CLINICAL REFERENCE | OPEN ACCESS

AMOIP: The Acute Multi-Organ Instability Phase

Why conventional pharmacovigilance wasn't designed to see the high-acuity window — and how to govern it.

AyurDatta Inc. · June 2026 · ayurdatta.com

KEY INSIGHT

The Acute Multi-Organ Instability Phase (AMOIP) is a clinically recognizable window during which the trajectory toward multi-organ failure in a high-risk relapsed/refractory patient is already in motion — but pharmacovigilance-aligned intervention can still change the outcome. Standard PVG infrastructure was not built to see that window. It was built to document what happens after it closes.

1. The Problem: A Structural Mismatch

Conventional pharmacovigilance infrastructure was not designed for the toxicity kinetics of advanced oncology therapeutics. CAR-T cell therapies, antibody–drug conjugates (ADCs), and radioligand treatments (RLTs) generate mechanism-driven toxicities that can progress from grade 1 onset to multi-organ failure within hours — a trajectory that standard case-intake and SUSAR reporting workflows are structurally unequipped to intercept.

The mismatch is architectural, not operational. Traditional PVG is built around a cadence of retrospective case assembly: an adverse event is observed, coded, narrativized, and reported according to timelines calibrated to pharmacokinetic profiles developed in the era of small-molecule chemotherapy. Those timelines assume days, not hours. They assume individual organ dysfunction, not cascading cross-system deterioration. They assume that by the time a case is processed, a clinician will still have options.

In high-acuity oncology, none of those assumptions hold.

1.1 Toxicity Velocity Has Changed

Cytokine release syndrome (CRS) in CAR-T cell therapy — the most widely studied high-acuity toxicity — typically presents within 1–14 days of infusion.

Cytokine release syndrome (CRS) in CAR-T cell therapy — the most widely studied high-acuity toxicity — typically presents within 1–14 days of infusion.[1] Initial symptoms — fever, tachycardia, mild constitutional signs — can progress over the course of hours to hemodynamic instability, vasopressor dependence, and multi-organ failure. Severe CRS is associated with mechanical ventilation and, in refractory cases, death.[2]

The same velocity characterizes ICANS: neuroinflammatory escalation driven by cytokine-mediated blood-brain barrier disruption can transition from confusion and agitation to seizure and cerebral edema within a clinical shift. ADC-related hepatotoxicity and marrow reserve collapse evolve on a similar compressed timeline in heavily pre-treated patients with limited physiologic reserve.

This is not a theoretical concern. Across the relapsed/refractory (R/R) populations most likely to receive these agents — patients who have exhausted prior lines of therapy and carry compromised baseline organ function — these cascades unfold faster than any asynchronous reporting pipeline can detect, let alone interrupt.

[1]CRS onset typically 1–14 days post CAR-T infusion; initial mild symptoms can progress over hours to vasopressor dependence, mechanical ventilation, and multi-organ failure. Source: ScienceDirect CRS overview; Springer Clinical Cancer Bulletin 2025.
[2]Incidence of CRS ranges 50–90% any-grade; grade ≥3 CRS 5–25% across products. Source: Gaffney et al., 2024 (CADTH Review); real-world CIBMTR data, JCO 2023; multicenter Greece cohort, Frontiers in Medicine 2025.

1.2 Existing Infrastructure Was Built for a Different Problem

Standard pharmacovigilance operations are optimized for post-market signal detection across large, heterogeneous populations. They excel at identifying patterns that emerge over time and across many cases. They were not designed to intercept individual-patient trajectories in real time. The core processes — case intake, medical coding, narrative development, aggregate reporting — are sequential and cadence-dependent. They produce a record of what happened. In high-acuity oncology, the clinical question is not 'what happened?' but 'what is happening, right now, in this patient?'

That distinction is the AMOIP problem in one sentence.

2. The AMOIP Window — A Clinical Definition

The Acute Multi-Organ Instability Phase is defined as the period in a high-risk R/R oncology patient during which:

- Mechanism-driven toxicity has been initiated (cytokine cascade, marrow suppression, radiation-associated organ injury);
- Clinical deterioration is in motion, but has not yet reached the point of irreversible multi-organ failure;
- Real-time pharmacovigilance-aligned intervention — signal identification, physician adjudication, escalation — can materially change the patient's trajectory.

AMOIP is not established clinical terminology. It is a framing construct developed to articulate the specific window that current PVG infrastructure systematically fails to govern. It is useful precisely because it names what has previously been left unnamed: the gap between 'toxicity detectable by real-time monitoring' and 'toxicity documented by retrospective case processing.'

In that gap, outcomes are decided.

2.1 The Four Organ System Cascades

AMOIP encompasses four clinically distinct but frequently co-occurring cascade patterns in advanced oncology patients:

Cytokine-mediated hemodynamic deterioration (CAR-T / bispecific)

Rapid CAR-T cell expansion drives IL-6, IFN-γ, IL-8, and MCP-1 release, activating vascular endothelium and triggering capillary leak, coagulopathy, and hemodynamic instability.[3] Any-grade CRS occurs in 50–90% of CAR-T recipients; grade ≥3 CRS in 5–25% across products and indications.[4]

Neuroinflammatory escalation (CAR-T / bispecific)

ICANS is mediated by cytokine-driven blood-brain barrier disruption and direct neuroinflammatory signaling. Pooled data from 75 trials (3,184 patients) demonstrate an all-grade incidence of 26.9% and high-grade incidence of 10.5%, with anti-CD19 constructs carrying significantly higher risk.[5]

Marrow reserve collapse (ADC / RLT)

ADC-related myelosuppression reflects both direct marrow toxicity from off-target payload release and baseline marrow compromise in heavily pre-treated patients. Any-grade hematotoxicity is observed in 89–93% of treated patients, with grade 3–4 events in 46–58%.[6] RLT (^{177}Lu-PSMA)-related anemia occurs at CTCAE grade I in approximately 73% of patients; grade ≥3 cytopenias in 11%.[7]

Radiation-associated renal and hepatic dysfunction (RLT)

Renal tubular PSMA expression results in ^{177}Lu retention and radiation dose to the kidney. CTCAE grade I/II nephrotoxicity by creatinine is observed in 22% of patients; eGFR-based classification identifies dysfunction in up

[5]ICANS: pooled incidence 26.9% all-grade (95% CI 21.7–32.7%), high-grade 10.5% (95% CI 8.1–13.6%). Anti-CD19 cohorts higher. Source: Systematic review & meta-analysis, PMC11518750, 2024.
[6]ADC hematotoxicity: any-grade AEs 89–93%; grade 3–4 in 46–58%. Source: PMC12231679, 2025; retrospective pharmacovigilance study PMC12558476.
[7]RLT (^{177}Lu-PSMA): anemia CTCAE I in 73%; grade ≥3 cytopenia 11%; nephrotoxicity CTCAE I/II creatinine 22%, eGFR 67%. Source: PMC8833540; Haematologic Toxicity study (PMC8001812).

to 67%.[8] ADC hepatotoxicity — particularly with calicheamicin conjugates — produces abnormal liver function tests in more than 30% of patients all-grade, with grade ≥3 events in approximately 18.8%.[9]

2.2 Toxicity Incidence Reference — CAR-T, ADC, and RLT

The following table summarizes published clinical and real-world incidence data across the three modality classes within which AMOIP risk is highest. All figures are sourced from peer-reviewed literature and pharmacovigilance databases.

Modality	Toxicity Class	Mechanism	Any Grade	Grade ≥3
CAR-T	CRS	Cytokine-mediated hemodynamic cascade	50–90%[1]	5–25%[1]
CAR-T	ICANS	Neuroinflammatory escalation / BBB disruption	20–60%[2]	10–30%[2]
ADC	Hepatotoxicity	Calicheamicin; off-target payload release	>30% (abnormal LFT)[3]	~18.8% grade ≥3[3]
ADC	Ocular Toxicity	MMAF/DM4 payload; corneal epithelial off-target	18–96%[4]	Variable by agent[4]
ADC	Myelosuppression	Marrow reserve collapse; dose-dependent cytopenia	Common (46–93%)[5]	~29–46%[5]
RLT	Myelosuppression	Radiation-associated marrow suppression	~73% (anemia)[6]	11% grade ≥3[6]
RLT	Nephrotoxicity	Renal tubular PSMA expression; radiation retention	22–67% (CTCAE I/II)[6]	4% grade ≥3[6]

Sources cited in footnotes 1–6. Incidence ranges reflect variation across product, indication, patient population, and grading system used.

3. Why Standard Pharmacovigilance Cannot See AMOIP

Pharmacovigilance as a discipline was designed around a specific model of drug harm: a substance administered to a patient produces an adverse biological response, which is identified through clinical observation, documented in a case report, coded to MedDRA, and submitted to a regulatory authority on a defined reporting schedule. That model is sound for the majority of therapeutic modalities.

In advanced oncology, it has a structural deficiency: it is retrospective by design. By the time a SUSAR is filed, a narrative is written, and a case is reviewed by a DSMB, the clinical window in which intervention was possible has often closed.

3.1 The Five Structural Gaps

Five specific structural characteristics of conventional PVG make it unsuited to govern the AMOIP window:

1. Asynchronous case intake

Cases are entered after the adverse event is clinically recognized — not at the point of early signal detection. In high-acuity settings, early signals (rising ferritin, IL-6 kinetics, cytokine-kinetic profiling) are available in real time but are not connected to the case-processing pipeline.

[9]ADC hepatotoxicity: abnormal LFT >30% all-grade; grade ≥3 ~18.8% per meta-analysis. Source: Navigating hepatotoxicity of ADCs, PMC12715376, 2025.

2. Sequential, not concurrent, workflows

Coding, narrative development, and medical review are performed sequentially. In a rapidly evolving AMOIP, the physician making the benefit-risk determination needs concurrent access to signal data, prior case context, and grading criteria — not a finished narrative produced 24–72 hours later.

3. Aggregate-cadence reporting

DSUR/PSUR/PBRER cycles aggregate safety data over defined periods. They are designed to detect population-level patterns. They are not designed to support individual patient management in real time. The cadence of aggregate reporting is orthogonal to the velocity of AMOIP.

4. No pre-specified escalation trigger for sub-grade-3 signals

Standard workflows escalate on confirmed grade 3/4/5 events. The AMOIP window is defined by the period before grade 3 is reached but after the trajectory toward it is detectable. Conventional PVG has no mechanism for acting on pre-collapse trajectories.

5. Documentation as endpoint, not input

In standard PVG, documentation is the output of the process — the record produced after medical review. In AMOIP governance, documentation must be the input to the process: timestamped, attributable, physician-signed records that constitute the audit trail of decisions made during the window, not a reconstruction of them afterward.

CRITICAL DISTINCTION

Conventional PVG produces a record of what happened. IHASG-aligned governance produces a record of what was decided, when, by whom, and on what evidence — while the window was still open. The difference is not administrative. In high-acuity oncology, it is clinical.

4. The Regulatory Direction of Travel

Global regulators have begun to recognize the mismatch between advanced therapeutic toxicity profiles and existing pharmacovigilance infrastructure. The FDA's January 2025 Draft Guidance on AI in regulatory decision-making, and the EMA's 2024 tools and guidelines for incorporating AI into pharmacovigilance, both signal an expectation that sponsors operating in high-acuity settings will implement proactive safety-risk characterization frameworks — not reactive case-processing pipelines.[10]

The implicit standard being set across FDA, EMA, MHRA, PMDA, and ICH guidance collectively is ICU-aligned safety governance: continuous signal detection, expedited SUSAR escalation pathways, and cross-regional safety adjudication operating at the speed of clinical deterioration rather than the cadence of aggregate reporting cycles.

This is not a future expectation. It is a live regulatory expectation, in place now, for any sponsor operating in CAR-T, ADC, or RLT programs with high-acuity R/R populations.

4.1 What Regulators Are Looking For

Based on recent guidance updates and inspection experience, sponsors can expect regulatory scrutiny across five specific areas when operating in AMOIP-risk settings:

- Pre-specified signal definitions: CRS, ICANS, DLT criteria mapped to source data elements before the trial begins — not defined retrospectively.
- Named physician accountability: a credentialed reviewer with documented decision rights for every benefit-risk determination. AI-assisted outputs require explicit physician review and sign-off.
- Part 11-aligned audit trails: attributable, timestamped, tamper-evident records retrievable on demand — not assembled from scattered documentation after the fact.
- Human-in-the-loop controls for AI: model-use logging, bypass prevention, and labeled AI outputs. The expectation is that no AI output becomes a record of decision without physician review.

[10]FDA Draft Guidance: 'Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products,' January 2025. EMA AI in pharmacovigilance tools and guidelines, 2024.

- Escalation governance: pre-specified SRC/DSMB/IDMC structures with defined expedited and SUSAR reporting pathways.

5. Governing the AMOIP Window — The IHASG Framework

AyurDatta's Integrated High-Acuity Safety Governance (IHASG) framework was developed specifically to close the gap between advanced therapeutic toxicity kinetics and conventional PVG infrastructure. It is a full-spectrum pharmacovigilance operations model that operates at the speed of clinical deterioration.

IHASG integrates case intake, real-time medical monitoring, MedDRA coding, narrative development, aggregate reporting (DSUR/PSUR/PBRER), and global regulatory submissions within a unified safety-governance architecture — with one non-negotiable architectural invariant at its center:

> **THE ARCHITECTURAL INVARIANT**
> No AI output becomes a record of decision without a named physician's review and signature. The bypass is engineered out — because the regulatory obligation is human.

5.1 The Five-Step Real-Time Review Flow

IHASG governance operates through a five-step clinical review cycle designed to function within the AMOIP window:

- Signal arrives from real-time data stream (physiologic monitoring, biomarker kinetics, EHR feed).
- AI assembles a draft narrative and suggested toxicity grade — explicitly labeled as suggested, never as a decision.
- The named physician reviews the AI output, the full signal context, and prior case trajectory — and decides. Override is documented with rationale.
- Physician sign-off is bound with a Part 11-style e-signature, creating an attributable, timestamped record of decision.
- A tamper-evident audit trail is generated as the work happens — not reconstructed after the clinical event concludes.

The result is a safety record that is inspection-ready not because it was assembled for inspection, but because it was built to be self-evidencing from the moment of clinical decision.

5.2 Readiness Assessment — Four Levels

IHASG evaluates sponsor readiness across four maturity levels. Level 4 — Inspection-Ready — is the operational standard required for AMOIP-aligned governance:

- Level 1 — Absent: No documented process, no designated owner, no records produced.
- Level 2 — Ad-hoc: Work happens, but is person-dependent; records are reconstructable only after the fact.
- Level 3 — Defined: Documented, owned process; but records lag, scatter, or require assembly.
- Level 4 — Inspection-Ready: Self-evidencing — attributable, timestamped records retrievable on demand. The answer is produced in the meeting.

6. Practical Implications for Safety Operations Leaders

The AMOIP framework has direct operational implications for any organization sponsoring or conducting advanced oncology trials in high-acuity R/R populations.

6.1 Assess Your Current Readiness

The first step is an honest assessment of where your current safety operations sit on the four-level IHASG maturity scale — specifically across the five safety domains most likely to be scrutinized in a high-acuity program:

- Signal definition and criteria: are your CRS, ICANS, and DLT thresholds pre-specified and mapped to source data elements?
- Medical review and benefit-risk adjudication: is there a named, credentialed physician with documented decision rights for every safety determination?
- Documentation and audit trail: are your records Part 11-aligned, attributable, and retrievable on demand — or are they assembled retrospectively?
- AI governance: if AI tools are in use, is there model-use logging, bypass prevention, and explicit physician sign-off on every AI-assisted output?
- Escalation governance: are your SRC/DSMB/IDMC structures, expedited reporting pathways, and SUSAR escalation triggers pre-specified?

6.2 Identify the Gap Between Your Cadence and Your Toxicity Velocity

The practical question is not whether your pharmacovigilance program is compliant with existing standards. It is whether your program can detect, adjudicate, and document a safety signal at the speed your therapeutic creates it.

In CAR-T programs, that window is hours. In ADC programs with heavily pre-treated patients, it is days. In RLT programs, it unfolds over cycles. In each case, the question is the same: by the time your current infrastructure produces a decision record, is the clinical window still open?

6.3 Understand the Regulatory Direction

The expectation that sponsors in high-acuity settings will implement proactive, real-time safety governance is not prospective regulatory guidance. It is current inspector expectation. Programs that cannot demonstrate ICU-aligned signal detection, physician-attributable decision records, and inspection-ready documentation are increasingly likely to face findings in FDA, EMA, and PMDA reviews of CAR-T, ADC, and RLT programs.

AMOIP is the clinical rationale for why that expectation is clinically appropriate. The governance gap it identifies is real, the toxicity velocity it describes is documented, and the inspection standard it implies is already in effect.

7. Conclusion

The Acute Multi-Organ Instability Phase is not a new clinical syndrome. It is a naming of a window that has always existed — the period between detectable pre-collapse trajectory and irreversible multi-organ failure — in which the standard pharmacovigilance infrastructure has no mechanism to intervene.

For CAR-T, ADC, and RLT programs operating in relapsed/refractory oncology populations, the toxicity incidence data are clear: CRS occurs in a majority of CAR-T recipients; high-grade events reach multi-organ involvement in a significant minority; ADC-related hepatotoxicity and myelosuppression are prevalent across heavily pre-treated cohorts; RLT-associated renal and marrow toxicity is common in patients with compromised baseline reserve. In every case, the clinical question is the same: can your safety governance operate at the speed of the toxicity it is governing?

IHASG is the answer AyurDatta has built. It is not a software tool. It is a physician-anchored, documentation-first, inspection-ready governance standard that makes the AMOIP window visible — and governable.

ABOUT AYURDATTA INC.

AyurDatta provides independent, physician-owned safety governance for AI-assisted and real-time oncology trials. The IHASG framework is built on the clinical expertise of Ashok Srivastava, MD, PhD, MBA —

board-certified oncologist, DSMB/IDMC Chair for novel-modality programs, and named physician reviewer across 135 oncology trials, 11 first-in-human studies, and 27 INDs — including AUCATZYL (obe-cel), the FDA-approved CD19 CAR-T. AyurDatta's programs carry a 100% inspection record with zero findings. This is cited as proof of capability, not a promise of client outcomes.

References

1. CRS incidence data: Gaffney et al. (2024), CADTH Health Technology Review; CIBMTR real-world registry, JCO 2023 41:7528; multicenter Greece cohort, Frontiers in Medicine 2025 (PMC12162571). CRS range 42–94% any-grade; grade 3–4 CRS 6–25%.

2. ICANS meta-analysis: pooled incidence 26.9% all-grade (95% CI 21.7–32.7%), 10.5% high-grade (95% CI 8.1–13.6%). PMC11518750, 2024.

3. ADC hepatotoxicity meta-analysis: abnormal LFT >30% all-grade; grade ≥3 ~18.8%. Navigating hepatotoxicity of ADCs, PMC12715376, 2025. FDA black-box warnings for hepatotoxicity across multiple approved ADCs.

4. ADC ocular toxicity: FAERS pharmacovigilance study Q3 2011–Q3 2023 (PMC11368736, 2024). Belantamab mafodotin ocular toxicity 51–96%: BCMA-ADC systematic review, PMC12774553.

5. ADC hematotoxicity: any-grade AEs 89–93%, grade 3–4 in 46–58%. PMC12231679, 2025. ADC hematotoxicity pharmacovigilance: PMC12558476. Sarah Cannon retrospective ADC trials (ESMO Open, 2025): grade 3–4 in 29%.

6. RLT toxicity: 177Lu-PSMA I&T study, PMC8833540. Haematologic toxicity study PMC8001812: anemia CTCAE I 73%, grade ≥3 cytopenia 11%.

7. CRS progression kinetics: initial symptoms progress over hours to hemodynamic instability, vasopressor dependence, multi-organ failure. ScienceDirect CRS Topics overview; Management of CRS — Springer Clinical Cancer Bulletin 2025; PMC7393694.

8. FDA Draft Guidance: 'Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products,' January 2025. EMA AI in pharmacovigilance tools and guidelines, 2024. ICH M14 real-world data safety assessment guideline (EMA, 2025).