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Agile, Collaborative, Efficient (ACE): A New Perspective on Data Monitoring Committee Data Review Preparation

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ABSTRACT

Data Monitoring Committee (DMC) has been part of clinical trials since 1960's. Nowadays, an increasing number of sponsors utilize DMC in various situations to monitor safety data, critical efficacy data, and ensure the integrity of study conduct. Given the different purposes of DMCs, there are diverse approaches to facilitate DMC data review. In this paper, we will discuss certain strategies and processes that Boehringer Ingelheim implement for DMC. To begin with, we will briefly describe the general purpose of a DMC as well as its roles and responsibilities in Boehringer, followed by an introduction to Boehringer's independent statistical analysis team (iSAT). The focus is to present three models that iSAT, as an independent team within sponsor, apply to efficiently and timely assist DMC data review. We will conclude by sharing experience/lessons learned from supporting DMCs in **randomized non-pivotal and/or open label registrational studies** to open further discussion.

KEY WORDS: DMC, data review, unblinding, trial integrity, independent team within sponsor

Background and Introduction

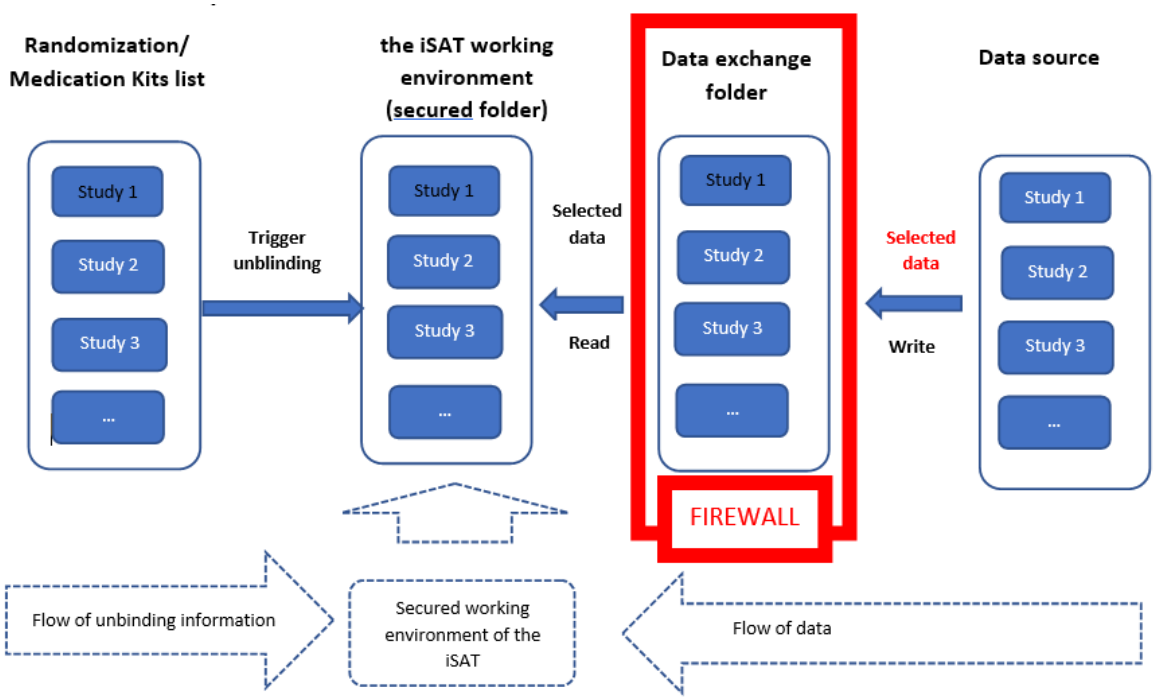
In general, "A Data Monitoring Committee is a group of **independent** experts **external** to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study." In addition, "other aspects of a clinical trial (e.g., study integrity, design aspects) might also be assessed by a DMC. Utilizing a DMC during trial conduct has tremendous benefits. However, not all the clinical trials need a DMC given its nature and purposes. Moreover, it is also a complex process to determine the necessity of a DMC, how to set up a DMC and select DMC members, etc. In this paper, we assume a DMC is already in place. Support is needed to produce blinded (unblinded) outputs for review in open (closed/executive) sessions. **The target audience** of this paper is statistical programmers, statisticians, data managers or functions that perform similar tasks. In addition, anyone who supported, are supporting, will support or have interest in supporting DMC could also benefit.

The Independent Statistical Analysis Team (iSAT)

The Independent Statistical Analysis Team (iSAT) consists of 2 statisticians and 3 statistical programmers, on average with over 10 years of experience from diverse therapeutic areas with the sponsor company. The primary task of the iSAT is to function as a dedicated independent team, preparing unblinded data handling and analysis **during trial conduct**. From this perspective, the iSAT is independent of any study and project team within the sponsor organization and is not involved in any trial or project related tasks during the conduct with the

exception for tasks requiring strict confidentiality handling such as DMC support, internal Interim Analysis, and/or IND safety reporting.

Firewall Set Up: Cornerstone for the Success of iSAT Supporting DMC



Both the iSAT and involved study teams have access to the data exchange folder, which provides the location where blinded study data can be stored. The iSAT will then copy the blinded data to the iSAT's own secured working environment for further use. Moreover, the setup of firewall is bi-directional: the iSAT does not have access to the study data sources directly. On the other hand, the study teams do not have access to the secured iSAT working environment. By doing so, the integrity and confidentiality of the iSAT work can be well maintained. Once study teams have completed their interactions with the iSAT, their access to the exchange folder will be revoked and they will no longer be able to access the exchange folder until new requests. Information for unblinding, such as randomization/medication kits information will be released to the iSAT following company standard procedure via secured channel.

Models of the iSAT Support DMCs

Being independent from study/project team within the sponsor is the iSAT's fundamental principal, which entitles the iSAT with the privilege to get involved in handling unblinded analysis **for randomized non-pivotal phase II and/or open label registrational studies**. To serve different purposes and fit into diverse scenarios, various models/methods are implemented, e.g., the conventional way of only unblinding blinded outputs, or provide full programming support as an independent team, or a hybrid of previous two.

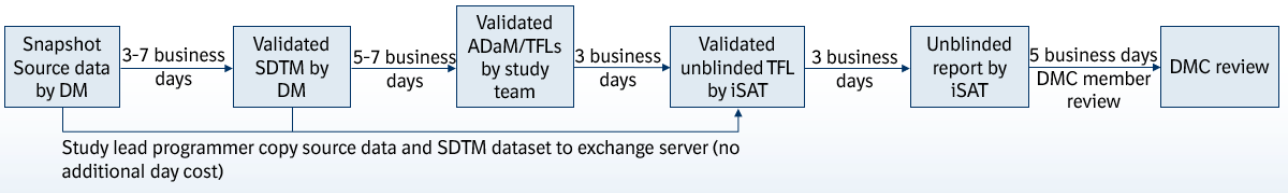
Model A – the iSAT Unblinds Blinded Outputs Only

This is the traditional and maybe the most popular approach within the pharmaceutical industry working on DMC if the sponsor gets involved. The scenario is that there are two teams, e.g., one with sponsor who provides blinded outputs. The other team is external to the sponsor who works on the unblinding and generates unblinded outputs. In our case, **for randomized non-pivotal phase II and/or open label registrational studies**, the iSAT can serve as the "external" team, unblind ADaM, generate unblinded tables, listings, and figures (TFLs), create summary report and address any additional closed session requests.

Key points:

- Study team prepares blinded ADaM and TFLs.
- The iSAT unblinds ADaM/TFLs, creates summary report.
- Addresses potential closed session requests.

Flow chart:



Challenges:

- Structure-wise, programs transferred from study team need to be executable in iSAT's unblinded working environment in the expected way, e.g., the iSAT needs to understand the use of macro variables, how to execute included programs smoothly, etc.
- Content-wise, the iSAT also needs to understand study team's programs/logics/algorithms and is ready to debug in case of anything unexpected.
- Accommodate sufficient time for mock/dry run.
- DMC might not review the freshest data: usually it takes up to 4/5 weeks from snapshot to the DMC meeting.

Model B – the iSAT Provides Full Programming Support

Given the challenges from model A, one potential solution is to consider full programming support from the iSAT **for randomized non-pivotal phase II and/or open label registrational studies**. In other words, trial statistician (TSTAT) and iSTAT (the independent statistician) will draft the initial DMC statistical analysis plan (SAP) and aligns with study team before DMC's kick off meeting. Afterwards iSTAT will take over the SAP. iPROG (the independent statistical programmer) programs ADaM and prepares unblinded outputs.

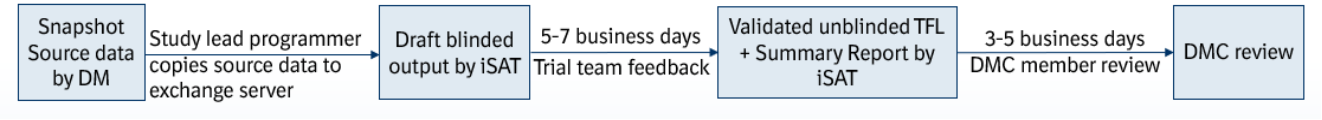
Key points:

The iSAT

- Prepares programs for ADaM and TFLs from source data.
- Shares draft blinded report with trial team as need.

- Creates unblinded TFLs and summary report.
- Addresses any potential requests from closed sessions.

Flow chart:



Benefits:

- It is efficient with fast delivery. For example, for the very first DMC, it can take up to approximately 12 business days from snapshot to the meeting. For later DMCs, the time can even be shortened by up to 5 business days, which is about 7 business days from the snapshot. In this way, DMC can review fresher data and make timely recommendation.
- The major task of DMC is to monitor safety/efficacy data and ensure the integrity during trial conduct. The request for data presentations at DMC might not be always the same as for interim analysis and/or final clinical trial report. As the independent team, the iSAT is agile and flexible enough to make appropriate adaptations and generate outputs that better fits review purposes.
- Requests from closed sessions can be addressed in a timely fashion with lower cost.

Studies that fit this model:

The iSAT gets involved only in **randomized blinded non-pivotal phase II and/or open label registrational studies.**

- Studies with high frequency DMC (e.g., every month)→ large amount of data is collected within short period and more up-to-date data need to be reviewed.
- Certain II/phase III studies → challenging to keep study team blinded during trial conduct due to the nature of study design.
- Studies with complex randomization scheme→technically difficult for study team to analyze/simulate blindedly.

Challenges:

- Being independent from study teams is a double-edged sword. Independence does not mean being isolated. The iSAT needs to be well informed of any important protocol updates, CRF updates, any changes in study conduct etc.
- Given the nature of maintaining data confidentiality and study integrity, the iSAT should be a small group with restrictions on team size, which makes us not capable to support large amount of DMCs in parallel.

Model C – A Hybrid of Model A and B

In some situations, study team prefers model A whereas certain outputs cannot be prepared appropriately in the blinded fashion. For example, in a double blinded study, one of the

objectives is to explore the relations between drug exposure (e.g., AUC) with clinical endpoints. In this case, we introduce the hybrid model: i.e., study team prepares all the outputs except those involve information that could lead to unblinding; instead, those outputs at the risk of releasing unblinded treatment will be handled by the iSAT. Another case that a hybrid model fits is to produce outputs for a subset of eligible patients. As an illustration, in a blinded study that allows cross over, a patient in the standard of care arm after progression, if qualified, can cross over to the investigational drug arm. In this case, it makes natural sense for the iSAT as an independent team to prepare all the required summary outputs after cross over.

Summary

In a nutshell, model B is our current preference for further DMC support after weighting the benefits and challenges. However, as is also well-known, there is no "one solution fits all". It is always recommended and encouraged to open the communication channel, discuss different scenarios, collaborate across teams, and choose the most optimum model that suits specific studies the best.

	Benefits	Challenges
Model A	• Widely accepted.	• Communication. • Mock/dry run takes time. Potential long lag time between snapshot and DMC meeting.
Model B	• Faster delivery and fresher data for review. • Address closed session requests timely. • Cost-wise efficient.	• Communication. • Potential lack of resources.
Model C [A variation of model A]	• Widely accepted. • More flexible compared with model A	• Communication. • Mock/dry run takes time. Potential long lag time between snapshot and DMC meeting.

The iSAT Supports DMC -- How Can We Do Better?

Nowadays the pharmaceutical industry is full of innovation, machine learning, Artificial Intelligence, ChatGPT, etc. How can we utilize these high-tech tools to better support DMC data review? One example is the implementation of data visualization to review data in a dynamic and interactive way. In one of the DMCs that we supported, in the closed session efficacy related data was presented using an interactive heat map based on R. With the rapid development of technologies, we believe that dynamic and interactive data review at DMC would be realized soon.

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