

General Considerations for the DSMB

This appendix lists some of the considerations to be taken into account by the DSMB. These issues 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 patients in the study. It is important for these issues to be stated in advance to assure both the patients and the investigators, that the DSMB will carefully consider the issues of safety and recommend protocol changes if questions of safety arise.

If important adverse experiences occur between planned meetings, and a substantial trend emerges, the Chair will call an emergency meeting of the DSMB. It is important to recognize that the DSMB will review all the relevant data available and may request additional data prior to making any suggestions, which will alter the study.

Interpretation of safety data is very complex and requires both clinical and statistical experts reviewing the data. 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 outcomes could be biased because of the differences in treatment programs;
- c. Whether the results are consistent for other variables which should be associated with the primary outcome variables in question;
- d. Whether the results are consistent among various subgroups of patients and across 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 results could be due to confounding factors and not due to the device;
- g. Whether it is likely that the current trends could be reversed if the trial were to be continued unmodified.

All of these considerations require expert evaluation and are 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 study are being evaluated and the patient's safety is being kept foremost in mind. At the point where the DSMB believes that evidence of a meaningful difference beyond a reasonable doubt exists between treatment arms such that a specific recommendation related to alteration of the study would be made, a statistician will identify the appropriate treatment groups and the Steering Committee will be notified.