Benefit-risk in early-phase trials: why PV must move from safety oversight to strategic decision partner

As uncertainty defines early-phase clinical development, how can proactive benefit–risk assessment and pharmacovigilance protect patients without slowing scientific progress?

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The inflection point: benefit–risk begins before benefit is proven

In early-phase development, benefit–risk (B/R) assessment is often treated as a downstream regulatory exercise. It should be one of the first strategic disciplines applied to a programme: the mechanism by which limited, uncertain and fast-moving evidence is translated into decisions that protect participants while preserving scientific momentum.

The European Medicines Agency (EMA) defines B/R assessment as a systematic, scientific process for evaluating whether a medicine's therapeutic benefits outweigh its risks. Its value is greatest when embedded from the first-in-human stage, before benefit is proven and uncertainty is highest.

This is where pharmacovigilance (PV) can shift the conversation. Rather than functioning only as a reporting and compliance mechanism, PV can become the discipline that continuously interrogates the emerging safety narrative: what do we know? What do we merely assume? What uncertainty is acceptable and what uncertainty should change the trial?

Regulators such as the EMA and the US Food and Drug Administration (FDA) do not ask whether a medicine is risk-free; they ask whether the risk is reasonable in relation to the expected benefit, the seriousness of the condition, the availability of alternatives and the reliability of the evidence.[1,2]

In early-phase trials, that evidence base is necessarily incomplete. The question, therefore, is not whether uncertainty exists, but whether the development team has made uncertainty explicit and built a credible process for acting on it.

As development becomes more complex – driven by innovative therapies, targeted mechanisms, precision approaches and accelerated pathways – the need for structured, transparent and continuous B/R assessment has become more urgent.[3] It is not a single milestone, but a living argument that evolves with every pharmacokinetic finding, biomarker trend, adverse event, dose-escalation decision and protocol amendment.[4,5]

The regulatory foundation: structure without complacency

The International Council for Harmonisation (ICH) guidelines provide the operating architecture for B/R assessment throughout clinical development. Their collective message is clear: participant protection depends not only on collecting safety data, but on interpreting that data rapidly and in context.

- ICH E6 (Good Clinical Practice) establishes the ethical and scientific standards for designing and conducting clinical trials, incorporating risk-based approaches to ensure participant safety and data integrity[5]
- ICH E2A and ICH E2D (Safety data collection and evaluation) define processes for adverse event detection, causality assessment and expedited reporting, forming the basis of early risk identification[6,7]
- ICH E2F (Development Safety Update Report) introduces a structured and periodic evaluation of cumulative safety data, explicitly requiring an ongoing assessment of the evolving benefit-risk profile during clinical development[4]
- ICH M4E (Common Technical Document – Efficacy) provides the framework for presenting efficacy and safety data in regulatory submissions, ensuring that B/R considerations are systematically summarised for regulatory decision-making.[8]

Together, these guidelines support a life cycle approach in which B/R assessment is continuously informed by emerging clinical and non-clinical evidence. For early-phase teams, the challenge is to avoid treating the framework as documentation. Its real value lies in forcing disciplined thinking when data is limited, ambiguous or evolving.

EMA and FDA perspectives: uncertainty must be managed, not hidden

For both the EMA and FDA, continuous evaluation of a drug's benefits against its risks is essential. In early development, it is especially consequential because assumptions can quickly become embedded in dose selection, cohort progression and go/no-go decisions.

The EMA's approach to first-in-human and early clinical trials places particular emphasis on defining the uncertainty associated with each development step and describing how potential risks arising from that uncertainty will be addressed.[9] Operationally, this requires high-frequency safety monitoring, rapid data verification loops, explicit escalation criteria and transparent documentation of trial decisions.

Similarly, the FDA's structured Benefit–Risk Framework assesses therapeutic context, clinical benefits, risks, risk management options and areas of uncertainty, promoting a more explicit and documented decision-making process.[2]

The shared regulatory direction is unmistakable: uncertainty is acceptable only if it is visible, interrogated and actively managed. Robust B/R assessment depends on integrating emerging safety and efficacy information into dose selection, study progression and development strategy in near real time.[2,9]

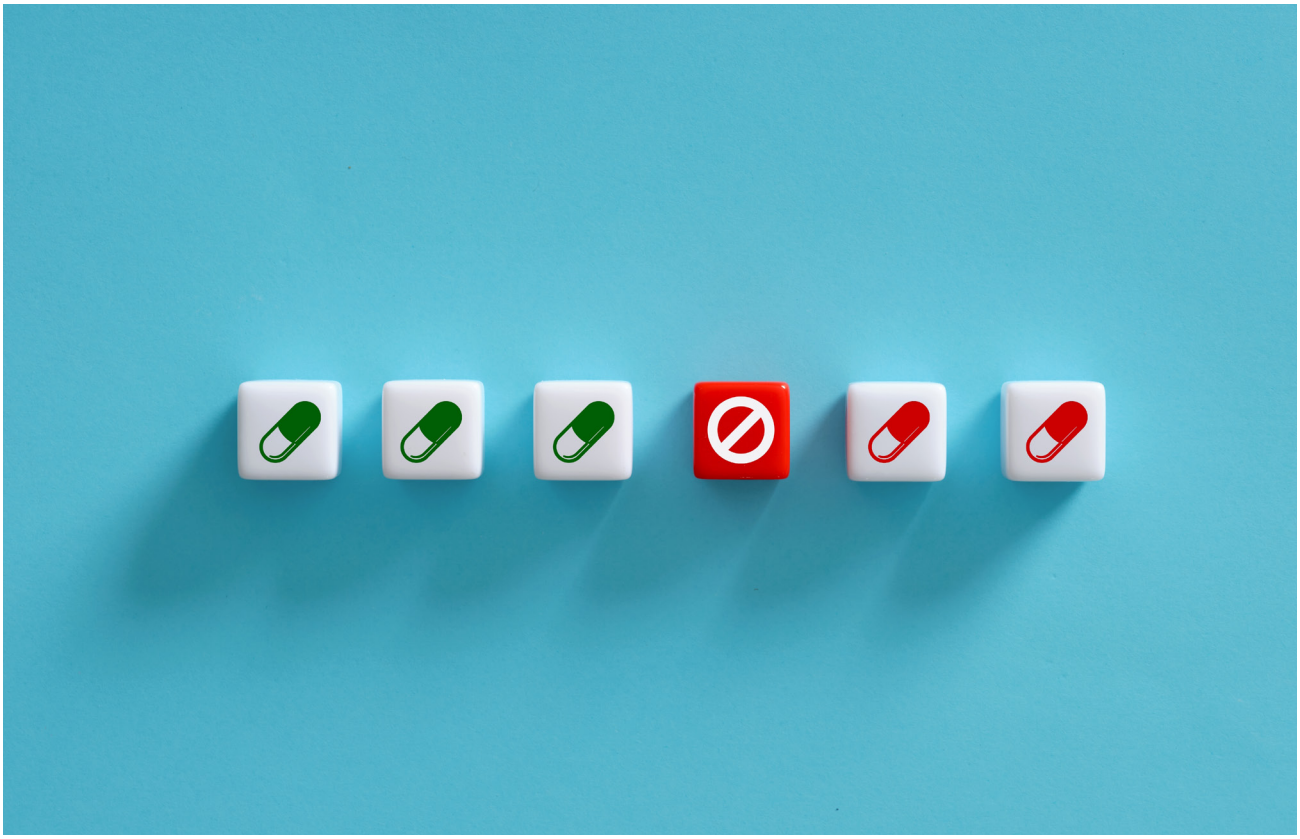
From implicit judgement to structured decisions

From a clinical research organisation (CRO) perspective, B/R assessment has evolved from an experience-based and largely implicit process into a more structured, operational discipline that supports consistent decision-making across clinical programmes.

Historically, B/R evaluations relied heavily on expert clinical judgement, with limited standardisation in how benefits and risks were documented, challenged or communicated. Regulatory expectations and scientific complexity have accelerated adoption of more structured methodologies, including qualitative frameworks and semi-quantitative tools such as effects tables, which organise safety and efficacy data consistently.

For CROs, this raises the bar. Sponsors increasingly need partners who can support standardised processes, robust data management and clear documentation practices that withstand regulatory scrutiny.

Quantitative approaches, including multi-criteria decision analysis (MCDA), may offer additional structure, although early-phase use remains constrained by limited data. Used appropriately, MCDA can translate complex, uncertain data and subjective preferences into a transparent and defensible decision. The opportunity is not to mechanise judgement, but to make judgement auditable. Structured B/R methods do not remove uncertainty; they prevent



uncertainty from being buried in assumptions, informal discussions or fragmented meeting minutes.

Defining benefit and risk when the evidence is still forming

In early development, 'benefit' and 'risk' are not yet conclusions; they are competing hypotheses tested and refined as evidence accumulates. Early trials rarely prove therapeutic value, yet they can reveal risks with immediate operational and ethical consequences.

- ***Exploratory benefits*:** early indicators of benefit are usually indirect and preliminary, such as PK/PD responses, biomarker movement, target engagement or early activity signals. They should be treated as directional evidence, not as proof of clinical efficacy
- ***Uncertain risks*:** early risks are often more visible than benefits and may emerge from preclinical models, class effects, pharmacology, individual participant experience or active first-in-human safety data.

This imbalance – where risk can appear before benefit is confirmed – demands caution without default conservatism. The aim is not to slow innovation, but to define what evidence is sufficient to continue, what should trigger modification and what should stop the trial. That is the essence of a mature early-phase B/R mindset.

PV as the early warning system – and the strategic interpreter

PV plays a critical role in early-phase clinical trials by enabling proactive identification, evaluation and communication of safety risks when exposure is small and clinical data is limited. Its value lies not only in detecting signals, but in interpreting them quickly enough to influence trial conduct.

In Phase 1 studies, PV supports systematic collection and review of safety data, enabling early signal detection despite small sample sizes and short exposure periods.[6,7]

Continuous safety monitoring is especially important during dose escalation, where emerging adverse events must be assessed rapidly to determine whether dosing should progress, pause, be modified or stop.[9] Timely communication of significant safety findings, including potential signals and suspected unexpected serious adverse reactions, is also essential to maintain participant safety and regulatory compliance.[4]

Effective PV in early development depends on close collaboration among PV, clinical operations, medical monitors, investigators, data management and sponsors. The most effective safety functions do not simply receive information; they create the forum in which information is interpreted, contested and translated into action.[2,5]

Embedding benefit–risk thinking into the clinical development plan

B/R assessment is increasingly incorporated into clinical development plans (CDPs) as a central principle guiding design, conduct and adaptation. Done well, it connects the scientific rationale, starting dose, escalation plan, safety monitoring strategy, decision points and future evidence-generation plan.

From the earliest stages, B/R considerations guide first-in-human design, starting dose selection – often based on the No Observed Adverse Effect Level or the more conservative Minimum Anticipated Biological Effect Level – dose escalation and safety monitoring plans.[3,9]

As data accumulates, CDPs should be refined to update the product's benefit-risk profile and risk minimisation strategies, supporting adaptive decision-making, proactive safety surveillance and efficient resource allocation.[2,4] Risk mitigation strategies may include sentinel dosing, controlled dose escalation, predefined stopping rules, robust adverse event review and ongoing safety governance.

Robust informed consent processes also sit within the B/R ecosystem. Clear communication of foreseeable and uncertain risks supports ethical conduct and reinforces the principle that trial participants are partners in knowledge generation, not passive sources of data. Integrated B/R assessment enables sponsors and CRO partners to anticipate safety questions, support regulatory interactions and keep participant protection at the centre of development without losing sight of scientific ambition.

The hard part: preventing optimism from outrunning evidence

Early-phase B/R assessment is difficult because the evidence is incomplete. Small cohorts, short exposure windows and heterogeneous populations create uncertainty in both safety and potential benefit evaluation.

Translational gaps further complicate prediction of human response, particularly for novel mechanisms, first-in-class compounds, complex biologics and highly targeted therapies. In these settings, absence of a signal may reflect limited exposure rather than absence of risk.

There is also a persistent risk of overinterpreting early signs of activity. Biomarker movement, target engagement or exploratory endpoint changes can be encouraging, but they may not translate into durable, clinically meaningful outcomes.

The discipline is to keep optimism useful but bounded. Stakeholder enthusiasm must be balanced with data-driven safety measures, transparent escalation logic and the willingness to adapt when the evidence changes. A rigorous B/R framework does not eliminate difficult judgement calls; it makes the reasoning behind them visible, defensible and patient-focused.

Future perspective: from reactive safety to predictive vigilance

Looking ahead, early-phase B/R assessment is likely to become more dynamic, data-rich and predictive. The next frontier is not simply better safety reporting, but earlier contextualisation



of safety findings within the broader evidence package.

Artificial intelligence, predictive analytics and translational modelling may help identify emerging patterns, prioritise review and better characterise uncertainty. Their value will depend on thoughtful governance: models must support scientific judgement, not obscure it.

Real-world data may complement limited trial data by adding context on natural history, comorbidities, background event rates and potential safety expectations. Precision medicine will also require more individualised B/R assessments that account for genetic, biomarker and disease-subtype differences.

Decentralised and hybrid clinical trials will also reshape PV practice by expanding remote safety monitoring, digital data capture and participant communication. These approaches can bring trials closer to patients, but they also place new pressure on data quality, signal triage and timely investigator oversight.

The central lesson is that B/R assessment in early-phase trials is not a regulatory afterthought; it is the operating system for responsible innovation. When PV is embedded early and empowered to interpret emerging evidence, it becomes more than a safeguard. For sponsors and CROs alike, the future will belong to teams that can move quickly without moving blindly – teams that treat uncertainty not as an obstacle to progress, but as the material from which better decisions are made.

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