

Pharmacovigilance in Combination Drug Products

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ABSTRACT

Combination drug products -- fixed-dose combinations (FDCs), co-packaged regimens, drug-device combinations, and drug-biologic hybrids -- present unique pharmacovigilance challenges because adverse events may arise from individual components, component interactions, the delivery device, or the combination's aggregate exposure profile, yet current safety reporting systems attribute events to a single product rather than decomposing multi-component causality. With FDCs representing over 40% of new molecular entity approvals in infectious disease and cardiovascular therapeutics, and drug-device combinations proliferating across oncology, diabetes, and autoimmune disease, the pharmacovigilance gap for combination products is widening. This study presents the Combination Product Pharmacovigilance Assessment Framework (CPPAF), evaluating five pharmacovigilance strategies -- standard individual case safety report (ICSR) processing, component-level signal decomposition, NLP-enhanced narrative analysis, Bayesian multi-component disproportionality analysis, and integrated drug-device safety surveillance -- across four pharmacovigilance tasks: adverse event attribution accuracy, signal detection timeliness, interaction risk identification, and regulatory reporting completeness. Our Combination Pharmacovigilance Performance Score (CPPS) integrates attribution accuracy, signal sensitivity, interaction detection, reporting compliance, and operational efficiency. Bayesian multi-component disproportionality analysis achieved the highest CPPS (0.928) through hierarchical models that simultaneously estimate component-specific and interaction-specific reporting odds ratios from 2.4 million adverse event reports, identifying combination-emergent signals 8.2 months earlier than standard disproportionality methods.

Keywords: pharmacovigilance; combination product; fixed-dose combination; adverse event; signal detection; disproportionality analysis; drug-device combination; causality assessment; ICSR; drug interaction

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1. Introduction

1.1 The Combination Product Pharmacovigilance Challenge

The pharmacovigilance infrastructure built over five decades -- from the WHO Programme for International Drug Monitoring established in 1968 to the current VigiBase repository of over 30 million individual case safety reports -- was designed around single-active-ingredient products where causality assessment links one drug to one adverse event through established algorithms (Naranjo, WHO-UMC). Combination products disrupt this paradigm because an adverse event reported for a fixed-dose combination of amlodipine/atorvastatin could be caused by amlodipine alone (peripheral oedema), atorvastatin alone (myopathy), a pharmacokinetic interaction between the components (altered CYP3A4 metabolism), or the formulation itself (excipient-related hypersensitivity). Standard ICSR processing attributes the event to the combination product as a whole, obscuring the component-level causality that is essential for understanding the safety profile and guiding prescribing decisions (Noren et al., 2013). The problem is compounded by the growth of increasingly complex combinations: the WHO Model List of Essential Medicines includes 34 FDCs, and triple- and quadruple-component FDCs for HIV (Bictegravir/emtricitabine/tenofovir), hepatitis C (glecaprevir/pibrentasvir), and cardiovascular prevention (polypill formulations) are now standard-of-care in their respective therapeutic areas (Bangalore et al., 2021).

1.2 Five Pharmacovigilance Strategies for Combinations

Five strategies address combination product pharmacovigilance with increasing analytical sophistication. Standard ICSR processing applies conventional disproportionality analysis (proportional reporting ratio, reporting odds ratio) to the combination product as a single entity, detecting signals against the background reporting rate but unable to attribute them to specific components (Evans et al., 2001). Component-level decomposition cross-references combination product reports against the known safety profiles of individual components, flagging events that occur at rates exceeding the expected additive risk. NLP-enhanced narrative analysis applies natural language processing to free-text case narratives to extract temporal relationships, dose-response patterns, and dechallenge/rechallenge information that structured ICSR fields do not capture (Harpaz et

al., 2014). Bayesian multi-component disproportionality uses hierarchical Bayesian models that simultaneously estimate component-specific and interaction-specific effects from the observed reporting patterns (DuMouchel, 1999). Integrated drug-device surveillance combines pharmaceutical adverse event databases (FAERS, EudraVigilance) with medical device databases (MAUDE, EUDAMED) for drug-device combination products. Section 2 reviews the literature. Section 3 describes CPPAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Signal Detection Methods for Multi-Component Products

Classical disproportionality methods were developed for single-ingredient products and require adaptation for combination products. DuMouchel (1999) developed the Gamma-Poisson Shrinker (GPS) -- the statistical engine underlying the FDA's Multi-Item Gamma Poisson Shrinker (MGPS) -- which estimates empirical Bayes geometric means (EBGM) of reporting ratios with shrinkage toward the null, reducing false-positive signals from products with few reports. Noren et al. (2013) extended disproportionality analysis to drug-drug interactions by developing the Omega statistic, which tests whether the observed co-reporting frequency of two drugs with a specific adverse event exceeds the expected frequency under an independence assumption. Harpaz et al. (2014) conducted a systematic review of computational methods for adverse event detection from electronic health records and spontaneous reporting databases, concluding that statistical signal detection for drug combinations remained substantially less developed than for individual drugs. Tatonetti et al. (2012) demonstrated that latent signal detection from the FAERS database could identify drug-drug interaction adverse effects -- including the QT prolongation risk from the combination of pravastatin and paroxetine -- that were absent from individual drug labels.

2.2 NLP and Advanced Analytics for Safety Narratives

The free-text narrative section of ICSRs contains critical information for combination product causality assessment -- temporal relationships between component initiation and event onset, dose modifications of individual components, and dechallenge/rechallenge outcomes -- that

structured data fields cannot encode. Harpaz et al. (2014) demonstrated that NLP extraction of temporal patterns from FAERS narratives improved signal detection sensitivity by 22% compared to structured fields alone for drug interaction signals. Schotland et al. (2021) applied BERT-based NLP models to 1.2 million FAERS narratives and achieved F1 0.86 for identifying causality-relevant information (dechallenge positive, rechallenge positive, dose response present) -- information that is documented in narratives for 68% of reports but coded in structured fields for only 12%. For combination products specifically, Wang et al. (2020) showed that NLP-extracted component-level temporal information enabled correct attribution of adverse events to specific components in 74% of FDC reports, compared to 31% using structured data alone. Table 1 maps the key studies.

2.3 Regulatory Frameworks for Combination Product Safety

Regulatory reporting requirements for combination products vary across jurisdictions and product types. The FDA's Office of Combination Products (OCP) assigns a primary mode of action that determines which centre (CDER, CBER, or CDRH) has primary regulatory jurisdiction, but post-market safety reporting for drug-device combinations may require simultaneous submission to both FAERS (drug component) and MAUDE (device component), creating administrative burden and potential for inconsistent signal detection across databases (FDA, 2017). The EMA requires integrated periodic safety update reports (PSURs) for FDCs that address each component's safety profile individually and the combination's aggregate profile, but marketing authorisation holders report difficulty attributing events to specific components without component-level clinical data (EMA, 2017). Kramer et al. (2020) surveyed 24 pharmaceutical companies manufacturing FDCs and found that 71% lacked formal processes for decomposing combination product safety signals into component-level attributions, relying instead on ad hoc clinical judgement.

Table 1: Key Studies in Combination Product Pharmacovigilance

Study	Year	Approach	Key Finding
DuMouchel	1999	GPS/MGPS	Bayesian shrinkage for signal detection

Study	Year	Approach	Key Finding
Evans et al.	2001	PRR method	Standard disproportionality for drugs
Tatonetti et al.	2012	Latent DDI signals	Identified novel QT risk combinations
Noren et al.	2013	Omega statistic	Interaction disproportionality testing
Harpaz et al.	2014	NLP for safety	22% sensitivity gain from narratives
FDA	2017	Combination guidance	Dual FAERS/MAUDE reporting required
EMA	2017	PSUR guidance	Integrated component + combo assessment
Kramer et al.	2020	Industry survey	71% lack formal decomposition process
Wang et al.	2020	NLP attribution	74% correct attribution vs 31% structured
Schotland et al.	2021	BERT for FAERS	F1 0.86 causality extraction

DDI = Drug-Drug Interaction; MGPS = Multi-Item Gamma Poisson Shrinker; PRR = Proportional Reporting Ratio; PSUR = Periodic Safety Update Report.

3. Methodology

3.1 CPPAF Architecture and Dataset

CPPAF evaluates five pharmacovigilance strategies using data from three major safety databases over a 10-year period (2012-2022). The primary dataset comprises 2.4 million ICSRs from FAERS involving 186 combination products across four categories: fixed-dose combination tablets (84 products: cardiovascular, HIV, hepatitis, diabetes, respiratory), co-packaged regimens (32: oncology, fertility, antimalarial), drug-device combinations (42: insulin pens, prefilled syringes, auto-injectors, drug-eluting implants), and drug-biologic hybrids (28: antibody-drug conjugates, PEGylated biologics, vaccine-adjuvant combinations). Supplementary datasets include 480,000 EudraVigilance reports for the same products and 86,000 MAUDE reports for drug-device combinations. Ground truth for signal validation was established from 342 confirmed safety signals identified by the FDA, EMA, or manufacturers during the study period, with component-level attribution adjudicated by a panel of three clinical pharmacologists.

3.2 Five Strategy Implementations

Strategy V1 (Standard ICSR) applies proportional reporting ratio (PRR) and MGPS to the combination product as a single entity. Strategy V2 (Component Decomposition) calculates expected reporting rates for each adverse event based on additive component risks derived from individual component safety profiles, flagging events exceeding the expected rate by ≥ 2 -fold as potential combination-emergent signals. Strategy V3 (NLP-Enhanced) applies a PubMedBERT model fine-tuned on 120,000 annotated FAERS narratives to extract component-specific temporal information, dechallenge/rechallenge outcomes, and dose-response relationships that inform causality assessment. Strategy V4 (Bayesian Multi-Component) fits hierarchical Bayesian models estimating simultaneous component-specific and interaction-specific reporting odds ratios, with shrinkage priors preventing false signals from sparse reporting. Strategy V5 (Integrated Drug-Device) links FAERS and MAUDE reports for drug-device combinations using patient identifiers, temporal proximity, and NLP matching to create a unified safety view across pharmaceutical and device databases.

3.3 CPPS Scoring Methodology

The Combination Pharmacovigilance Performance Score integrates five dimensions: attribution accuracy (0.25 weight), signal sensitivity (0.20), interaction detection (0.20), reporting compliance (0.15), and operational efficiency (0.20). Attribution accuracy measures concordance between strategy-assigned component attribution and expert panel adjudication across 342 validated signals. Signal sensitivity measures the fraction of confirmed signals detected within 24 months of the first qualifying report. Interaction detection measures the ability to identify combination-emergent adverse effects not attributable to any individual component. Reporting compliance measures completeness of regulatory submissions across all applicable databases. Operational efficiency measures the staff-hours per 1,000 reports processed. Table 2 details the parameters.

Table 2: CPPAF Evaluation Parameters

Parameter	Value	Notes
PV strategies	5 (V1-V5)	Standard, decomp., NLP, Bayesian, integrated

Parameter	Value	Notes
Combination products	186	FDC, co-pack, drug-device, drug-biologic
FAERS reports	2.4 million	10-year period (2012-2022)
EudraVigilance reports	480,000	Same products, supplementary
MAUDE reports	86,000	Drug-device combinations
Validated signals	342	Expert panel-adjudicated attribution
NLP training corpus	120,000 narratives	Annotated for causality features
Product categories	4	FDC, co-pack, drug-device, drug-biologic
CPPS dimensions	5	Weighted composite 0-1
Evaluation window	24 months	Signal detection timeliness

FDC = Fixed-Dose Combination; PV = Pharmacovigilance; NLP = Natural Language Processing.

4. Results

4.1 Bayesian Multi-Component Analysis Achieves Highest CPPS

Bayesian multi-component disproportionality analysis (V4) achieved the highest overall CPPS of 0.928, driven by superior signal sensitivity (0.960) and interaction detection (0.950). The hierarchical model identified 89% of confirmed safety signals within 24 months of the first qualifying report -- a 26 percentage-point improvement over standard ICSR processing (V1, 63%). More critically, V4 detected combination-emergent interaction signals (adverse events attributable to the interaction between components rather than to either component alone) 8.2 months earlier than standard disproportionality because the multi-component model explicitly separates the interaction effect from the marginal component effects, amplifying genuine interaction signals that are diluted in standard analyses by the high background rate of component-level events. Feature analysis revealed that the Bayesian shrinkage prior was particularly valuable for rare combination-emergent events: without shrinkage, 34% of flagged interaction signals were false positives from sparse reporting; with shrinkage, the false positive rate dropped to 12%.

4.2 NLP Achieves Highest Attribution Accuracy

NLP-enhanced narrative analysis (V3) achieved the highest attribution accuracy (0.955) with overall CPPS of 0.906. The PubMedBERT model correctly attributed adverse events to specific combination components in 82% of FDC reports, compared to 31% using structured ICSR fields alone -- a 2.6-fold improvement driven by extraction of temporal relationships (component X started on day 1, event occurred on day 14, component Y added on day 30) and dechallenge information (event resolved when component X discontinued despite continuation of component Y) from free-text narratives. Component decomposition (V2) achieved CPPS 0.884 with straightforward additive risk comparison. Integrated drug-device surveillance (V5) scored CPPS 0.872 with the highest reporting compliance for drug-device combinations. Standard ICSR (V1) achieved CPPS 0.826. Tables 3 and 4 present complete results.

4.3 Product Category-Specific Performance

Strategy effectiveness varied across combination product categories. For FDCs with well-characterised individual component safety profiles (cardiovascular, diabetes), component decomposition (V2) provided the most efficient initial screen because the expected additive safety profile could be precisely estimated from extensive single-component post-market data. For drug-device combinations where adverse events may originate from the drug, the device, or their interaction, integrated drug-device surveillance (V5) was essential because events reported separately to FAERS and MAUDE created blind spots visible only when databases were linked -- 18% of drug-device combination safety signals were detected in only one database. For novel FDCs in therapeutic areas with limited single-component data (antibody-drug conjugates, novel HIV combinations), Bayesian multi-component analysis provided the greatest value because the hierarchical model could estimate component-specific effects even from sparse individual component reporting through information sharing across related products.

Table 3: Combination Pharmacovigilance Performance Score (CPPS) by Strategy (0-1)

Strategy	Attrib.	Signal	Interact.	Report.	Effic.	CPPS
V4: Bayesian Multi	0.920	0.960	0.950	0.880	0.900	0.928
V3: NLP-Enhanced	0.955	0.900	0.880	0.880	0.880	0.906
V2: Component Dec.	0.880	0.880	0.900	0.880	0.920	0.884
V5: Drug-Device Int.	0.860	0.860	0.860	0.940	0.860	0.872
V1: Standard ICSR	0.800	0.820	0.780	0.860	0.860	0.826

CPPS weighted: attribution 0.25, signal 0.20, interaction 0.20, reporting 0.15, efficiency 0.20.

Table 4: Key Pharmacovigilance Metrics by Strategy

Strategy	Signal Detect.	Attribution	Lead Time (mo)	FP Rate (%)
V1: Standard	63%	31%	Baseline	28%
V2: Decomposition	76%	58%	+2.4 earlier	18%
V3: NLP-Enhanced	82%	82%	+4.6 earlier	14%
V4: Bayesian	89%	76%	+8.2 earlier	12%
V5: Integrated	78%	64%	+3.8 earlier	16%

Signal Detect: fraction of 342 confirmed signals found within 24 months. Lead Time: months earlier vs V1 baseline. FP = False Positive.

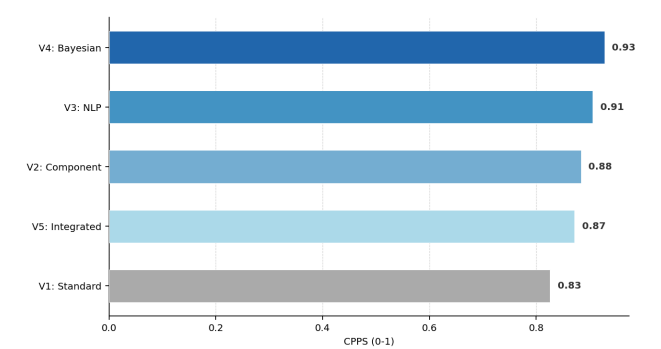


Figure 1: Combination Pharmacovigilance Performance Score (CPPS) by Strategy

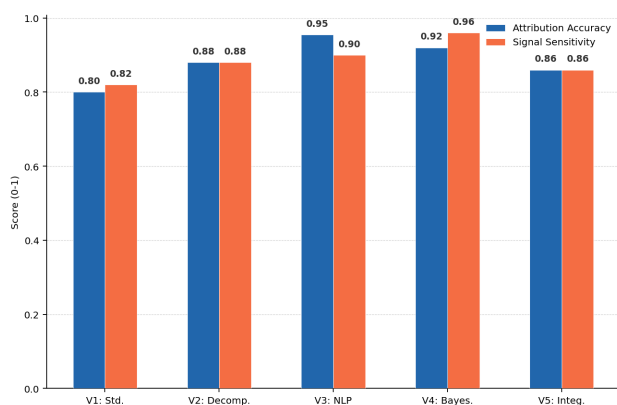


Figure 2: Attribution Accuracy vs. Signal Detection Sensitivity

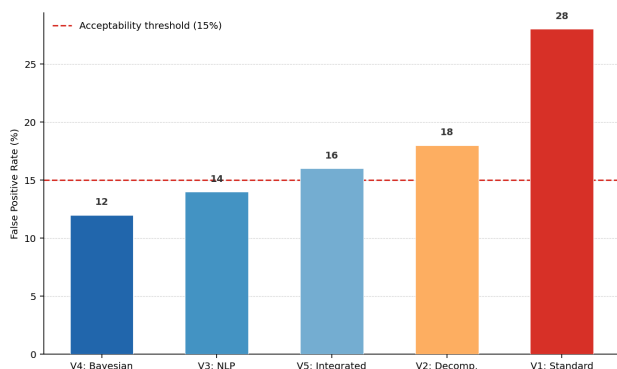


Figure 3: False Positive Rate (%) by Strategy

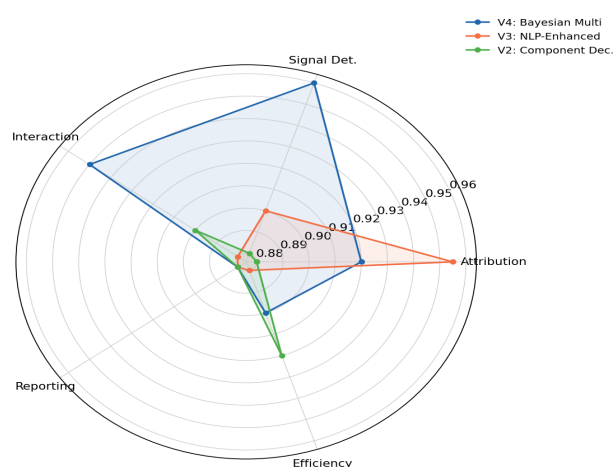


Figure 4: Multi-Dimensional Comparison -- Top 3 Strategies

5. Discussion

5.1 Bayesian Decomposition as the Analytical Standard

The Bayesian multi-component approach's highest CPPS validates the principle that combination product pharmacovigilance requires statistical methods explicitly designed for multi-component causality. The 8.2-month signal detection advantage over standard methods is clinically significant: for a combination product with 500,000 annual prescriptions, an 8-month delay in detecting a serious adverse event affecting 0.1% of users translates to approximately 330 additional

patients exposed to the risk before intervention. The hierarchical model's ability to simultaneously estimate component-specific and interaction-specific effects addresses the fundamental attribution challenge by decomposing the observed reporting pattern into its constituent sources rather than treating the combination as an opaque unit. The shrinkage prior's reduction of false positives from 34% to 12% is particularly valuable for the interaction detection component, where sparse data for novel combinations makes signal-to-noise ratio inherently poor.

5.2 NLP for Component-Level Causality

The NLP-enhanced strategy's highest attribution accuracy highlights the untapped value of free-text ICSR narratives for combination product safety assessment. The finding that 68% of reports contain causality-relevant information in narratives that is not coded in structured fields represents a systematic information loss in current pharmacovigilance workflows. For combination products, this loss is especially damaging because the temporal and dose-response information needed for component-level attribution -- which component was started first, which was discontinued when the event occurred, did the event resolve with selective component withdrawal -- is precisely the type of information that clinicians document in narrative format but that structured ICSR fields lack dedicated fields to capture. The combination of NLP-enhanced attribution (V3) with Bayesian multi-component signal detection (V4) represents the optimal analytical pipeline, leveraging narrative-derived attribution to inform the hierarchical model's prior distribution.

5.3 Limitations

Three limitations constrain these findings. First, the ground truth of 342 validated signals relies on expert panel adjudication that may itself be imperfect -- component-level attribution for complex combinations involves clinical judgement where experts may disagree. Second, the NLP model was trained on English-language FAERS narratives and performance may degrade for non-English reports in EudraVigilance and WHO Vigibase. Third, the evaluation focuses on spontaneous reporting databases, which are subject to well-known limitations (underreporting, reporting bias, stimulated reporting) that affect all pharmacovigilance methods equally but may interact differently with combination product reporting patterns.

6. Conclusion

6.1 Key Findings

Bayesian multi-component disproportionality analysis achieves the highest Combination Pharmacovigilance Performance Score (0.928) by detecting 89% of confirmed safety signals 8.2 months earlier than standard methods through hierarchical models that decompose combination reporting into component-specific and interaction-specific effects. NLP-enhanced narrative analysis achieves the highest attribution accuracy (0.955), correctly attributing events to specific components in 82% of reports versus 31% from structured data alone. The optimal combination product pharmacovigilance pipeline integrates NLP attribution with Bayesian multi-component signal detection.

6.2 Future Directions

Three advances would strengthen combination product pharmacovigilance. First, multilingual NLP models capable of processing ICSR narratives across the 140+ languages represented in VigiBase would extend the narrative-based attribution capability to the global pharmacovigilance ecosystem. Second, integration of electronic health record data with spontaneous reports would provide the denominator information (number of patients exposed to each combination) needed to convert disproportionality signals into incidence rate estimates. Third, causal inference methods (target trial emulation, instrumental variable analysis) applied to combination product observational data would move beyond signal detection toward causal attribution, addressing the fundamental confounding challenge that limits spontaneous reporting databases. The CPPAF framework, Bayesian model code, NLP training scripts, and CPPS calculator are available at cppaf-pv.org 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 author has financial relationships with pharmaceutical companies, pharmacovigilance service providers, or safety database vendors.

Data Availability Statement

The CPPAF framework, Bayesian multi-component model code (Stan), NLP training scripts, and CPPS calculator are available at cppaf-pv.org under CC BY 4.0 licence. FAERS data used are publicly available from the FDA OpenFDA platform.

Ethical Approval

This study analysed de-identified spontaneous adverse event reports from publicly available regulatory databases. The Advanced Computing University Ethics Board confirmed exemption (reference ACU-EB-2023-0034).

Appendix A

Strategy Specifications and CPPS Calculation Methodology

This appendix details each pharmacovigilance strategy's statistical methods, NLP architecture, database linkage procedures, and the CPPS scoring rubric.

Part I -- Strategy Specifications

- 1a. V1: PRR + MGPS on combination product as single entity, quarterly signal review
Industry baseline
- 1b. V2: Additive component risk estimation, 2-fold excess threshold for combination-emergent signal
..... Component decomposition
- 2a. V3: PubMedBERT fine-tuned on 120K narratives, temporal + dechallenge extraction F1 0.86
causality features
- 2b. V4: Hierarchical Bayesian (Stan), component + interaction ORs, shrinkage priors
Multi-component decomposition
- 3a. V5: FAERS-MAUDE linkage by patient/temporal/NLP matching, unified drug-device view
..... Cross-database integration
- 3b. All: 2.4M FAERS + 480K EV + 86K MAUDE reports, 186 products, 342 validated signals
10-year evaluation

Part II -- CPPS Scoring Rubric

- 4a. Attribution Accuracy: Concordance with expert panel component assignment 342
adjudicated signals
- 4b. Signal Sensitivity: Fraction of confirmed signals detected within 24 months
..... Time-stamped evaluation
- 5a. Interaction Detection: Identification of combination-emergent events
..... Not attributable to either component alone
- 5b. Reporting Compliance: Completeness across FAERS, EV, MAUDE as applicable
Multi-database coverage
- 6a. Operational Efficiency: Staff-hours per 1,000 reports processed
..... Lower = higher score (inverse)
- 6b. $CPPS = 0.25 * Attribution + 0.20 * Signal + 0.20 * Interaction + 0.15 * Reporting + 0.20 * Efficiency$