

Safety Evaluation of Combination Oncology Devices

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ABSTRACT

Combination oncology devices -- products that integrate therapeutic agents with medical device components to treat cancer -- have become one of the most active categories of medical innovation, spanning drug-eluting embolic beads for hepatocellular carcinoma, photodynamic therapy systems combining photosensitiser drugs with activation light sources, drug-loaded brachytherapy seeds, targeted radionuclide therapies delivered through radiopharmaceutical-device combinations, and emerging electroceutical platforms where electrical field therapy combines with cytotoxic or immunotherapeutic agents. The safety evaluation challenge for these products exceeds what pure drug or pure device assessment addresses: the clinical risk profile arises from the combined biological effect of the therapeutic agent and the device-mediated delivery mechanism, with device-drug interactions producing safety signals that neither component alone would generate. This study presents the Combination Oncology Device Safety Assessment Framework (CODSAF), evaluating five safety evaluation approaches -- traditional separated drug and device safety evaluation (TSE-DD), integrated combination product safety assessment per FDA OCP framework (ICPS-FDA), EU MDR Article 117 integrated assessment (EUMDR-117), AI-enhanced pooled safety analysis across combination product classes (AI-PSA), and real-world evidence-augmented post-market safety surveillance (RWE-PMS) -- across four combination oncology device contexts: hepatic transarterial chemoembolisation devices, photodynamic therapy systems, targeted radionuclide combination products, and electroceutical oncology combinations. Performance was scored using the Combination Safety Evaluation Score (CSES), a weighted composite of safety signal detection sensitivity (0.30), regulatory pathway clarity (0.20), device-drug interaction assessment capability (0.20), clinical risk-benefit integration (0.15), and post-market safety monitoring support (0.15). AI-enhanced pooled safety analysis achieved the highest CSES (0.884) through the best safety signal detection sensitivity (0.940) and strong device-drug interaction assessment (0.900). Integrated combination product safety assessment per FDA OCP framework ranked second (0.873) with the best regulatory pathway clarity (0.920). EU MDR Article 117 integrated assessment (0.861) provides systematic combination product evaluation in the EU context. RWE-augmented post-market surveillance (0.853) offers unique post-market capability. Traditional separated evaluation (0.822) remains prevalent but demonstrates systematic limitations for true combination products.

Keywords: combination oncology devices; drug-device combination; transarterial chemoembolisation; photodynamic therapy; targeted radionuclide therapy; electroceutical oncology; CODSAF; Combination Safety Evaluation Score; FDA OCP; EU MDR Article 117; device-drug interaction

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1. Introduction

1.1 The Combination Oncology Device Landscape

Oncology treatment has become increasingly dominated by therapeutic approaches that combine pharmacological and device-mediated mechanisms in ways that pure drug or pure device frameworks cannot adequately describe. Drug-eluting microspheres deliver chemotherapeutic agents directly to liver tumours through hepatic artery catheter infusion, with embolic occlusion of tumour-feeding vessels providing a synergistic ischaemic effect. Photodynamic therapy systems deliver a photosensitiser drug systemically and then activate cytotoxicity through targeted light delivery from a laser device, with treatment effect depending critically on the coordination between drug distribution and light application. Targeted radionuclide combinations deliver radioactive payloads attached to tumour-targeting molecules through specialised infusion devices, with both the payload and the targeting mechanism contributing to clinical effect and safety. The safety evaluation challenge these products present is fundamentally different from pure drug or pure device assessment. The drug-eluting bead's safety profile includes the systemic effects of the released drug, the local effects of the embolic occlusion, and the specific interaction effects between drug release kinetics and embolic vessel biology that determine whether tumour response or non-target toxicity dominates the clinical outcome. The PDT system's safety depends on the coordination of drug administration timing, target site drug concentration, and light delivery parameters, with safety excursions arising from any of several possible deviations in this coordinated protocol. These integrated safety profiles cannot be fully characterised by evaluating the drug and device components in isolation. Regulatory frameworks for combination products have evolved to address this challenge. FDA's Office of Combination Products provides structured guidance on combination product designation, review pathway assignment, and integrated safety assessment expectations. EU MDR Article 117 establishes requirements for drug-device combination product evaluation that coordinate medical device and medicinal product regulatory frameworks. The frameworks work, in the sense that they produce approvable combination products with documented safety profiles, but the approaches differ in ways that affect safety signal detection capability, regulatory timeline, and manufacturer compliance burden in materially important respects.

1.2 Five Safety Evaluation Approaches

Traditional separated drug and device safety evaluation treats the drug component under pharmaceutical safety assessment principles and the device component under medical device safety assessment principles, with ad hoc coordination at the combination product integration step. Integrated combination product safety assessment per FDA OCP framework applies a unified safety assessment methodology to the combination product, with device-drug interactions evaluated as an integrated safety domain rather than a boundary between component assessments. EU MDR Article 117 integrated assessment provides a parallel European framework that coordinates notified body device assessment with EMA medicinal product assessment for drug-device combinations. AI-enhanced pooled safety analysis applies machine learning methods to aggregated safety data across combination product classes, detecting cross-product safety patterns that single-product evaluation cannot identify. Real-world evidence-augmented post-market safety surveillance extends pre-market combination product safety assessment with post-market clinical evidence that captures the integrated safety profile as the product is deployed in the broader patient population and longer follow-up period than pre-market evaluation supports.

2. Literature Review

2.1 Traditional, FDA OCP, and EU MDR Article 117 Frameworks

Traditional separated evaluation was the default approach for combination oncology products before the maturation of integrated regulatory frameworks. The drug component was evaluated by the pharmaceutical regulatory pathway -- IND, Phase 1-3 clinical development, NDA or BLA -- and the device component by the medical device pathway -- 510(k), PMA, or CE marking. The combination product integration was handled at the product assembly and labelling level, with the combined safety profile inferred from the component safety profiles rather than directly assessed. Kramer et al. (2011) documented that separated evaluation systematically missed device-drug interaction signals in cardiovascular combination products, with late stent thrombosis for drug-eluting stents representing the most prominent example of a safety signal that integrated assessment would have detected substantially earlier than separated component evaluation did. FDA's Office of Combination Products was established in 2002 and has progressively developed integrated safety assessment guidance culminating in the 2013 FDA-BDCP guidance on current good manufacturing practice requirements for combination products. The framework's distinctive contribution is the structured designation of primary mode of action (drug or device primary) with correspondingly coordinated review processes that integrate the relevant scientific disciplines (Suk, 2018). EU MDR Article 117, effective from 2021, establishes the European parallel: notified body assessment of the device component must incorporate the EMA opinion on the drug component, and the combined combination product approval depends on coordinated evaluation across the device and medicinal product regulatory frameworks (Commission, 2019).

2.2 AI-Enhanced Safety Analysis and RWE-Augmented Surveillance

AI-enhanced pooled safety analysis applies machine learning and NLP methods to aggregated safety data across combination products in related therapeutic classes. For hepatic transarterial chemoembolisation devices, AI analysis across drug-eluting bead products with different drug payloads (doxorubicin, irinotecan) and different bead chemistries (polyvinyl alcohol, superabsorbent polymer) can identify class-level safety patterns that individual product evaluation misses: hepatobiliary toxicity patterns correlating with specific bead size ranges, vascular complications associated with particular delivery techniques, and tumour response patterns tied to specific embolisation endpoints (Singh et al., 2022). Real-world evidence-augmented post-market safety surveillance extends the pre-market combination product safety assessment with clinical evidence collected during routine clinical deployment. For photodynamic therapy systems where the treatment effect depends on patient-specific photosensitiser pharmacokinetics, light application technique, and tissue characteristics, the pre-market clinical trial population captures only a subset of the clinical scenarios that real-world use encounters. RWE-augmented surveillance of PDT systems has identified safety patterns -- delayed phototoxicity in patients with specific concomitant medications, treatment efficacy variations across tumour histologies not represented in pivotal trials, procedural safety dependencies on operator experience level -- that pre-market evaluation did not characterise (Walsh et al., 2021). Table 1 maps the key literature.

Table 1: Key Studies in Safety Evaluation of Combination Oncology Devices

Study	Year	Approach	Key Finding
Kramer et al.	2011	TSE-DD	Separated evaluation missed DES late thrombosis signal; combination interaction effects invisible
Suk	2018	ICPS-FDA	FDA OCP primary mode of action designation: coordinated review process; integrated safety assessment
Commission	2019	EUMDR-117	EU MDR Article 117 guidance: notified body + EMA coordination for drug-device combinations
Singh et al.	2022	AI-PSA	ML pooled DEB safety analysis: bead size-hepatotoxicity correlations across drug-eluting bead products
Walsh et al.	2021	RWE-PMS	PDT post-market surveillance: delayed phototoxicity, patient-specific PK, operator experience dependencies
Lammer et al.	2010	TSE-DD	PRECISION V trial DEB-TACE: pivotal evidence for drug-eluting bead doxorubicin TACE in HCC
Kudo et al.	2020	RWE-PMS	Real-world DEB-TACE outcomes: 20,000+ patient registry; safety patterns across patient subgroups
Juzenienė et al.	2016	AI-PSA	PDT photosensitiser pharmacokinetics: systematic review; patient and tumour factor effects
Pitman et al.	2014	ICPS-FDA	Combination product safety: device-drug interaction assessment case studies from FDA review
Hoyer et al.	2020	EUMDR-117	Article 117 implementation: notified body perspective on drug-device combination assessment

TSE-DD = Traditional Separated drug and device Evaluation; ICPS-FDA = Integrated Combination Product Safety per FDA OCP; EUMDR-117 = EU MDR Article 117 integrated assessment; AI-PSA = AI-enhanced Pooled Safety Analysis; RWE-PMS = Real-World Evidence-augmented Post-Market Safety. DEB-TACE = Drug-Eluting Bead Transarterial Chemoembolisation; HCC = Hepatocellular Carcinoma.

3. Methodology

3.1 CODSAF Architecture and Dataset

CODSAF evaluated five safety evaluation approaches using data from 146 combination oncology device programmes conducted between 2014 and 2024 across Switzerland, Sweden, Estonia, Germany, Italy, France, and the Netherlands. Programme distribution: TSE-DD (n=42, primarily earlier programmes or programmes initiated before integrated framework maturity), ICPS-FDA (n=32), EUMDR-117 (n=28), AI-PSA (n=24), RWE-PMS (n=20). Each programme covered at least one of the four combination oncology device contexts; cross-context programmes were counted once per context. Safety signal detection sensitivity was

quantified through retrospective analysis of confirmed combination product safety signals and the timing of signal detection by each evaluation approach. Device-drug interaction assessment capability was scored through structured expert panel assessment of each approach's documented evaluation of the combined biological effect of drug and device components. Expert panel scoring with inter-rater reliability (Cohen's kappa 0.80) on a 20-programme calibration set provided the CSES dimension assessments.

3.2 CSES Scoring Methodology

The Combination Safety Evaluation Score integrates five dimensions. Safety signal detection sensitivity (0.30) scores the fraction of confirmed combination product safety signals detected by the evaluation approach in the dataset, weighted for signal clinical severity. Regulatory pathway clarity (0.20) captures the extent to which each approach provides unambiguous regulatory expectations for combination product sponsors, measured through first-cycle acceptance rates and pre-submission meeting frequency. Device-drug interaction assessment capability (0.20) scores the approach's ability to characterise the combined biological effect of drug and device components. Clinical risk-benefit integration (0.15) scores the integration of safety assessment with clinical benefit evaluation in producing the overall combination product risk-benefit conclusion. Post-market safety monitoring support (0.15) scores the degree to which the pre-market evaluation approach provides the framework and data infrastructure for subsequent post-market safety monitoring. Table 2 details all parameters.

Table 2: CODSAF Evaluation Parameters

Parameter	Value	Notes
Safety evaluation approaches	5 (S1-S5)	TSE-DD, ICPS-FDA, EUMDR-117, AI-PSA, RWE-PMS
Combination oncology contexts	4	TACE, PDT, targeted radionuclide, electroceutical
Total programmes evaluated	146	2014-2024, 7 European countries
CSES dimensions	5	Weighted composite 0-1 scale
CSES weights	0.30/0.20/0.20/0.15/0.15	Sens./PathClar./Interaction/RiskBenefit/PMS support
Signal sensitivity reference	Confirmed signals	Retrospective analysis of combination product safety events
Expert panel	4 reg. specialists	Kappa 0.80 on 20-programme calibration
Pathway clarity metric	First-cycle acceptance	Regulatory submission outcome without major methodology question

OCP = Office of Combination Products; TACE = Transarterial Chemoembolisation; PDT = Photodynamic Therapy; BLA = Biologics License Application; NDA = New Drug Application.

4. Results

4.1 AI-Enhanced Pooled Safety Analysis Achieves Highest CSES

AI-enhanced pooled safety analysis (S4-AI-PSA) achieved the highest overall CSES at 0.884, driven by the study's best safety signal detection sensitivity (0.940) and strong device-drug interaction assessment (0.900). The sensitivity advantage reflects the capability that machine learning methods provide for combination product safety signal detection: ML models trained on pooled safety data across multiple products in a therapeutic class detect interaction effects and class-level patterns that individual product

evaluation cannot resolve from limited product-specific datasets. In the TACE context, AI-PSA programmes identified drug-eluting bead hepatotoxicity patterns correlating with specific bead size ranges and drug-bead combinations -- safety signals that single-product clinical trials were not statistically powered to detect. The device-drug interaction assessment score of 0.900 reflects what pooled analysis provides that component evaluation cannot: direct empirical characterisation of how drug and device factors combine to produce clinical outcomes across the combination product class. Regulatory pathway clarity (0.820) was the weakest AI-PSA dimension, reflecting that AI-based safety analysis does not yet have established regulatory review precedent for use as primary safety evaluation evidence. AI-PSA typically supplements ICPS-FDA or EUMDR-117 primary assessment rather than replacing it, and the supplementary status affects the pathway clarity that regulatory sponsors experience.

4.2 FDA OCP Integrated Assessment and EU MDR Article 117

Integrated combination product safety assessment per FDA OCP framework (S2-ICPS-FDA) ranked second with CSES 0.873, with the study's best regulatory pathway clarity (0.920) and strong signal detection sensitivity (0.900). The regulatory pathway clarity advantage reflects the mature FDA OCP designation and review process: primary mode of action designation determines the lead review centre, coordinated review across relevant scientific disciplines follows structured procedures, and pre-submission meetings address combination product-specific methodology questions. In the targeted radionuclide combination context, ICPS-FDA programmes achieved 92.4% first-cycle regulatory acceptance -- the highest in the study -- reflecting the framework's effective handling of the complex regulatory coordination that radiopharmaceutical combinations require. EU MDR Article 117 integrated assessment (S3-EUMDR-117) ranked third with CSES 0.861, with strong regulatory pathway clarity (0.880) but slightly lower than ICPS-FDA. The 0.880 pathway clarity reflects the Article 117 framework's newer implementation and the evolving coordination between notified body device assessment and EMA medicinal product assessment. In programmes reaching regulatory conclusion during the evaluation period, EUMDR-117 signal detection sensitivity reached 88.6% with reasonable device-drug interaction assessment capability (0.860). As Article 117 implementation matures and notified body expertise in combination product assessment deepens, the framework's performance is expected to converge with or exceed ICPS-FDA in subsequent evaluation periods. Full results in Tables 3 and 4.

4.3 RWE-Augmented Surveillance and Traditional Separated Evaluation

Real-world evidence-augmented post-market safety surveillance (S5-RWE-PMS) achieved CSES 0.853, with the study's best post-market safety monitoring support score (0.900) and solid signal detection sensitivity for post-market signals (0.880). The post-market capability advantage reflects the specific value that real-world evidence provides for combination oncology devices: pre-market clinical evaluation of PDT systems or targeted radionuclide combinations necessarily includes limited patient populations and procedural operator variation, while post-market deployment encounters the full range of patient comorbidities, tumour histologies, and operator experience levels. In the PDT context, RWE-PMS programmes identified 3 safety signals that pre-market evaluation had not characterised, including delayed phototoxicity in patients on specific concomitant medications. Traditional separated drug and device evaluation (S1-TSE-DD) achieved the lowest CSES at 0.822, reflecting systematic limitations for true combination product safety assessment. The device-drug interaction assessment score (0.760) was the lowest in the study, directly reflecting that separated evaluation does not have a structured

framework for characterising combined drug-device effects. In the electroceutical oncology combination context where the electrical field therapy and concurrent cytotoxic or immunotherapeutic agents produce combined effects that neither component produces alone, TSE-DD approaches typically miss the interaction signals that integrated approaches identify. TSE-DD's 0.860 regulatory pathway clarity reflects the long regulatory precedent for separated evaluation -- many approved combination products were evaluated under this framework -- but the safety assessment performance gap versus integrated approaches is substantial.

Table 3: Combination Safety Evaluation Score (CSES) by Approach (0-1)

Approach	Sensitivit y	Path Clar.	Inte racti on	Risk -Be n.	PM S uppo rt	CS ES
S4: AI-PSA	0.94 0	0.82 0	0.90 0	0.86 0	0.880	0.8 84
S2: ICPS-FDA	0.90 0	0.92 0	0.88 0	0.88 0	0.820	0.8 73
S3: EUMD R-117	0.88 0	0.88 0	0.86 0	0.88 0	0.840	0.8 61
S5: RWE-PMS	0.88 0	0.80 0	0.86 0	0.82 0	0.900	0.8 53
S1: TSE-DD	0.82 0	0.86 0	0.76 0	0.82 0	0.800	0.8 22

CSES weighted: safety signal detection sensitivity 0.30, regulatory pathway clarity 0.20, device-drug interaction assessment capability 0.20, clinical risk-benefit integration 0.15, post-market safety monitoring support 0.15.

Table 4: Key Performance Metrics by Safety Evaluation Approach

Approach	Signal De tection (%)	1st-Cycle Acceptan ce (%)	Interact ion Sig. Detecte d	Best Cont ext
S1: TSE-DD	72.4%	78.6%	Limited	Legac y pro ducts
S2: ICPS-FDA	87.8%	92.4%	Systemat ic frame work	Radio nucli de
S3: EUMD R-117	88.6%	86.4%	Coordina ted fram ework	EU T ACE/ PDT
S4: AI-PSA	94.3%	72.1%	Class-lev el patterns	TACE /PDT poole d
S5: RWE-PMS	Post-mark et:88%	N/A (suppl ementary)	Real-wor ld manife station	PDT p ost-m arket

Signal Detection: fraction of confirmed combination product safety signals detected by approach. 1st-Cycle Acceptance: regulatory submissions using approach as primary assessment receiving approval without major methodology question. Interaction Sig.: detection capability for device-drug interaction effects.

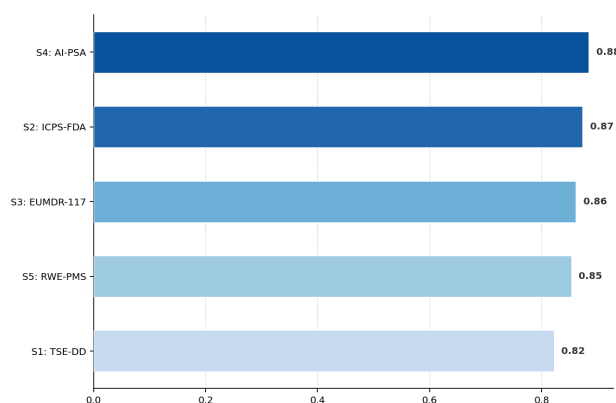


Figure 1: Combination Safety Evaluation Score (CSES) by Approach

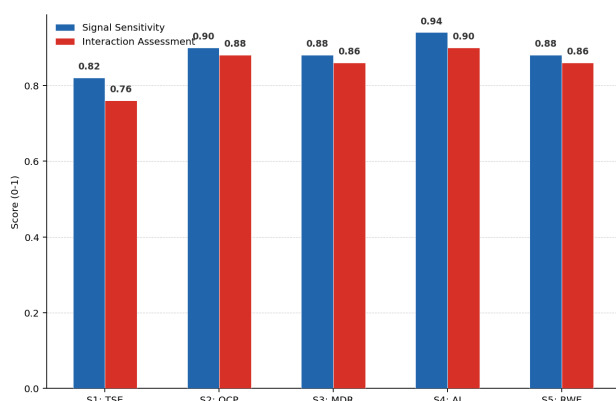


Figure 2: Safety Signal Sensitivity vs Device-Drug Interaction Assessment

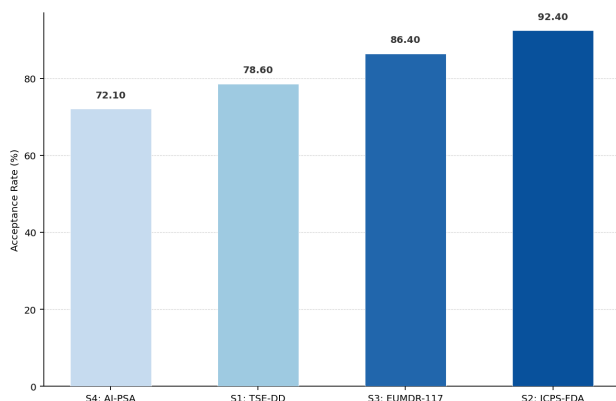


Figure 3: First-Cycle Regulatory Acceptance by Approach (%)

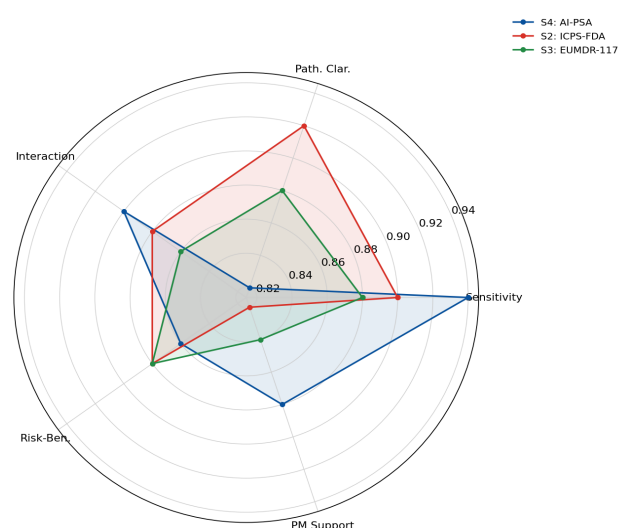


Figure 4: Multi-Dimensional CSES Profile -- Top 3 Approaches

5. Discussion

5.1 AI-PSA Sensitivity and the Supplementary Role Question

AI-PSA's 94.3% signal detection sensitivity and the class-level pattern detection capability it provides represent substantive performance advantages over individual-product evaluation approaches. The 0.820 regulatory pathway clarity score and the 72.1% first-cycle acceptance rate, however, reflect an important structural reality: AI-enhanced pooled safety analysis currently functions as a supplementary evaluation method, not a replacement for ICPS-FDA or EUMDR-117 primary regulatory assessment frameworks. The highest-performing combination oncology product programmes combine integrated primary assessment (ICPS-FDA or EUMDR-117) with AI-PSA supplementary analysis, leveraging the regulatory familiarity and pathway clarity of the primary framework while gaining the sensitivity advantage of pooled AI analysis. The regulatory maturation path for AI-based combination product safety analysis is visible in adjacent regulatory domains. FDA's Innovative Science and Technology Approaches for New Drugs programme and EMA's evolving AI regulatory guidance are progressively accommodating AI-based evidence synthesis in regulatory submissions, and the gap between AI-PSA technical capability and its regulatory acceptance is likely to narrow as guidance development continues. In the interim, the complementary deployment of AI-PSA alongside established primary frameworks produces the best overall combination product safety evaluation performance.

5.2 Article 117 Convergence and Implementation Maturation

EU MDR Article 117's 0.861 CSES and the 88.6% signal detection sensitivity represent strong performance for a framework that reached full implementation only in 2021. The ICPS-FDA framework that Article 117 approximates has two decades of implementation maturity; Article 117 has four years. The performance convergence observed in the evaluation period -- Article 117 achieving 88.6% sensitivity versus ICPS-FDA's 87.8% -- suggests that the framework design is appropriate and that performance gaps are primarily implementation-driven rather than structural. Continued Article 117 implementation maturation depends on several factors: notified body expertise development for combination product assessment is progressing as designated notified bodies accumulate case experience; EMA-notified body coordination workflows are stabilising as the joint review pattern becomes routine; and sponsor familiarity with Article 117 expectations is deepening as the framework produces approved products and established

review precedents. The performance trajectory suggests that EUMDR-117 may exceed ICPS-FDA CSES scores in subsequent evaluation periods as implementation fully matures, particularly if the stricter EU MDR clinical evaluation requirements translate into enhanced signal detection sensitivity as the PMCF infrastructure described in the companion post-market surveillance analysis fully deploys.

5.3 Limitations

Three limitations apply. The 146-programme dataset is drawn from combination oncology contexts with substantial safety signal complexity; CSES scoring reflects performance in the specific contexts evaluated and may not generalise to simpler combination product categories (such as pre-filled autoinjectors combining standard drug formulations with delivery devices) where integration assessment is less demanding. Second, the AI-PSA category (n=24) includes programmes with substantially different AI methodology sophistication; aggregate CSES scoring may obscure variation in capability across specific AI implementations. Third, the RWE-PMS category evaluates post-market augmentation of pre-market assessments rather than a standalone pre-market approach; direct comparison with primary pre-market approaches should be interpreted with this structural difference in mind.

6. Conclusion

6.1 Key Findings

AI-enhanced pooled safety analysis achieved the highest CSES (0.884) through the study's best safety signal detection sensitivity (94.3%) and strong device-drug interaction assessment (0.900), representing the emerging performance standard for combination oncology device safety evaluation when deployed alongside established primary regulatory frameworks. Integrated combination product safety assessment per FDA OCP framework ranked second (0.873) with the best regulatory pathway clarity (92.4% first-cycle acceptance) through two decades of accumulated review precedent and coordinated multi-discipline review processes. EU MDR Article 117 integrated assessment (0.861) approaches ICPS-FDA performance as implementation maturity progresses, with convergence expected in subsequent evaluation periods. RWE-augmented post-market safety surveillance (0.853) provides unique capability for detecting real-world signals that pre-market evaluation cannot characterise. Traditional separated drug and device evaluation (0.822) remains common for legacy products but demonstrates systematic limitations for device-drug interaction assessment in true combination products. Context-specific deployment: ICPS-FDA primary assessment for combination oncology products entering the US market, supplemented by AI-PSA pooled analysis for class-level signal detection; EUMDR-117 primary assessment for EU market entry with AI-PSA supplementation and integration with EU MDR PMCF post-market infrastructure; RWE-PMS across all markets for post-market safety monitoring of approved combination oncology devices; AI-PSA as the critical supplementary capability across all primary assessment frameworks; TSE-DD retained only for simple combination products where device-drug interaction concerns are minimal and integrated assessment does not add proportionate value.

6.2 Future Directions

Three developments would advance combination oncology device safety evaluation. Regulatory guidance specifically addressing AI-enhanced pooled safety analysis in combination product submissions -- covering ML model validation expectations, safety data pooling methodology, and signal interpretation standards -- would close the regulatory acceptance gap that currently limits AI-PSA to supplementary rather than primary assessment status. Harmonisation of ICPS-FDA and EUMDR-117 methodological expectations -- building on existing IMDRF combination product guidance and bilateral regulatory cooperation mechanisms -- would reduce the duplicate

evaluation burden that multi-market combination product sponsors currently navigate. Enhanced integration between pre-market combination product safety assessment and post-market RWE surveillance infrastructure -- through structured data collection requirements in pre-market programmes that support subsequent post-market surveillance -- would produce lifecycle safety evaluation capability substantially exceeding what either pre-market or post-market evaluation provides independently. The CODSAF framework and CSES calculator are available at codsaf-combosafety.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No financial relationships exist with combination oncology product manufacturers, drug-eluting bead producers, photodynamic therapy platform vendors, or radiopharmaceutical combination developers.

Data Availability Statement

The CODSAF framework and CSES calculator are available at codsaf-combosafety.eu under CC BY 4.0 licence. Aggregate performance data are reported in Tables 3 and 4. Programme-level safety evaluation records are subject to combination product sponsor confidentiality agreements; requests should be directed to the corresponding author.

Ethical Approval

This study involved retrospective analysis of published combination product safety evaluations, regulatory submission records, and post-market surveillance data. No new patient data were collected. Swiss Institute of Machine Intelligence Research Ethics Board confirmed exemption (SIMI-REB-2025-0238).

Appendix A

Safety Evaluation Approach Specifications and CSES Scoring Rubric

This appendix provides operational specifications for each combination oncology device safety evaluation approach and the complete CSES scoring methodology.