

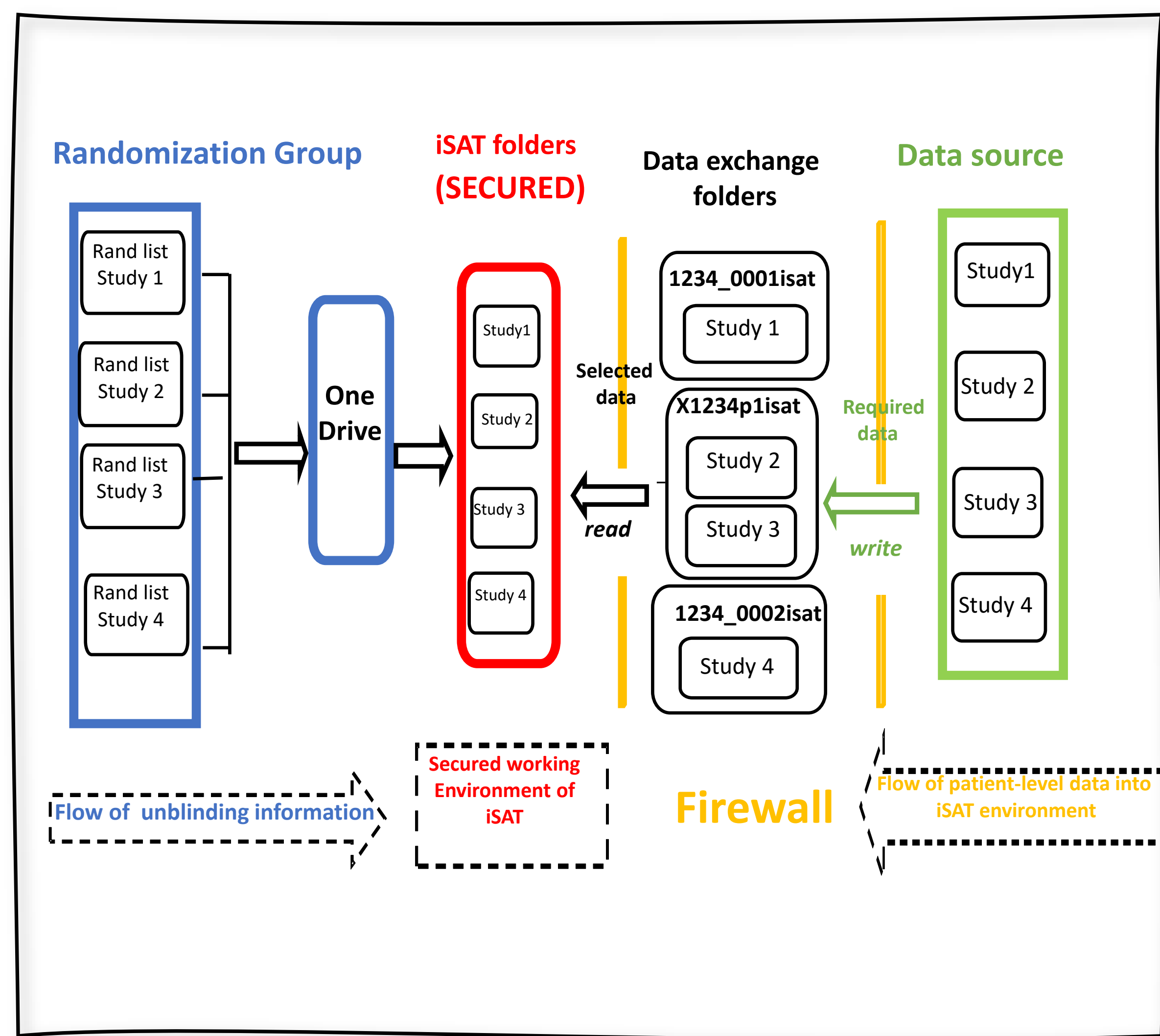
INTRODUCTION

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 (BI) implement for DMC. To begin with, we will briefly describe the general purpose of a DMC as well as its roles and responsibilities in BI, followed by an introduction to BI'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.

iSAT (INDEPENDET STATISTICAL ANALYSIS TEAM)

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. Firewalls - both physically and electronically - were defined and established to ensure that only the iSAT has access to unblinded information (see **Figure 1**)

FIGURE 1: FIREWALL SETUP



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

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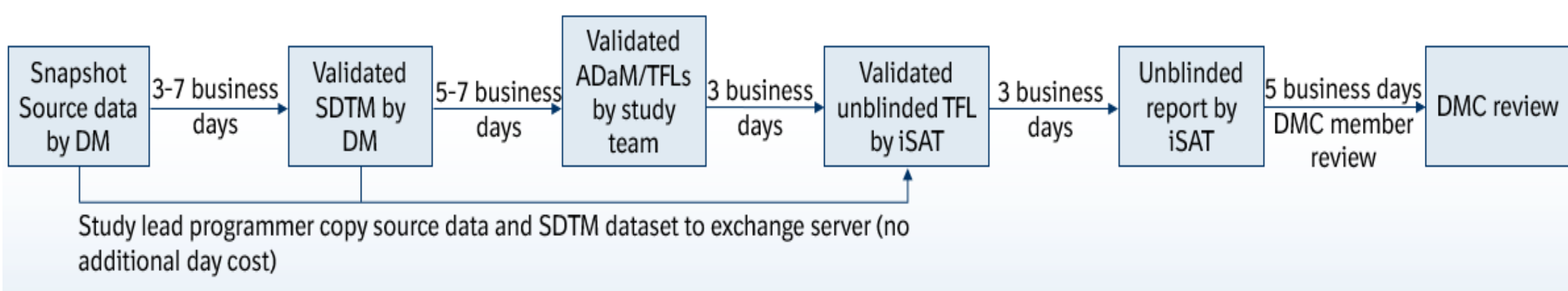
MODELS OF ISAT SUPPORT DMCs

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.

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

Workflow:

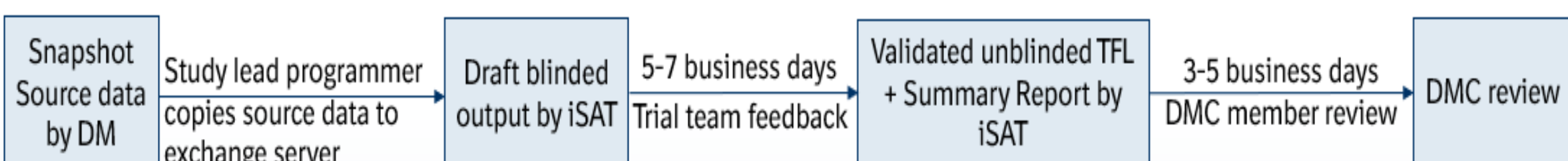


Model B – the iSAT Provides Full Programming Support

For randomized non-pivotal phase II and/or open label registrational studies, 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. 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.

Workflow:



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 AND DISCUSSION

	Benefits	Challenges
Model A	Widely accepted.	- High demand on understanding trial/study team’s work both tructure-wise and Content-wise Accommodate sufficient time for mock/dry run. - DMC might not review the freshest data.
Model B	- Efficient with fast delivery. - Agile and flexible enough to make appropriate adaptations. review purposes. - Requests from closed sessions can be addressed in a timely fashion with lower cost.	- Communication. - Potential lack of resources.
Model C [A variation of mode A]	- Well accepted. - Flexible to adapt diverse scenarios.	- High demand on understanding trial/study team’s work both structure-wise and Content-wise Accommodate sufficient time for mock/dry run. - DMC might not review the freshest data.

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. With the rapid development of technologies, we believe that dynamic and interactive data review at DMC would be realized soon.