Out of sight, out of mind? A simulation study assessing the use of Quantitative Bias Analysis for Outcome Misclassification in Single-Arm Trials with External Control Comparisons

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Inizio Advisory

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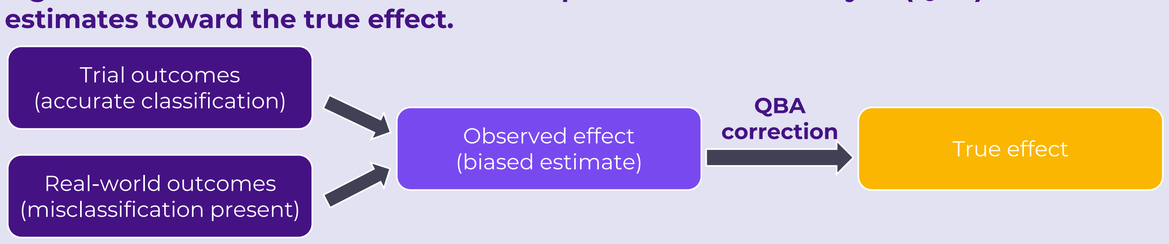
RWD132

Introduction

- **Single-arm trials with external controls** are increasingly used in regulatory and HTA submissions.[1]
- **Key challenge**: Outcomes in real-world data may be defined or recorded differently than in trials, creating risk of **differential misclassification**, e.g. in oncology, many studies have identified concordance between physician reported response and response measured using trial definitions.[2]
- **Bias risk**: Even modest outcome misclassification can meaningfully distort estimated treatment effects.[3]
- **Quantitative bias analysis (QBA)** is more commonly used for unobserved confounding,[4] but its application to outcome misclassification remains limited.

Figure 1. Outcome misclassification and quantitative bias analysis (QBA) correct estimates toward the true effect.



- **Objective**: To assess how differential outcome misclassification affects treatment effect estimates in external control arm studies comparing single-arm trial and real-world comparator outcomes, and to evaluate whether deterministic and probabilistic QBA methods can reduce or eliminate misclassification bias.

Methods

- **Simulation setup**: A hypothetical single-arm trial with a single binary endpoint and no outcome misclassification was simulated, alongside external control datasets generated under varying outcome misclassification scenarios.
- **Misclassification scenarios**: Sensitivity and specificity varied to mimic three real-world outcome definitions with increased severity of misclassification.

Table 1. Sensitivity and specificity values used to generate misclassification scenarios for the external control datasets.

	Scenario 1	Scenario 2	Scenario 3
Sensitivity	0.95	0.85	0.60
Specificity	0.98	0.95	0.90

- **Bias correction approaches**:
  - **Deterministic QBA**: Applied correction using assumed sensitivity/specificity.[5]
  - **Probabilistic QBA**: Sensitivity/specificity treated as random variables (e.g., uniform priors); adjustment via Monte Carlo simulation (10,000 iterations).[6]
- **Performance assessment**: We compared corrected estimates against the true effect to quantify bias reduction using the Ratio of Odds Ratios

$$\mathbf{RoOR = OR_{estimate} / OR_{true}}$$

- **True effect:** The simulated "truth" was **OR = 0.53 (95% CI: 0.30–0.94)**.

Results

- **Simulated effects showed that misclassification led to bias towards the null (OR→1) in all scenarios.** Across misclassification scenarios, the observed ORs ranged 0.60–0.84 (larger OR = less apparent benefit) [**Figure 2**].
- **Deterministic QBA reduced bias:** Applying fixed sensitivity/specificity corrections produced ORs ≈ 0.43–0.57, moving estimates back toward the true effect [**Figure 2**].

Figure 2. Simulated odds ratios under increasing outcome misclassification bias compared with bias-adjusted estimates from deterministic and probabilistic quantitative bias analysis. The dashed line indicates the true effect (OR = 0.53).

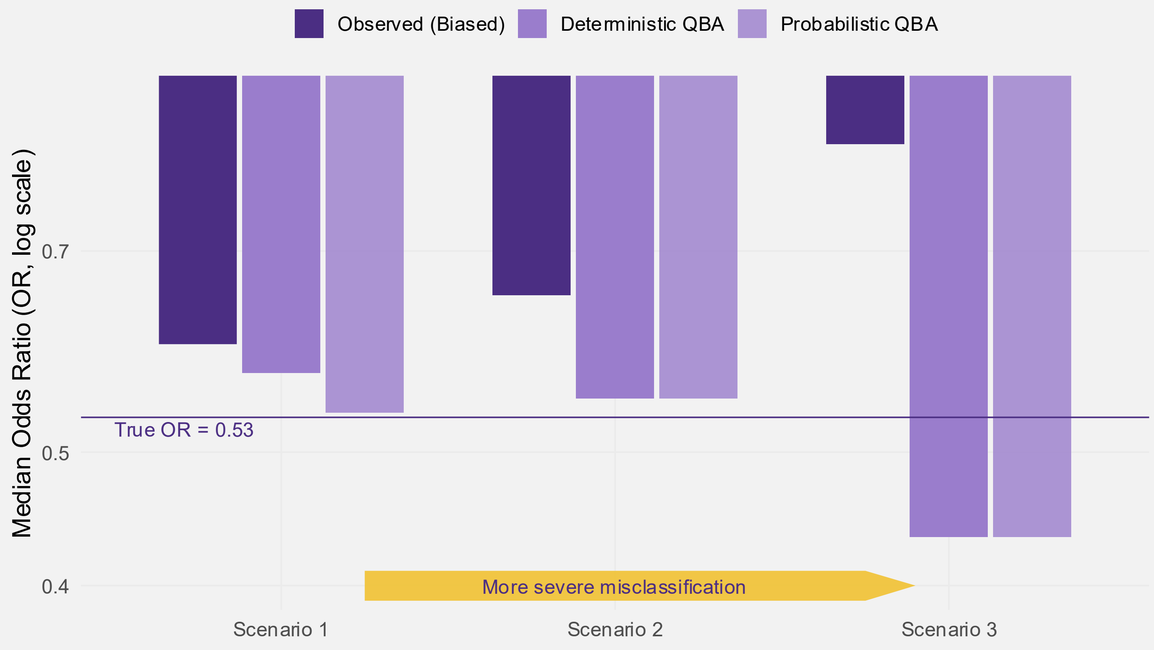
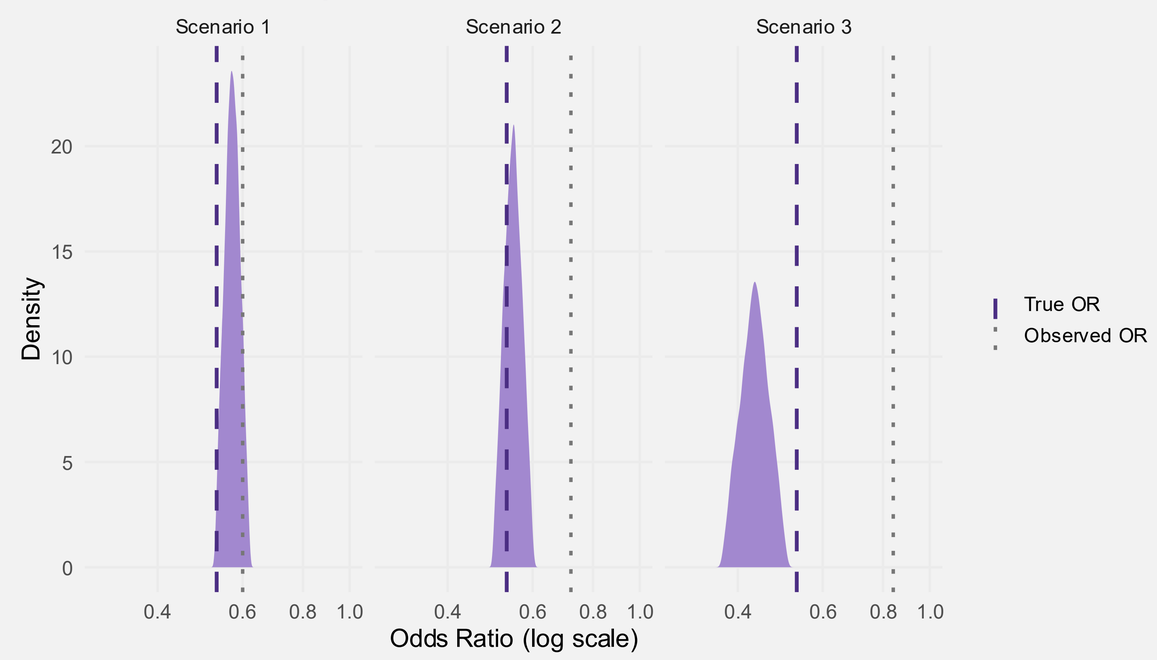


Figure 3. Probabilistic QBA (systematic error only): distributions of bias-adjusted odds ratios across misclassification scenarios. Densities are Monte Carlo draws from probsens using priors on sensitivity/specificity; dashed line = true effect (OR = 0.53), dotted line = observed OR).



- **Probabilistic QBA** produced central estimates [**Figure 2**] close to the true effect **(median ORs ≈0.43–0.57)** while also generating **scenario-specific distributions** of adjusted ORs [**Figure 3**]. These distributions show how uncertainty in sensitivity and specificity propagates into treatment effect estimates: corrected effects remain centered near the truth but with wider intervals.
- Following correction with QBA, Ratio of Odds Ratios ranged between 0.81–1.08 and 0.87–1.06 for deterministic and probabilistic QBA, respectively [**Table 2**].

Table 2. Simulated and bias-adjusted odds ratios (OR) and ratios of odds ratios (RoOR) across misclassification scenarios.

Approach	Scenario 1	Scenario 2	Scenario 3
True effect	OR = 0.53	OR = 0.53	OR = 0.53
Before correction (observed)	OR = 0.60, RoOR = 1.13	OR = 0.72, RoOR = 1.36	OR = 0.84, RoOR = 1.58
After deterministic QBA (fixed Se/Sp)	OR = 0.43, RoOR = 0.81	OR = 0.50, RoOR = 0.94	OR = 0.57, RoOR = 1.08
After probabilistic QBA (systematic only, medians)	OR = 0.46, RoOR = 0.87	OR = 0.51, RoOR = 0.96	OR = 0.56, RoOR = 1.06

Discussion & Conclusion

- **Outcome misclassification** in RW external-control comparisons **meaningfully biases estimated effects** even when misclassification is modest.
- **Deterministic QBA**, using fixed sensitivity/specificity, **substantially reduces this bias** and recovers ORs close to the simulated truth across scenarios.
- **Probabilistic QBA** treats sensitivity/specificity as distributions, producing similar central estimates while **explicitly conveying parameter uncertainty** via Monte Carlo simulation, offering a transparent way for decision-makers to assess robustness of treatment effects under parameter uncertainty.
- Probabilistic QBA can further **incorporate random error from sampling variability** beyond the systematic error correction.
- **Recommendations**: pre-specify QBA in SAPs; report observed and bias-adjusted effects and ratio-of-ORs or other relevant measures; examine systematic-only and systematic and random uncertainty to inform decision makers.

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Abbreviations

HTA, health technology assessment; OR, Odds Ratio; Se, sensitivity; Sp, specificity; QBA, quantitative bias analysis; SAP, statistical analysis plan; RW, real-world; RoOR, ratio of odds ratios;

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