SIGNAL

SAFETY THAT SCALES: PRACTICAL CLINICAL SAFETY STRATEGIES FOR EARLY-STAGE BIOTECHS

JUNE 2026

AGENDA

01 What Is Drug Safety?

02 How Safety Operates in Trials

03 Pitfalls for First-Time Sponsors

04 Building a Scalable Framework

05 Practical Case Studies

06 Actionable Takeaways

WHAT IS DRUG SAFETY IN CLINICAL DEVELOPMENT?

WHAT IS DRUG SAFETY / PHARMACOVIGILANCE?

WHO Definition: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problems.

DETECT

Identify adverse events & product problems from all sources

ASSESS

Evaluate causality, severity, expectedness & population risk

UNDERSTAND

Characterise benefit-risk profile across patient populations

PREVENT

Minimise risk through labelling, RMPs and regulatory action

THREE INTERCONNECTED DISCIPLINES

Pharmacovigilance
Continuous monitoring from IND to NDA. Focuses on capturing, coding, and assessing adverse reactions.

Risk Management
Aggregate synthesis. Evaluating the global benefit-risk profile through signal detection and data analysis

Medical Monitoring
Active clinical oversight. Ensures protocol adherence and participant safety in real time at the site level.

All three disciplines operate simultaneously and the sponsor is accountable for all of them.

WHY SAFETY IS THE #1 DRIVER OF CRITICAL FINDINGS IN EARLY TRIALS

60%

of trial discontinuations are safety-driven[1]

~50%

of GCP inspection findings relate to safety reporting[2]

72 hrs

expedited SAE reporting window to authority

Why Early Phase Is Most Vulnerable

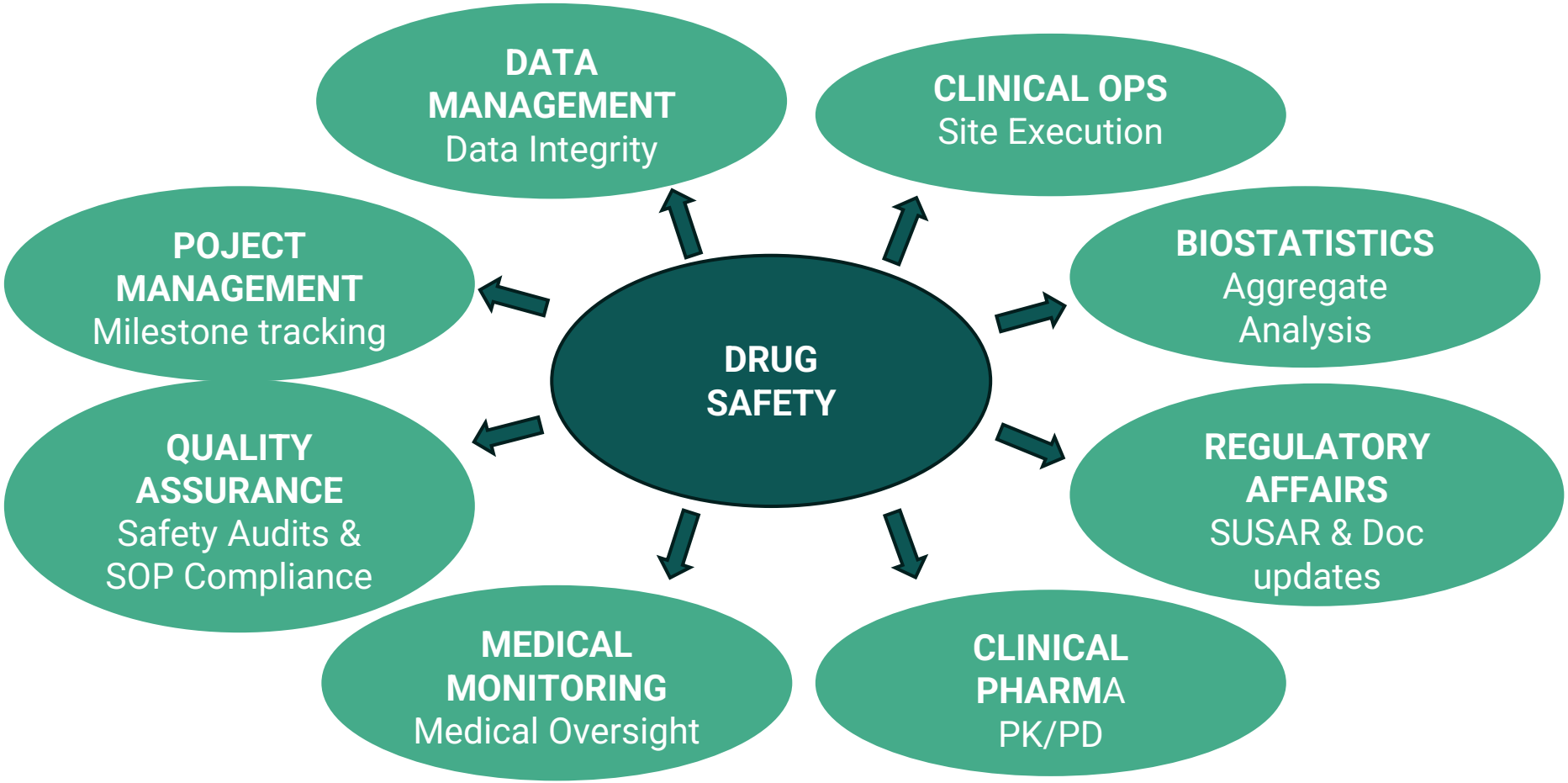
- First exposure in humans — no established safety profile
- Small teams, limited drug safety expertise
- Investigators unfamiliar with sponsor obligations
- Complex multi-site governance with limited oversight
- Regulatory scrutiny is highest at this stage

[1] Tufts Center for the Study of Drug Development (CSDD) Pipeline Database. [2] European Medicines Agency (EMA) GCP Inspectors Working Group Annual Report (CHMP Inspection Metrics).

HOW DRUG SAFETY OPERATES WITHIN CLINICAL TRIALS

DRUG SAFETY INTERFACES

CROSS-FUNCTIONAL COLLABORATION DRIVES TRIAL SAFETY EXCELLENCE



The safety of a trial is not maintained by a single department, but by the structural integrity of the entire cross-functional ecosystem.

CORE SAFETY ACTIVITIES IN CLINICAL TRIALS

Strategy & Setup

- Protocol Development
- SOP Development
- Study Specific SMP
- RSI management (IB)
- Vendor Selection

Case Operations

- Database Management
- Safety Narratives
- Triage & Processing
- MedDRA Coding
- Medical Review

Analytics & Reporting

- Signal detection
- Aggregate Reports
- Database Reconciliation
- Expedited SUSARs
- Trend analysis

Governance & Oversight

- DSMB/DSMC Support
- Vendor Management
- Quality Compliance
- Inspection Readiness
- Safety Governance

Clinical Engagement

- Site Safety Training
- Patient Education
- HA Communications
- Risk Mitigation
- Ethics Committee Submissions

COMMON PITFALLS

COMMON PITFALLS IN DRUG SAFETY

THE DELEGATION TRAP
Delegating execution to a CRO does not remove ultimate sponsor accountability

ABSENCE OF CLEAR DOCUMENTATION
Missing or poorly defined Safety Management Plans (SMP) and clear operational SOPs

UNCLEAR ROLE & RESPONSIBILITIES
Overlapping or poorly mapped roles create communication gaps in reporting

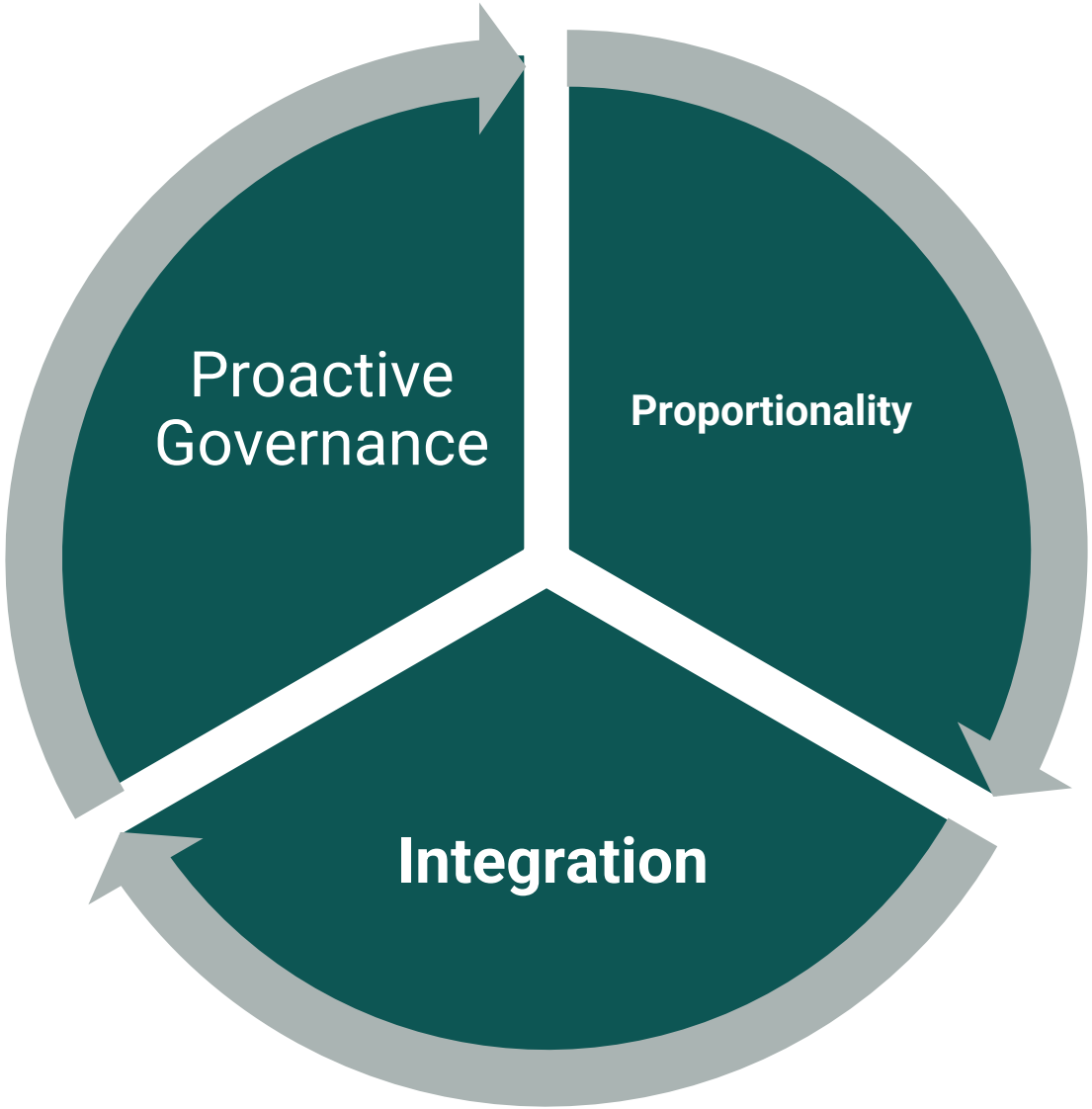
INFASTRUCTURE OVERKILL
Over-engineered systems for early trials. Implementing heavy, post-marketing systems too early.

NO EARLY SIGNAL DETECTION
Omitting early signal detection and waiting for aggregate annual reviews risks missing critical signals and puts patients at risk

DATABASE SILOS
Clinical and safety databases treated as silos. Reconciliation not performed. Discrepancies only discovered pre-lock

FOUNDATIONS THAT PREVENT SAFETY FAILURES

MOVING FROM REACTIVE COMPLIANCE TO STRUCTURAL TRIAL RESILIENCE



BUILDING A SCALABLE SAFETY FRAMEWORK FROM FIRST-IN-HUMAN

RIGHT-SIZING YOUR SAFETY INFRASTRUCTURE

A PHASED APPROACH TO SCALING COMPLIANCE WITHOUT CRUSHING EARLY-PHASE AGILITY

Early Phase

Lean Agility (Phase I/II)

- A minimalist footprint focused on accurate signal capture while preserving startup development speed.
- **Core Requirements:** Deploy foundational Safety Management Plans (SMP), establish internal Sponsor Safety Management Teams (SMT), and enforce non-negotiable 24-hour investigator site SAE reporting timelines.

Mid to Late Phase

Expanded

- Transitional scaling to handle multifold increases in data complexity, international endpoints, and patient volume.
- **Core Requirements:** Implement full MedDRA dictionary coding, introduce independent Data Safety Monitoring Boards (DSMB) for unblinded data analysis, and automate aggregate data compilation workflows to prevent signal detection latency.

Registration & Commercial

Fully Integrated

- A robust, heavily validated, globally compliant environment optimized to safeguard immense real-world patient exposure.
- **Core Requirements:** Formulate long-term regulatory Risk Management Plans, establish automated, expedited global SUSAR reporting pipelines directly to health authorities, and institutionalize continuous Periodic Safety Update Reports (PSUR / PBRER).

Safety infrastructure must be proportionate to the product's known risks and trial complexity.

PRACTICAL CASE STUDIES

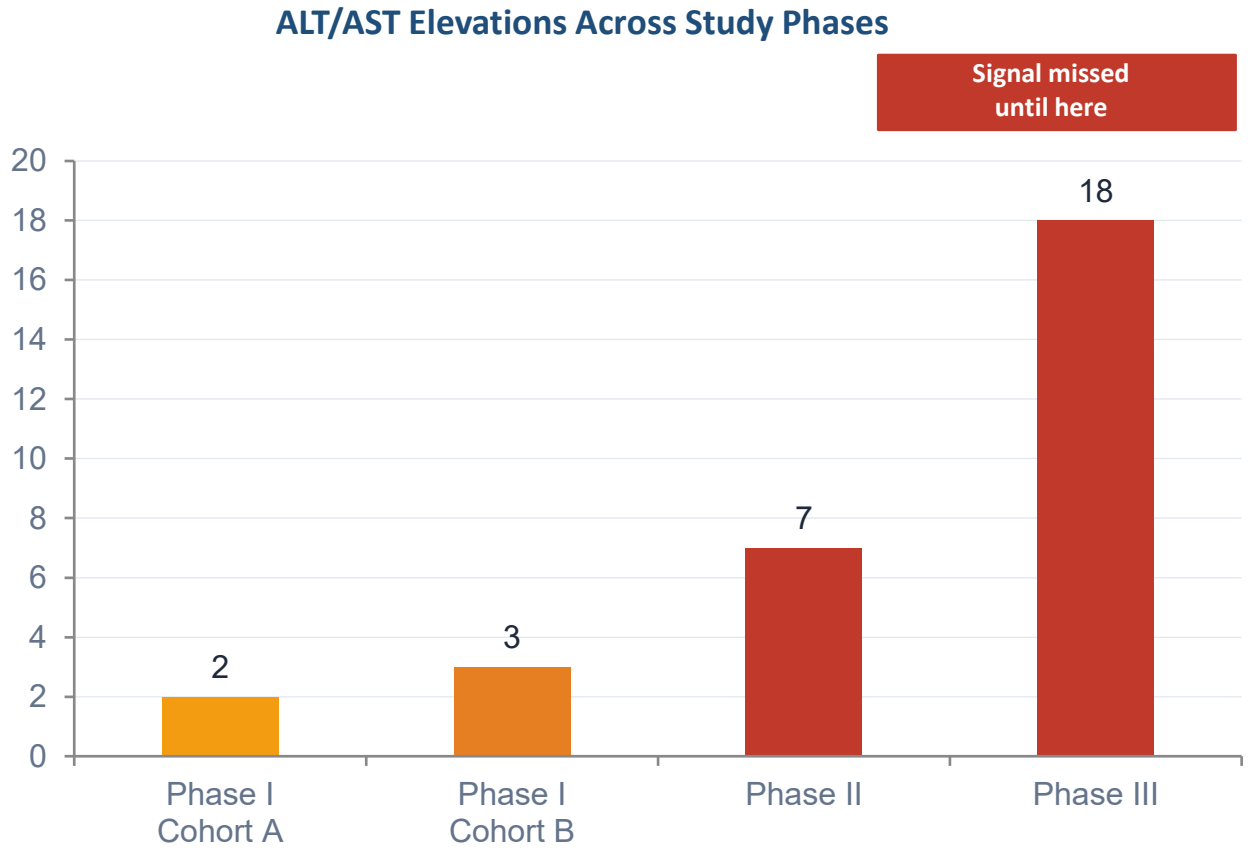
THE SILENT SIGNAL: MISSED LIVER ENZYME TRENDS

Background

- A Phase I–II oncology trial recorded individual ALT/AST elevations within case report forms.
- Cases were reviewed in isolation.
- No trend analysis/aggregate signal detection was performed until Phase III.

What Happened

- Hepatotoxicity cluster emerged in Phase III data review
- Pattern had been present since Phase I but invisible without aggregate view
- DSUR submissions lacked cumulative safety analysis
- Regulatory agency flagged delayed signal detection during inspection



THE SILENT SIGNAL: MISSED LIVER ENZYME TRENDS

Root Cause Analysis

•Treating safety data as isolated, rather than performing aggregate review.
• Complete absence of a safety signal detection plan.
•The Safety Management Plan lacked pre-defined, standardized thresholds to automatically flag hepatotoxicity signals.

Regulatory Findings

•Major Finding & Clinical Hold - Trial halted due to systemic non-compliance with ICH E2A and ICH E6(R2) standards.
•Deficient DSUR Submissions - Annual safety reporting was cited for completely lacking cumulative safety analysis.
•Outdated Reference Safety Information - The Investigator's Brochure failed to reflect current, updated risk profiles.
•Delayed Signal Detection - Regulatory inspectors formally flagged a systemic lag in identifying critical safety signals.
•Ethical & Informed Consent Breach - Failure to update and inform active participants of newly emerging hepatic risks in a timely manner

INSPECTION READINESS : MOCK AUDIT FINDINGS

Background

- A Phase I FIH sponsor team utilizing a CRO for SAE intake and database management.
- A pre-inspection gap analysis conducted after the first cohort completed dosing to ensure the Trial Master File (TMF) was audit-ready.

Mock Audit Observation

- No SMP was finalized or signed before the trial started.
- No defined Roles and Responsibilities for Medical Coding Queries or SAE Reconciliation.
- 15% of the SAEs had incorrect MedDRA coding, and the clinical database did not match the safety database.

Would have resulted in a Major Finding for Lack of Sponsor Oversight and Inadequate Quality System

INSPECTION READINESS : MOCK AUDIT FINDINGS

Root Cause

- The team prioritized speed to FIH over the establishment of a foundational safety framework
- The absence of an SMP, the delegation of tasks was verbal and implied rather than documented specific roles and responsibilities.

Actions

- Conducted a manual reconciliation between the clinical and safety databases to fix coding errors
- Drafted, approved, and implemented a SMP detailing the specific roles and responsibilities

ACTIONABLE TAKEAWAYS

KEY TAKEAWAYS

1	Safety infrastructure must be established before FIH
2	Safety infrastructure must be proportionate to product risk and trial complexity
3	Outsource operational execution but the sponsor has ultimate responsibility
4	Establish clear Safety Management Plans with roles & responsibilities early
5	Implement real-time aggregate trend analysis to detect signals before they become regulatory findings.

SAFETY READINESS CHECKLIST

People & Governance

- [ ] Named Safety Physician / Medical Monitor appointed
- [ ] DSMB/IDMC established with signed charter
- [ ] Sponsor safety team clearly defined in org chart
- [ ] CRO delegation log in place (signed both parties)

Documents & Systems

- [ ] Core safety SOPs approved
- [ ] Safety database selected and validated
- [ ] Safety Management Plan finalised
- [ ] TMF structure established with index
- [ ] IB or SmPC finalized with RSI approved.

Reporting & Oversight

- [ ] SAE timelines defined and communicated to sites
- [ ] Safety Review Meeting cadence scheduled
- [ ] Regulatory submission process tested
- [ ] 24/7 SAE intake process confirmed operational
- [ ] Annual aggregate report submission timelines mapped

Training & Inspection Readiness

- [ ] All staff GCP + drug safety trained with documented evidence
- [ ] Investigators trained on SAE reporting obligations
- [ ] Response to inspection strategy documented

THANK YOU

SUSAN FITZPATRICK

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sfitzpatrick@signalpharmaexperts.com

info@signalpharmaexperts.com