HTA83

Data Transportability Analyses for Addressing Generalizability Challenges in Non-Local Real-World Evidence (RWE)

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Background & Problem Statement

- Health Technology Assessment (HTA) bodies are increasingly turning to real-world evidence (RWE) to inform decisions, particularly when randomized trials are unavailable – such as in rare diseases, early access settings, or with single-arm trials. In these cases, **non-local** RWE – from other countries or health systems – may be needed to supplement or replace local data when local data are limited.
- However, differences in practice, populations, and infrastructure can limit generalizability of non-local RWE. The **target population**, or the jurisdiction-specific population to whom results are intended to apply, may not be fully represented.
- **Transportability methods** can offer a structured, quantitative approach to adjust non-local RWE for better alignment with the target population, improving its credibility in HTA submissions.

Objectives

- Describe key assumptions required for data transportability in HTA.
- Outline statistical methods used to adjust non-local RWE.
- Discuss how transportability methods can help address common concerns cited by HTA bodies for non-local RWE.

Conceptual Overview & Assumptions

Key Assumptions for Transportability *(Table 1)*

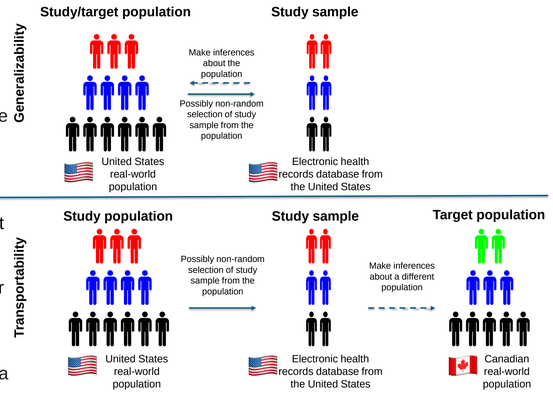
- For non-local RWE to be considered suitable for decision-making, **three core assumptions**[1] must be met to ensure generalizability is feasible:
  - 1) Consistency, 2) Positivity and 3) Conditional Exchangeability.

Table 1: Key assumptions required for valid transportability

Assumption	Description	Possible Threats	Resolution
Consistency	The treatment and outcome definitions must remain the same across the study and target populations.	Different treatment regimens or dosages across jurisdictions (e.g., US vs Japan) lead to differences in treatment outcomes. Inconsistencies in concomitant or subsequent therapies.	Analyze treatment effects by regimen/dosage subgroups. Use structured target trial specifications (i.e., define index date, exposure, and follow-up) to identify variation in treatment versions that may bias outcome comparisons.
Positivity	Requires that individuals in the target population have comparable counterparts in the study population.	Target population includes individuals with no equivalent in study data (e.g., Epidermal Growth Factor Receptor (EGFR) mutation differences between populations in Asia and North America/Europe).	Adjust for underlying biological drivers (e.g., EGFR mutation prevalence) or augment study data with external information. If ignorable, omit variable.
Conditional Exchangeability	Assumes that all key confounding variables and effect modifiers between the study and target populations are properly adjusted for.	Unmeasured variables such as Socioeconomic Status or Quality of Life affect outcomes and differ across jurisdictions. Time-varying confounders not captured in datasets.	Link datasets for missing covariates or use proxies. Perform Quantitative Bias Analysis to assess impact of unmeasured confounding.

Conceptual Overview & Assumptions (cont.)

Figure 1: Conceptual framework distinguishing generalizability and transportability



This diagram illustrates the difference between generalizing from a study population to a broader population (generalizability) versus transporting findings to a different, external population (transportability). Different colours (red, blue, black and green) represent different subgroups with respect to differences in prognosis or treatment response. Green figures represent segments of the target population not represented in the study population, where external data is needed for transportability.

Overview of Methods

Evaluating Generalizability and Transportability Research Trends

- Conducted a PubMed search of studies published on generalizability and transportability in recent years from 2004 to 2023.

Describe Statistical Approaches for Transportability Adjustment *(Table 2)*

- Summarized four statistical methods that can be used to adjust for population differences in transportability analyses:
  - Matching, Weighting, Standardization/Outcome models and Doubly Robust Methods

Targeted Review of HTA Submissions *(Table 3)*

- Reviewed past HTA submissions to Canada's Drug Agency (CDA-AMC) and to the UK's National Institute to Health and care Excellence (NICE) that included RWE as either primary or supportive evidence to assess how transportability analyses might have directly addressed HTA committee concerns regarding external validity.

Table 2: Statistical methods to adjust for differences in non-local RWE

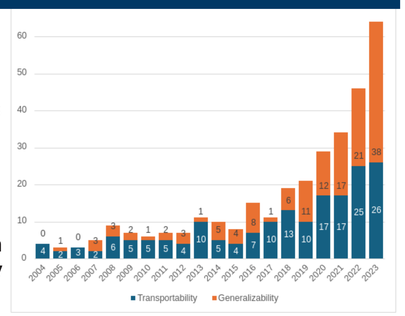
Method	How It Works	Advantages	Limitations	Example
Matching	Rebalance the study sample to match the target population by matching on prognostic variables (e.g., propensity scores).	Simple to explain; transparent assumptions.	Less scalable with high-dimensional or time-varying data.	Stuart 2010
Weighting	Apply weights to the study sample so the covariate distribution mimics that of the target population (e.g., inverse odds of sampling weighting).	Flexible for incorporating time-varying covariates; Covariate balance can be assessed post-weighting.	Less statistically efficient (may require larger sample sizes); Sensitive to outliers.	Westreich et al. 2017; Ling et al. 2022
Standardization / Outcome models	Use stratified or model-based outcome estimation from study sample, then apply predictions across target population covariates (e.g., G-formula).	Statistically efficient; no need to merge datasets; handles positivity violations.	Model misspecification risk; can't test covariate balance directly.	Ramago-palan et al. 2022
Doubly Robust Methods	Combine weighting and modeling. Asymptotically unbiased if either the weight or outcome model is correctly specified.	More robust to model misspecification.	More complex to implement and interpret.	Bang & Robins 2005

Applications & Impact

Intensifying Research on Topic of Generalizability and Transportability Over Time

- The number of PubMed-indexed publications that reference generalizability or transportability concepts has increased from 4 in 2004 to 64 in 2023, reflecting growing academic and regulatory interest.

Figure 2: Trend in published literature on generalizability and transportability



Case Studies and HTA Applications

Table 3: HTA case examples using non-local RWE

Drug	HTA Body	HTA Report #	Key Issue (Data Source & Critique)	Violated Assumptions
Teclistamab	CDA-AMC	PC0332	• External control arm from US RWE (Flatiron). • The data did not reflect Canadian treatment pathways; flagged unmeasured confounding due to differences in prior therapies and standard of care.	Consistency, Positivity, Exchangeability
Elranatamab	CDA-AMC	PC0315	• External control arm using US RWE. • The control population was not representative of Canadian practice, and dosing/treatment regimens varied significantly.	Consistency, Exchangeability
Tepotinib	NICE	TA789	• Single-arm trial with indirect treatment comparisons using US claims/RWE. • Issues with subsequent therapies not aligned to National Health Service practice.	Consistency, Exchangeability, Positivity

Overall Implications for HTA Applications

- In each of the case studies, the application of transportability methods provides a structured framework to:
  - Adjust for clinical and demographic differences.
  - Address key reviewer concerns (e.g., comparator choice, population mismatch).
  - Increase confidence in non-local RWE when local data are limited.

Strengths & Limitations

- **Strengths:**
  - Demonstrates how transportability methods may systematically overcome generalizability challenges faced by non-local RWE in HTA submissions.
  - Case studies illustrate how these methods may quantitatively resolve issues related to consistency and comparator alignment.
  - Timely and relevant: aligns with increasing HTA and regulatory interest.
- **Limitations:**
  - Case studies reflect selected examples and may not be broadly generalizable.
  - Does not evaluate the impact of transportability on HTA decision outcomes.

Conclusions

Transportability analyses offer a systematic approach to improve the relevance and credibility of non-local RWE in HTA submissions. By applying methods such as matching, weighting, and standardization, these techniques aim to better align external control data with local clinical and demographic contexts. This approach may support the credible use of non-local evidence when local data are unavailable or limited in regulatory and reimbursement decisions.

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Disclosures

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