

Appendix IIIC

The DRAFT Charter of the

Data Safety Monitoring Board (DSMB) for POINT

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1. Introduction

The Charter will define the primary responsibilities of the DSMB, its relationship with other trial committees, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMB, and an outline of the content of the Open and Closed Reports that will be provided to the DSMB.

2. Primary responsibilities of the DSMB

The DSMB will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about stopping or continuing the trial to the trial Executive Committee. To contribute to enhancing the integrity of the trial, the DSMB may also formulate recommendations relating to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMB will be advisory to the Executive Committee. The Executive Committee will be responsible for promptly reviewing the DSMB recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

3. Membership of the DSMB

3.1 Members

The DSMB is an independent multidisciplinary group consisting of clinician-scientists that collectively, has experience in the management of patients with stroke and in the conduct and monitoring of randomized clinical trials. An independent statistician from the NETT SDMC will be assigned to the DSMB to facilitate data presentation and analyses, but will have no voting rights for any decisions that are taken. The NINDS will select members of the DSMB.

3.2 Conflicts of interest

DSMB membership is restricted to individuals free of relevant significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Individuals who fulfill any of the following criteria are automatically disqualified from membership: the study investigators, individuals employed by UCSF, the University of Michigan, or the Medical University of South Carolina, and individuals employed or consulting with Sanofi, Bristol-Myers Squibb, Boehringer-Ingelheim, or another company making a competing antiplatelet agent. The DSMB members will disclose to fellow members any potential conflicts of interest, and the DSMB will be responsible for deciding whether any materially impact on their objectivity.

DSMB membership is to be for the duration of the clinical trial. If any member leaves the DSMB during the course of the trial, the NINDS will promptly appoint their replacements.

4. Timing and purpose of the DSMB meetings

4.1 Organizational meeting and early safety/trial integrity reviews

This charter was written to be ready by the start of the trial. This draft charter was developed by the UCSF trial statistician and Principal Investigator. In finalizing the DSMB charter, the trial leadership will provide an advisory review of scientific and ethical issues relating to study design and conduct and will discuss with the DSMB the standard operating procedures for the role and functioning of the DSMB, and the format and content of the Open and Closed Reports that will be used to present trial results at future DSMB meetings.

4.2 Formal interim analysis meetings

Two 'Formal Interim Analysis' meetings will be held to review data relating to treatment efficacy, patient safety and quality of trial conduct.

The major interim efficacy analysis will be done when 33% (177) and 66% (353) of 530 expected events have occurred. The first analysis meeting of the DSMB is planned for 6 months from the start of the study to review initial safety data and finalize form of reports, and subsequent meetings of the DSMB will occur at 6 month intervals afterwards either by teleconference or face to face. Reports will be sent to the DSMB prior to these meetings. The date of each DSMB meeting will be made available to the trial statistician with at least six weeks notice. The first formal interim efficacy analysis is planned for approximately 18 months from initiation of enrollment, with the second occurring approximately 15 months later. The trial Principal Investigator and other members of the Trial Operations Committee will attend an open session at the beginning of the meeting, and will be available at the end of the meeting to answer any questions. An unblinded statistician from the NETT SDMU will prepare the reports and attend the whole meeting to assist with the interpretation of the results.

5. Procedures to ensure confidentiality & proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMB has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment arm. The NETT SDMC will provide the Chair of the DSMB with information on any serious *unexpected* adverse reactions to the study treatment, as reviewed by the medical monitors, and will also be responsible for satisfying the standard requirements for reporting of relevant events to the regulatory authorities.

At the same time, procedures will be implemented to ensure proper communication is achieved between the DSMB and the trial investigators and the sponsor. To provide a forum for exchange of information among various parties that share responsibility for the successful conduct of the trial, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the DSMB to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMB and others who have valuable insights into trial-related issues.

All materials, discussions and proceedings of the DSMB are completely confidential. DSMB members and other participants in DSMB meetings (such as the trial statistician) are expected to maintain

confidentiality, and will refrain from revealing to the trial Executive Committee, or any other party, information that would lead to compromising the integrity of the trial unless such release is required to protect patient safety.

5.1 Closed sessions

Sessions involving only DSMB membership and the unblinded statistician who generated the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DSMB will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMB will be unblinded in its assessment of safety and efficacy data (at formal interim analysis). During these sessions, the DSMB will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

5.2 Open sessions

In order to allow the DSMB to have adequate access to information provided by the trial investigators, or by members of the regulatory authorities, a joint session between these individuals and DSMB members (called an Open Session) will be held before the Closed session. If necessary, a further Open Session can be held, on request either in the middle or end of the Closed Session. Open sessions give the DSMB an opportunity to query these individuals about issues that have arisen during their review in the initial Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved. These individuals will either be present at the DSMB meeting or be provided a telephone link.

5.3 Open and closed reports

For each DSMB meeting, Open and Closed Reports will be provided (see Section 8 for outlines of the content of these reports). Open Reports, available to all who attend the DSMB meeting, will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up and compliance.

Closed Reports, available only to those attending the Closed Sessions of the DSMB meeting, will include analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of adverse events and symptom severity, and Open Report analyses that are displayed by intervention group.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within approximately one month of the date of the DSMB meeting. The Reports should be provided to DSMB members approximately two weeks prior to the date of the meeting.

5.4 Minutes of the DSMB meeting

The minutes of the DSMB meetings closed session will be prepared by unblinded statisticians who will also attend the DSMB meetings. A POINT clinical coordinating center member will prepare the minutes of the open session. Two sets will be prepared: the Open Minutes and the Closed Minutes.

The Open Minutes will describe the proceedings in the Open Session of the DSMB meeting, and will summarize all recommendations by the DSMB. Since these minutes will be circulated immediately to the trial Principal Investigator, it is necessary that these minutes do not unblind the efficacy and safety data if the DSMB is not recommending early termination.

The Closed Minutes will describe the proceedings from all sessions of the DSMB meeting, including the listing of recommendations by the Committee. Because it is likely that these minutes will contain unblinded information, it is important that they are not made available to anyone outside the DSMB. Rather, copies will be kept by the DSMB chair and unblinded statistician(s). These will be archived at the time of study closure.

5.5 Recommendations to the trial Executive Committee

At each meeting of the DSMB during the conduct of the trial, the DSMB will make a recommendation to the Executive Committee to continue or to terminate the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter. Should the DSMB consider a recommendation by any member to terminate the trial early, a full vote of the DSMB will be required. In the event of a split vote, the decision will go with the majority vote, but a report should be provided to the Executive Committee, written by the DSMB members who are in the minority, for the purposes of officially stating their position on the issue. This report should unblinded data only when absolutely necessary to inform the Executive Committee. This information should be forwarded to the trial Principal Investigator as rapidly as possible.

The Executive Committee is convened to review the recommendations. The Executive Committee takes responsibility for the design, conduct and analysis of the clinical trial. The Executive Committee is a multidisciplinary group that, collectively, has the scientific, medical and clinical trial management experience to conduct and evaluate the trial.

The Executive Committee is ultimately responsible for safeguarding the interests of participating patients and for the conduct of the trial, acting on the advice of the DSMB. Recommendations to amend the protocol or conduct of the study made by the DSMB will be considered and accepted or rejected by the Executive Committee. The Executive Committee will be responsible for deciding whether to continue or to stop the trial based on the DSMB recommendations. If the trial statistician feels conflicted in decision making by having knowledge of the unblinded data, he will recommend an independent statistician be brought in to advise the Executive Committee.

The DSMB will be notified of all changes to the protocol or to study conduct. The DSMB concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to their implementation.

The Executive Committee will maintain confidentiality of all information it receives other than that contained in the Open Reports until after the trial is completed or until a decision for early termination has been made.

6. Statistical monitoring guidelines

During the period of recruitment into the study, interim analyses of the proportion of patients alive and independent, or dead, or with other major outcome events will be supplied, in strictest confidence, to all members of the DSMB, along with any other analyses that the DSMB may request.

In the light of these analyses, the DSMB will advise the chairman of the Executive Committee if, in their view, the randomized comparisons have provided both

(i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and

(ii) evidence that might reasonably be expected to lead many clinicians conversant with the available evidence to materially change their practice with regard to the choice of early antiplatelet therapy after acute TIA.

Criteria for stopping or modifying the trial for safety will also consider the balance of ensuring safety for trial participants and how early stopping will impact on clinical practice. For the interim analyses of the composite event for the primary efficacy analysis, O'Brien and Fleming (1979) stopping boundaries are adopted. The two interim analyses will occur after approximately 177 (1/3 of 530 total events) and 353 (2/3) events have been observed. Depending upon the DSMB request, additional interim analyses may be conducted. The spending function approach gives flexibility in the timing and frequency of interim analyses. The most current version of the EAST[®] software (Cytel Corporation) will be used as the interim monitoring tool.

At any interim analysis, if the stopping boundary is crossed, the DSMB may recommend stopping the study for overwhelming efficacy of one treatment over the other, although the better treatment may not necessarily be clopidogrel. If and only if the stopping boundary is crossed, prior to making the final decision for recommendation to stop the study, it is expected that the DSMB would request thorough analyses of secondary outcomes and subgroup analyses to confirm the findings of the primary outcome results.

Futility analyses are planned to be conducted to coincide in timing with the tentatively scheduled interim analyses for efficacy (at three equal intervals of information). However, if the recruitment is much slower than anticipated or if new information from sources external to the study about the clopidogrel treatment becomes available, the futility of the therapy may be assessed earlier or in-between planned intervals of interim analyses.

The stochastic curtailment method is adopted based on conditional power (Lan KKG et al, 1982). The informal criterion for determination of futility is that at each interim look, if the conditional power (defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated so far and under the assumption that the alternative is true) falls below 20%, then the DSMB evaluates all study information (such as overall recruitment rate and secondary outcome assessment data) to consider stopping the study for futility. The evaluation is conducted in a blinded manner.

Evaluation of futility using conditional power allows flexibility in that it can be calculated and assessed at anytime during the study without inflation of the Type I error probability and that the threshold does not necessarily have to be pre-specified. The drawback is that the overall Type II error probability may not be preserved, whereas a formal but less flexible hypothesis testing approach using the beta-spending function for futility boundaries (Pampallona S et al, 2001) does preserve power. However, for the POINT Trial, the flexibility of this informal approach to assessing futility holds more appeal because it allows other information to be taken into consideration, such as recruitment and safety data and conditional power at other alternative effect sizes (Friedlin B and Korn EL, 2002).

An interim monitoring tool, the most current version of the EAST[®] software will be used to estimate the conditional power.

Following a report from the DSMB, the Executive Committee will decide whether to modify entry to the study (or seek extra data). Unless this happens, however, the Executive Committee, the collaborators and central administrative staff will remain ignorant of the interim results.

7. Content of the DSMB's open and closed reports

7.1 Open statistical report: an outline

- Statistical commentary explaining issues presented in Open Report figures and tables
- Major protocol changes
- Study accrual by month and by site, including an assessment of whether recruitment targets are being met and whether enough sites are randomizing patients.
- Details of the number of pending and missing case report forms (including the number of seriously overdue follow-ups), and the number with outstanding data items.
- Baseline characteristics (pooled by treatment regimen)
- Eligibility violations
- Time between randomization and initiation of treatment
- Adherence to medication schedule (pooled by treatment regimen)
- Any other relevant information (such as updated Cochrane reviews)
- Pooled analysis of primary outcome

7.2 Closed statistical report: an outline

- Statistical commentary explaining issues raised by Closed Report figures and tables
- Repeat of the Open Report information, in greater detail by treatment group
- Details of any patients in the double-blind part of the trial for whom treatment was unblinded.
- Analyses of primary and secondary efficacy endpoints
- Subgroup analyses and analyses adjusted for baseline characteristics
- Analyses of adverse events and overall safety data, including:
 - Mortality within 90 days from randomization
 - Symptomatic intracranial hemorrhages within 90 days
 - Severe bleedings events within 90 days
 - Moderate bleeding events within 90 days
 - Other serious adverse events within 90 days

- Discontinuation of medications
- Information on crossover patients

8. Acknowledgements

This document was adapted from a section in 'Data Monitoring Committees in Clinical Trials-A Practical Perspective' (Ellenberg SS, Fleming TR, DeMets DL. Data Monitoring Committees in Clinical Trials-A Practical Perspective. Statistics in Practice, John Wiley and Sons, Chichester, England, 2002).