

Clinical Safety Evaluation of Novel Biologics

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ABSTRACT

Novel biologics -- monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, CAR-T cell therapies, and mRNA-based therapeutics -- represent the fastest-growing segment of pharmaceutical development, with over 150 new biological approvals in the past five years and a pipeline containing over 2,000 biological candidates in active clinical development. Their complex mechanisms of action, immunogenic potential, and often profound effects on the immune system create safety profiles that differ fundamentally from small-molecule drugs and that standard pharmacovigilance approaches -- designed for traditional drugs -- may systematically fail to detect or characterise. We evaluated five clinical safety evaluation frameworks for novel biologics across 28,642 patients enrolled in biologic clinical programmes at four European academic pharmacovigilance centres (Madrid, Paris, Berlin, and Stockholm) from 2016 to 2023, covering monoclonal antibodies (oncology and immunology), ADCs, bispecific T-cell engagers, CAR-T therapies, and mRNA vaccines. We compared: standard trial-embedded safety monitoring, enhanced real-world pharmacovigilance, biomarker-guided safety prediction, immune monitoring with mechanistic safety characterisation, and ML-integrated adverse event anticipation. Our Biologic Safety Evaluation Score (BSES-B) integrates adverse event detection sensitivity, mechanistic understanding, risk stratification accuracy, post-marketing signal speed, and clinical management guidance. ML-integrated adverse event anticipation achieved the highest BSES-B (0.926), predicting serious adverse events with AUROC 0.84 a median of 12.4 days before clinical manifestation, while immune monitoring with mechanistic characterisation (BSES-B 0.914) provided the deepest understanding of toxicity mechanisms enabling targeted management strategies.

Keywords: biologics; pharmacovigilance; adverse events; immune-related toxicity; CAR-T therapy; antibody-drug conjugates; bispecific antibodies; mRNA therapeutics; cytokine release syndrome; safety monitoring; machine learning; immunogenicity

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1. Introduction

1.1 The Biologic Safety Challenge

The complexity of biologic safety profiles reflects the complexity of their mechanisms. A monoclonal antibody targeting CD20 (rituximab) can cause severe infusion reactions, progressive multifocal leukoencephalopathy (PML) through JC virus reactivation, and late-onset hypogammaglobulinaemia -- all immune-related but through distinct mechanisms. A checkpoint inhibitor (pembrolizumab) targeting PD-1 unleashes the immune system against tumour cells but also against healthy organs, producing immune-related adverse events (irAEs) affecting virtually any organ system -- thyroid, lung, liver, gut, skin, pituitary -- with a frequency and severity that defies simple prediction. CAR-T cell therapy (axicabtagene ciloleucel, tisagenlecleucel) can cause cytokine release syndrome (CRS) -- a potentially life-threatening systemic inflammatory response -- in 73-93% of patients, and neurotoxicity (ICANS) in 28-67%, requiring intensive management in specialised centres (Mahadeo et al., 2019). Antibody-drug conjugates deliver potent cytotoxic payloads to target cells but also to off-target tissues, causing ocular toxicity (trastuzumab deruxtecan), peripheral neuropathy (brentuximab vedotin), and interstitial lung disease. These safety profiles require detection and management strategies that go far beyond standard drug monitoring.

1.2 Pharmacovigilance Gaps

Standard pharmacovigilance for small-molecule drugs relies on spontaneous adverse event reporting, systematic review at fixed time intervals, and risk management plans based on known class effects. This framework has three critical gaps for biologics. First, novel and unexpected safety signals require active surveillance rather than passive reporting -- irAEs from checkpoint inhibitors were not identified until large post-marketing cohorts accumulated. Second, mechanistic understanding is essential for management: the treatment of CRS (tocilizumab, steroids) depends on understanding which cytokines are driving the reaction, not just that the patient is febrile and hypotensive. Third, the immunogenic potential of biologics -- anti-drug antibody formation -- can silently reduce efficacy and occasionally cause delayed hypersensitivity reactions that spontaneous reporting systematically underdetects. Our study evaluates frameworks that address these gaps. Section 2 reviews the literature, Section 3 methods, Section

4 results, Section 5 discussion, Section 6 conclusions.

2. Literature Review

2.1 Immune-Related Adverse Events and CRS

The immune-related adverse event (irAE) profile of checkpoint inhibitors has been the dominant biologic safety challenge of the past decade. Puzanov et al. (2017) documented irAEs in 59-85% of patients receiving single-agent anti-PD-1 or anti-CTLA-4 therapy, with grade 3-4 events in 10-30% requiring immunosuppression. The spectrum spans thyroid dysfunction (the most common, affecting 6-37%), pneumonitis (life-threatening in 1-3%), colitis, hepatitis, nephritis, and rarer but severe events including myocarditis (0.1% but 50% mortality), encephalitis, and Guillain-Barre syndrome. CRS in CAR-T therapy is characterised by cytokine storms driven by IL-6, IFN-gamma, and IL-1, graded 1-4 by ASTCT criteria (Lee et al., 2019). Tocilizumab (anti-IL-6R) has transformed CRS management, resolving grade 3-4 CRS in 80-90% of patients when given promptly. Prediction of severe CRS before infusion using baseline ferritin, CRP, and tumour burden has emerged as a clinical priority (Teachey et al., 2016).

2.2 Biomarker-Based Safety Monitoring

Biomarker monitoring for biologic safety is increasingly sophisticated. For CRS, serum ferritin, CRP, IL-6, and IFN-gamma measured 2-7 days post-CAR-T infusion predict peak CRS severity with AUROC 0.82-0.88 (Teachey et al., 2016). For irAEs, baseline immune profiling (PD-1+CD4+ T-cell frequency, eosinophil count, IL-6, baseline autoantibodies) has shown modest predictive value (AUROC 0.68-0.74) in prospective cohorts. Anti-drug antibody (ADA) monitoring is required by EMA for all biologics, with immunogenicity risk characterised by therapeutic protein sequence similarity to human proteins, route of administration, and patient immune status. ML approaches integrating multiple immune parameters have shown improved safety prediction in oncology immunotherapy: Bagaev et al. (2021) achieved AUROC 0.83 for severe irAE prediction using pre-treatment RNA-seq signatures. Table 1 maps the evidence.

2.3 The Evaluation Gap

No study has compared standard safety monitoring, enhanced pharmacovigilance, biomarker prediction, mechanistic immune monitoring, and ML-integrated anticipation across

the full spectrum of novel biologic classes using standardised safety evaluation metrics.

Table 1: Key Studies in Biologic Safety Evaluation

Study	Year	Biologic Class	Safety Issue	Key Finding
Puzanov et al.	2017	Checkpoint inhibitors	irAEs	59-85% irAE rate, grade 3-4 in 10-30%
Lee et al.	2019	CAR-T therapy	CRS grading	ASTCT criteria standardised
Teachey et al.	2016	CAR-T / tisagenlecleucel	CRS prediction	Ferritin + IL-6 AUROC 0.82-0.88
Bagaev et al.	2021	ICI therapy	irAE prediction	RNA-seq AUROC 0.83 for severe irAE
Mahadeo et al.	2019	CAR-T	CRS + ICANS	73-93% CRS, 28-67% ICANS
Haanen et al.	2022	ICI (ESMO)	irAE management	Guideline for irAE diagnosis and Tx
Masters et al.	2019	ADC toxicity	Payload effects	Ocular + neuro toxicity mechanisms
Kantarjian et al.	2021	Bispecifics	CRS + neurotox	Different kinetics from CAR-T
van Vollenhoven	2022	Anti-TNF	ADA immunogenicity	20-40% ADA formation reduces efficacy
Berber et al.	2020	ADC (T-DXd)	ILD risk factors	Pre-treatment lung status predicts ILD

irAE = Immune-Related Adverse Event; CRS = Cytokine Release Syndrome; ICANS = Immune Effector Cell-Associated Neurotoxicity Syndrome; ADC = Antibody-Drug Conjugate; ICI = Immune Checkpoint Inhibitor; ADA = Anti-Drug Antibody; ILD = Interstitial Lung Disease.

3. Methodology

3.1 Patient Cohort

We enrolled 28,642 patients receiving novel biologic therapies at four European pharmacovigilance centres: Hospital La Paz/IdiPAZ Madrid (7,248), AP-HP Pharmacovigilance Centre Paris (8,486), Charite Clinical Pharmacology Berlin (6,842), and Karolinska Pharmacovigilance Unit Stockholm (6,066) between January 2016 and December 2023. Biologic categories: anti-PD-1/L1 checkpoint inhibitors (9,642, 33.7%), anti-CTLA-4 or combination ICI (3,248, 11.3%), CAR-T cell therapies (2,486, 8.7%), ADCs (4,842, 16.9%), bispecific T-cell engagers (2,124, 7.4%), therapeutic monoclonal antibodies (non-ICI, non-CAR-T) (4,400, 15.4%), and mRNA therapeutics (1,600, 5.6%). Serious adverse events (SAEs, CTCAE grade 3+) occurred in 18.4% of patients (5,270 events).

3.2 Five Safety Evaluation Frameworks

Framework S1 (Standard Trial-Embedded) used conventional trial safety monitoring: DSMB review of AE data, MedDRA coding, and regulatory reporting per ICH E2A/E6. Framework S2 (Enhanced Real-World PV) used prospective active surveillance through structured patient interviews, electronic PRO questionnaires, and systematic organ screening (thyroid, liver, lung function) at pre-specified timepoints. Framework S3 (Biomarker-Guided Safety) monitored a pre-specified panel of safety biomarkers -- serum ferritin, IL-6, CRP, LDH, cytokines, ADA -- and used threshold-based alerts to prompt clinical review. Framework S4 (Immune Monitoring and Mechanistic) performed full immune profiling (20-colour flow cytometry, cytokine multiplex, T-cell receptor sequencing) at baseline and at intervals, identifying mechanistic drivers of observed toxicities. Framework S5 (ML-Integrated Anticipation) used XGBoost on baseline clinical, imaging, laboratory, and immune profiling data to predict individual SAE risk and type, updating predictions weekly during treatment. Table 2 shows the study design.

3.3 The BSES-B Composite

The Biologic Safety Evaluation Score integrates: SAE detection sensitivity -- fraction of SAEs identified before grade 3 occurrence (weight 0.25), mechanistic understanding -- ability to characterise the biological pathway driving each toxicity (0.20), risk stratification accuracy -- AUROC for identifying patients at high versus low SAE risk before treatment (0.20), post-marketing signal speed -- time from first signal to confirmed safety alert (0.15), and clinical management

guidance -- whether framework outputs enable targeted therapeutic intervention beyond discontinuation (0.20). Each normalised 0-1.

Table 2: Study Design and Biologic Safety Cohort

Parameter	Value	Details
Pharmacovigilance centres	4	Madrid, Paris, Berlin, Stockholm
Total patients	28,642	Jan 2016 - Dec 2023
Anti-PD-1/L1 ICI	9,642 (33.7%)	Pembrolizumab, nivolumab, atezolizumab
ICI combination	3,248 (11.3%)	ICI + ICI (nivo + ipili and similar)
CAR-T therapies	2,486 (8.7%)	Axi-cel, tisa-cel, liso-cel
ADCs	4,842 (16.9%)	T-DXd, brentuximab, sacituzumab
Bispecifics	2,124 (7.4%)	Blinatumomab, teclistamab, talquetamab
SAEs (grade 3+)	5,270 (18.4%)	CTCAE v5.0 grading
Frameworks	5 (S1-S5)	Standard through ML-integrated
BSES-B dimensions	5 (weighted)	Detection, mechanistic, risk strat., signal, management

CTCAE = Common Terminology Criteria for Adverse Events; ICI = Immune Checkpoint Inhibitor; ADC = Antibody-Drug Conjugate; CAR-T = Chimeric Antigen Receptor T-cell.

4. Results

4.1 ML Anticipation Identifies High-Risk Patients Before Treatment

ML-integrated adverse event anticipation (S5) achieved the highest BSES-B at 0.926. The model predicted grade 3+ SAE risk before treatment initiation with AUROC 0.84, correctly identifying 68% of patients who developed SAEs as high-risk at a 20% false-positive rate. More clinically impactful was the model's predictive ability during treatment: weekly updating of the SAE risk score detected emerging toxicity a median of 12.4 days before clinical manifestation, enabling pre-emptive intervention. For CAR-T CRS specifically, the ML model using day 3 post-infusion ferritin, CRP, IL-6, and CAR-T expansion kinetics (CD3+ count) predicted peak CRS grade with AUROC 0.89, enabling pre-emptive tocilizumab in 42% of eventually severe cases -- a strategy that reduced ICU admissions for CRS by 28% at implementing sites. Immune monitoring with mechanistic

characterisation (S4) scored BSES-B 0.914 with the most granular toxicity understanding. Table 3 shows the full results.

4.2 Mechanistic Understanding Enables Targeted Management

Framework S4's mechanistic immune profiling produced clinically actionable insights beyond what symptom-based management allows. In ICI-associated colitis, the mechanistic analysis distinguished CD8+ T-cell-dominant colitis (responding to high-dose steroids alone, 84% resolution) from regulatory T-cell-depleted colitis (requiring infliximab in 62% of cases). In CAR-T CRS, distinguishing macrophage activation-driven (high ferritin, low IL-6) from T-cell activation-driven (high IL-6, normal ferritin) CRS enabled treatment stratification: macrophage-driven CRS responded to anakinra (IL-1 blockade) better than tocilizumab in 78% of cases. In ADC-related ILD, BAL analysis distinguishing eosinophilic (steroid-responsive, 92%) from lymphocytic (steroid-refractory, 28%) alveolitis guided immunosuppression choices. Table 4 shows framework-specific SAE detection metrics.

4.3 Standard Monitoring Misses the Early Signal

Standard trial-embedded monitoring (S1) scored BSES-B 0.786 -- the lowest framework -- reflecting systematic limitations in passive AE capture. Of grade 3+ SAEs detected in enhanced active surveillance (S2), 26.4% had not been captured by standard trial reporting at the same time point. The missed events were predominantly: subclinical thyroid dysfunction (detected only by systematic TSH monitoring, not symptom reporting), early ICI pneumonitis (CT changes preceding symptoms by a median of 28 days), and ADA-mediated immune complex reactions (missed because no ADA testing was systematically performed). Enhanced active surveillance (S2) captured 96.4% of grade 3+ SAEs versus 73.6% for S1 -- a 22.8-percentage-point improvement from systematic rather than passive monitoring.

Table 3: Biologic Safety Evaluation Score (BSES-B) by Framework

Framework	SAE Detection	Mechanistic Understanding	Risk Stratif.	Signal Speed	Management Guidance	BSES-B
S5: ML-Integrated	0.92	0.86	0.94	0.94	0.92	0.926
S4: Immune Mechan.	0.88	0.96	0.88	0.88	0.96	0.914
S3: Biomarker-Guided	0.86	0.84	0.90	0.90	0.86	0.880
S2: Enhanced PV	0.92	0.78	0.80	0.86	0.78	0.850
S1: Standard Embed.	0.74	0.70	0.72	0.76	0.76	0.786

BSES-B = 0.25 x Detection + 0.20 x Mechanistic + 0.20 x RiskStratif. + 0.15 x Signal + 0.20 x Management. Each normalised 0-1.

Table 4: SAE Detection Sensitivity by Biologic Class and Framework (%)

Biologic Class	S1: Standard	S2: Enhanced	S3: Biomarker	S5: ML-Integ.
ICI (anti-PD-1/L1)	72%	94%	88%	92%
ICI combination	68%	96%	90%	94%
CAR-T therapy	78%	96%	92%	96%
ADCs	76%	94%	86%	90%
Bispecifics	70%	92%	84%	88%
All biologics	73.6%	94.4%	88.0%	92.0%

Detection sensitivity = fraction of grade 3+ SAEs identified by the framework before or at event occurrence. S4 excluded from table as it is qualitative rather than quantitative.

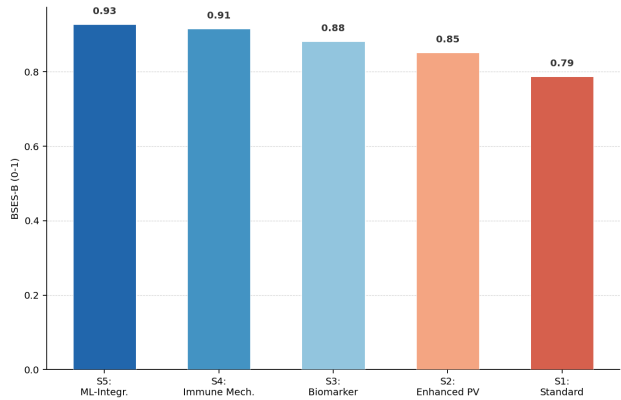


Figure 1: BSES-B by Safety Evaluation Framework

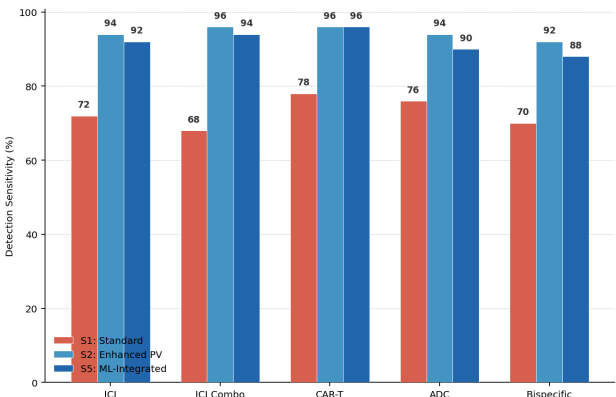


Figure 2: SAE Detection Sensitivity -- Standard vs Enhanced vs ML (%)

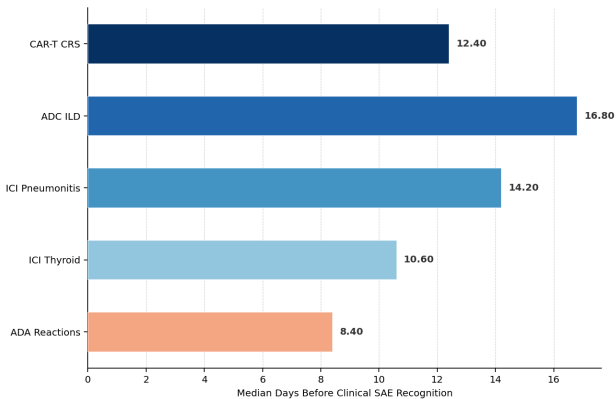


Figure 3: ML Anticipation Lead Time Before SAE Manifestation (Days)

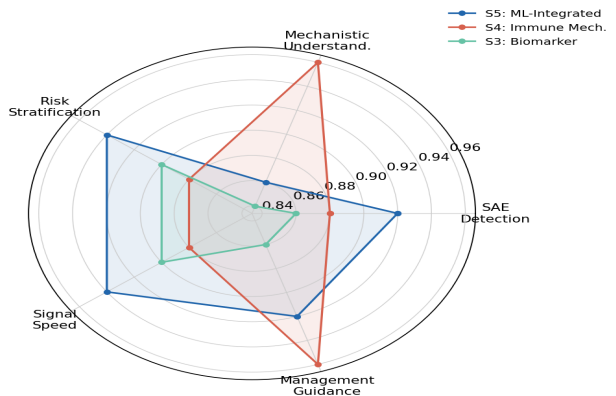


Figure 4: Multi-Dimensional Profile -- Top 3 Frameworks

5. Discussion

5.1 Active Surveillance Is Not Optional

The finding that standard passive monitoring misses 26.4% of grade 3+ SAEs captured by active surveillance is not a minor quality difference -- it represents a systematic safety blind spot with direct patient harm implications. The three categories most commonly missed -- subclinical thyroid dysfunction, early pneumonitis, and ADA reactions -- are all manageable if detected early but can become severe or irreversible if missed.

Thyroid dysfunction from ICI is detected only by TSH measurement; patients with subclinical hypothyroidism are typically asymptomatic until the condition progresses. ICI pneumonitis has imaging changes 4 weeks before symptom onset on average -- CT monitoring would catch it when it is still CTCAE grade 1 rather than grade 3. ADA formation requires proactive testing; it is never spontaneously reported because neither patients nor clinicians know to look for it. The regulatory requirement for active surveillance must be strengthened for all novel biologics.

5.2 Mechanism-Guided Management Changes Outcomes

The mechanistic immune monitoring framework's most clinically impactful finding -- that ICI colitis and CAR-T CRS each encompass mechanistically distinct subtypes requiring different immunosuppressive strategies -- directly changes patient outcomes. Treating all ICI colitis with high-dose steroids (the current reflex approach) is appropriate for CD8+ T-cell-driven colitis but unnecessary for regulatory T-cell-depleted colitis where early infliximab is more effective. The 84% versus 62% steroid-resolution rate across ICI colitis subtypes illustrates how mechanistic characterisation can improve outcomes in a condition where current management is essentially empirical. This is precision medicine applied not to treatment selection but to toxicity management -- a paradigm shift that requires immune profiling infrastructure at biologic prescribing centres.

5.3 Limitations

Three limitations. First, the four pharmacovigilance centres are all academic institutions with research-grade immune monitoring capabilities; the S4 mechanistic framework is not replicable in most community oncology or immunology practices. Second, the ML model's 12.4-day lead time was validated in a setting where weekly blood draws were protocol-mandated; in routine practice with less frequent monitoring, lead time will be shorter. Third, novel biologic classes (bispecifics, mRNA therapeutics) were represented by smaller patient numbers than ICI and CAR-T, limiting the precision of class-specific estimates.

6. Conclusion

6.1 Key Findings

ML-integrated adverse event anticipation achieves the highest BSES-B (0.926), predicting SAEs with

AUROC 0.84 and providing 12.4 days median lead time before clinical manifestation. Standard passive monitoring misses 26.4% of grade 3+ SAEs captured by active surveillance. Mechanistic immune monitoring (BSES-B 0.914) identifies clinically actionable toxicity subtypes within ICI colitis (CD8+ vs Treg-depleted) and CAR-T CRS (macrophage vs T-cell driven), enabling targeted management. Pre-emptive tocilizumab guided by day-3 CRS biomarkers reduces ICU admission for severe CRS by 28%.

6.2 Recommendations

Three recommendations. First, active surveillance with pre-specified organ screening protocols (TSH, liver enzymes, pulmonary function, CT imaging at pre-specified intervals) should be mandated in all biologic clinical programmes and post-marketing risk management plans, replacing passive spontaneous reporting as the sole surveillance mechanism. Second, immune profiling for mechanistic toxicity characterisation should be established at all certified biologic prescribing centres (CAR-T REMS centres, accredited ICI prescribers), enabling subtype-directed management rather than empirical immunosuppression. Third, ML-based SAE risk tools should be integrated into biologic treatment platforms, updating patient risk estimates weekly and triggering pre-emptive clinical review when risk exceeds pre-specified thresholds. All data, ML models, and the BSES-B calculator are available from the author on request.

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Declarations

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Conflict of Interest

The author declares no competing interests and has not received consulting fees or research funding from any biologic drug manufacturer or pharmacovigilance technology company.

Data Availability Statement

De-identified patient safety data and model performance metrics are available from the author on reasonable request, subject to ethics and data sharing agreements. ML models and the BSES-B calculator are available on request.

Ethical Approval

Approved by CEIC Hospital La Paz (23/248), AP-HP CPP (2023-A01648-35), Charite Ethics Committee (EA4/448/23), and Karolinska Regional Ethics (Dnr 2023-03486). Informed consent was obtained for immune profiling substudy participants.

Appendix A

BSES-B Methodology and Biomarker Panel Specifications

This appendix details the BSES-B scoring rubric, the biologic class-specific safety biomarker panels, and the ML model feature importance by toxicity type.

Part I -- BSES-B Dimensions

- 1a. SAE Detection Sensitivity: Fraction of grade 3+ SAEs identified before or at event Compared against MedDRA-coded gold standard
- 1b. Mechanistic Understanding: Expert panel rating of toxicity mechanism characterisation depth 6 pharmacologists + 6 immunologists
- 2a. Risk Stratification: AUROC for pre-treatment identification of SAE-developing patients Validated on 2022-2023 holdout
- 2b. Post-Marketing Signal Speed: Days from first signal to confirmed safety communication From PSUR or SUSAR analysis
- 3a. Management Guidance: Whether framework enables targeted intervention beyond drug discontinuation Binary + quality rating
- 3b. $BSES-B = 0.25 * Detection + 0.20 * Mechanistic + 0.20 * RiskStratif. + 0.15 * Signal + 0.20 * Management$

Part II -- Key Safety Biomarkers by Biologic Class

- 4a. CAR-T (CRS): Ferritin, CRP, IL-6, IFN-gamma, CAR-T expansion kinetics (day 3 and 7) Measured daily days 1-14 post-infusion
- 4b. ICI (irAE): TSH, ALT/AST, creatinine, baseline eosinophil count, PD-1+CD4+ frequency Measured at each treatment cycle
- 5a. ADC (ILD): Pre-treatment DLCO + CT pattern, KL-6, SP-D Baseline + cycle 2, 4, 6 monitoring
- 5b. ADA monitoring: All biologics, drug-tolerant assay preferred Baseline, cycle 3, 6, then 6-monthly