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A model for sponsors to support independent operation of IDMCs in clinical trials

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ABSTRACT

The Independent Data Monitoring Committee (IDMC) is entrusted with monitoring patients' safety and benefits along with the power to stop a trial for safety, futility or efficacy based on pre-specified stopping rules. Since IDMC is a wholly independent entity appointed by sponsor, sponsors often engage a third party, like a contract research organization (CRO), to produce reports using the accumulated data for IDMC review and assessment. Therefore, ensuring IDMCs have the highest quality of reports for their review is critical to ensure trials are only stopped for the right reasons or, just as importantly, kept going based on valid conclusions. The question then becomes how a sponsor can best ensure quality of such reports without infringing upon the independence principle. In this paper we will share a working model we found to be successful, with special focus as follows:

1. Development of Scope of Work (SOW), charter, DTP, timelines, and meetings
2. Data sharing between the sponsor and CRO, and blinding of treatment arms
3. Prioritizing data sets and variables for IDMC analysis
4. Open versus closed reports i
5. CRO output verification process to promote accurate IDMC review meetings

INTRODUCTION

According to the guidelines of good clinical practices of the International Council for Harmonisation (ICH), the Independent Data Monitoring Committee (IDMC) is an independent group of clinicians and biostatisticians appointed by study sponsors to provide an independent evaluation of clinical trials, assessing their safety, scientific validity, and integrity. The Food and Drug Administration (FDA) in the United States recommends the establishment of an IDMC for any controlled clinical trial, of any scale, which assesses mortality or major morbidity rates. The IDMC is charged with the responsibility of ensuring patient safety and efficacy, with the authority to make recommendations to stop clinical trials based on predetermined stopping rules around safety, futility, or benefit. In the event of safety concerns, overwhelming benefits observed in the treatment arm, or futility of continuing the trial once the study hypothesis becomes unproveable, the IDMC may recommend study termination in accordance with stopping rules pre-specified in the study protocol. Therefore, guaranteeing the highest quality of reports for IDMC review is pivotal in ensuring that clinical trials are stopped for valid reasons or maintained based on reliable findings. The challenge lies in how sponsors can optimize the quality of these reports without infringing upon the principle of independence.

This paper introduces a successful working model for ensuring report quality while preserving independence.

DEVELOPMENT OF SCOPE OF WORK, CHARTER, DATA TRANSFER PLAN TIMELINES, AND MEETINGS

Alignment of expectations is critical for both the sponsor study biometrics team and independent statistical reporting group (ISRG) in supporting IDMC data reviews and activities, encompassing project clarifications on scope, timelines, quality and communication. Therefore, it is recommended the sponsor study biometrics team engage with the ISRG to establish these expectations ahead of significant project deliverables. Sponsor study biometrics team may develop and/or review the following documents:

SOW (SCOPE OF WORK)

Describes all ISRG deliverables and activities such as facilitating the IDMC meetings, performing randomization checks, generating test runs and quality check runs, interim efficacy analyses (if applicable), establishing key ISRG membership (e.g., Biostats lead and Programming lead).

IDMC CHARTER

This document articulates the objectives and outlines the governance, activities, and roles and responsibilities of the various groups involved in IDMC efforts as well as operating principles, including the purpose of IDMC meetings, meeting frequency, open and closed session procedures, and measures to ensure confidentiality and proper communication.

ROLES AND RESPONSIBILITY FOR EACH STAKEHOLDER GROUP

Table below outlines the components of each stakeholder groups and their corresponding responsibilities. The components and roles and responsibilities should be evaluated based on specific studies and disease areas.

Stakeholder Group	**Roles and Responsibilities**
Independent Data Monitoring Committee (IDMC): • Clinicians with expertise in relevant clinical specialties • Biostatistician • (Optional) For example medical ethicist (for trials with high risks or with broad public health implications)	• Review accumulating data, attend IDMC meeting and monitor safety and efficacy on a regular basis for ongoing clinical trials • Advise sponsor regarding continuing safety of trial subjects and continuing trial validity and scientific merit • Review unblinded interim data and recommend early termination of trial based on pre-specified stopping rules for efficacy or futility at interim analysis (if applicable) • Call adhoc meeting if necessary
Sponsor Liaison Team (SLT) • Study Medical Monitor & Clinical Development Lead • Study Clinical Project Manager • Study Biostatistician & Program Lead Statistician • Study Product Safety Lead	• Attend IDMC open sessions, provide scientific details and answer questions IDMC members may have in the open session • Respond to IDMC recommendations if applicable •
Sponsor Study Biometrics (SSB) • Study Biostatistician • Study lead programmer	• Develop IDMC Charter • Verify open and closed reports (based on dummy randomization code) produced by ISRG for IDMC meetings • Prepare statistical programs for analysis verification based on dummy treatment code to be used by the Independent Sponsor Biometrics Team in case such verification is required • Develop verification plan for interim analysis

Stakeholder Group	Roles and Responsibilities
Independent Sponsor Biometrics Team (ISBT) • Independent statistician (may be an employee of the sponsor, but not a member of the study team) • Independent statistical programmer(s)	• Independently verify important closed-session results from the interim analysis upon notification from DRB, if the IDMC recommendation is to stop the study for safety, efficacy, or futility • Verify randomization information accuracy
Sponsor Data Review Board (DRB) • Chief Medical Officer • Head of Regulatory • Head of Biometrics • Head of Drug Safety	• Review the IDMC recommendations, determine whether they are acceptable, and convey such recommendations to the SLT • Notify the ISBT to validate interim analysis results upon receipt of an IDMC recommendation to stop the study early due to safety, efficacy, or futility
Independent statistical reporting group (ISRG) • Independent statistician from a contract research organization (CRO) • Independent statistical programmers from a CRO	• Generate open and closed IDMC reports • Schedule IDMC meetings • Participate in IDMC meetings for both open and closed sessions
Randomization & Trial Supply Management (RTSM)	• Transfer unblinded data related to randomization to ISRG for unblinded analysis for IDMC • Transfer unblinded data related to randomization to ISBT upon request from sponsor for verification of important closed results if IDMC recommends to stop the trial early due to safety, efficacy, or futility

The following diagram shows the parties involved in the IDMC-related aspects of the trial, their roles, and the relationships between them.

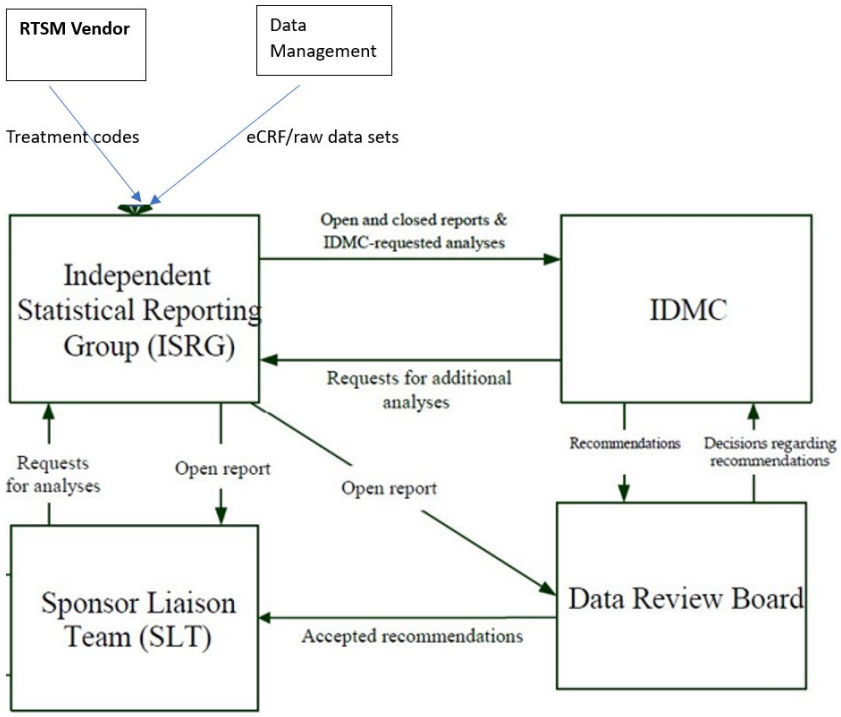

Figure 1. Trial Organization

DATA TRANSFER PLAN (DTP)

This document describes the transfer and data scope and structure requirements for safety and efficacy data sets, and dummy randomization codes (if applicable) from sponsor to ISRG and vice versa.

TIMELINES

This document should clearly describe the dates or durations for key data deliverables and activities supporting the IDMC meetings, such as data cut-off date, data cleaning, data transfer dates, dry runs, final reports, QC activities and reviews. Ensure the timelines are agreed by all stakeholders. We recommended to include the accountable team from each stakeholder to ensure transparency and accountability.

DATA SHARING BETWEEN THE SPONSOR AND CRO, AND BLINDING OF TREATMENT ARMS

This section outlines the transfer of data sets and documents between the sponsor and the ISRG at the CRO. The data and document sharing processes are bi-directional, encompassing transfers from the sponsor to the ISRG, ISRG to sponsor and RTSM to ISRG. All transfers must adhere to the guidelines laid out in the sponsor-approved DTP. A secure platform must be planned in advance to transfer these documents and data to protect data integrity and minimize potential risk of transfers inadvertently becoming available to parties outside those listed in the DTP.

Examples of covered Documents are the study protocol, IDMC charter, SAP, open and/or closed TLF shells. The sponsor will share raw data sets with the ISRG based on the IDMC charter to produce IDMC-specific TLFs.

Below DTPs will describe expectations for the transfer of the following:

1. Blinded clinical data from the sponsor to the ISRG,

2. TLF output data sets from the ISRG to the sponsor, and
3. Randomization data sets from the RTSM vendor to the ISRG.

BLINDED CLINICAL DATA FROM SPONSOR TO ISRG

The DTP should clearly list out the cumulative data sets that will be included in each transfer. The “Data sets” section will list out all the blinded data sets that are required for ISRG programming and output generation, such as:

- Safety data sets
- Efficacy data sets, if applicable
- “Other” data sets including dummy treatment code information which allows sponsor verification on the same dummy codes as needed, protocol deviations, etc., if applicable
- Additional considerations for the DTPs may include data cut-off date for all the data sets prior to each transfer, naming convention and formats, mode of transfer, transfer schedule, test data transfer, dry run, production, and ad-hoc transfers if required

TLF OUTPUT DATA SETS FROM ISRG TO SPONSOR

This DTP outlines transfer specifications for the delivery of the ISRG output data sets and TLFs to sponsor. These data sets refer to those produced by the ISRG as a byproduct of all closed and open TLFs. They contain all info shown in these TLFs in SAS ® data set format, which can be electronically compared against the sponsor TLF output data sets of open and closed TLFs. This process makes the QC of ISRG and sponsor outputs more efficient in addition to the output review and cross-check. Also, it allows the sponsor study biometrics team further confidence in pre-defined analysis and overall quality of the data and TLF reports.

RANDOMIZATION DATA SETS FROM RTSM VENDOR TO ISRG

This DTP outlines transfer specifications for the randomization data with unblinded treatment codes from the external RTSM vendor to the ISRG for the generation of closed reports for IDMC review.

PRIORITIZING DATA SETS AND VARIABLES FOR IDMC ANALYSIS

This section describes the scope of IDMC-driven data sets determined by the IDMC charter and the TLF shells. The planning and development of these data sets should be consistent with the study CSR scope and all derivation rules should be aligned with the study SAP.

Based on the IDMC charter document, the sponsor study biometrics team can choose to program SDTM and ADaM data sets to produce IDMC-specific TLFs and QC ISRG outputs. IDMC-driven SDTM and ADaM data sets are recommended, but optional, based on the study-specific requirements and the urgency of the IDMC.

To assist with QC of important ISRG outputs, it is recommended to prepare the list of SDTM and ADaM data sets based upon IDMC report shells. The recommended list should conform to the IDMC standard analysis scope.

OPEN VERSUS CLOSED REPORTS

For each IDMC meeting, the ISRG will prepare an open report to be used in the open session and a closed report for the closed session.

OPEN REPORT

The open report is available to all who attend the IDMC meeting. It typically presents a pooled “Total” column which includes all treatment groups without breaking down by treatment arm. In the open session of the IDMC, the sponsor may prepare presentations based on the open report to summarize the overall patient demographics, disease characteristics, disposition, treatment-emergent adverse events and/or AEs of special interest.

CLOSED REPORT

The closed report is available to only those attending the closed sessions of the IDMC meeting (IDMC members and ISRG representatives). The closed report includes analyses displayed by treatment arms with masked labels (e.g., Arm A, Arm B). To maintain trial integrity, it is important to ensure the closed report is not accessible to the sponsor.

VERIFYING THE CRO (ISRG) OUTPUTS

Both the open and closed reports should be produced in high accuracy. That requires clean raw data set and quality-checked statistical program to process and summarize the data. To optimize confidence in the reports an ISRG shares with the IDMC, sponsor may choose to have the study biometrics team perform QC on the open reports and on the closed reports using the dummy treatment codes shared with the ISRG, before the first IDMC meeting.

If the IDMC recommends stopping the trial early for efficacy, futility or safety concerns based on the open/closed report, the ISBT should promptly verify the key safety and efficacy outputs (if applicable). The scope and timeline of the verification may be pre-specified and documented, for example, as a verification plan that kicks in once the DRB receives the early stopping recommendation from the IDMC. The verification plan should clearly define the roles and responsibilities of stakeholders who contribute to the procedure. For example, the study programmers are responsible for developing and testing the blinded data sets and blinded outputs using dummy treatment variables. They should also inform the ISBT on key information such as analysis folder structure, unblinding process, location of relevant datasets, variables, files and specifications to be used in the verification procedure. The study statistician can be responsible for developing the verification plan, reviewing and verifying the blinded outputs, and informing the ISBT on study design, statistical analysis plan and TLF details for outputs to be verified.

The scope of the verification should be highly focused. It should include only the key safety outputs and key efficacy outputs (if applicable) because the verification should be executed and completed promptly within a matter of x days, depending on the scope of specified verification.

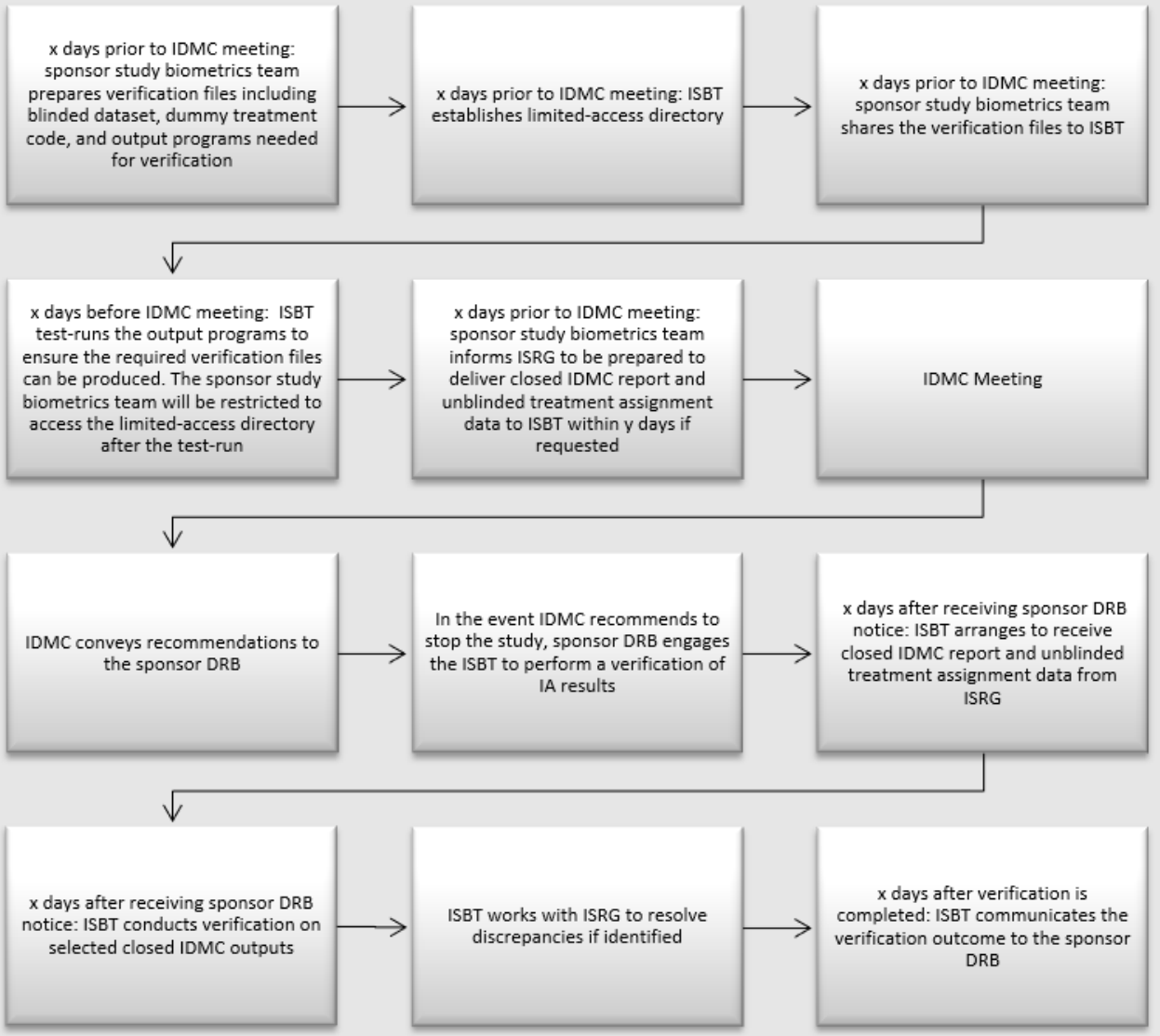

Figure 2. Example of Verification Flowchart for the IDMC Procedure and Timeline

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