Joint PSI/EFSPI, Phuse, ASA Safety Working Group Webinar Series

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

Scientific Evaluation of Safety Data: A Learning and Decision-Making Approach

October 8, 2026, webinar
Overview of Safety Analysis and Implementation Process of Safety Surveillance in Ongoing Studies

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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)

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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

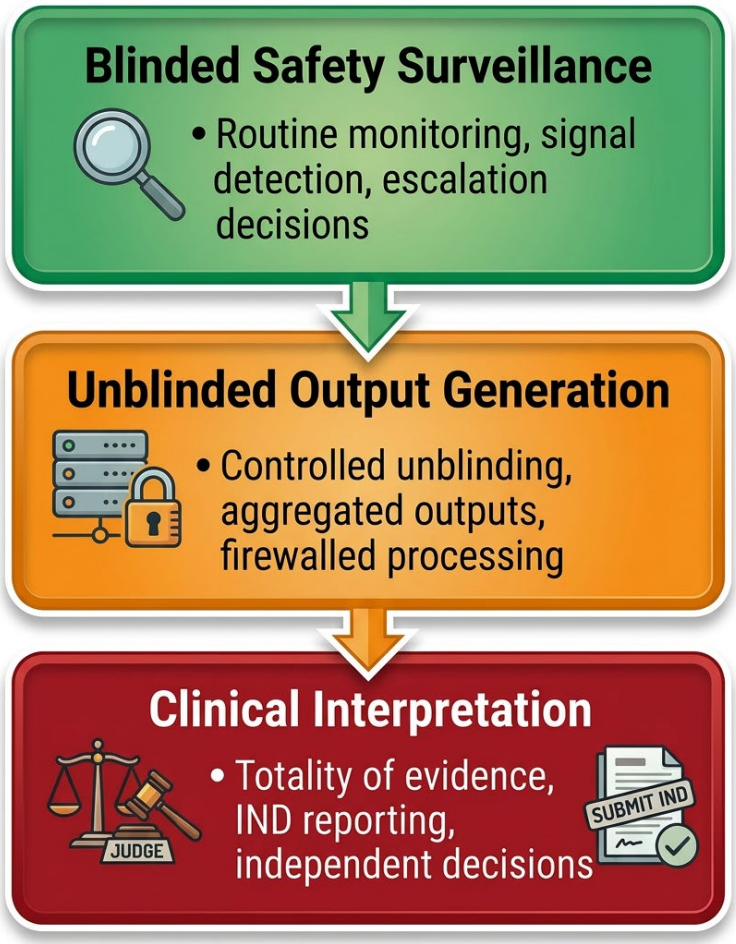
Key Questions

- 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:

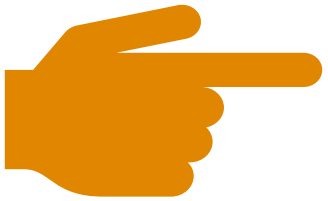
1. **ASAP** (Aggregate Safety Assessment Planning)
   - aligns stakeholders and safety topics
2. **SSP** (Safety Surveillance Plan)
   - defines cadence, triggers, roles, escalation
3. **Firewall controls**
   - protect trial integrity through restricted access and communication

☛ **Who does what, how and when?***

*We assume that we have an SSP available, which identifies and describes the analysis of anticipated SAEs.

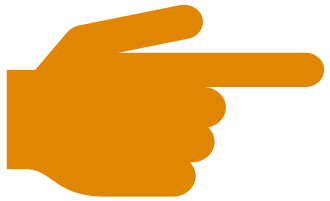
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The Operational Framework



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)

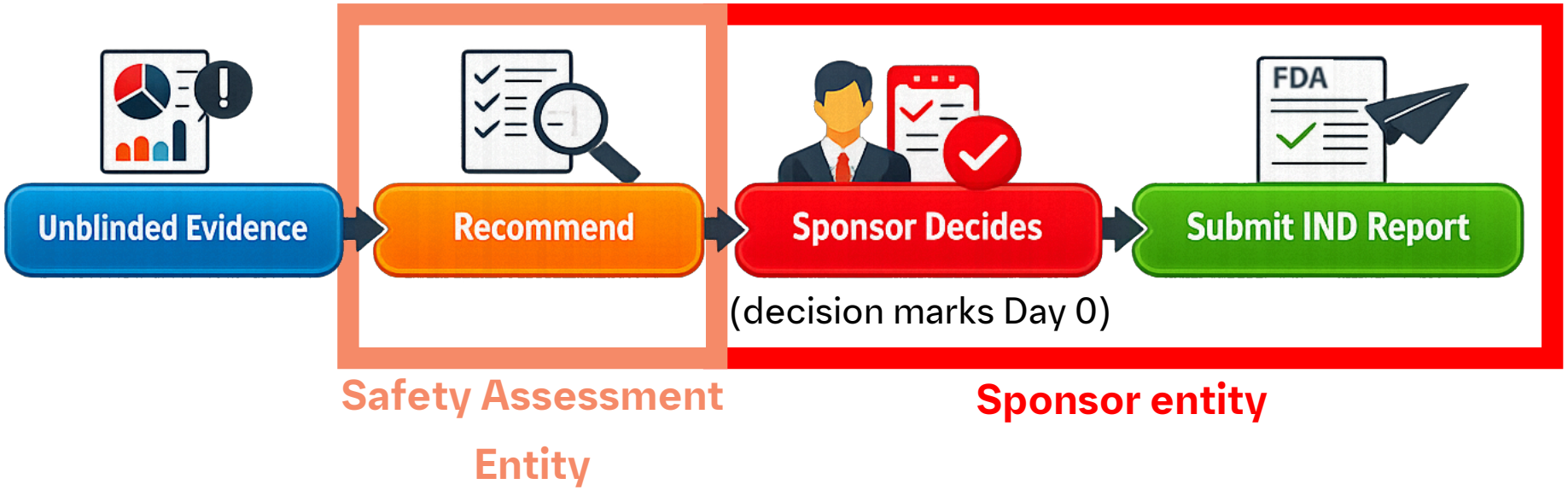
- Additional independence and credibility.
- Sponsor retains reporting responsibility



3. Hybrid (combination of both)

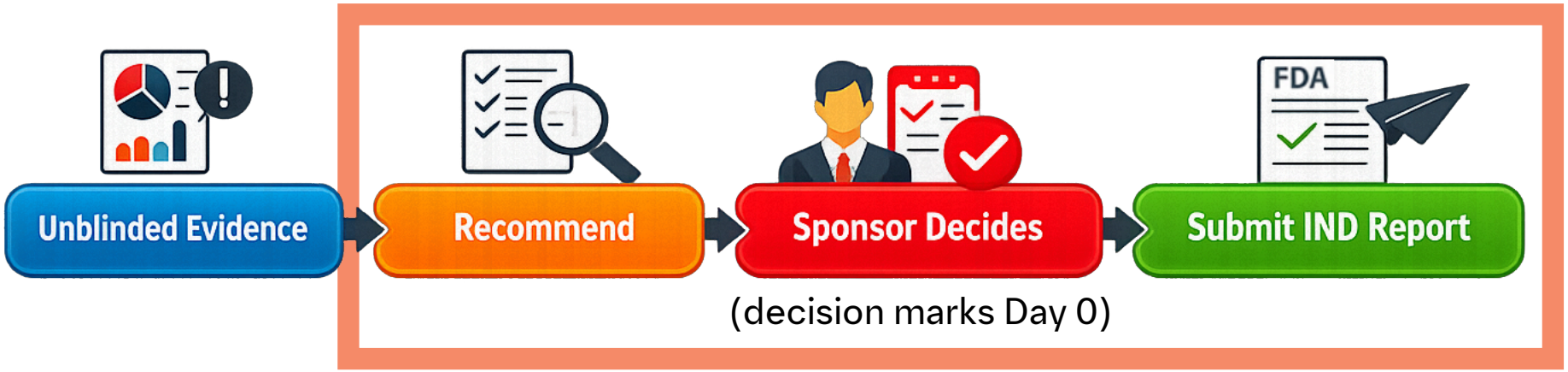
- Balances context and independence.
- Needs precise rules for escalation and communication.

The Who: Responsibilities



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

The Who: Responsibilities



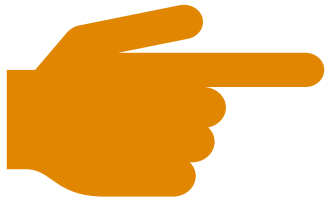
An **internal** or **hybrid** Safety Assessment Entity may take over the sponsor responsibilities, if prospectively defined.

The Who: entities involved

- **Safety Assessment Entity**
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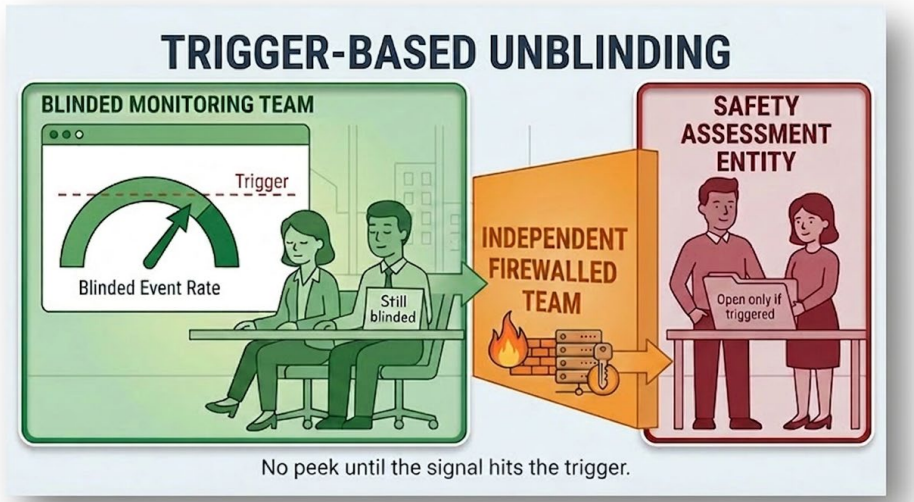
The Operational Framework

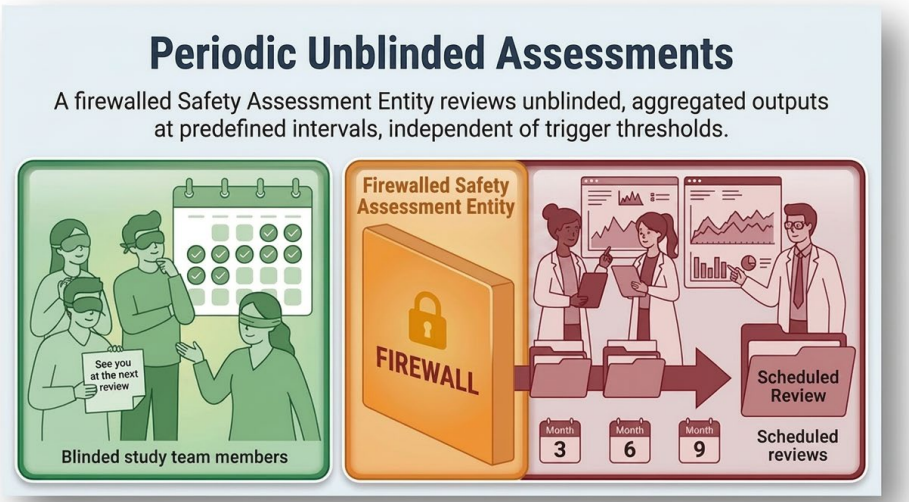


Who does **what**, how and when?

The What: analysis of anticipated SAEs

2 approaches are described*

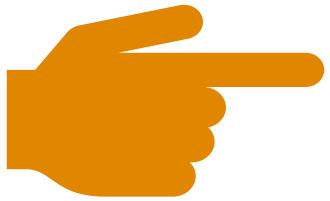




Both require prospective planning to minimize unnecessary unblinding.

*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

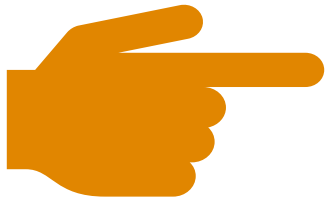
Contracted firewalled output generation.

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 recommendation

(unblinding of Sponsor entity)

Sponsor entity (responsible for reporting)

What happens once the sponsor entity is unblinded?

Two options

1) Reporting decision (aggregate analysis supports a causal relationship with the investigational drug)

- Sponsor reports the anticipated event as a **Serious and Unexpected Suspected Adverse Reaction (SUSAR)**.
- Update of relevant safety information (e.g., Investigator's Brochure) makes the event **expected**, i.e., a **serious expected suspected adverse reaction**.
- Once included in the Investigator's Brochure, **subsequent events generally no longer require IND safety reporting**, unless there is a **clinically important increase in the event rate**

2) No reporting decision (aggregate analysis does NOT support a causal relationship with the investigational drug)

- Regardless of the initial approach, monitoring now uses **Periodic Unblinded Assessments**
- On each review, a new reporting decision is being made, restarting this decision flow.

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

Example (Periodic Unblinded Assessments)



What does the Safety Assessment Entity “see”?

Example Outputs: Current Incidence Rates and Rate Ratios for all anticipated events

	Total # of SAEs	Observed Exposure (PY)	Incidence Rate per 100 PY (60% CI)		Rate Ratio** (60% CI)	
Anticipated Event #1						
Current Risk*						
Reference	7	5.83	120.09	(81.21, 175.55)		
Treatment #1	9	2.45	367.70	(262.64, 511.46)	3.06	(2.00, 4.68)
…				…		
Treatment #n	11	1.42	777.13	(576.28, 1043.94)	6.47	(4.31, 9.72)
Pooled Treatments	20	3.86	517.72	(418.64, 640.11)	4.31	(2.98, 6.24)
Anticipated Event #2						
…						

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PY = Patient Years; CI = Confidence Interval; * At database snapshot date: DDMMMYYYY; ** Rate Ratio vs Reference Treatment

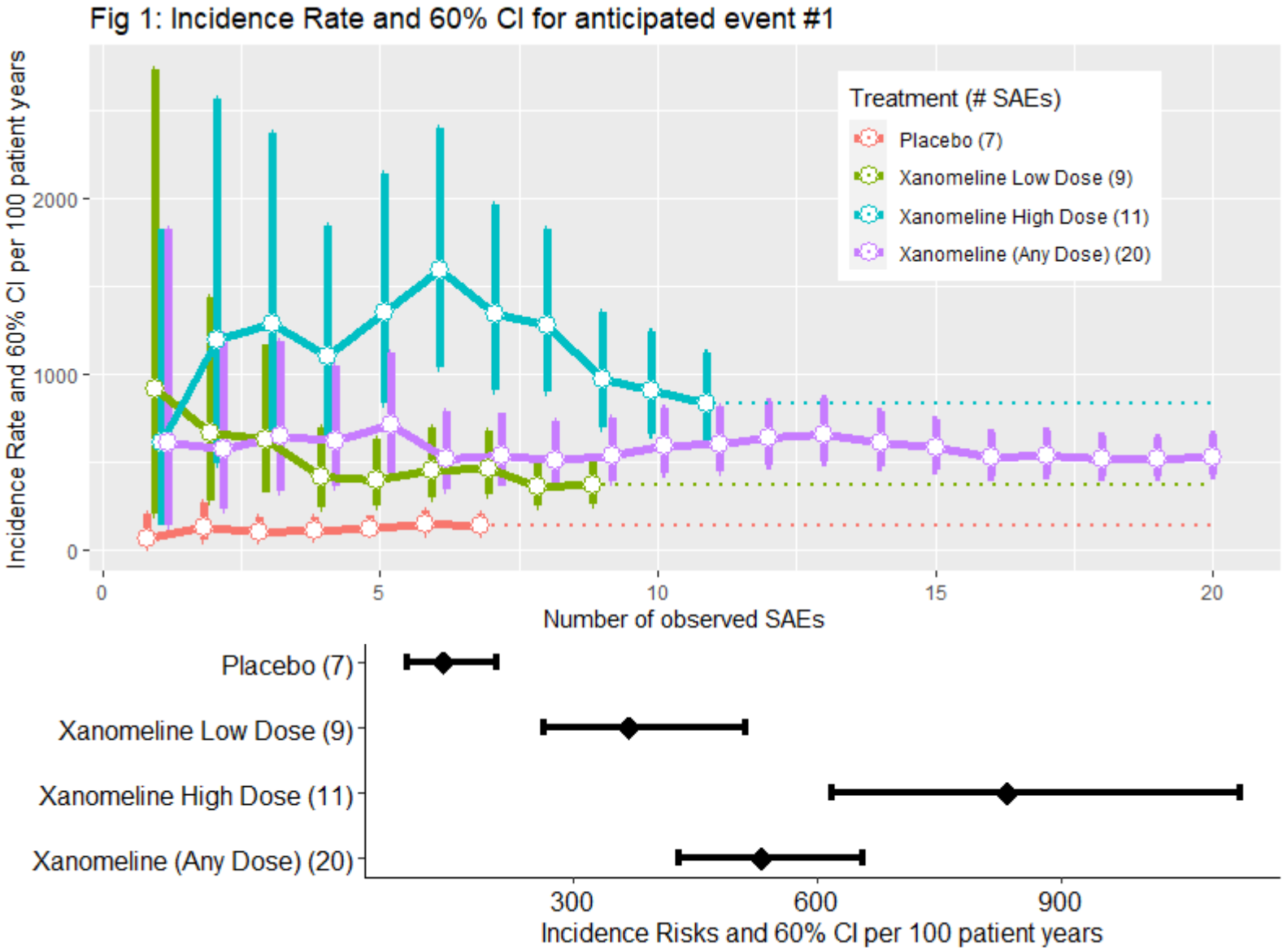
Example Outputs: Anticipated Events by treatment

Anticipated Event #1

Number of Events	AE Onset Date	Observed Exposure PY	Incidence Rate	CI lower	CI upper
Placebo					
1	2013-05-01	1.50	66.53	14.85	199.21
2	2013-05-09	1.60	125.09	51.56	267.62
3	2013-09-12	2.92	102.60	52.50	188.61
4	2013-11-02	3.68	108.71	62.42	182.65
5	2013-12-12	4.10	122.08	75.43	193.03
6	2013-12-19	4.16	144.37	93.93	218.37
7	2014-05-08	5.00	139.87	94.58	204.45
Xanomeline Low Dose					
1	2012-11-17	0.11	913.12	203.76	2734.18
2	2013-01-19	0.30	670.18	276.25	1433.87
3	2013-02-11	0.47	633.38	324.09	1164.38
4	2013-04-02	0.96	415.06	238.32	697.40
5	2013-05-07	1.25	399.62	246.93	631.87
6	2013-05-18	1.31	456.56	297.04	690.58
7	2013-07-02	1.52	460.68	311.53	673.41
8	2014-01-10	2.23	359.41	250.51	511.25
9	2014-04-07	2.44	368.11	262.93	512.04
Xanomeline High Dose					
1	2012-12-27	0.16	608.75	135.84	1822.79
2	2013-02-20	0.17	1197.54	493.62	2562.16
3	2013-04-16	0.23	1289.12	659.62	2369.85
4	2013-05-23	0.36	1098.50	630.75	1845.74
5	2013-06-20	0.37	1352.78	835.89	2139.01
6	2013-08-02	0.38	1588.04	1033.20	2402.02
7	2013-10-13	0.52	1345.66	909.98	1967.07
8	2013-11-12	0.62	1281.58	893.27	1823.01
9	2014-01-30	0.93	972.56	694.67	1352.80
10	2014-03-09	1.10	906.33	660.64	1237.20
11	2014-04-21	1.32	833.56	618.12	1119.75
1	2012-11-17	0.16	608.75	135.84	1822.79
2	2012-12-27	0.35	570.70	235.24	1221.03
3	2013-01-19	0.47	644.56	329.81	1184.92
4	2013-02-11	0.64	624.36	358.50	1049.08
5	2013-02-20	0.70	710.60	439.09	1123.60
6	2013-04-02	1.15	521.79	339.48	789.23
7	2013-04-16	1.31	533.77	360.95	780.26
8	2013-05-07	1.56	512.63	357.31	729.20
9	2013-05-18	1.66	540.67	386.18	752.05
10	2013-05-23	1.69	590.06	430.11	805.48
11	2013-06-20	1.82	603.27	447.35	810.39
12	2013-07-02	1.89	634.30	477.36	840.30

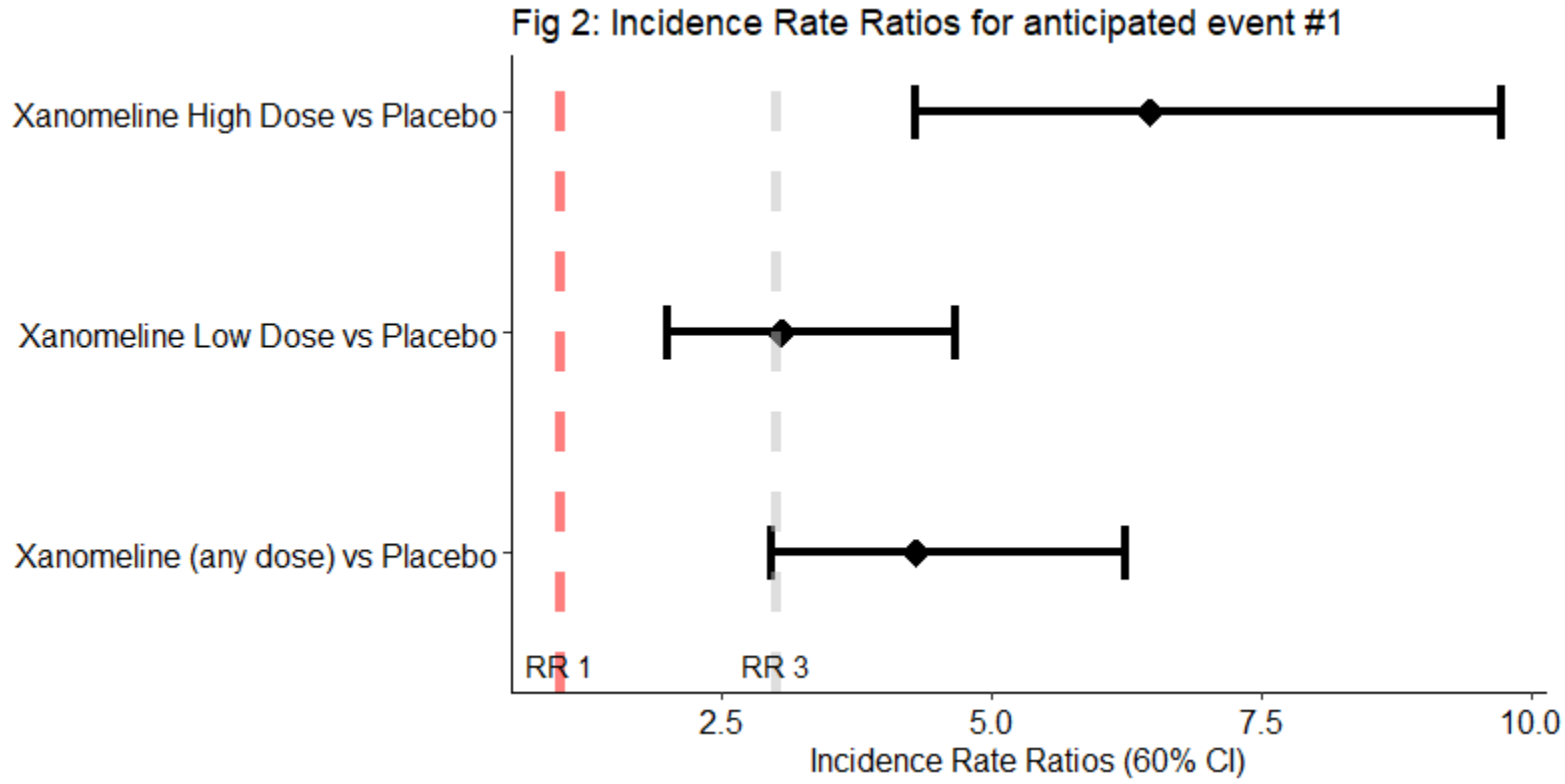
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Example Outputs: Incidence Rates for Anticipated Event #1



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Example Outputs: Incidence Rate Ratios for Anticipated Event #1

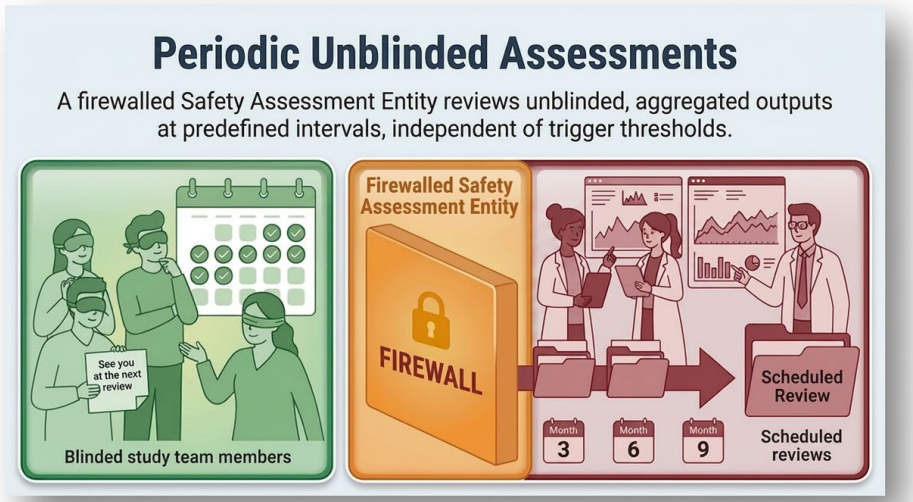


Why 60% 2-sided? Why RR > 3? Why?!?

Janet Wittes, Brenda Crowe, Christy Chuang-Stein, Achim Guettner, David Hall, Qi Jiang, Daniel Odenheimer, H. Amy Xia & Judith Kramer (**2015**) **The FDA's Final Rule on Expedited Safety Reporting: Statistical Considerations**, Statistics in Biopharmaceutical Research, 7:3, 174-190, DOI: 10.1080/19466315.2015.1043395

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Examples (Periodic Unblinded Assessments)



Example 1: fully external



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

Example 2: fully internal

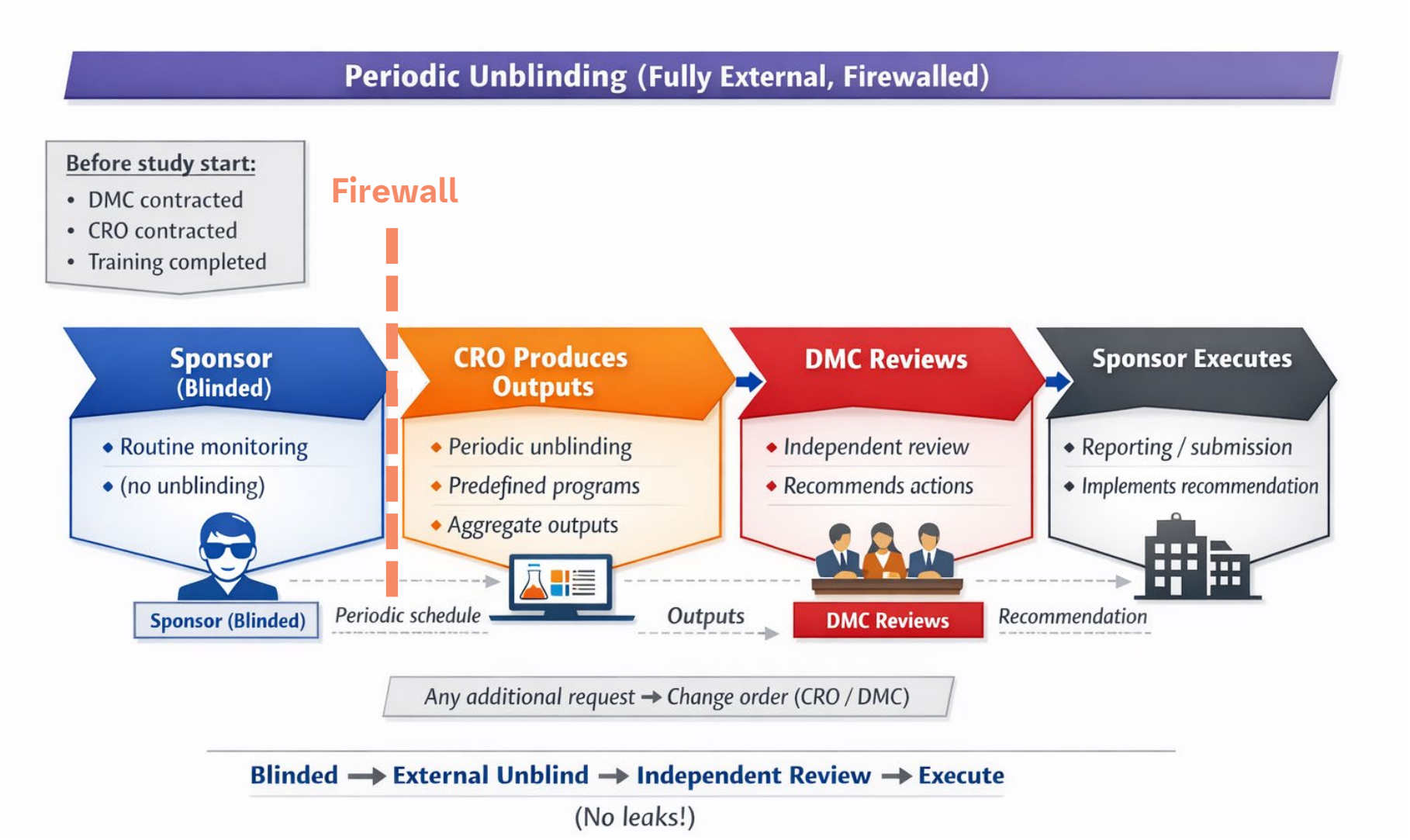


- **SDAC**: iSAT
- **Safety Assessment Entity**: independent internal team

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

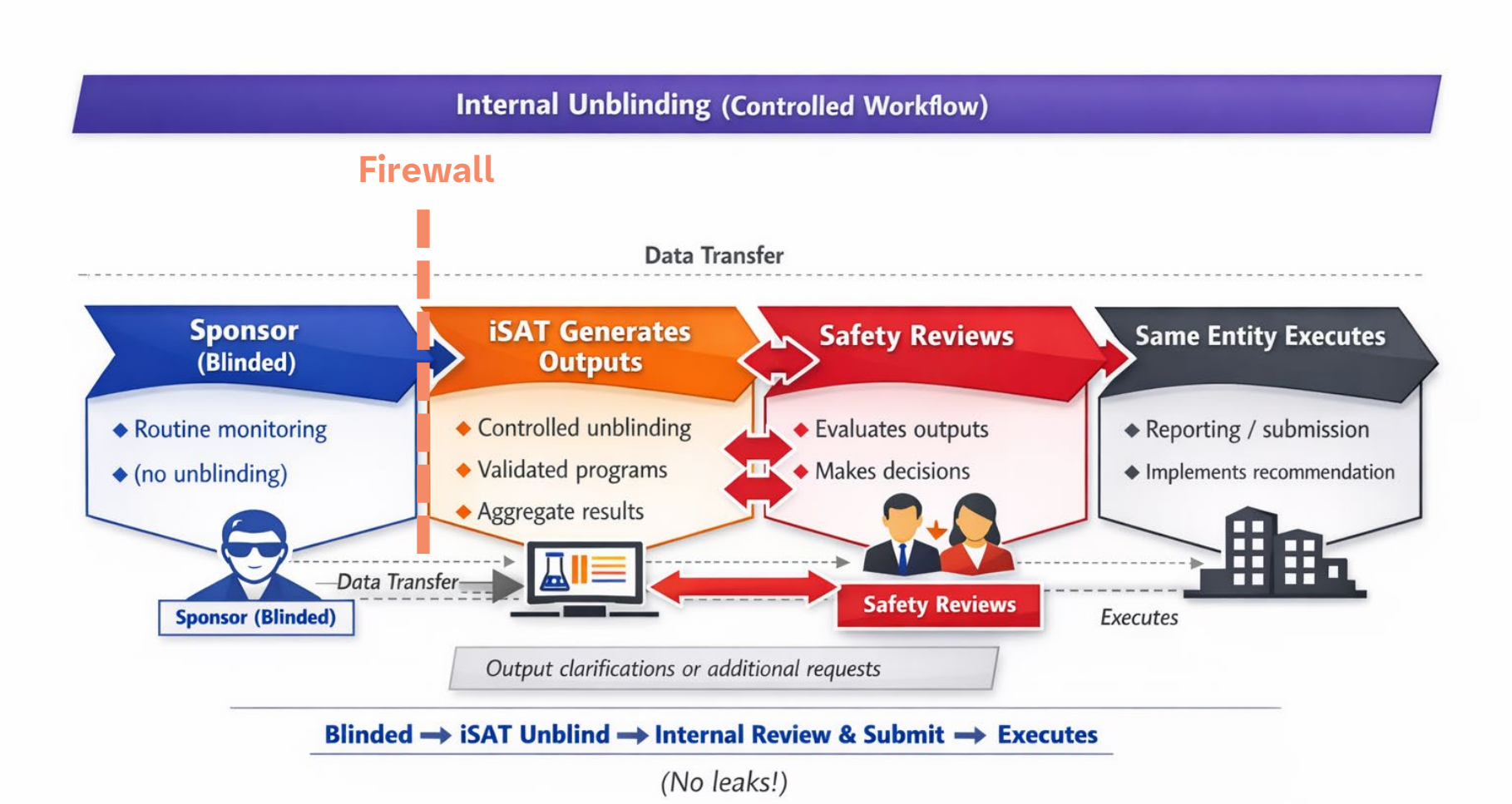
Strengths

- Independent perception
- Established DMC model

Watch-outs

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

Example #2: fully internal



Example #2: fully internal

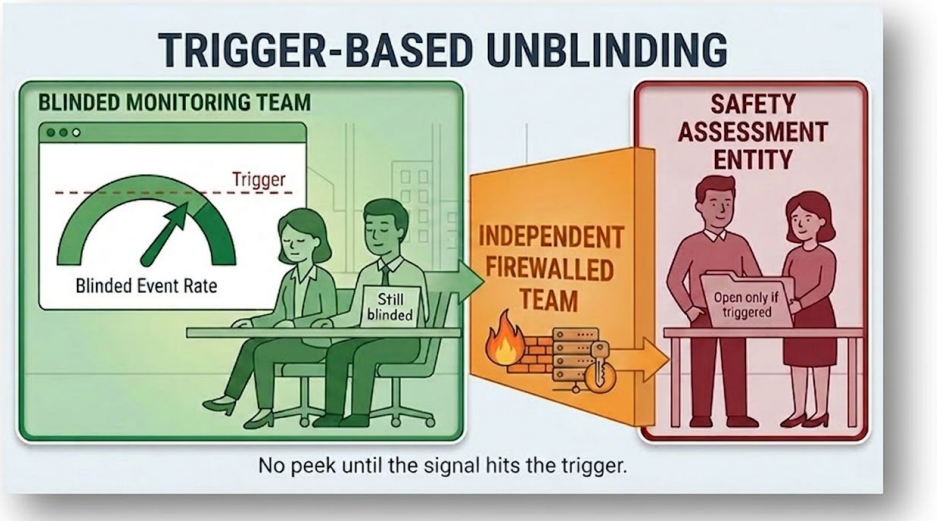
Strengths

- 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

Example (Trigger Based Unblinded)



Alex Spiers *and* ***Matteo Pedone*** *from GSK will give you an example for this now.*

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From Theory to Practice: Implementing BDRIBS for Blinded Safety Surveillance

Some references (in no particular order)

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