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**Data Monitoring Committee Charter Template**

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| **Data Monitoring Committee (and Interim Analysis Group) Charter** |
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| **Protocol Number(s):** insert number(s)  If the trial will have multiple protocol numbers over time it might be impractical to list them here (and have to keep updating the list), in which case omit them and use the trial’s name. |
|  |
| **[Insert Trial Name]** |

[**Amendment [#]**, if applicable]

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1. ABBREVIATIONS

* Only abbreviations actually used in the text should be in the Abbreviations section of the document. Common abbreviations listed below do not need to be spelled out at first use in the text; however, they must be included in the Abbreviations section of the document.

|  |  |
| --- | --- |
| AE | Adverse Event |
| COIMS | Council for International Organizations of Medical Sciences |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DMC | Data Monitoring Committee |
| EDMS | Electronic Document Management System |
| FOIA | Freedom of Information Act |
| IAG | Interim Analysis Group |
| IB | Investigator’s Brochure |
| ISA | Intervention Specific Appendix |
| IVRS/IWRS | Interactive Voice/Web Response System |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System |
| SSG | Statistical Support Group |
| TA | Therapeutic Area |

This template is based on the combined experience of a number of companies, it is intended to be useable “as is” with the following necessary modifications:

1. Items bracketed / highlighted in blue indicate optional or modifiable text.
2. Items bracketed / highlighted in green indicate fill-in-the-blank or require an action (eg, insert drug name).

Remove highlighting and brackets as items are completed.

HOWEVER no template can anticipate all uses and circumstances, users should feel free to further refine it for their specific trial.

# PURPOSE OF THE DATA MONITORING COMMITTEE CHARTER

This document provides the plan [for monitoring the safety of subjects] [and/or] [for evaluating risk/benefit when formal interim analyses are pre-defined] in the study [insert Protocol number (s)]. It details the roles and responsibilities of the [independent] Data Monitoring Committee (DMC) [and Interim Analysis Group] and identifies the members of the committee[s]. It also outlines what data will be provided to the DMC, the process for disseminating study data, and the communication plan.

In any cross-organizational Platform Trial the DMC should be independent (regardless of whether the trial is confirmatory or not), if the trial is within an organization (a large Pharma testing its own interventions) and the trial is not confirmatory, the DMC need not be independent and can be composed of employees from within the organization.

An Interim Analysis Group (IAG), if used, reports to the DMC, preparing the results of the interim data analysis for their review and deliberation. The members of the IAG should be thoroughly familiar with the method and code to be used in the interim analysis and the SAP.

An IAG is recommended if the analysis at each interim is anything other than straightforward. It helps preserve the blinding from the larger Statistical Support Group (SSG) and allows the use of the specialist statisticians required to be limited to this delicate and important task.

# BACKGROUND

This DMC Charter is for a Platform Trial that will study multiple “interventions” over time, with new interventions being added as earlier interventions complete. The overall study is described in the Master Protocol with each intervention’s specific aspects being described in an Intervention Specific Appendix. We use the term “sub-study” to refer to the part of the trial that is relevant to a particular intervention.

Simply insert here the one paragraph summary of the trial protocol from the title page of the trial’s Master Protocol.

[Summary from the Master protocol]

# PURPOSE OF THE DATA MONITORING COMMITTEE

[The primary purpose of this DMC is to ensure the safety of the subjects in this study by monitoring safety data collected in the clinical program [, and to evaluate the efficacy data in the pre-defined interim analyses], and to provide recommendations to the Trial Management Group concerning the conduct of the study including changes to the informed consent. Details of specific committee member roles are described in Section 5 below.

If the trial has pre-planned adaptions it is not the job of the DMC to second guess the adaptation decisions, but it is the job of the DMC to check that the adaptations are still appropriate, in particular:

* That the data extracted from the CRF database and analyzed appears to be complete and correct.
* That the analysis has been performed correctly.
* That any assumptions behind the analysis have been met, and that no serious unexpected circumstances have arisen.
* That the results of the last interim have been applied correctly.

# .ORGANIZATIONS

## Data Monitoring Committee

### Data Monitoring Committee Members

Provide a list of the DMC members with position on the DMC and contact information in Attachment 1.

The DMC should consist of a minimum of three members with at least one medical expert in each of the relevant therapeutic area(s) (TA) and at least one Statistician knowledgeable about the design of the trial; one of these individuals will chair the Committee. In the case of a multinational trial, clinician representation should reflect regional participation in the trial. For trials with unusually high risks or with broad public health implication (e.g., HIV), a patient group community representative should be included in the DMC. Consideration should be given to include a bioethicist as a DMC member as well. If the study protocol includes adaptive design elements that may modify some components of the study design during its course, at a minimum, the DMC Statistician should have experience with adaptive design features. Prior data monitoring experience of the DMC members is useful, but not essential. However, at least one of the DMC members, especially the Chairperson of the committee must have considerable experience on data monitoring committees. DMC members must not be investigators in the study or otherwise associated with the study (e.g., Steering Committee member). Provide rationale if an intervention owner employee is selected as a member of DMC (this is discouraged because of the risk of unblinding due to the employee’s possibly conflicting loyalty).

If the trial has pre-defined adaptations, these normally require the execution of a sophisticated analysis of a snapshot of a subset of the trials data. It is recommended that the extraction and preparation of the data is by the SSG (that also prepares charts and tables for the DMC for its review of safety and risk/benefit), but that the task of the analysis is performed by a separate Interim Analysis Group [IAG]. This should comprise a statistician familiar with the trial design and a supporting statistician/programmer and allows specialists to perform the analysis and for the SSG to remain blinded.

A Platform Trial DMC should be a particularly good place to train the next generation of DMC experts (for this trial and others) and consideration should be given to having “shadow DMC members” who can observe but have no voting/recommendation rights.

The names of the DMC [and IAG] members, affiliations, and the contact information are listed in Attachment 1.

[In addition, consultants representing the fields of [insert field] have been identified prospectively to assist the DMC. Consultants to the DMC cannot be involved in ongoing Steering Committee’s trials. They have also disclosed their financial interests. Consultants are not considered DMC members and cannot participate in formulating recommendations in DMC meetings. Their details are also listed in Attachment 1.]

### Confidentiality Agreement, Financial and Non-financial Disclosure, and Conflict of Interest

The DMC [and IAG] members must disclose financial and non-financial/intellectual involvement in the product being developed or service on DMCs of the same, related or competing product. Each DMC [and IAG] member must evaluate his or her own potential conflicts of interest and complete the assessment of conflict of interest form. Members of the DMC [and IAG] are responsible for advising the Steering Committee of any changes in financial and non-financial/intellectual interests in pharmaceutical and/or biotechnology companies, including consultancies. Any DMC [or IAG] member who develops potential or significant conflicts of interest during the course of the study that could impact his/her objectivity may resign/could be asked to resign from the DMC [or IAG].

At the start of every DMC [or IAG] meeting the chair should check if any member’s conflict of interest has changed.

The conflict of interest assessment and confidentiality agreement of any consultants to the DMC is the responsibility of the DMC Chairperson, working in consultation with the Steering Committee as needed.

### Insider Trading

It is prohibited for any DMC [or IAG] member to use any material non-public information received in connection with their role as DMC [or IAG] member to make decisions about buying or selling shares or other securities in any company involved in the trial, or whose products are being evaluated in the trial. It is also prohibited to disclose to any person such material non-public information, whether or not the disclosing person has actual knowledge of the use of the information by the recipient. A DMC [or IAG] member using or disclosing “insider” information may commit a severe criminal offence, the penalty of which may be fines and imprisonment.

### Duration of Data Monitoring Committee Membership

Due to the unknown duration of a platform trial, and that duration being typically much longer than for a conventional trial it recommended members of the DMC be given rolling fixed term appointments so that succession planning is explicitly managed.

The DMC [and IAG] membership will last for a planned fixed term of [X] years, renewable by mutual agreement with the Trial Management Group. When a member leaves the DMC, the Trial Management Group may seek a replacement.

## Statistical Support Group

An SSG typically constitutes at least a Statistician (SSG Statistician), a Project Manager, and a Programmer (one person may serve more than one role).

A Statistical Support Group (SSG) independent of the Trial Management Group, will support the DMC [and IAG]. The SSG will perform the duties as described in Section 5.2.1. The roles and responsibilities of the SSG are detailed in Section 5.2.

The SSG is composed of personnel from [CRO name, academic or internal group]. Their names, roles in the project, and the contact information are included in Attachment 2.

## Steering Committee

The Steering Committee will include the senior medical and statistical members who can make scientific and business decisions based on the DMC recommendations. The Steering Committee must include a representative who understands the technical aspects of platform trial design. The Steering Committee must also include a senior clinical safety member and senior level statistician.

The names of the Steering Committee, their roles, and contact information are included in Attachment 3.

The Chairperson will serve as the point of contact between the DMC and Steering Committee. The roles and responsibilities of the Steering Committee are detailed in Section 5.3. The Steering Committee members must be independent of the study conduct.

## Trial Management Group

The Trial Management Group is composed of a group of people including Clinician(s), Statistician(s)[[1]](#footnote-1), and others who are responsible for the design, conduct, and analyses of the study. The roles and responsibilities of the Trial Management Group are detailed in Section 5.5.

## Interim Analysis Group

The Interim Analysis Group is composed of a small group of people (possibly as few as 2), statistician programmers who are thoroughly versed in the trial’s statistical design, particularly its adaptive elements. The roles and responsibilities of the Interim Analysis Group are detailed in Section 5.3.

# ROLES AND RESPONSIBILITIES

## Roles and Responsibilities of Data Monitoring Committee Members

### Data Monitoring Committee Members

Each member is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the DMC except as described in this charter. The DMC may contact the SSG Statistician directly with questions regarding the operational details associated with the data analyses and summary tables. The SSG Project Manager must be copied in all correspondence from the DMC to the SSG Statistician.

The DMC will have the following meetings:

1. Initial convening meeting
2. Initial review meeting to review the format and contents of reports from the SSG [and IAG]
3. Full safety reviews.
4. Interim action review meetings.
5. Ad hoc safety/interim reviews called by the DMC Chairperson.

See Section 9 for the schedule of the meetings.

At or before the convening meeting DMC members must:

1. Provide their CVs to the Steering committee.
2. Review and sign the DMC charter.

During their membership of the DMC, members must:

1. Attend all scheduled and ad hoc meetings, making themselves available in a timely manner in order to not unduly delay a meeting.
2. Prior to each meeting, review the data package from the SSG [and formal interim recommendations from the IAG].
3. If they believe that they may have a potential intellectual or financial conflict of interest must inform the Chairperson of the DMC. In such cases, the DMC meeting minutes must document the disclosure of the potential conflict of interest and the outcome of the discussion, e.g., abstention of member from formulating recommendations, no action needed
4. Review and finalize the draft meeting minutes.
5. Ensure that all points of view are adequately summarized in the minutes.

At or before the initial meeting the DMC must:

1. Review and comment on the DMC SAP.

The DMC SAP must be approved before the next DMC meeting.

The DMC will perform the following data reviews:

1. Detailed individual reports of serious adverse events (SAEs).
2. The enrollment status (number of patients screened, number of patients screening failures, number of patients randomized if applicable), demographic data and baseline characteristics, and discontinuation rate and reasons for discontinuations.
3. Summarized safety data (AEs, SAEs, AEs of special interest, laboratory data, ECG data and any other data applicable for the study) as well as efficacy data as appropriate.
4. Any individual event thought to be of major significance by the Trial Management Group such as major protocol deviations (e.g. under/overdosing, missed visits). In addition, safety letters for the specific study agent will be reviewed. The DMC should address the Trial Management Group’s concern provided that no unblinded information/conclusion will be implied by answering these questions.
5. The DMC is responsible for review of formal interim analysis results, evaluating the pre-planned adaptations, and formulating recommendations for the Steering Committee.

The DMC is responsible for alerting the Steering Committee if they have safety concerns. In addition, they are responsible for making recommendations to the Steering Committee concerning the conduct of the study including changes to the inform consent.

### Overruling pre-planned adaptation

If the IAG or DMC decide that a particular pre-planned behavior should be overruled then:

* If the IAG and DMC agree that a one-off overruling is required then the DMC and IAG must inform the Steering Committee of the change along with the reasons for change.
* If the IAG and DMC agree that permanent change to the adaption rules is required then the DMC and IAG must inform the Steering Committee of the change along with the reasons for change and ensure the trial SAP is updated appropriately.
* If the IAG and DMC disagree on what is required then the DMC must inform the Steering Committee of the disagreement, the DMCs recommendation and their reasons for overriding the recommendation of the IAG.

### Data Monitoring Committee Chairperson

In addition to the roles and responsibilities detailed in Section 5.1.1, the DMC Chairperson must:

1. Set the open DMC meeting agendas in collaboration with the TMG, [IAG,] and SSG.
2. Set the closed DMC meeting agenda.
3. Lead and guide discussions in both the Open and Closed sessions of the DMC meetings.
4. Make executive decisions, if necessary.
5. Inform DMC members of the completion of their responsibilities.
6. Collect feedback from DMC members.
7. Seek consensus among the DMC members.
8. Ensure that requests from DMC members for additional information are communicated to the SSG Statistician and/or the Steering Committee Chairperson.
9. Report DMC safety issues and related recommendations as well as recommendations from any formal interim analyses to the Steering Committee Chairperson
10. Seek logistical input from the Steering Committee Chairperson prior to finalization of DMC recommendations if necessary; ensuring that all recommendations from the DMC are clearly formulated and shared with the Steering Committee Chairperson within [XX] days of the meeting.
11. Sign the DMC meeting minutes and the DMC Meeting Report summarizing the conclusions and recommendations of the DMC from each meeting
12. Act as the contact between the DMC and the Steering Committee Chairperson by discussing the issues and representing the views of the DMC with the Steering Committee Chairperson without jeopardizing the integrity of the data
13. Inform the Steering Committee Chairperson of the need for additional DMC meetings and identified issues, proposed meeting date(s), and specifications for data review

## Roles and Responsibilities of the Statistical Support Group

### Statistical Support Group

The SSG has the following major responsibilities,

Before the trial starts they must:

1. Implement a secure data transfer/storage mechanism (such as a secure document portal or Electronic Document Management System (EDMS)) for giving and controlling access to the sensitive data and documents pertaining to the trial.
2. Create and validate the programs to process the data for charts and tables to be presented to the DMC and create the dataset to be used for interim analyses.

During the trial they must:

1. Request transfers of the clinical datasets from [specify the Steering Committee or CRO, as applicable] [and randomization code from [specify IVRS/IWRS vendor, if necessary] ].
2. Merge the randomization data and producing programmed tables for DMC review.
3. [Immediately inform DMC members of the death of study subjects.]
4. [Send the DMC Chairperson SAE reports (submitted by sites) weekly.]
5. [Requesting pharmacovigilance data from Trial Management Group overseeing trial safety data, if asked by the DMC.]
6. [Serve as a minute-taker to appropriately document the Open and Closed sessions of the DMC meetings.]
7. Schedule DMC meetings and notifying DMC meeting attendees and the Steering Committee’s Study Statistician and Steering Committee Chairperson of the meeting dates.

When an intervention completes, they must:

1. Collect all personal working documents from the DMC members or remove access to them in the EDMS. The checklist in Attachment 6 should be used to determine if all documents/data packages that were sent to the DMC members have been returned. See Section 10 for information on what constitutes a personal working document and what should be done with the documents once they are collected from the DMC members.
2. To prepare the release of the relevant data for publication/transfer to the intervention owner when an intervention completes.

When the trial is complete, they must:

1. Archive the data packages, meeting minutes, evaluation forms, and any other documents that were needed during the course of the DMC activities (e.g., additional requests for information) in a secured filing system.
2. The archived documentation must be sent to the Trial Management Group at the end of the trial according to the Steering Committee’s specifications. Prior to sending the documentation to the Steering Committee, the SSG Statistician should ensure that the electronic files are readable/useable. After receiving the archived documentation, the Trial Management Group must verify that all of the appropriate documentation has been returned and that all of the electronic files are readable/useable.

### Statistical Support Group Statistician

The SSG Statistician must:

1. [Prepare the mockup tables, listings, and graphs of the DMC Statistical Analysis Plan (DMC SAP) overseen by the SSG statistician].
2. Oversee the SSG programming staff to ensure that the tables, listings and graphs are programmed as intended based on the mock-ups as per the DMC SAP, conducting a quality control review of all tables and listings using the SSG organization’s procedures for QC review prior to making the data package available to the DMC members, a checklist (Attachment 5) that documents this review must be signed by the SSG Statistician
3. Obtain the treatment assignment data from [specify the source of the assignment data,].
4. Work with the SSG programming staff to maintain an archive of electronic copies of the datasets and the programs used to generate DMC reports
5. Provide selected summary tables and listings with test data and dummy treatment assignments to the Study Statistician for review prior to production of the first data package

## Roles and Responsibilities of the Interim Analysis Group (IAG)

If the trial uses a complex analysis, an IAC, a separate, specialist, group specifically for executing the interim analyses is usually constituted. There will be no need for an IAC if there are no interims, or the interim analysis is very straightforward, in which case the role of the IAC can be performed by the SSG. Having a separate IAC allows it to be staffed with specialists familiar with the analysis and the execution of adaptive trials, leaving the more straightforward statistical work to the SSG.

The role of the IAC vis-à-vis the DMC is to prepare for the DMC the interim analysis report and to inform them of any problems such as: missing or late data, unanticipatedly fast/slow accrual, unanticipated patterns in the data, technical problems with the analysis.

The IAC further supports the DMC by providing explanations to DMC questions of the interim report and propose possible solutions to problems that arise.

The Interim Analysis Group is responsible for performing the interim analysis, ensuring its correctness, and producing the interim analysis report for the DMC, it must:

Before the trial starts they must:

1. Approve the DMC charter and DMC SAP.
2. Prepare the programs to receive the interim data and perform the interim analysis.
3. Prepare the code to produce the interim analysis report for the DMC.
4. Agree the form and content of the interim analysis report with the DMC.

During the trial they must:

1. Receive and check the interim analysis data from the SSG before each interim.
2. Report any problems with the interim analysis data to the SSG.
3. Perform the interim analysis and produce the interim analysis report and send the report to the DMC.
   1. Modifications to randomization probabilities in a RAR design are to be communicated directly to the relevant persons running the Randomization system.
   2. More significant adaptations (e.g. closing an intervention for success or futility, promoting an intervention to a confirmatory stage, stopping an intervention being allocated to a particular participant subgroup) are communicated to the DMC for their approval and communication to the Steering Committee.
4. If there were any problems with the data or analysis, this should be reported to the DMC along with the interim analysis report.
5. Respond to DMC questions concerning the interim analysis report.
6. Suggest to the DMC possible solutions to unanticipated problems that arise.

## Roles and Responsibilities of the Steering Committee with respect to the DMC

The Steering Committee is responsible for communicating the DMC recommendations to the Trial Management Group and identifying appropriate actions based on the recommendations of the DMC.

Before the trial starts the Steering Committee must:

1. Constitute the DMC and draw up its charter. There should be a single point of contact in the Steering Committee with responsibility for the DMC charter.
2. Selecting the DMC and appointing its Chairperson.
3. Ensure the DMC approves the DMC charter and DMC SAP.

During the trial the Steering Committee must:

1. Manage and adjudicate on any conflicts of interest arising for any DMC member.
2. Address any Trial Management Group concerns with the DMC.
3. Communicate the DMC recommendations to Trial Management Group.
4. Request additional information, even unblinded summary data, from the DMC if the DMC recommends stopping or making any major unplanned modification to the study. However, the unblinded information will not be shared with the Trial Management Group until the study is completed.
5. Communicate the action(s) taken to the DMC.

## Roles and Responsibilities of the Trial Management Group(s) with respect to the DMC

The Trial Management Group has the following major responsibilities.

Before the trial starts it must:

1. Select the SSG [and IAG]
2. Review and approve the DMC SAP.
3. Ensure that the appropriate documents (e.g., protocol, Investigator’s Brochure (IB), and any amendments to these documents) are compiled and sent/made accessible to the DMC members in accordance with the established timeframes and obtaining acknowledgement that the DMC members received the documents/data packages. A checklist to facilitate this process must be utilized and is provided in Attachment 5.

During the trial it must:

1. Provide the SSG/DMC with relevant information regarding the interventions and the conduct of the platform trial.
2. Provide the SSG with the appropriate database in accordance with the established timeframes.
3. Before each DMC meeting, provide a list of concerns (if any) to the [Steering Committee. If in agreement, the Steering Committee will provide the list to the] DMC.
4. In collaboration with the SSG, [IAG,] and DMC setting the DMC open session agenda.
5. Communicate the Steering Committee decision/action to appropriate external parties, e.g., global regulatory authorities, IRB and the study investigators as necessary.
6. Prior to each DMC review, collaborate with SSG to ensure in a blinded fashion that all outputs are programmed as intended per the DMC SAP.
7. Attending open sessions of the DMC meeting.
8. Reviewing the open session DMC meeting minutes.

### Study Statistician

The Study statistician has the following major responsibilities with respect to the DMC, they must:

1. Prepare the DMC Statistical Analysis Plan (DMC SAP) [including mockup tables, listings, and graphs in collaboration with SSG / oversees the preparation of the mockup tables, listings and graphs by the SSG statistician].
2. Ensure the DMC SAP is agreed by the DMC members, the Steering Committee and the Trial Management Group

# DATA MONITORING COMMITTEE MEETINGS

A DMC meeting may be either a face-to-face meeting or a teleconference, unless the type of meeting is specified. The DMC meeting may include an open session. Steering Committee Trial and Management Group members may present pertinent study information to the DMC members during the open session. Investigators or experts serving as ad hoc advisors may be requested to attend an open session of the meeting. The closed session will be limited to the DMC members, consultants to the DMC if needed, and designated staff from the SSG for presentation of the unblinded data. An executive session can be called with DMC members only. Steering Committee and SSG members are excluded from the executive session. A joint session may be held with all representatives from the DMC, Steering Committee, and SSG after the closed/executive session is completed.

All meetings require attendance by the DMC Chairperson (or delegate to other DMC member should the Chairperson not be able to attend) and the DMC Statistician. If the DMC Statistician cannot attend but conveys his opinion to the Chairperson prior to the meeting, the Chairperson may hold the meeting. While the SSG will attempt to schedule the meeting at a time when all DMC members can attend, a quorum of at least three DMC members, including the medical expert for the TA for which the data will be discussed, is required at all meetings or teleconferences for consensus on the recommendation. For meetings that will address recommending early termination of the trial or other major decisions affecting the trial, it is strongly encouraged that all members attend. The Chairperson has the authority to cancel or change the meeting if he feels more members should attend for the decision.

If there are 3 DMC members only, then the above paragraph can be simply replaced by ‘All meetings require attendance by all 3 DMC members, as all 3 members are required for consensus on the recommendation’

## Decision Making

DMC members decide on:

* approval of the DMC Charter
* changes or amendments to the Charter
* all recommendations to be submitted to the Sponsor.

To participate in the decision, a DMC member must be present or a participant in a conference call meeting; only for deciding on a recommendation to stop an intervention or the whole trial will the DMC Chair contact members who were not present to obtain their view. Decisions are preferably by consensus, but if necessary by voice vote, but any member may request a secret written ballot.

Initial endorsement of the DMC Charter requires unanimous agreement by the DMC. For all other matters, but particularly in reference to any amendments to the Charter or a recommendation of intervention termination, every effort will be made by the DMC to achieve consensus. However, if unanimous agreement cannot be reached, recommendations based on majority of all DMC members will be put forth by the DMC chair, to the Steering Committee, as the official recommendation of the DMC. The DMC Chair will convey the rationale of the majority decision, as well as those of DMC members voting in the minority.

## Initial Meeting

It is strongly recommended that the organizational meeting be a face-to-face meeting. A teleconference organizational meeting may be utilized if appropriate. The protocol, DMC charter, DMC SAP, and IB should be provided to the DMC members at least one week prior to the initial meeting.

The meeting should at least one month be before the first participant is enrolled (the meeting schedule is in section 9)

All DMC members will be required to attend the initial organizational meeting. The purposes of the meeting are as follows:

1. Present relevant background safety data for the initial interventions.
2. Review the study protocol.
3. Review the DMC charter, including roles and responsibilities and the communication plan.
4. Review table and listing mockups that will be provided in the DMC SAP.
5. Review a mockup of the report they will receive from the IAG
6. Select tentative timing of DMC meetings, especially the first scheduled DMC meeting.

The Steering Committee and/or SSG will set up the organizational meeting. The attendees will include the DMC members, the SSG Statistician, [a representative from the IAG], and any other representatives from the SSG and the Steering Committee’s Trial Management Group.

If items 4 & 5 are not available at the initial meeting they must be reviewed at a second ‘initial’ meeting before the first scheduled meeting, sufficiently in advance of it for any issues to be resolved.

## Scheduled Meetings

Data review meetings will occur via [specify whether the meetings will be face-to-face, teleconference, or a combination of both] after the DMC members have reviewed the data package. The SSG will set up these scheduled meetings and all DMC members, the SSG Statistician, and other SSG representatives will attend the meetings. The purpose of these scheduled meetings is to discuss the data and formulate a recommendation to the Steering Committee. See Section 9 for a schedule of meetings.

## New Intervention Meetings

All DMC members will be required to attend a new intervention meeting. The purposes of the meeting are as follows:

1. Present relevant background safety data for the new intervention.
2. Review the ISA for the new intervention and any changes to the master protocol.

## Unscheduled Meetings

The DMC or Steering Committee has the option to call an unscheduled meeting at any time. The DMC need not inform the Steering Committee of the meeting. The attendees for this meeting are the DMC members and the SSG Statistician. The DMC may request that a Steering Committee or Study Management Group representative attend a portion of an unscheduled meeting.

The DMC members should not disclose to the Steering Committee the reasons behind the perceived need for unscheduled meetings or additional data requests and strenuously minimize any unblinding that such a meeting might cause.

## Meeting Report/Minutes

DMC meeting minutes summarizing the conclusions and recommendations of the DMC will be drafted after each open and closed meeting, separately. A SSG representative is responsible for preparing draft minutes of each DMC scheduled or unscheduled meeting. This individual will ensure that the date of the meeting, a summary of the discussions, the committee recommendations, the rationale for the recommendations, and the list of attendees are included in these minutes. The SSG will send the draft minutes to the DMC Chairperson who will review and modify the minutes. The DMC Chairperson will then sign and date the finalized minutes and return them to the SSG for confidential distribution to DMC members. The DMC Chairperson will sign the DMC meeting minutes. The DMC meeting minutes should include important considerations that led to the DMC recommendations.

The DMC meeting report containing open session summaries, and the conclusions or recommendations without reference to unblinded data will be sent to the Steering Committee within [XX] working days after the meeting. A template of a meeting report is provided in Attachment 4 as a guideline. If the DMC meeting minutes for open sessions are not included in the open session summaries mentioned above, they will be sent to the Steering Committee within [XX] days after the meeting.

The DMC meeting minutes for closed sessions, however, will not be sent to the Steering Committee until after the completion of the sub-studies extant at the time and database lock of the relevant clinical database(s)/unblinding of the trial.

All meeting minutes from each scheduled or unscheduled meeting will be archived, along with a copy of the corresponding data package, in a secure manner until [specify when the archived information should be sent to the Steering Committee or if it will be by request of the Steering Committee, at which time all archived information should be transferred to the Steering Committee’s Trial Management Group]. [In case of internal SSG: All archived information should be transferred to the Trial Management Group after the database lock of the relevant sub-studies.]

# STATISTICAL GUIDELINE FOR PROTOCOL SPECIFIED INTERIM ANALYSIS

## Pre-planned Interim Analysis

If there is no interim analysis, state it and say it is not applicable. The details of the interim analysis will be in the DMC SAP, do not repeat them here, except to make clear what the planned decisions of the DMC are.

The DMC must review and approve the DMC SAP [and IAG interim analysis report] at the initial DMC meeting. This will describe the interim analysis and pre-planned adaptations to be reviewed and approved by the DMC.

If the DMC believe that external data (on interventions with similar methods of action or changes in standard of care) justifies adjustment of the SAP they should agree changes with the SSG [/ IAG].

## Protection of Study Integrity and Control of Operational Bias

For trials with an adaptive design, document the plan for protection of study integrity and control of operational bias in Attachment 8. For all other studies, indicate that this does not apply and delete the attachment.

[The plan for protection of study integrity and control of operational bias is included in Attachment 7.]

# DATA REVIEWS AND COMMUNICATIONS

## DMC Statistical Analysis Plan

[In collaboration, the SSG Statistician and Study Statistician] will draft a DMC SAP including an analysis plan for both safety and efficacy data as appropriate. The DMC SAP must be agreed to by the DMC members, the Trial Management Group, and the Steering Committee. The DMC SAP provides the details of the statistical methods and analyses to be applied to the data. The DMC SAP also describes in detail the scope of the data, the data cut-off criteria for each DMC review, the contents to be included in the data package, and whether and how the treatment groups will be blinded in the data package.

## Data Reviews

Provide information on:

1. Type of data review and frequency of each type of review:

Example: Comprehensive data review of an intervention’s data meeting will take place when approximately 10%, 30%, 50%, 70%, and 90% of planned subjects are enrolled to that intervention in the study. In addition, survival data and selected AEs of clinical interest will be reviewed every three months (by the DMC Chairperson or by all DMC members). Other meetings or data reviews may be scheduled at the discretion of the DMC or upon request by the Steering Committee.

2. Data handling: Specify what kind of data will be provided and how the SSG will receive data.

Example: Before each scheduled DMC meeting, data cut-off dates will be identified and the clinical database will be made as clean as practicable in preparation for the creation of SAS data sets. Data cut-off dates should be at least [XX] weeks, but no greater than [XX] weeks prior to a DMC meeting. Approximately [XX] weeks prior to a DMC meeting, the Trial Management Group will transfer the blinded data to the SSG and the IVRS/IWRS vendor will transfer the randomization code to the SSG. Clinical data may include dosing information, coded adverse events,…CIOMS report will be provided upon request for serious adverse events.

3. Unblinding: Specify whether the summary tables in the data package will be displayed with real treatment identity or masked treatment group code. Please note if there is a separate data package for open session; the summary data can only be presented based on dummy codes or based on the combined data.

4. Distribution of data package:

Example: Data packages be will be uploaded to the EDMS and made accessible to the DMC members who will be sent notification of its availability. All data and output should be held in strict confidence. The data package will be available to the DMC members no later than five business days prior to the scheduled meeting.

1. [Type of data review and frequency of each type of review:
2. Data handling: …
3. Unblinding: …
4. Distribution of data package: …]

DMC data packages should begin with a protocol synopsis, a listing of new amendments, a reminder of previous recommendations of the DMC, a concise summary of interim data, an explanation of complex medical or statistical issues that may underlie the interpretation of the data, and a copy of the informed consent form so that the DMC knows of the adverse reactions about which the participants are aware.

Thoughtful development of figures and tables is important; these should focus on what is necessary for discussion and formulating recommendations. Graphical presentations of data, with backup tables in an organized appendix for reference as needed, are encouraged.

In the event that the DMC requires additional safety information beyond the standard summary tables and listings that were provided, the request will be made to the SSG Statistician. The SSG will provide all analytical support for this effort and will forward the results to each of the DMC members. If the SSG Statistician does not have the required information, he/she will request that the Study Statistician obtain the information. The information request should be worded in such a way that if possible the Study Statistician does not know the intent of the data inquiry. In the event that the Study Statistician is not able to appropriately address the request, the Study Clinician may provide additional information. Additional data requests should be limited to those that are considered essential by the DMC.

The DMC must not divulge the contents of the unblinded data to members of the Trial Management Group or to any members of the Steering Committee unless specifically requested by the Steering Committee Chairperson until the study has completed.

### Data Monitoring Committee Recommendations

At the end of each DMC meeting, the DMC will senda copy of the completed DMC recommendation form (see Attachment 4) to the Steering Committee Chairperson within [XX] days of the meeting.

The possible recommendations the DMC members can make are:

1. To continue the study according to the protocol rules until next scheduled meeting.
2. To continue the study according to the protocol but plan an additional meeting.
3. To continue the study according to the protocol but request additional expert review/analyses.
4. To override the protocol and not carry out the per-planned adaptation. This must be discussed with the [SSG / IAG] See section 5.3 above.
5. To continue the study and amend the protocol.
6. To set up a meeting with the Steering Committee to discuss concerns of safety and/or efficacy within the clinical study.
7. To stop an intervention.
8. To stop the study.

[Add additional study specific options if necessary]

The DMC recommendations, which are sent to the Steering Committee Chairperson, will include DMC conclusions and recommendations without reference to unblinded data.

### Steering Committee Communications and Decisions

If the recommendation is to stop an intervention/treatment arm, close a sub-group, stop the whole trial, modify the trial, or to override the pre-planned adaptation rules (whether to make an un-planned adaptation or to refuse to make a planned adaptation), the DMC should provide the rationale for their recommendation to the Steering Committee. The DMC Chairperson should call or email the Steering Committee Chairperson to communicate the DMC recommendation and send an evaluation form to the Steering Committee Chairperson conveying the same information. The Steering Committee will review such recommendations, request additional blinded or unblinded data analysis if needed, consult with regulatory agencies or other consultants if needed, and form the decision to follow or not follow the DMC recommendations within [XX] days of receipt of the DMC’s recommendations. The Steering Committee will form an action plan that will minimize the risk of revealing unblinded information and communicate the action plan with the Trial Management Group. The Steering Committee should take measures to protect data confidentiality and trial integrity during the decision-making process.

If the Steering Committee decide not to follow the DMC recommendation this must be communicated to the DMC along with the Steering Committee’s rationale. If the DMC recommends terminating the trial (or a treatment arm or indication), but the Steering Committee decides to continue, the Trial Management Group will notify the appropriate regulatory authorities, the participating IRBs or IECs, and investigators of the DMC’s recommendation and the Steering Committee’s decision.

If the DMC and the Steering Committee agree to stop the trial (or a treatment arm or indication), the Trial Management Group will inform the appropriate regulatory agencies and investigators.

1. The DMC recommendations and the Steering Committee decisions will be described in the clinical study report.

### Concerns about Subjects’ Safety

If the DMC determines that there is a safety risk for subjects in the trial, they will note their concerns on the DMC meeting report, and the Chairperson will alert the Steering Committee Chairperson via a phone call. The Steering Committee Chairperson will immediately call an urgent meeting to discuss the safety issues. The meeting attendees should be the members of the Steering Committee, members from the Safety Management Team (SMT), and, at a minimum, the DMC Chairperson or delegate. The Steering Committee Chairperson or delegate is responsible for recording the minutes of this meeting and getting approval for the final minutes from the meeting attendees. Once the Steering Committee has the appropriate information from the DMC, they will make a decision regarding the possible modification of the study design or termination of the trial.

The intention to modify or stop the study by the Steering Committee may then be made in consultation with the regulatory agencies. The final decision will be conveyed to the Trial Management Group, the DMC, and the investigators along with the rationale for any modifications to the trial. The Trial Management Group will implement the required changes.

# PROJECTED TIME TABLE FOR DATA MONITORING COMMITTEE MEETINGS AND DATA PACKAGES

Select which types of meeting are going to take place from the following and specify their timing.

First participant enrolled:

The enrollment of the first participant is projected to be around [DD/MON/YYYY]

Initial Meeting:

The initial meeting will be at least [XX] months before the enrollment of the first participant.

**Initial Run-through Meeting:**

A meeting to review the SSG [and IAG] data reports using the live trial data systems, before an actual analysis is due will be [XX] months after the enrollment of the first participant.

**First data package:**

The first data package including survival and SAE data should be available [XX months] after the enrollment of the first participant.

**First face-to-face meeting:**

The first face-to-face meeting will take place after [planned information available for first face-to-face] which is projected to be around [DD/MON/YYYY]

**Full Safety Reviews**

There will be full safety reviews [every XX months / every XX participants complete / other planned schedule]

**Interim Analysis Reviews**

There will be reviews of the interim analysis report after each interim analysis, which will occur reviews [every XX months / every XX participants complete / other planned schedule]

# DOCUMENTATION

Original documents (meeting agendas, meeting minutes, safety reports/tables/line listings, DMC members' faxed DMC meeting reports, QC checklists, document checklists, DMC members’ faxed signature pages, correspondence, etc.) will be managed by the SSG Statistician.

After evaluation of an intervention’s final data and at study completion, the SSG Statistician will be responsible for transferring all an intervention’s / the study’s final documents to [the Trial Management Group] for filing in the central file (as outlined in Section 6.6).

Personal working documents (copies of safety reports/tables/line listings, safety reports/tables/line listings with handwritten notes, notes taken during a meeting, original signature DMC meeting reports, correspondence, etc.) reviewed or created by a DMC member to support or back-up decisions captured in the minutes are also subject to the Steering Committee's current record retention schedule or policy.

DMC members should retain all the personal working documents during the study and return them to the SSG Statistician at the end of their participation. Alternatively, the personal working documents may be returned to the SSG Statistician during the trial if they are no longer needed for instance once an intervention has completed.

The SSG Statistician will then need to contact the Trial Management Group to inquire whether there are any hold notices on the intervention. If there are no relevant active hold notices, the Trial Management Group will inform the SSG Statistician that the working documents, with the exception of the original signed DMC meeting reports, should be destroyed/deleted as soon as possible in a secure manner. If there is a relevant hold notice, the SSG Statistician will forward the documents to the Trial Management Group upon request. In either situation, the original signature DMC meeting reports must be returned to the Trial Management Group.

The SSG will compile and maintain the following documents:

* Copy of the DMC charter (and all amendments to the charter) and associated attachments and addenda, DMC SAP
* Copy of the IB
* Protocols and protocol amendments for the clinical studies subject to the DMC
* Curriculum vitae for each DMC member
* Curriculum vitae for staff of the SSG
* Copies of the data package provided to the DMC members for each data review
* Minutes of each DMC meeting, including conclusions or recommendations concerning the conduct or evaluation of the sub-studies and any important considerations that led to the conclusions/recommendations
* DMC reports provided to the Steering Committee Chairperson containing conclusions or recommendations without reference to unblinded data
* [Copies of blinded data provided to medical specialists for evaluation and scoring]
* Copies of all correspondence related to this DMC
* Upon completion of the sub-studies and closure of the relevant clinical database(s), the documents will be forwarded to the Trial Management Group for archiving.

# DATA AND COMMUNICATION FLOWCHART

*Final Decision*

*Unblinded Interim Data*

*Interim Analysis Report*

Interim Analysis Group

**Statistical Support Group**

*Tables, Listings, Figures, Meeting Minutes, DMC Meeting Report*

*Additional Data and Analysis Requests*

**Data Monitoring Committee**

*Blinded Datasets, Protocol, DMC Charter, DMC SAP, IB*

**Trial Management Group**

**Steering Committee**

*Recommendations*

*Final Decision*

*Treatment Codes*

Attachment 1: Data Monitoring Committee Members

|  |  |  |
| --- | --- | --- |
| **DMC Chairperson:** | |  |
| Name, Title: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Clinical Specialist:** | |  |
| Name: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Clinical Specialist:** | |  |
| Name: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Clinical Specialist:** | |  |
| Name: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
| **Statistician:** | |  |
| Name: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
| **[Patient representative:]** | |  |
| Name: |  |  |
| Affiliation: |  | |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |

Attachment 2: Steering Committee Members

|  |  |  |
| --- | --- | --- |
| **Chairperson (Clinician or Statistician):** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Head of Safety:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Clinician:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Statistician:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |

Attachment 3: Statistical Supporting Group

|  |  |  |
| --- | --- | --- |
| **Name of the Company or Steering Committee internal group** | | |
| **Statistician:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Project Manager:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Programmer:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |

Attachment 4: Interim Analysis Group

|  |  |  |
| --- | --- | --- |
| **Name of the Company or Steering Committee internal group** | | |
| **Statistician:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |
|  | | |
| **Programmer:** | |  |
| Name: |  |  |
| Address: |  | |
| Phone: |  | |
| E-mail address: |  | |

Attachment 5: Data Monitoring Committee Meeting Report

To: Steering Committee Chairperson

Meeting Date:

Protocol:

Meeting Attendees:

The DMC charged with the review of safety data for the [trial name] reviewed Data package number [ ] dated [dd/Mon/yyyy].

Summary of discussion in the open session of the meeting:

As a result, the DMC recommendation is:

|  |  |
| --- | --- |
|  | To continue study according to the protocol until next scheduled meeting |
|  |  |
|  | To continue study according to the protocol, and plan an additional meeting |
|  | The following date is proposed for the additional meeting: [dd/Mon/yyyy] (to be confirmed with Steering Committee Chairperson) |
|  |  |
|  | To continue study according to the protocol, and request additional expert review/analysis |
|  | The review will be performed by the SSG / IAG / external consultant and is expected to report to the DMC by : [dd/Mon/yyyy] (to be confirmed with Steering Committee Chairperson) |
|  |  |
|  | As a consequence of the above choice we recommend making adaptations following the pre-planned rules. |
|  | The following adaptations are to be performed: |
|  |  |
|  | In agreement with the IAG we recommend temporarily overriding the protocol. |
|  | The following adaptations are/are not to be performed: |
|  |  |
|  | In agreement with the IAG we recommend permanently modifying the protocol. |
|  | The following modifications are to be made: |
|  |  |
|  | Contrary to the IAG we recommend temporarily overriding the protocol. Our rationale is attached. |
|  | The following adaptations are/are not to be performed: |
|  |  |
|  | To continue study retaining the pre-planned adaptation rules but amending the protocol as described: |
|  | [Describe sections below and list protocol(s) to be amended] |
|  |  |
|  | To set up a meeting with the Steering Committee to discuss concerns of safety and/or efficacy |
|  | within the clinical study as outlined below, within [#] weeks after the DMC meeting |
|  |  |
|  | Additional Comments: |

|  |  |
| --- | --- |
|  |  |
| Chairperson, Data Monitoring Committee for Study [insert study number(s)] | Date |

Attachment 6: Checklist for Quality Review of Prepared Tables/Listings

**Protocol [insert number (s)]**

|  |  |
| --- | --- |
|  | Planned data package |
|  |  |
|  | Additional requests |
|  |  |
|  | I have reviewed all of the programmed tables and/or listings for accuracy. |

|  |  |
| --- | --- |
|  |  |
| Signature SSG Statistician: | Date (dd/Mon/yyyy) |

Attachment 7: Checklist of Documents Prepared for Data Monitoring Committee Members

**Protocol [insert number (s)]**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Planned data package |  | Additional request review |
|  |  | | |
|  | Other, specify: | | |

For SSG Statistician or designee:

I have prepared the following documents for the DMC members

|  |  |
| --- | --- |
|  | Final DMC charter |
|  |  |
|  | DMC charter amendment |
|  |  |
|  | IB, updated IB |
|  |  |
|  | Protocol |
|  |  |
|  | Protocol amendment |
|  |  |
|  | DMC SAP |
|  |  |
|  | Safety letters |
|  |  |
|  | Planned data package |
|  |  |
|  | Additional requests |
|  |  |
|  | Other: [specify] |

|  |  |
| --- | --- |
|  |  |
| Signature | Date (dd/Mon/yyyy) |

For DMC member:

|  |  |
| --- | --- |
|  | I have received all the documents listed above. |
|  |  |
|  | I have the following items missing from the package: |
|  | [specify] |

|  |  |
| --- | --- |
|  |  |
| Signature | Date (dd/Mon/yyyy) |

For SSG Statistician or designee:

|  |  |
| --- | --- |
|  | I have verified that all the documents from the DMC members have been returned. |
|  |  |
|  | Not all the documents were returned from the DMC members. |
|  | [Specify the missing items and reasons (if the DMC member is not able to produce these items)] |

|  |  |
| --- | --- |
|  |  |
| Signature | Date (dd/Mon/yyyy) |

Attachment 8: Plan for Protection of Study Integrity and Control of Operational Bias in [insert Trial Name]

**General Directions:**

* This attachment is required for studies with an adaptive design feature. Possible exceptions to this rule are studies with routine group sequential design or simple blinded sample size re-adjustment.
* This attachment is completed by the Study Statistician in consultation with the Adaptive Clinical Trial Experts.
* If additional subheadings are needed for clarity, add as appropriate.
* The Study Statistician must distribute this completed Plan to the Trial Management Group to ensure implementation.

BACKGROUND AND RATIONALE

The purpose of this document is to:

* Provide sufficient and necessary background of the trial to understand and interpret the adaptive design features and the operational measures to be implemented for protection of data integrity and minimization of bias (e.g., impact of accrual rate and dropout rate on the patient’s distribution and drift of patient’s characteristics over time).
* Identify, if applicable, regulatory guidelines and meetings between the Steering Committee and regulatory authorities that contributed to the finalization of the adaptive design and any regulatory recommendation and/or concerns (e.g., at the end of Phase 2a meeting).

POTENTIAL CONCERNS

The following questions should help the team focus on and plan for implementation measures aiming at the protection of study integrity and minimization of operational bias. Text should be added which identifies the potential concern applicable to the specific planned adaptations. Not all questions may be applicable, but they may help trigger other evaluations related to the logistics and operational details for implementation.

* How often will the unblinded analyses be performed, and to whom should the data be unblinded?
* To what extent are the patients and/or investigators aware of the details on the adaptation(s)? Will their behavior be impacted by knowledge of the adaptations?
* Will the unblinding cause potential bias in treatment assessment?
* How is the blind of the treatment assignment maintained through the execution of the study? For example, in trials with IA for dropping/adding an arm, will the information of this change introduce any unblinding (e.g., due to expected and observable adverse events?)
* Will the implementation of the adaptive design impact the randomization scheme of the trial?
* Will protocol deviations or violations invalidate the adaptive method?
* How might an unexpected DMC action affect the power and validity of the design?

**NOTE**: Measures describing the communication flow and preventing premature release of the interim results to the team/sites/general public is beyond the scope of this attachment and they should be addressed in the DMC Charter/ IA SAP.

[EXAMPLE] A response-adaptive randomization is typically used to assign more patients to the superior treatment groups by changing the randomization schedule. However, for ethical reasons, the patients should be informed that the later they come into the study, the greater the chance of being assigned to the superior groups. For this reason, patients may prefer to wait for late entry into the study. This could cause bias because sicker patients might enroll earlier than those with less severe symptoms. This would trigger a treatment effect confounding with the patient’s disease background. For this reason the team has not included in the protocol the exact timing of the IA for determining the superior active treatment arm…

Data Integrity and Validity

Operational Bias

The application of adaptive design methods may introduce some unexpected operational bias, to the detriment of the accuracy and reliability of the obtained statistical inference. This section should describe operational bias sources that are beyond the statistical methodologies or simulations that were used to demonstrate the adequate control of Type I error.

The following operational aspects are concerns that the team may need to address to control the operational bias, as deemed applicable to the design in question. This is not an exhaustive list but a tool to prompt the team’s evaluation of the operational details to be considered.

Examples of bias sources outside of statistical methodologies or simulations includes but is not limited to:

* Documentation of actual DMC monitoring process, extent of compliance to the protocol such as actual time of IA against the pre-specified cutoff.
* The stopping rule chosen in the design phase serves as a (statistical) guideline to the DMC, which will make a recommendation regarding whether to continue or stop the trial early due to safety, efficacy, or futility as pre-specified in the protocol and charter. What if the DMC deviates from the pre-specified rules because of unexpected results in the whole benefit/risk assessment?
* Ensure complete awareness of the purpose and implications of the adaptive design in terms of efforts for the more complex implementation to all stakeholders (e.g., site staff, investigators, DMC, IRB). Acceptance and understanding of the benefits of an adaptive design balanced against the operational complexity is an important ingredient to the successful implementation and conduct of the clinical trial. For example, investigators/sites may be more motivated to comply with real time data entry and contribute to high quality/clean data.
* Assess whether the information around the interim analysis timing and consequent actions (or lack thereof) may
* Trigger inferential guessing and back calculation of treatment effect and impact on the perception of the efficacy/safety of the tested drug.
* Cause unwanted changes in the perceived probability of success of the trial
* Affect patient enrollment and screening due to involuntary preconception of the benefit of the current treatment arm(s)
* Affect the administration of the intervention
* Changes investigator’s behavior and attitude towards his patients’ participation to the trial
* Identify if any of the following modifications that are potentially a source of bias might be of concern for the study conduct:
* Expected and controllable (such as changes in laboratory testing procedures and/or diagnostic procedures),
* Expected but not controllable (such as change in study dose and/or treatment duration),
* Unexpected but controllable (such as patient non-compliance),
* Unexpected and uncontrollable (the random error in observing the clinical responses/outcomes)
* Evaluate the potential risk of information (assessment) biases:
* patient enrollment,
* differential dropouts in favor of one treatment,
* crossover to the other treatment,
* protocol deviation due to additional medications or treatments,
* differential assessment of the treatments (e.g., subjective clinical evaluations or PRO’s)
* Drift in patients baseline/demographic characteristics over time (e.g., treatment by “stage” interaction)
* Determine how to combine data collected from different stages for a final data analysis (e.g., seamless Phase II/III design)
* Assess whether the knowledge of the current enrollment overall and by country will introduce any bias, e.g., in the study with an IA for sample size re-estimation
* Plan the drug supply management and timing of campaigns for the different stages and adaptations

PROTECTION OF STUDY INTEGRITY AND VALIDITY

Based on the identified risks above, describe in details the measures planned to protect the study integrity and validity.

EXAMPLES

* The central core Trial Management Group will have no access to the aggregated data in unblinded fashion during the implementation of the planned analyses based on the interim data for study adaptive purpose.
* Separate data (eCRF) and IWRS access rights will be given to blinded and unblinded team members. Access will be limited to what is required to perform an individual function.
* No aggregate data access or analyses will be allowed until the study is considered complete as defined by the protocol.

CONTROL OF OPERATIONAL BIAS

Based on the identified risks above, describe in details the measures planned to avoid or minimize operational bias in this trial.

EXAMPLES

* Extensive training is conducted regarding the flow of communication between the central team and the investigational site.
* To ensure blinding, investigators performed training (with signed documentation) with study staff to ensure proper patients handling for the second stage of the study, when patients are re randomized based on failure of treatment in the first stage….
* The baseline patient characteristics were masked to protect of the integrity of the data, because of potential manipulation of borderline PRO scores to increase their probability to be randomized to treatment X….
* Disguise information on the timing of the sample size re estimation and the total number of subjects enrolled at a given time. Avoid disclosing all the details related to the sample size thresholds, treatment effect estimates and decision rules stemming from the IA, to avoid back guessing of the actual interim results.
* Disguise in the protocol the details around the possible shifts in randomization probabilities or probabilities of dropping or adding a treatment arm.
* The following measures were undertaken to prevent dissemination of knowledge of decisions resulting from the interim analysis of unblinded results which conveys information about accumulating data, even to investigators and other site staff members who remain blinded to study treatment assignment:...

OTHER IMPLEMENTATION DETAILS

Based on the identified risks above, describe in details any other measures planned in the implementation of the adaptive design clinical trial.

1. Including the Study Statistician [↑](#footnote-ref-1)