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Managing Unblinded Activities Internally: The Independent Statistical Analysis Team (iSAT) Model

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ABSTRACT

The independent Statistical Analysis Team (iSAT) was established in 2017 as a sponsor-employed, fully unblinded, and independent analysis group to manage unblinded activities internally. Initially created to support Pharmacovigilance for anticipated event reporting, iSAT's role has expanded to include Data Monitoring Committees (DMCs) and Interim Analyses (IAs). The team operates under strict firewalls—physical, electronic, and organizational—to ensure confidentiality and maintain study integrity. Processes include secure data environments, hierarchical separation, and controlled communication. For anticipated event analyses, iSAT receives limited datasets excluding efficacy data, while IA workflows involve blinded teams providing programs that iSAT executes post-unblinding. For DMCs, iSAT functions as both independent statistician and programmer, enabling rapid turnaround times and confidential handling of additional requests. Over eight years, this model has supported more than 30 trials, demonstrating advantages such as expert internal resources, streamlined communication, elimination of external data transfers, and improved efficiency. While external perception of internal unblinding remains a potential concern, restricting iSAT involvement to non-pivotal studies mitigates this risk. Overall, the iSAT model offers a robust, efficient, and secure approach for managing unblinded activities within a sponsor organization.

INTRODUCTION

Double-blind randomized clinical trials are designed to minimize bias in treatment evaluation. However, during trial conduct, access to unblinded data may be necessary for specific purposes, including:

- Safety reporting of anticipated events for IND submissions,
- Ongoing benefit–risk evaluation by Data Monitoring Committees (DMCs),
- Interim analyses supporting internal development decisions.

Traditionally, these unblinded activities are performed by external independent statistical groups to maintain separation from the sponsor's blinded trial team. While effective, this approach introduces challenges, including data transfer complexities, contracting delays, limited familiarity with internal systems, and potential inefficiencies in timelines.

To address these limitations, Boehringer Ingelheim established an **independent Statistical Analysis Team (iSAT)** in 2017. The iSAT is an internal group of statisticians and programmers who conduct unblinded analyses while remaining organizationally and operationally isolated from study teams. This paper describes the iSAT model, its governance and firewall setup, and lessons learned from eight years of implementation.

ISAT MODEL AND ORGANIZATIONAL SETUP

TEAM STRUCTURE AND SCOPE

The iSAT consists of dedicated statisticians and programmers with extensive experience across multiple therapeutic areas. The team currently includes two statisticians and three programmers, all sponsor employees.

Initially, iSAT was created to support pharmacovigilance by performing unblinded anticipated events analyses for IND safety reporting. Over time, its remit expanded to include:

- Acting as independent statistician and programmer for Data Monitoring Committees (DMC),

- Performing interim analysis (IA) for non-pivotal trials.

Across these activities, iSAT operates fully unblinded while being independent from the blinded study team.

FIREWALL AND GOVERNANCE FRAMEWORK

This framework ensures that unblinded information remains confined to iSAT and authorized stakeholders.

The primary concern with an internal unblinded team is the potential risk of operational bias or inadvertent unblinding of the study team. To mitigate this, iSAT operates under a comprehensive firewall framework.

Key Firewall Components

The iSAT firewall includes:

- Restricted Data Access
  iSAT members only have access to ongoing trial data for studies they actively support.
- Secured Study-Specific Environments
  Each study has dedicated, access-controlled folders managed by the iSAT.
- Organizational Separation
  iSAT is hierarchically separated from development teams within the organization.
- Controlled Communication
  Communications between iSAT and blinded study team members is minimized after unblinding and governed by predefined logistics and access plans.

USER CASES

ANTICIPATED EVENTS ANALYSES

For unblinded analyses of anticipated safety events, iSAT receives a restricted data set that explicitly excludes efficacy information. This allows safety monitoring and reporting while minimizing unnecessary exposure to treatment effect data.

Additionally, the iSAT supports:

- Continued use of blinded trigger approaches when feasible,
- Early adoption of DMC-based unblinded monitoring in pharmacovigilance contexts.

DATA MONITORING COMMITTEES

For trials requiring a DMC, iSAT acts as:

- Independent Statistician,
- Independent Programmer,
- Occasionally Project Manager.

Key features of the iSAT DMC model include:

- Participation in closed DMC sessions, presenting unblinded outputs directly to DMC members,
- Use of source data rather than SDTM, allowing highly efficient production timelines,
- Ability to deliver unblinded outputs in less than two weeks from data snapshot to DMC meeting when required.

During DMC setup, iSAT collaborates closely with the blinded study team to define roles, responsibilities, and workflows.

INTERIM ANALYSES

For interim analyses, the blinded trial team typically:

- Develops analysis programs while still blinded,
- Transfers programs/blinded ADaM datasets to iSAT according to prespecified timelines.

The iSAT then:

- Unblinds the data within the secured environment,
- Executes the programs which the trial team provides,
- Shares unblinded results strictly according to a pre-approved Logistics and Access Plan.

This approach maximizes efficiency while preserving the integrity of the blinded study team.

FLEXIBLE PROGRAMMING MODELS

Three programming responsibility models are supported:

1. Study Team–Led Model
   The blinded team leads analysis data set (ADS) and table, listing, and figure (TLF) programming, and iSAT does the unblinding the ADS which the study team provides, and run the TFL programs based on unblinded ADS.
2. iSAT-Led Model
   iSAT assumes responsibility for ADS and TLF programming. The study team only needs to provide the source datasets.
3. Hybrid Model
   Tasks are shared depending on data restrictions.

In all models, iSAT exclusively produces unblinded outputs, while quality control activities are shared as appropriate.

RESULTS AND EXPERIENCE

Over eight years, the iSAT model has been applied to approximately 30 clinical trials involving:

- IND safety reporting,
- Data Monitoring Committees,
- Interim analysis,
- Unplanned unblind analysis.

FEEDBACK FROM STAKEHOLDERS

Including study teams, DMC members, and pharmacovigilance partners, the feedback has been consistently positive. Key observed benefits include:

- Faster turnaround times,
- Improved communication efficiency,
- Higher procedural consistency,
- Enhanced integration with internal standards and systems.

ADVANTAGES OF THE INTERNAL ISAT MODEL

Compared with outsourcing unblinded activities, the sponsor-employed iSAT offers several advantages:

- Immediate access to experienced statisticians and programmers,
- Direct communication with internal trial teams,
- Familiarity with company procedures and governance,
- No need to transfer sensitive data to external vendors,
- Flexible resourcing without contract renegotiations,
- Improved operational efficiency for DMC meetings and interim analyses.

LIMITATIONS AND RISK PERCEPTION

The primary limitation of the iSAT model is external perception risk, namely concern that sponsor employees have access to unblinded data. This risk is mitigated by:

- Restricting iSAT involvement primarily to non-pivotal trials,
- Maintaining strict firewall procedures,
- Clearly documenting roles, access controls, and governance.

Protecting trial integrity remains a core responsibility of the iSAT, and adherence to firewall principles is treated with high priority.

CONCLUSION

An internal, sponsor-employed independent Statistical Analysis Team can successfully support unblinded clinical trial activities when robust governance and firewall structures are in place. Based on eight years of practical experience across multiple studies, the iSAT model demonstrates that internal independence is feasible, efficient, and well-accepted. This approach represents a viable alternative to outsourcing for non-pivotal trials requiring unblinded analyses, offering operational advantages without compromising trial integrity.

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