gail, M., DeMets, D.L., Slud, E.V., Simulation studies on increments of the two-sample logrank score test for survival data, with applications to group sequential boundaries. *Survival Analysis Monograph Series 2* (R Johnson and J Crowley, Eds.) 1981; IMS Lecture Notes, Hayward, CA.
11. DeMets, D.L., Gail, M. Use of logrank tests and group sequential methods at fixed calendar times. *Biometrics* 1985; 41:1039-1044.
12. Jennison C and Turnbull BW. Repeated confidence intervals for group sequential trials. *Controlled Clinical Trials*. 5:33-45, 1984.

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13. Kim K and DeMets DL. Confidence intervals following group sequential tests in clinical trials. *Biometrics*. 43:857-864, 1987.
14. Tsiatis AA, Rosner GL, Mehta CR. Exact confidence intervals following a group sequential test. *Biometrics*. 40:797-803, 1984.
15. Miller RG. *Simultaneous Statistical Inference*. McGraw Hill, New York, NY, 1966.
16. Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*. 6:65-70, 1979.
17. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 75:800-802, 1988.

APPENDIX II - GENERAL CONSIDERATIONS FOR THE DATA AND SAFETY MONITORING BOARD

In addition to the statistical considerations discussed in Appendix I, other considerations in making recommendations for protocol changes will be taken into account by the *DSMB*. These issues are discussed below and include both the magnitude of the observed differences and their consistency as well as the importance of the differences to the health and the safety of the individuals in the trial. It is important for these issues to be stated in advance to assure both the patients and the Investigators, who will be masked to the aggregate data, that the *DSMB* will carefully consider the issues of safety and recommend protocol changes if questions of safety arise.

Those safety and adverse experiences will be monitored by the *DSMB* *at least twice yearly*. Obviously, if important adverse experiences occur in the interim, and a substantial trend emerges, an emergency meeting of the *DSMB* will be called. It is important to recognize that the *DSMB* will review all the relevant data available and additional analyses may be required before they will make the suggestions that the trial be modified.

Whereas statistical considerations have been discussed in Appendix I, interpretation of interim data is very complex and requires both clinical and statistical experts reviewing the data in concert. A number of considerations for interpretation of these data can be stated and these include:

- a. Whether the results could be explained by possible differences in the baseline variables between the groups;
- b. Whether the ascertainment of outcomes could be biased because of the differences in treatment programs (ascertainment bias);
- c. Whether the results are consistent for other variables which should be associated with the primary outcome variable in question;
- d. Whether the results are consistent among various subgroups of patients and across the various centers involved in the study;
- e. Whether the risk which is under consideration is outweighed by assessment of the overall benefits of therapy;
- f. Whether the results could be due to concomitant therapy and not due to the differences in the treatment programs;

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- g. Whether the statistical considerations discussed in the earlier sections have been considered;
- h. Whether it is likely that the current trends could be reversed if the trial were to be continued unmodified;
- i. Whether and how much additional precision could be obtained by continuing the trial under the present protocol; and,
- j. Whether there would be significant loss in overall considerations of the validity of the trial by the medical community by discontinuation or change in protocol.

All of these considerations require expert evaluation and are considered the major role of the *DSMB*. The *DSMB* will consider these issues on a regular basis to assure the safety of the patients and to assure the investigators and the medical community that the risks of this trial are being evaluated and the patient's safety is being kept foremost in mind. In addition, as a general rule the *DSMB* will make no recommendation to terminate the study early for effectiveness until approximately 50% of the projected patient's months of follow up are accrued.

Thus, a recommendation to modify or terminate the trial would not be based totally on statistical grounds, nor should it be. Rather, the *DSMB* supports the view voiced by Canner, on behalf of the Coronary Drug Project¹, that for decision making in clinical trials, "No single statistical decision, rule, or procedure can take the place of the well reasoned consideration of all aspects of the data by a group of concerned, competent, and experienced persons with a wide range of scientific backgrounds and points of view."

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Coronary Drug Project Research Group. Practical aspects of decision making in clinical trials: the Coronary Drug Project as a case study, *Controlled Clinical Trials*. 1:363-376, 1981.