Wednesday 17th June 2026 | ICC Belfast
Hall 2b: 11:15 – 12:30

2026 CONFERENCE

Benefit-Risk SIG: Advancing the Implementation of Safety Methodologies

Beyond Individual Cases: Operationalizing FDA IND Safety Reporting for Anticipated Serious Adverse Events

Matthias Trampisch
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Str. 173
55216 Ingelheim am Rhein, Germany
matthias.trampisch@boehringer-ingelheim.com

Greg Ball
ASAPprocess
43 Eastwood Blvd
Manalapan, NJ 07726, USA
greg.ball@asapprocess.co

Barbara Hendrickson
Department of Pediatrics, University of Chicago
Chicago, IL USA
bhendric@bsd.uchicago.edu

Marianna Grinberg
UCB BioSciences GmbH
Rolf-Schwarz-Schütte-Platz 1
40789 Monheim, Germany
Marianna.Grinberg@ucb.com

Kevin Don Roberts
Pfizer Inc.
610 Main Street
Cambridge, MA 02138, USA
Kevin.Roberts@pfizer.com)

Life forward

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The Core Challenge

➢Anticipated serious adverse events

Events anticipated in the study population, independent of drug exposure

Why Individual Case Review Falls Short

In many IND programs, serious events are common because of:

- advanced disease
- baseline morbidity
- background therapies

Therefore, isolated cases may be plausibly unrelated to IND treatment and insufficient for reporting decisions.

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Regulatory Background

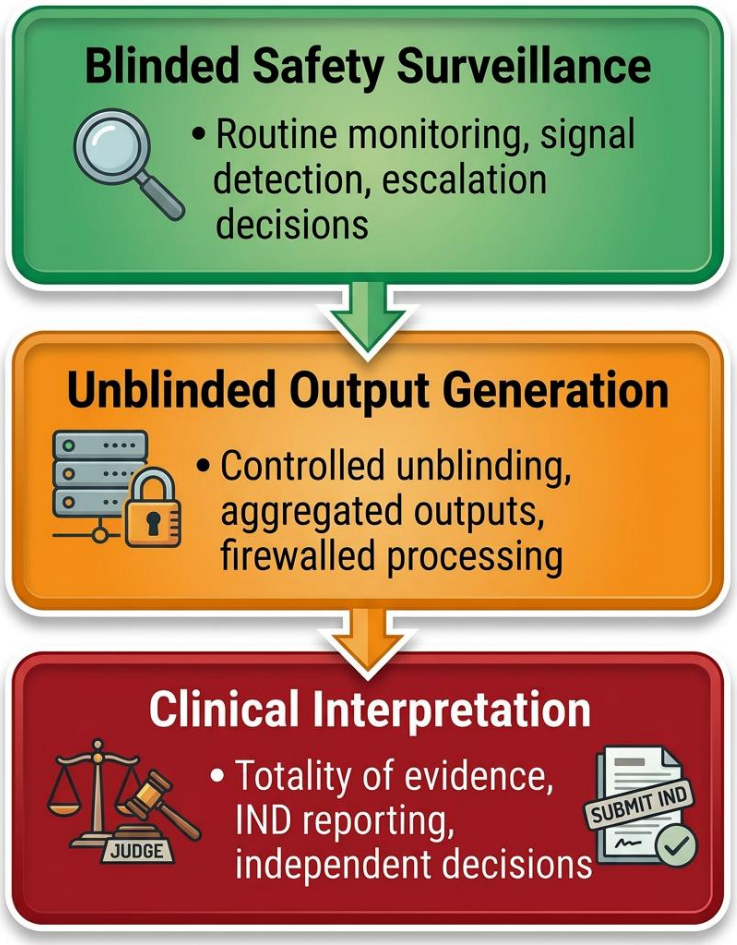
- The ***FDA final guidance***[1] on ***Sponsor Responsibilities for IND Safety Reporting*** (based on ***21 CFR 312.32***[2]) expects sponsors to assess **anticipated Serious Adverse Events** using **aggregated, unblinded analysis** when event rates suggest increased product risk during trial conduct.
- The guidance is principle based
- Operational challenge is left to the sponsor

Key Questions

- How do we perform unblinded aggregate assessment?
- How do we preserve trial integrity?
- Who reviews, decides, and reports?

[1]FDA. Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. Guidance for Industry. [Online].; 2025. Available from: https://www.fda.gov/media/150356/download.
[2]Administration USFaD. Code of Federal Regulations. Title 21, Part 312.32 - IND Safety Reporting. 2025 Available from: https://www.ecfr.gov/current/title-21/section-312.32

The Operational Framework

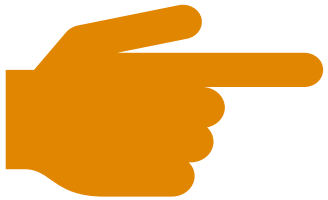


Planning for Safety Surveillance and Aggregate Analysis

A workable model needs three things:

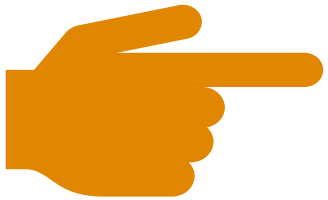
1. **ASAP** (Aggregate Safety Assessment Planning)
   - aligns stakeholders and safety topics
2. **SSP** (Safety Surveillance Plan)
   - defines cadence, triggers, roles, escalation
3. **Firewall controls**
   - protect trial integrity through restricted access and communication

The Operational Framework



Who does what, how and when?

The Operational Framework



Who does what, how and when?

The Who: entities involved

- **Safety Assessment Entity**
  - **Unblinded**, can be composed of internal and/or external[1] (e.g. CRO, DMC) personnel; reviews and recommends reporting
  - **Independent**: firewalled entity for unblinded safety review, with no role in trial conduct, efficacy evaluation, or operational decision-making on trial level
- **Sponsor entity for reporting**
  - **Unblinded**, sponsor employed; executes reporting requirements to the FDA
- **Statistical Data Analysis Center (SDAC)**
  - **Unblinded**, can be internal (independent Statistical Analysis Team) or external (CRO); creates unblinded outputs for the Safety Assessment Entity
  - Least-privilege data access, ensuring that the assessment entity receives only the data necessary to evaluate the safety question at hand
- **(opt) Safety Monitoring Team (SMT)**
  - **Blinded**, usually internal personnel; may conduct blinded safety assessments

[1]internal refers to sponsor employed personnel, external to sponsor contracted personnel

The Who: Safety Assessment Entity - Three Models

All models are unblinded and must be firewalled.

1. Internal (Sponsor-employed personnel)

- Fast setup, strong program context.
- Requires demonstrable firewall integrity

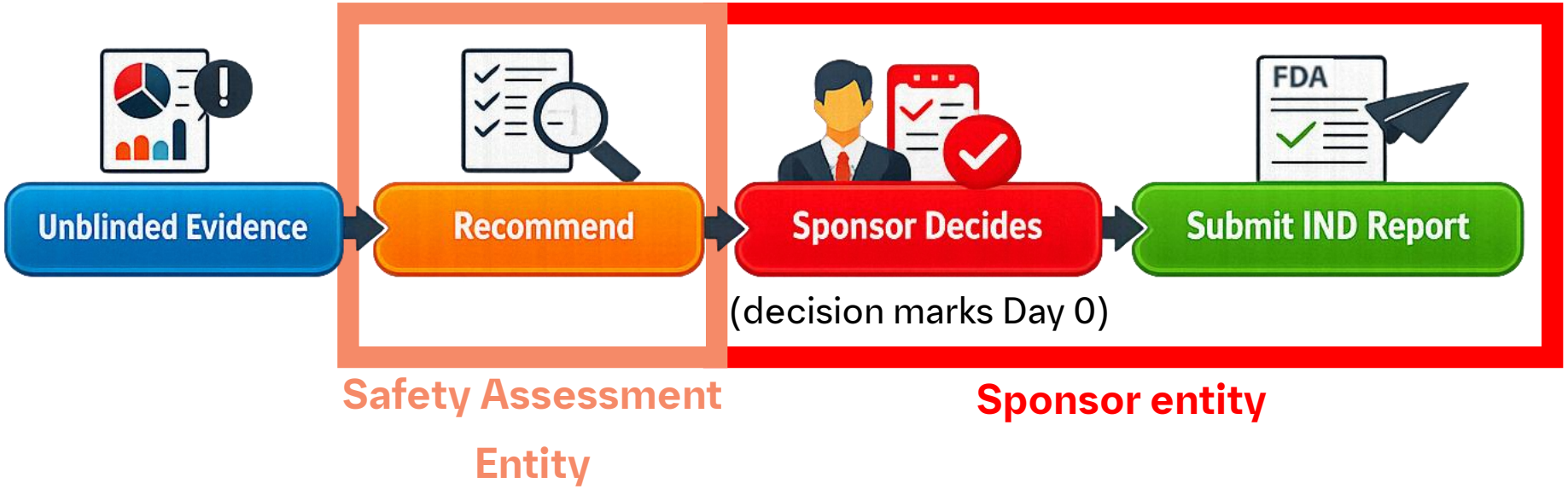
2. External (e.g. DMC)

- Additional independence and credibility.
- Sponsor retains reporting responsibility

3. Hybrid (combination of both)

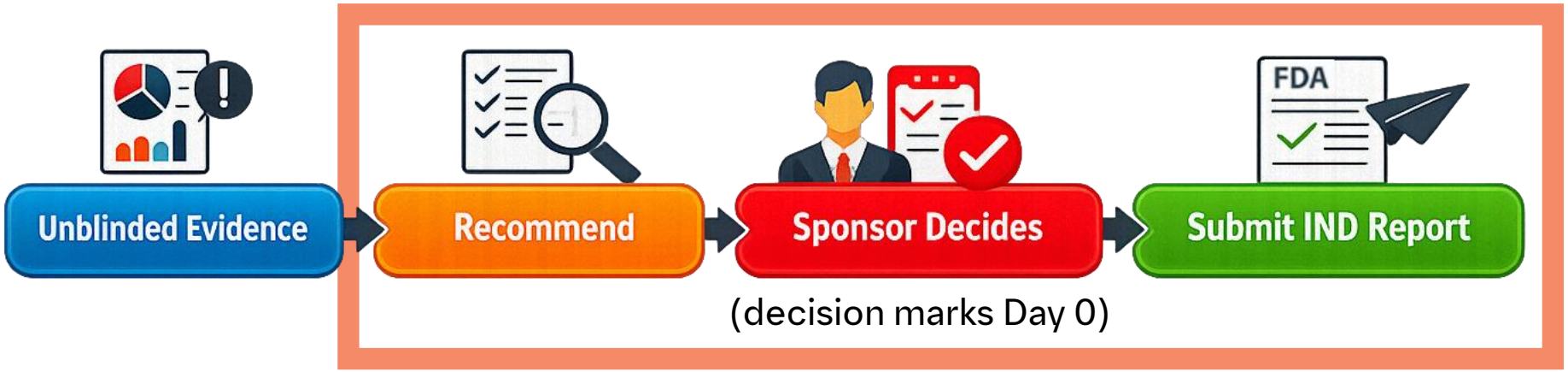
- Balances context and independence.
- Needs precise rules for escalation and communication.

The Who: Responsibilities



For an **external** Safety Assessment Entity, a sponsor entity must decide and execute

The Who: Responsibilities



An **internal** or **hybrid** Safety Assessment Entity may take over the sponsor responsibilities, if prospectively defined.

The Who: entities involved

- Safety Assessment Entity
  - Unblinded, can composed of internal and/or external[1] (e.g. CRO, DMC) personnel; reviews and recommends reporting
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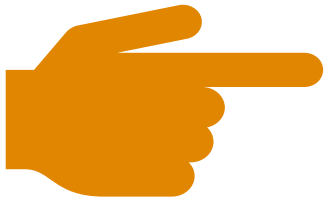

Who does what, how and when?

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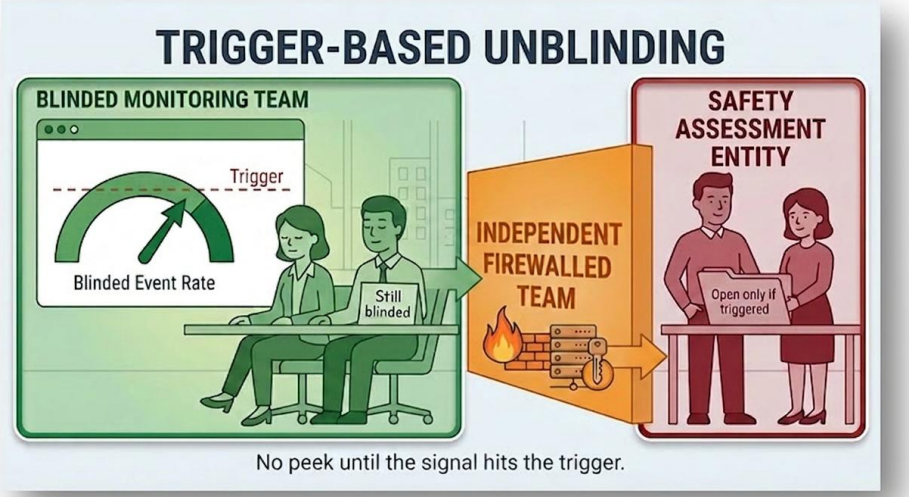
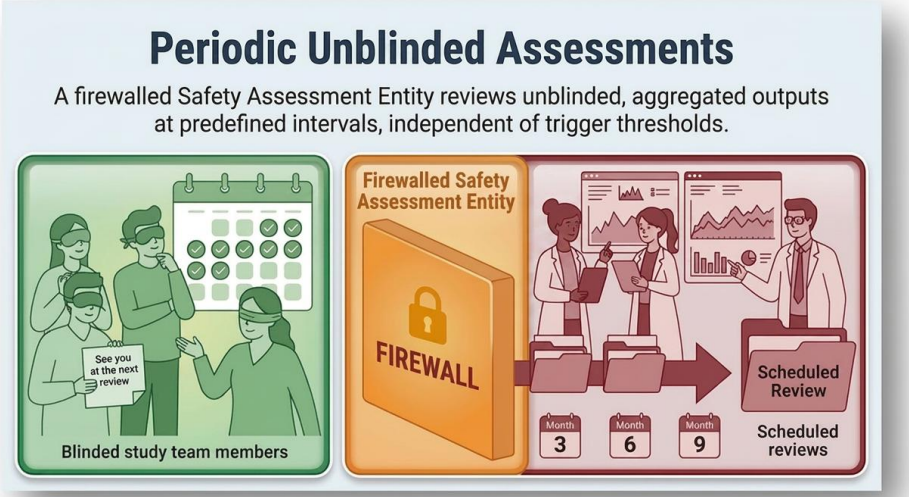
The What: analysis of anticipated SAEs

2 approaches are described*

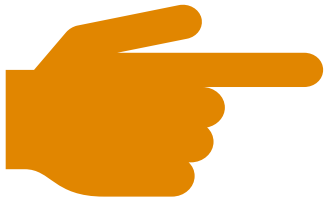




Both require prospective planning to minimize unnecessary unblinding.

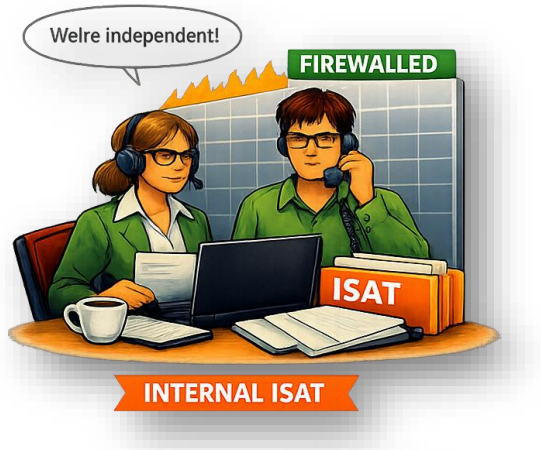
*Statistical methods for both assessment types are available elsewhere, see references at the end

The Operational Framework



Who does what, how and when?

The How: Statistical Data Analysis Center (SDAC): Output Generation Models



Internal, independent[1] Statistical Analysis Team (iSAT)

Sponsor-employed, independent, firewalled statisticians/programmers.

Efficient iteration; requires robust separation.

External CRO

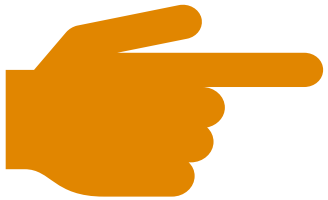
Contracted firewalled output generation.

Clear scope, deliverables, and timelines needed.

SDAC generates outputs
Safety Assessment Entity interprets

[1]Independent: not involved in trial or project related tasks or design decisions

The Operational Framework



Who does what, how and when?

The When: Process flow

Blinded Safety Surveillance

- Routine monitoring, signal detection, escalation decisions

Unblinded Output Generation

- Controlled unblinding, aggregated outputs, firewalled processing

Clinical Interpretation

- Totality of evidence, IND reporting, independent decisions

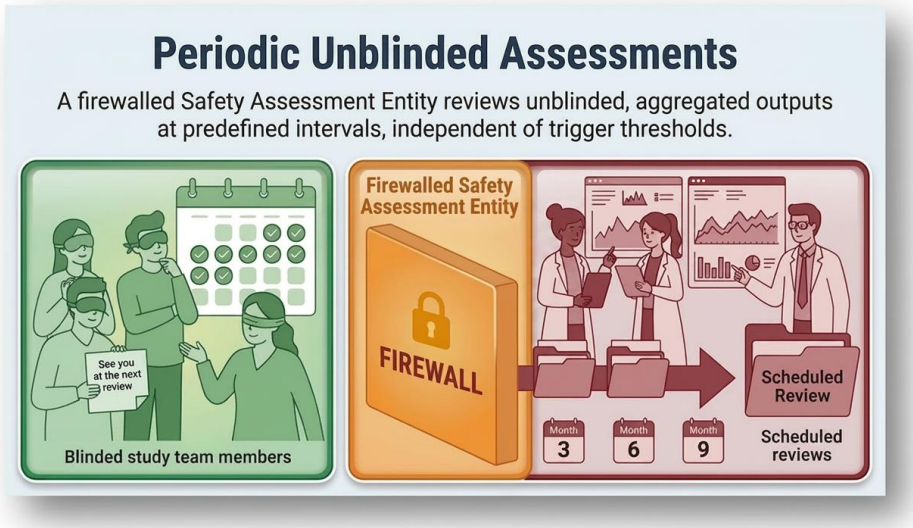
Reporting decision

Sponsor entity (responsible for reporting)

Examples: prerequisites for anticipated SAE monitoring

- ✓ SOP-defined process
- ✓ SSP in place
- ✓ Anticipated SAEs and background rates defined if applicable
- ✓ Trigger / cadence / escalation rules agreed
- ✓ Outsourcing, DMC charter, and training completed if applicable
- ✓ Blinded safety monitoring continues in parallel

Examples (Periodic Unblinded Assessments)



Example 1: fully external

- **SDAC**: CRO
- **Safety Assessment Entity**: DMC

Example 2: fully internal

- **SDAC**: iSAT
- **Safety Assessment Entity**: independent internal team

Side note: mixed models are possible if roles and firewalls are prospectively defined

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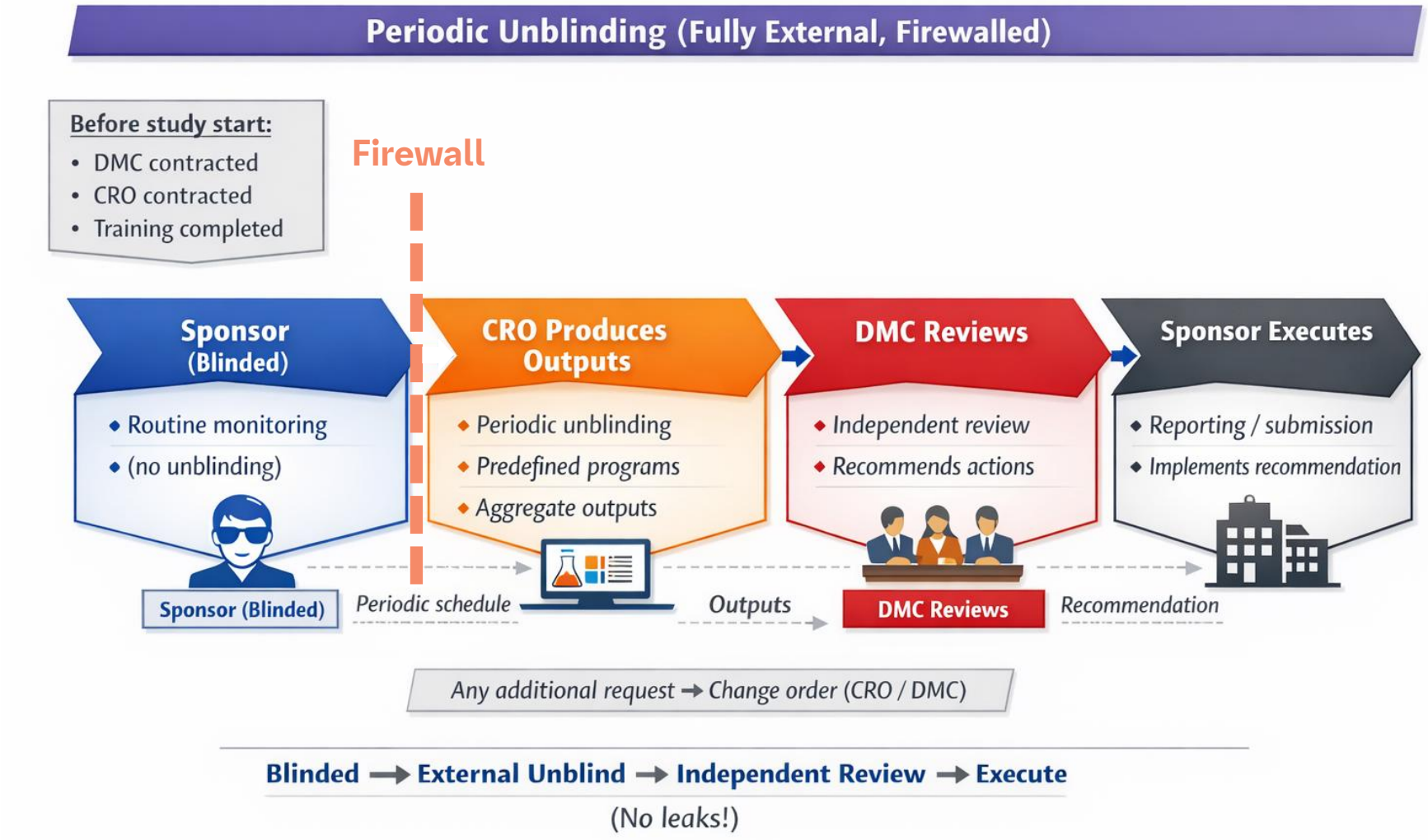
Example #1: fully external



Example #1: fully external

Strengths

- Independent perception
- Established DMC model

Watch-outs

- Contracting/training burden
- Sponsor oversight still required
- Pathway needed for additional unblinded information
- Sponsor still decides/reports

Example #1: “fully” external

Strengths

- Independent perception
- Established DMC model

Watch-outs

- Contracting/training burden
- Sponsor oversight still required
- Pathway needed for additional unblinded information
- Sponsor still decides/reports

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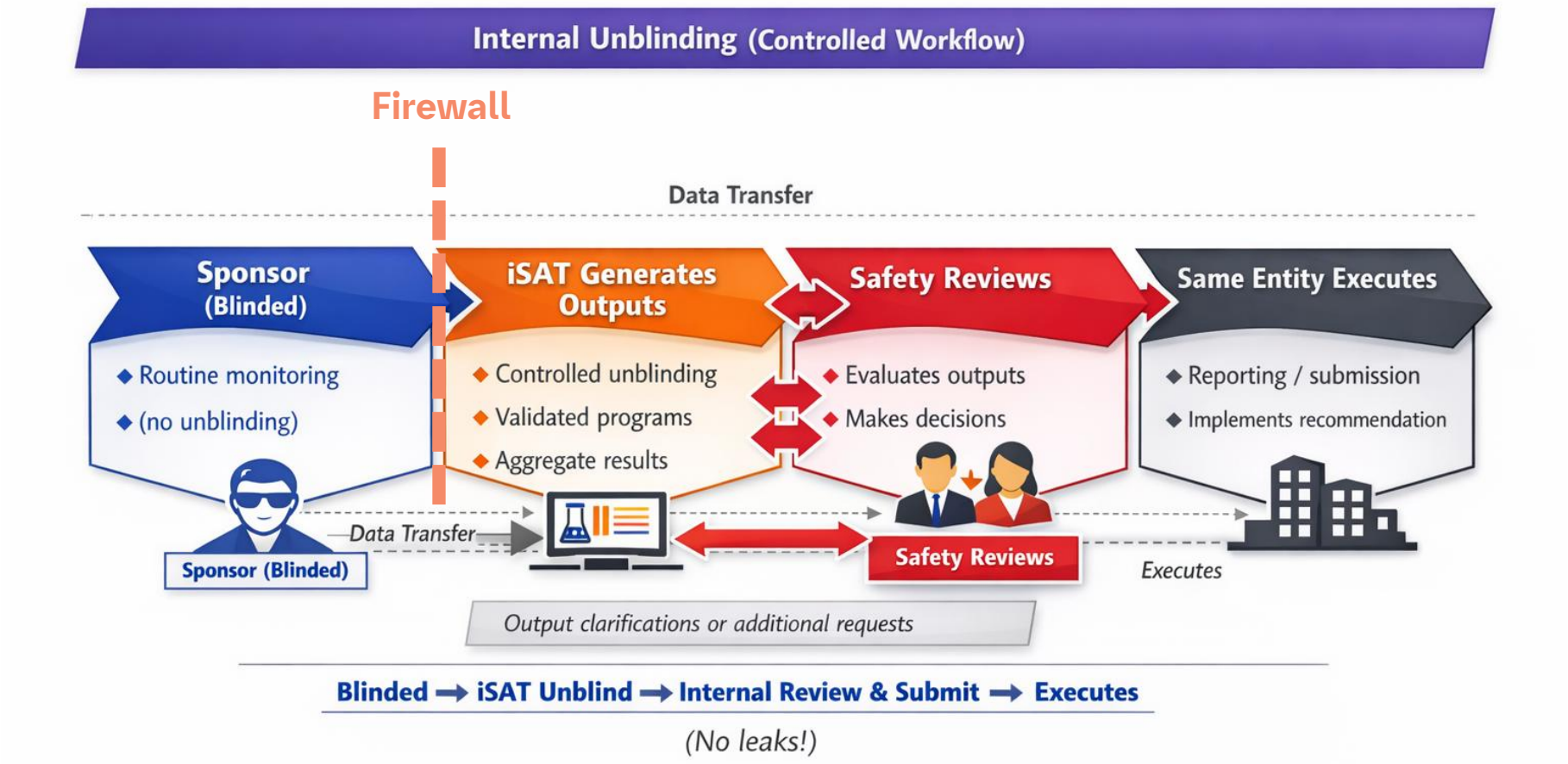
Example #2: fully internal



Example #2: fully internal

Strengths

- Faster setup
- Efficient iSAT / Safety Assessment Entity interaction
- Follow-up analyses easier

Watch-outs

- Requires enough independent personnel
- External perception matters
- Firewall documentation must be strong

Summary

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Breaking Silos

PHUSE Safety Analytics WG, PSI Safety Methodology Implementation WG and ASA BIOP Safety WG **are collaborating!**

Goal: Co-creation of standard tools and methods together with Safety Clinicians, Knowledge share, and create systematic impact

Two Initiatives:

1. Interactive Safety Visualization for ongoing safety monitoring (contact: Dooti Roy)

2. Aggregate Safety Analyses and Reporting (contact: Matthias Trampisch)


THANK YOU!
Beyond Individual Cases: Operationalizing FDA IND Safety Reporting for Anticipated Serious Adverse Events
ASAP
Aggregate Safety Plans
ASAP
SSP
Unblinded Outputs
FDA
FDA
NAILED IT!
DATA ROCKS!
SAFETY FIRST!
TEAM EFFORT

Some references (in no particular order)

- FDA. Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. Guidance for Industry. [Online].; 2025. Available from: https://www.fda.gov/media/150356/download.
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Abstract

Beyond Individual Cases: Operationalizing FDA IND Safety Reporting for Anticipated Serious Adverse Events

How should sponsors assess serious adverse events that are anticipated in the study population and therefore not informative as isolated cases? This presentation addresses a key challenge in FDA IND safety reporting: the aggregate assessment of anticipated serious adverse events (anticipated SAEs) in ongoing blinded clinical trials. Rather than relying on individual-case review, the session shows how sponsors can operationalize aggregate approaches when clinically meaningful treatment-arm imbalances must be assessed while preserving trial integrity.

The talk presents a practical framework for translating FDA expectations into operational practice. It highlights how sponsors can prospectively define roles, responsibilities, review cadence, triggers, escalation pathways, and documentation standards through an Aggregate Safety Assessment Planning (ASAP) process and a Safety Surveillance Plan (SSP). The framework supports both trigger-based unblinding after blinded rates exceed projected thresholds and periodic unblinded review at prespecified intervals.

A major focus is governance. Attendees will learn how routine safety surveillance and unblinded output generation and clinical interpretation can be separated through a model involving a Statistical Data Analysis Center (SDAC) and a firewalled Safety Assessment Entity. The presentation compares internal and external implementation options, including use of an internal independent Statistical Analysis Team (iSAT) or an external CRO for controlled unblinded output generation, and illustrates safeguards that support compliant, timely, and audit-ready decision-making regarding IND safety reporting.

Using practical examples, the session will show how different operating models can help sponsors maintain blinding, support regulatory decision-making, and strengthen the credibility of ongoing trials.