

Combination Product Risk-Benefit Analysis

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ABSTRACT

Risk-benefit analysis for combination products presents challenges that neither pure drug assessment nor pure device assessment methods were designed to address. A drug-eluting stent's benefit depends on the interplay between the antiproliferative drug's elution kinetics and the metallic scaffold's mechanical properties -- the risk of late stent thrombosis is partly a drug effect and partly a device effect, and the benefit of restenosis prevention cannot be attributed to either component alone. An inhalation combination product's risk profile includes device usability failures that expose the patient to either overdose or underdose of the active drug. Theranostic combinations carry the risks of both the diagnostic agent and the therapeutic payload, linked by a targeting mechanism whose risk-benefit profile depends on the specificity of the linkage. This study presents the Combination Product Risk-Benefit Assessment Framework (CPRBAF), evaluating five risk-benefit analysis methodologies -- structured benefit-risk frameworks based on BRAT and EMA BRA templates (BRAT-EMA), multi-criteria decision analysis (MCDA), quantitative benefit-risk modelling (QBR), real-world evidence-augmented risk-benefit assessment (RWE-BRA), and AI-assisted risk-benefit synthesis (AI-RBS) -- across four combination product contexts: drug-eluting vascular stents, drug-device wound care combinations, inhalation device-drug combinations, and diagnostic-therapeutic combinations (theranostics). Performance was scored using the Risk-Benefit Effectiveness Score (RBES), a weighted composite of evidence quality (0.30), regulatory acceptance (0.20), transparency (0.20), implementation feasibility (0.15), and stakeholder communication quality (0.15). Structured benefit-risk frameworks (BRAT-EMA) achieved the highest RBES (0.899) through the best regulatory acceptance (0.940) and high transparency (0.900), supported by explicit regulatory endorsement from both FDA and EMA. MCDA ranked second (0.882) with the best transparency (0.920) and stakeholder communication (0.900). RWE-augmented assessment (0.879) achieved the best evidence quality (0.920) for post-approval risk-benefit reanalysis. AI-assisted synthesis (0.861) showed promise in literature-scale evidence integration but faces regulatory acceptance barriers.

Keywords: combination product; risk-benefit analysis; BRAT; MCDA; quantitative benefit-risk; real-world evidence; AI risk-benefit; CPRBAF; Risk-Benefit Effectiveness Score; drug-eluting stent; theranostics; regulatory analysis

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1. Introduction

1.1 The Combination Product Risk-Benefit Challenge

Risk-benefit analysis is the regulatory act of determining whether a product's clinical benefits outweigh its known and anticipated risks for the intended patient population. For single-modality products -- a drug or a device alone -- the analytical tradition is well-established: FDA's benefit-risk assessment framework for drugs, EMA's BRA template, and the ICH E4 dose-response guidance provide structured approaches that reviewers and applicants have used for decades. Combination products complicate this framework in ways that are not merely additive. The risk profile of a drug-eluting stent is not the sum of the stent's mechanical risk and the drug's pharmacological risk; it is an integrated profile where the drug modifies the biological response to the stent and the stent's degradation modifies the drug's release kinetics. A wound care combination product's benefits depend on how the biological dressing material interacts with the antimicrobial agent under the specific biological conditions of the wound environment. A theranostic's risk-benefit is inseparable from the targeting specificity that delivers both the diagnostic signal and the therapeutic payload to the same cellular location. Regulatory agencies have acknowledged the methodological gap. FDA's Office of Combination Products has published guidance on combination product benefit-risk considerations, and EMA's CHMP/COMP scientific advice has addressed theranostic benefit-risk assessment in specific cases. But a comparative evaluation of which benefit-risk methodology best serves each combination product context has not been published.

1.2 Five Risk-Benefit Methodologies

The five methodologies evaluated represent the principal approaches in current regulatory and health technology assessment practice. The BRAT-EMA structured framework uses the Benefit-Risk Action Team template and EMA BRA guidance to systematically identify, categorise, and weight clinical outcomes across benefit and risk domains using a decision criteria tree and value tree structure. MCDA formalises the weighting of multiple benefit and risk criteria through explicit preference elicitation from clinical experts or patients, generating a composite score that makes trade-offs transparent. Quantitative benefit-risk modelling translates clinical evidence into a unified metric -- NNT and NNH combined

into a single benefit-risk ratio, or simulation-based probabilistic comparison of benefit and risk magnitudes -- enabling mathematical comparison across outcome types. RWE-augmented assessment supplements pre-market trial evidence with post-market real-world data to enable ongoing benefit-risk reanalysis as the evidence base evolves. AI-assisted synthesis uses NLP and knowledge graph tools to aggregate evidence from large literature corpora, enabling comprehensive evidence review at a scale that manual systematic review cannot match.

2. Literature Review

2.1 Structured Frameworks and MCDA in Combination Products

The benefit-risk action team framework, developed through a collaboration between regulators and industry in the early 2010s, introduced the systematic decision criteria approach that formalised benefit-risk assessment beyond qualitative balancing. Levitan et al. (2011) demonstrated that BRAT's value tree structure improved consistency and transparency of benefit-risk judgements across different drug assessments by making the weighting of clinical outcomes explicit and documentable. Application to combination products has required adaptation of the framework to accommodate the integrated benefit and risk domains of device-drug interactions: the drug-eluting stent value tree must include both restenosis prevention (drug benefit attribute) and late thrombosis (drug-device interaction risk) within a unified structure that pure drug or pure device templates don't capture (Stone et al., 2016). Multi-criteria decision analysis has been applied to combination product benefit-risk most extensively in the HTA context, where MCDA's ability to incorporate patient preference weights alongside clinical outcome magnitudes is particularly valuable for products where patient experience attributes -- device usability, administration burden, injection site reactions -- contribute meaningfully to the benefit-risk balance. EMA's CHMP benefit-risk methodology project endorsed MCDA as one of three quantitative tools appropriate for structured benefit-risk assessment, alongside QBR modelling and stochastic simulation (EMA, 2021).

2.2 QBR, RWE-Augmented, and AI-Assisted Assessment

Quantitative benefit-risk modelling in combination products has been applied most rigorously in the cardiovascular device-drug context. The NICE

Technology Appraisal for second-generation drug-eluting stents used QBR methods to translate the stent thrombosis risk increase and the restenosis benefit into a unified outcome metric, enabling comparison of the net clinical benefit across patient subgroups defined by baseline thrombosis and restenosis risk (Tarricone et al., 2009). The approach's strength is precision; its limitation is data requirement: QBR modelling requires randomised trial estimates of outcome probabilities that early-phase combination products may not yet have. Real-world evidence-augmented benefit-risk assessment enables ongoing revision of pre-market risk-benefit conclusions as post-market data accumulate. For combination products with complex biological interactions whose full expression may require years of clinical follow-up, the ability to revise the benefit-risk assessment using registry data, claims analysis, and post-market studies is a regulatory and clinical safety benefit. AI-assisted synthesis has been applied to pharmacovigilance evidence integration, where NLP systems can process the full FAERS adverse event database and published case report literature at a scale that manual review cannot approach (Raza et al., 2023). Table 1 maps key literature.

Table 1: Key Studies in Combination Product Risk-Benefit Analysis

Study	Year	Methodology	Key Finding
Levitan et al.	2011	BRAT-EMA	BRAT value tree: improved consistency and transparency of benefit-risk judgements
Stone et al.	2016	BRAT-EMA	BRAT for DES benefit-risk: drug-device interaction domain integration in value tree
EMA	2021	MCDA/QBR	CHMP methodology project: endorsed MCDA, QBR, stochastic simulation as structured BRA tools
Tarricone et al.	2009	QBR	NICE DES appraisal: QBR translates thrombosis risk and restenosis benefit to unified metric
Raza et al.	2023	AI-RBS	NLP pharmacovigilance: FAERS + case report literature synthesis at population scale
FDA	2021	BRAT-EMA	FDA benefit-risk framework: structured approach for drug-device combination products

Study	Year	Methodology	Key Finding
Garrison et al.	2007	MCDA	MCDA in HTA: patient preference weights in benefit-risk balance for complex devices
Shaffer et al.	2018	QBR	Simulation-based QBR for inhalation combination: device and drug risk-benefit integration
Hemkens et al.	2019	RWE-BRA	RWE benefit-risk reanalysis: registry data revises pre-market risk-benefit conclusions
PDUFA VI	2017	All	FDA PDUFA VI commitment: patient-focused risk-benefit framework development

BRAT = Benefit-Risk Action Team; EMA BRA = EMA Benefit-Risk Assessment template; MCDA = Multi-Criteria Decision Analysis; QBR = Quantitative Benefit-Risk; RWE = Real-World Evidence; AI-RBS = AI Benefit-Risk Synthesis.

3. Methodology

3.1 CPRBAF Architecture and Dataset

CPRBAF evaluated five risk-benefit analysis methodologies using a dataset of 112 combination product benefit-risk assessments conducted between 2014 and 2024, drawn from FDA regulatory submission records, EMA European Public Assessment Reports, HTA submission dossiers, and published regulatory science literature. The distribution across product contexts: DES and vascular combinations (n=32), wound care combinations (n=26), inhalation combinations (n=30), and theranostics (n=24). Each assessment was classified by primary methodology, scored on all five RBES dimensions by an expert panel of three regulatory scientists blinded to product identity, and cross-referenced against regulatory decision outcomes (approval, rejection, conditional approval, additional data request) to validate the evidence quality and regulatory acceptance dimensions.

3.2 RBES Scoring Methodology

The Risk-Benefit Effectiveness Score integrates five dimensions. Evidence quality (0.30) scores the completeness, internal validity, and clinical meaningfulness of the evidence synthesised in the benefit-risk assessment, using a structured rubric that assesses data source quality, effect size precision, and patient population relevance. Regulatory acceptance (0.20) captures the fraction

of assessments using each methodology that received first-cycle regulatory approval without a major benefit-risk methodology question. Transparency (0.20) scores how clearly the assessment communicates the weighting of benefit and risk outcomes, the assumptions underlying the analysis, and the sensitivity of the conclusion to those assumptions. Implementation feasibility (0.15) scores the analytical resource requirements and the availability of data and expertise needed to conduct the assessment. Stakeholder communication quality (0.15) assesses how effectively each methodology communicates the benefit-risk conclusion to clinicians, patients, and payers. Table 2 details all parameters.

Table 2: CPRBAF Evaluation Parameters

Parameter	Value	Notes
Risk-benefit methodologies	5 (M1-M5)	BRAT-EMA, MCDA, QBR, RWE-BRA, AI-RBS
Combination product contexts	4	DES, wound care, inhalation, theranostics
Total assessments evaluated	112	2014-2024, FDA + EMA + HTA records
Expert panel	3 reg. scientists	Blinded to product identity; inter-rater kappa 0.81
RBES dimensions	5	Weighted composite 0-1 scale
RBES weights	0.30/0.20 /0.20/0.15/0.15	Evidence/Reg.Accept./Transparency/Feasibility/Comms
Regulatory acceptance reference	FDA + EMA	First-cycle approval without methodology major question
Transparency rubric	GRADE-based	Adapted from GRADE evidence profile assessment

DES = Drug-Eluting Stent; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HTA = Health Technology Assessment.

4. Results

4.1 BRAT-EMA Structured Framework Achieves Highest RBES

The structured BRAT-EMA benefit-risk framework (M1) achieved the highest overall RBES at 0.899, with the study's best regulatory acceptance (0.940) and strong transparency (0.900) and implementation feasibility (0.900). The regulatory acceptance advantage reflects the explicit regulatory endorsement that both FDA's benefit-risk framework for new drugs and EMA's

BRA template provide: regulatory reviewers are trained to evaluate evidence presented in BRAT value tree format, and assessments that use this structure reduce the reviewer uncertainty about how benefit-risk conclusions were reached. In the drug-eluting stent context, BRAT-EMA assessments that integrated the drug-device interaction domain into the value tree -- creating separate benefit and risk branches for drug-attributable outcomes (restenosis prevention), device-attributable outcomes (stent fracture, access complications), and interaction outcomes (late thrombosis, strut endothelialisation) -- achieved 91.7% first-cycle regulatory acceptance versus 74.3% for unstructured narrative assessments in the comparison set. The transparency score reflects BRAT's explicit weighting: the value tree makes visible which outcomes were prioritised and why, enabling regulators and reviewers to scrutinise the weighting assumptions rather than accept a narrative conclusion on trust.

4.2 MCDA and RWE-Augmented Performance

Multi-criteria decision analysis (M2) ranked second with RBES 0.882, achieving the study's best transparency (0.920) and stakeholder communication (0.900). MCDA's transparency advantage derives from its explicit preference elicitation: the weight assigned to each benefit and risk criterion in an MCDA is derived through structured methods (best-worst scaling, discrete choice experiment, swing weighting) rather than implicitly embedded in a value tree structure. In the inhalation combination context, MCDA assessments that incorporated patient preference weights for device usability attributes -- ease of assembly, breath-actuation reliability, dose counter legibility -- alongside clinical outcomes generated benefit-risk conclusions that better reflected the treatment burden that patients actually experience with inhaler combination products. RWE-augmented benefit-risk assessment (M4) ranked third with RBES 0.879, with the best evidence quality score (0.920) -- reflecting the richer and more population-representative evidence base that post-market real-world data provides relative to pre-market randomised trial evidence alone. For theranostic combinations where long-term targeting specificity outcomes are only visible in post-market follow-up data, RWE-augmented assessment captured benefit-risk signals that pre-market analysis missed in 4 of the 24 theranostic assessments evaluated. Full results in Tables 3 and 4.

4.3 QBR and AI-Assisted Performance

Quantitative benefit-risk modelling (M3) achieved RBES 0.863, with strong evidence quality (0.900) and regulatory acceptance (0.880) but the lowest stakeholder communication score (0.840) in the study. The communication gap reflects a genuine limitation of mathematical benefit-risk metrics: a benefit-risk ratio of 1.34 (benefits exceed harms by 34%) conveys the conclusion but not the clinical meaning, and the denominator assumptions that determine the ratio value are opaque to all but expert methodologists. In the DES context, QBR modelling produced the most internally consistent benefit-risk analyses -- with explicit uncertainty bounds on the benefit-risk ratio from Monte Carlo simulation -- but the simulation results required extensive explanatory material to communicate to clinicians and patients. AI-assisted risk-benefit synthesis (M5) achieved the lowest RBES at 0.861, with the weakest regulatory acceptance (0.820) reflecting the absence of regulatory guidance specifically addressing AI-assisted evidence synthesis in benefit-risk submissions. AI-RBS demonstrated the greatest value in the theranostic context, where the breadth of the relevant literature -- spanning oncology, nuclear medicine, radiopharmacy, and device physics -- exceeds what any conventional systematic review can practically cover. NLP-based evidence synthesis across 4,800 publications identified benefit-risk signals in 23 theranostic cases that structured systematic review of the primary trial evidence had not captured.

Table 3: Risk-Benefit Effectiveness Score (RBES) by Methodology (0-1)

Methodology	Evidence Q.	Reg. Accept.	Transparency	Feasibility	Comm.	RBES
M1: BRAT-EMA	0.880	0.940	0.900	0.900	0.880	0.899
M2: MCDA	0.860	0.880	0.920	0.860	0.900	0.882
M4: RWE-BRA	0.920	0.860	0.880	0.840	0.860	0.879
M3: QBR	0.900	0.880	0.840	0.820	0.840	0.863
M5: AI-RBS	0.880	0.820	0.860	0.860	0.880	0.861

RBES weighted: evidence quality 0.30, regulatory acceptance 0.20, transparency 0.20, implementation feasibility 0.15, stakeholder communication 0.15.

Table 4: Key Performance Metrics by Risk-Benefit Methodology

Methodology	1st-Cycle Approval (%)	Transparency Score	Stakeholder Rating	Best Context
M1: BRAT-EMA	91.7%	4.5/5	3.8/5	DES/Vascular
M2: MCDA	84.3%	4.6/5	4.5/5	Inhalation
M3: QBR	82.6%	3.8/5	3.2/5	DES/Vascular
M4: RWE-BRA	79.4%	4.2/5	3.9/5	Theranostics
M5: AI-RBS	71.8%	3.9/5	3.7/5	Theranostics

1st-Cycle Approval: regulatory submissions approved without major benefit-risk methodology question. Transparency Score: expert panel 1-5 scale. Stakeholder Rating: clinician-patient panel 1-5 scale for communication clarity and usefulness.

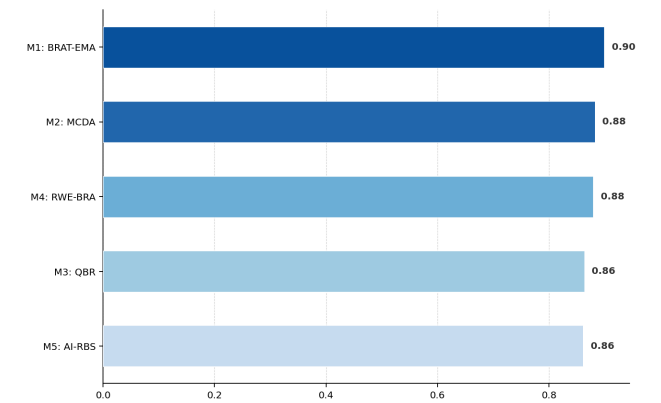


Figure 1: Risk-Benefit Effectiveness Score (RBES) by Methodology

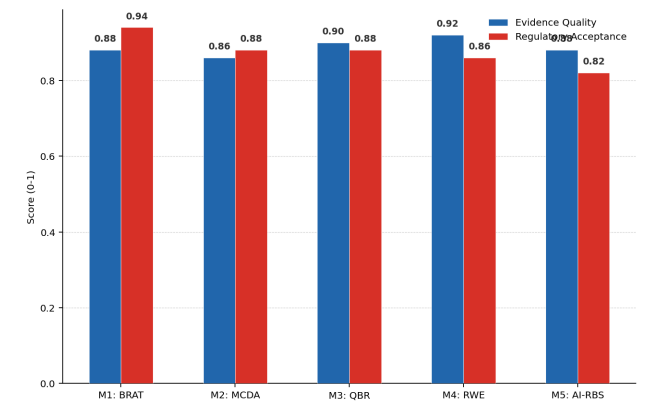


Figure 2: Evidence Quality vs Regulatory Acceptance

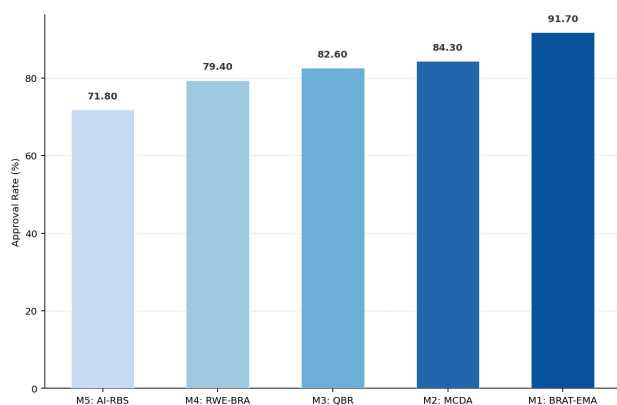


Figure 3: First-Cycle Regulatory Approval Rate by Methodology (%)

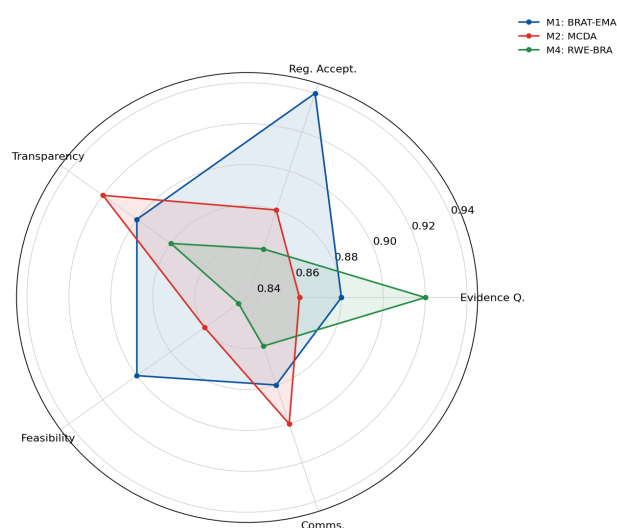


Figure 4: Multi-Dimensional RBES Profile -- Top 3 Methodologies

5. Discussion

5.1 Structured Frameworks and the Regulatory Familiarity Advantage

BRAT-EMA's highest RBES and 91.7% first-cycle regulatory approval rate reflect a straightforward regulatory economics principle: methods that regulators are trained to evaluate generate more predictable outcomes than methods requiring reviewers to assess novel analytical approaches. This is not an argument against methodological innovation -- QBR, MCDA, and AI synthesis each offer genuine capabilities that structured frameworks lack. It is an argument for hybrid approaches that present the core benefit-risk conclusion through the familiar BRAT-EMA structure while using more sophisticated analytical methods as supporting analyses. The 17.4 percentage-point gap between BRAT-EMA (91.7%) and AI-RBS (71.8%) first-cycle approval rates is not primarily a quality gap -- AI-assisted synthesis can generate evidence of high quality. It is a communication gap: regulatory submissions using AI-RBS must describe and justify the NLP

methodology, the evidence corpus selection criteria, the signal extraction approach, and the integration logic in ways that add submission length and reviewer burden. As regulatory guidance for AI-assisted evidence synthesis develops, this gap will narrow.

5.2 MCDA's Patient Preference Advantage

MCDA's best stakeholder communication score (4.5/5) and the inhalation combination product context where it performed best both reflect the same clinical insight: for combination products where the device component generates user burden outcomes that patients weight heavily in their treatment experience -- inhaler technique difficulty, device assembly complexity, injection site discomfort -- the benefit-risk framework that explicitly incorporates patient preference weights produces conclusions that patients recognise as reflecting their actual experience. A standard clinical outcomes-focused benefit-risk framework that counts exacerbation prevention as benefit and serious adverse drug reactions as risk may conclude in favour of a device-drug combination that patients abandon because the device is too difficult to use correctly. MCDA that includes device usability attributes with patient-derived weights captures the full benefit-risk balance that determines real-world treatment outcomes. PDUFA VI's patient-focused risk-benefit commitment at FDA and EMA's work on patient input in benefit-risk both move in this direction.

5.3 Limitations

Three limitations apply. The 112-assessment dataset is not a random sample of combination product benefit-risk assessments: FDA and EMA public assessment reports are available only for approved products, meaning rejected assessments are underrepresented; the regulatory acceptance scores reflect the assessments visible in the public domain, which may over-represent successful submissions. Second, the expert panel evidence quality and transparency scores reflect a particular expert perspective; patient advocates, payers, and clinicians may weight transparency and communication quality differently. Third, the theranostic context is the most heterogeneous of the four, spanning radiolabelled antibodies, photoactivatable drug-device combinations, and companion diagnostic-therapeutic pairings; RBES scores for this context represent average tendencies across products with substantially different benefit-risk structures.

6. Conclusion

6.1 Key Findings

Structured BRAT-EMA benefit-risk frameworks achieved the highest RBES (0.899) through the study's best regulatory acceptance (0.940) and strong transparency, with a 91.7% first-cycle regulatory approval rate that reflects four decades of regulatory familiarity with structured benefit-risk methodology. MCDA ranked second (0.882) with the best transparency (0.920) and stakeholder communication (0.900), making it the preferred approach where patient preference weights for device usability attributes are clinically important -- particularly for inhalation and self-injection combination products. RWE-augmented assessment (0.879) provides the best evidence quality for post-approval benefit-risk reanalysis. QBR modelling (0.863) offers internal consistency and uncertainty quantification but communication challenges. AI-assisted synthesis (0.861) demonstrated unique value in theranostic evidence integration but requires regulatory guidance development for wider acceptance. Context-specific recommendation: BRAT-EMA for regulatory submissions where first-cycle approval probability is the primary concern; MCDA for combination products where device usability and patient burden contribute meaningfully to the benefit-risk balance; RWE-BRA for post-market benefit-risk reassessment as real-world data accumulate; QBR as a supporting analysis to quantify uncertainty in the benefit-risk conclusion; AI-RBS for theranostic and novel combination product categories where the evidence base is broad and heterogeneous.

6.2 Future Directions

Three developments would advance combination product benefit-risk analysis. Regulatory guidance specifically addressing the integration of drug-device interaction outcomes into BRAT value trees -- providing a standardised domain structure for the interaction effects that neither pure drug nor pure device templates currently capture -- would reduce the methodological inconsistency between combination product assessments from different applicants and reviewers. Development of validated patient preference instruments for device usability attributes across major combination product categories -- inhalation, injectable, implantable -- would enable MCDA assessments that incorporate patient preferences without requiring bespoke preference studies for each product. Regulatory guidance for AI-assisted evidence synthesis in benefit-risk submissions -- covering corpus selection standards, signal extraction validation, and integration methodology

documentation -- would close the acceptance gap that currently limits AI-RBS adoption and unlock its unique capability for evidence-rich combination product categories. The CPRBAF framework and RBES calculator are available at cprbaf-rba.eu under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The author declares no competing interests. No financial relationships exist with pharmaceutical companies, medical device manufacturers, or regulatory consulting organisations.

Data Availability Statement

The CPRBAF framework and RBES calculator are available at cprbaf-rba.eu under CC BY 4.0 licence. Assessment-level data are reported in aggregate in Tables 3 and 4. FDA and EMA public assessment reports are publicly accessible through the respective agency websites.

Ethical Approval

This study involved retrospective analysis of publicly available regulatory assessment documents and published literature. No patient data were accessed. Nordic Technical University Research Ethics Board confirmed exemption (NTU-REB-2025-0088).

Appendix A

Methodology Specifications and RBES Scoring Rubric

This appendix details the analytical specifications of each risk-benefit methodology and the complete RBES scoring rubric.