AMS Advanced Medical Services

A Standardized Framework

Acceptance of Non-Randomized Evidence from Real-World Data in HTA

Insights from EU HTA Methodology & German Practices

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INTRODUCTION

The EU HTA guidelines acknowledge the relevance of non-randomized evidence (NRE) from real-world data to address evidence gaps when more robust evidence is unavailable. A likely scenario in EU HTA, as comparative evidence for multiple PICOs has to be provided.

However, the absence of randomization necessitates robust methods to mitigate confounding bias. Among available methods, propensity score (PS) techniques are particularly emphasized for addressing confounding in effect estimation.

Challenges

Although the EU HTA guidelines outline criteria on how to adjust for bias using PS methods, uncertainty remains regarding acceptance of NRE in Joint Clinical Assessments (JCA) and the required level of rigor.

German HTA practices in the context of routine practice data collection (RPDC) offer valuable insights as NRE is already integrated into HTA processes with rigorous methodologies.

METHODS

- **Review** of EU HTA and German HTA (IQWiG) **methodological guidelines.**
- **Comparative Analysis** of requirements for NRE evaluating differences in methodological rigor and acceptance thresholds with a **focus** on the evaluation of confounding bias adjustment by **PS methods**.
- **Case Study** Examination of Germany's RPDC framework and its implications for HTA acceptance standards, based on insights from published statistical analysis plans.

CONCLUSION

While EU guidance on NRE remains high-level and offers a certain amount of freedom in method choice, learnings from German RPDC may help inform analysis strategy for successful submission of NRE analyses in EU HTA. In any case, a well-justified, prospectively planned analysis strategy is crucial.

Abbreviations

ATE: average treatment effect; ATT: average treatment effects among the treated; IQWiG: Institute for Quality & Efficiency in Health Care; JCA: joint clinical assessment; MAIC: matching adjusted treatment comparison; ML NMR: multilevel network meta-regression; NMA: network meta-analysis; NRE: non-randomized evidence; PS: propensity score; RPDC: routine practice data collection; SD: standard deviation; STC: simulated treatment comparison

Type of Treatment Comparison

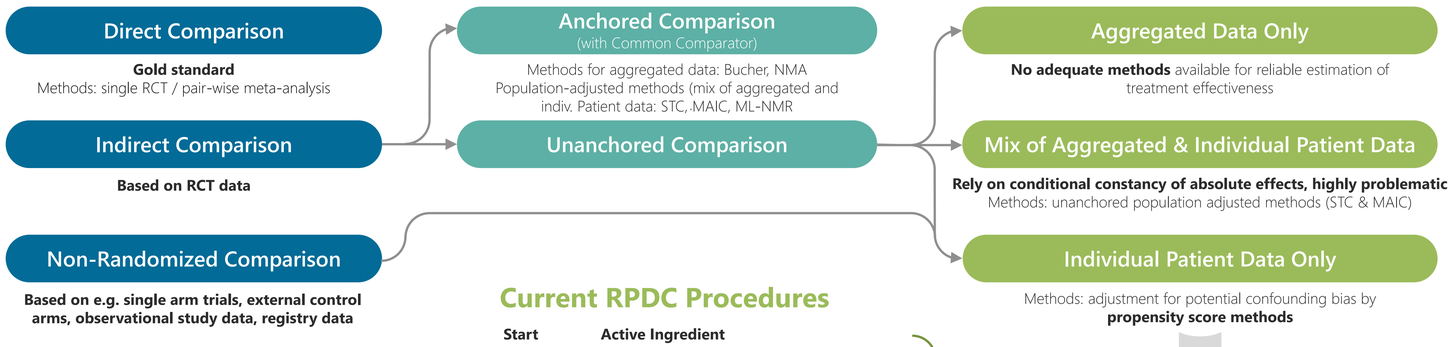

Figure 1 Flow Chart
When to consider NRE according to HTA CG methodological guidelines.

Current RPDC Procedures

	Start	Active Ingredient
1	01 Feb 22	Onasemnogene abeparvovec (Zolgensma®)
2	21 Aug 23	Brexucabtagene autoleucel (Tecartus®)
3	30 Aug 24	Etranacogene dezaparvovec (Hemgenix®)
4	30 Aug 24	Valoctocogene roxaparvovec (Roctavian®)
5	30 Oct 24	Risdiplam (Evrysdi®)

Figure 2 Analysis Table
EU HTA & German methodology on NRE & German use cases from RPDC.

	Methodology for the Use of NRE in EU & German HTA		German Use Cases
	Consensus	Differences	RPDC SAP Assessments
Method for Confounder Adjustment	Various methods listed with focus on **PS methods**. Full access to individual patient data needed. No unmeasured confounders; pre-specification of all model covariates.	EU: Covariate selection based on transparent approach GER: Systematic review + clinical expertise to identify confounders and their interactions	Prospective **definition** of complete confounder set [1,2,3,4,5]; **Weighting** by standardized mortality ratios [1]; fine stratification [1,3] inverse probability of treatment (IPTW) [3,4,5]; **PS matching**: [2]
Positivity	All included patients must be eligible for all treatment options defined by research question.	EU: Violations include contraindications to one of treatments; PS near 0/1 GER: Eligibility described and evaluated in inclusion criteria	**Inclusion/exclusion criteria** were adjusted to ensure positivity [2]
Overlap	Sufficient overlap of PS distributions between groups required.	EU: Visually determined (histograms, density plots) GER: Overlap must additionally be quantified	>50% areal overlap in PS densities sufficient [1,2,5]; **Trimming**: above 5%-/95%- percentiles [3]; based on extreme stabilized IPTW weights; if sufficient overlap remained, PS matching with 0.2*SD caliper [4]
Balance	Sufficient balance with regard to confounders required.	EU: Assessed by absolute standardized differences for each covariate before/after adjustment Acceptable cut-offs for differences range from 0.1 to 0.25 - if above, balance assumption is violated	All confounders must be balanced after adjustment. **Threshold of 0.25** accepted, but noted to be least conservative [2]
Further Criteria			
Missing Data	Transparent reporting of extent/reasons for missing data required. Use of appropriate methods to handle missing data. Assessment of potential impact on results (e.g., via sensitivity analyses).		**No imputation** for missing endpoint data [1]; **Multiple imputation** for confounders [2,3,4,5]; clear criteria for complete case analysis outlined (e.g. if missing ≤5%) if specified as alternative to multiple imputation [2,5]
Inferential Goal	Excluding patients from analysis through trimming/ matching may alter target population: Adjusted populations must be clearly described & assessed for consistency with original research question.	EU: Choice of PS method must align with inferential goal (e.g., average treatment effect [ATE]; average treatment effect among treated [ATT]) GER: Analysis based on treatment policy strategy	ATE is to be estimated, not ATT [3]; Treatment policy estimand as primary analysis [4]; Hypothetical estimand as sensitivity analysis only [4,5]
Shifted Null-Hypothesis	Effect estimates must be large enough to rule out residual confounding.	EU: Effect estimates with confidence interval beyond prespecified/justified threshold from no effect GER: Confidence intervals shall be above dramatic effect thresholds; e.g. RR 5–10	RR=0.5 for sample size calculation [1,3,4]/ for hypothesis testing [2,5]

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FACT SHEET

Non-Randomized Evidence

NRE refers to clinical or real-world data used to compare treatments without using random assignment to groups. Unlike RCTs, NRE arises from study designs where the choice of treatment is influenced by clinical decisions, patient preferences, or other factors.

Common Sources of NRE

- Single-arm trials
- Observational studies (e.g., cohort or case-control studies)
- Real-world data such as registries, electronic health records, or insurance claims
- External control arms or historical controls
- Unanchored indirect comparisons, even if based on separate RCTs

Key Characteristics

- No randomization, so higher risk of bias and confounding
- May better reflect routine clinical practice and broader patient populations
- Increasingly used for evaluation of comparative effectiveness and safety in HTA when RCTs are unavailable or infeasible

Propensity Score Methods

A PS is the probability of receiving a treatment given observed covariates and is estimated by modelling treatment assignment as function of those covariates.

Underlying Assumptions

Conditional exchangeability must be met and can be assessed by investigating the properties of

1. **Positivity** Patients in both groups must be theoretically eligible for both treatments of interest.
2. **Overlap** There must be sufficient overlap in PS between the treatment groups to ensure comparability.
3. **Balance** Populations in the groups being compared must be sufficiently balanced after adjustment for confounding.

References

EU HTA CG (2024). Methodological Guideline for Quantitative Evidence Synthesis: Direct & Indirect Comparisons.

EU HTA CG (2024). Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons.

IQWiG (2024). General Methods. Version 7.0.

IQWiG (2020). Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln, Rapid Report. Nr. 863.

RPDC procedural documents & resolutions: https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/