RWD30

APPLYING TRANSPORTABILITY METHODS TO REAL-WORLD DATA: A SCOPING REVIEW

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Introduction

- Real-world data (RWD) has emerged as an additional evidence source for health technology assessment (HTA) agencies. Its importance is apparent in the case of rare diseases, where real-world evidence (RWE) may provide the most robust information available.
- However, the most available or high quality RWD may be derived from a geography that is different to that of the target population. This can introduce uncertainty for the HTA agency as to whether or not results are valid for their population of interest.
- Applying transportability methods to analysis using a suitable data source may help to reduce this uncertainty. These methods provide an estimate of what the treatment effect would have been had the original study been conducted in the target population by adjusting for differences between the source and target population.

Objectives

- To conduct a scoping review to identify and describe studies applying transportability methods using RWD.

Methods

- A search strategy was implemented in PubMed/Medline, Cochrane, and Google Scholar using keywords related to transportability and real-world data. Reference lists were also scanned for relevant full-text articles applying transportability methods in real-world contexts. Studies transporting from randomised controlled trial (RCT) to RWD, or RWD to RWD, were included.
- Studies applying methods to synthetic data or assessing the generalisability of findings without applying transportability methods were excluded.
- Data were extracted from the included articles on the transportability scenario considered, transportability method used, and disease area examined.
- Study characteristics and findings were summarised and presented in tabular form.

Results

- A total of 491 articles were retrieved, of which 7 were eligible for inclusion (**Figure 1**)
- Most of the included articles (4 out of 7)[1-3,6] transported an estimate (e.g., treatment effect or overall survival outcome) from an RCT to a target population identified in RWD. Two studies[5,7] transported an estimate from one RWD population to another, and one study[4] transported estimates from both RCT to RWD and RWD to RWD.

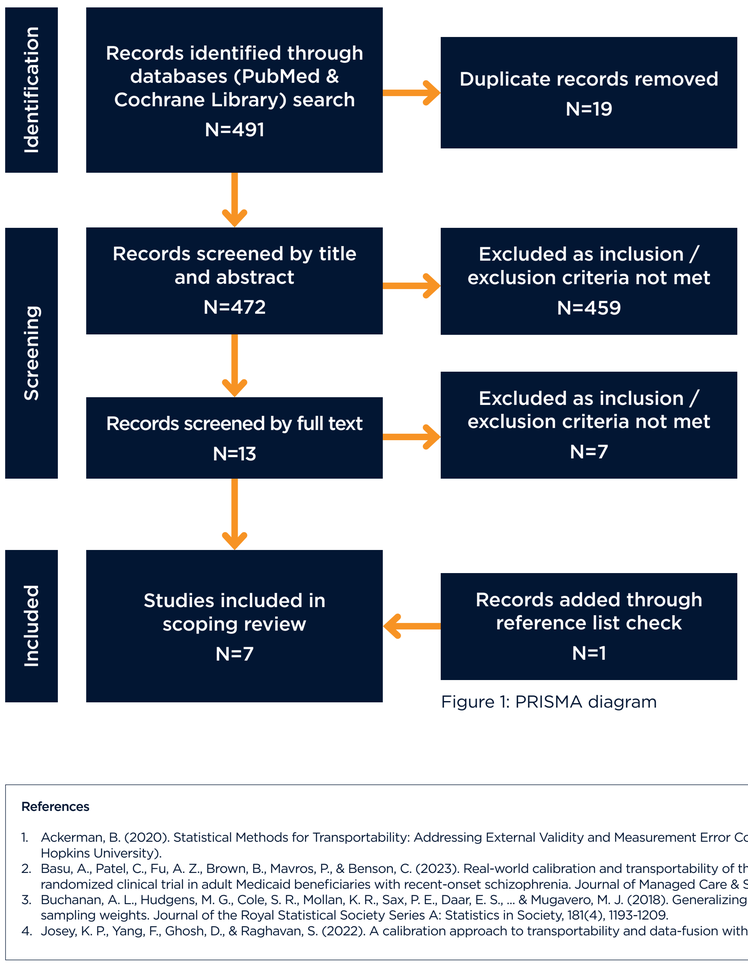


Figure 1: PRISMA diagram

Table 1: Main characteristics of included studies

Author, Year, First Author Country	Population and Setting	Study Measures	Transportability Method	Results/Conclusions
1. Ackerman 2022, US*	**Study sample:** 810 randomised participants in the PREMIER lifestyle intervention trial **Target populations:** 1. 2,180 adults sampled from the National Health and Nutrition Examination Survey (NHANES) with above-optimal blood pressure (BP) meeting trial inclusion criteria 2. 2,180 adults in NHANES sample weighted with survey weights to reflect all U.S. adults with above-optimal BP	**Exposure:** Lifestyle intervention treatment for blood pressure reduction relative to standard care **Outcome:** Change in systolic blood pressure between baseline and 6-month study follow-up **Transported outcome:** Absolute treatment effect: difference between treatments arms in mean BP change from baseline to follow-up	Inverse odds of sample membership weighting incorporating survey weights	The treatment effect in the RCT sample for the lifestyle intervention vs. standard of care (difference in mean change of -4.66, 95% CI -6.10, -3.23) was very similar to the transported estimates in the unweighted and weighted target samples (exact numbers not reported in text).
2. Basu et al., 2023, US	**Study sample:** 132 participants with a diagnosis of schizophrenia in the Disease Recovery Evaluation and Modification (DREaM) RCT **Target population:** 1,000 individuals identified through Medicaid Managed Care (MMC) dataset with a schizophrenia diagnosis between 2015-2019	**Exposures:** Three treatment strategies including oral antipsychotics (OAP) -OAP, OAP- paliperidone palmitate (PP) and PP-PP **Outcomes:** 18- and 30-month psychiatric hospitalisations identified by ICD-9 codes or ICD-10 codes, and reported as the primary diagnosis during hospitalisation **Transported outcome:** Absolute difference: the (cumulative) number of psychiatric hospitalisations per patient	Inverse probability weighting	The transported treatment effect for OAP-OAP treatment was comparable to the original observed treatment effect in MMC cohort; however, the transported treatment effects for OAP-PP and PP-PP demonstrated reduced psychiatric hospitalizations per patient over 18 months (-0.77, 95%CI: -1.08, -0.47 and -0.83, 95%CI: -1.15 to -0.60, respectively). The transported treatment effects were consistent when extrapolated from 18-months to 30 months.
3. Buchanan et al., 2021, US	**Study samples:** 1. 200 women from AIDS Clinical Trial Group (ACTG) 320 2. 1,156 men & women from ACTG320 3. 322 women from ACTG A5202 4. 1,857 men & women from ACTG A5202 **Target populations:** 1. 493 women from the Women's Interagency HIV Study (WIHS), which is considered to be a representative sample of all women living with HIV in the USA 2. 6,158 men & women from the Center for AIDS Research Network of Integrated clinical Systems (CNICS), which is considered to be a representative sample of all people living with HIV in the USA 3. 1,012 women from the WIHS 4. 12,302 men & women from the CNICS	**Exposures:** 1. For ACTG 320: Adding protease inhibitor (PI) as an HIV treatment with two nucleoside analogues 2. For ACTG A5202: Abacavir-lamivudine (ABC-3TC) or tenofovir disoproxil fumarate-emtricitabine (TDF-FTC) pus efavirenz or ritonavir-boosted atazanavir **Outcomes:** (1) Differences in mean change in clusters of differentiation 4 (CD4) cell count from baseline to week 4 for ACTG320 and its corresponding target population (2) Differences in mean change in CD4 cell count from baseline to week 48 for A5202 and its target population **Transported outcome:** Absolute difference: mean change in CD4 cell count from baseline to week 4 or 48	Inverse probability of sampling weighting	For HIV affected women, the transported estimates indicated that the within-trial result underestimated the effects of PIs in HIV-infected women in the USA (46 vs. 24, respectively); the weighted estimates (differences in mean change of CD4 cell count from baseline to week 48 for A5202 and target population) also indicated a much stronger protective effect of ABC-3TC (vs. TDF-FTC) in the target population of all HIV-infected women in the USA (35 vs. 1, respectively). In the target population of all women and men living with HIV in the USA, the weighted estimates were comparable with the within-trial effect estimates (17 vs. 19 in terms of mean change of CD4 cell count from baseline to week 4), suggesting that both the effect of PIs and the effect of ABC-3TC (versus TDF-FTC) from the trials may be transportable to all people living with HIV in the USA.
4. Josey et al., 2022, US	**Study samples:** 1. 84,003 patients from 2004-2009 cohort of Veterans Affairs (VA) population who initiated the first-line diabetic medication metformin monotherapy 2. 29,447 patients from 2004-2009 cohort of VA who initiated the first-line diabetic medication sulfonylurea 3. 2,368 diabetes patients from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) clinical trial, of which 1,185 receiving insulin provision treatment and 1,183 receiving insulin sensitization treatment **Target population:** 1. 100,612 patients from 2010-2014 cohort of VA who initiated the first-line diabetic medication metformin 2. 11,736 patients from 2010-2014 cohort of VA who initiated the first-line diabetic medication sulfonylurea 3. 30,393 patients from 2010-2014 cohort of VA who received either insulin provision or insulin sensitization therapy after diagnosis with diabetes mellitus	**Exposure:** (1) metformin monotherapy (2) sulfonylurea (3) Insulin sensitization treatment relative to insulin provision treatment strategy for treating diabetes **Outcome:** (1 & 2) 1-year, 2-year and 5-year all-cause mortality after first prescriptions (3) All-cause mortality 3 years after randomisation **Transported outcome:** Absolute difference: risk difference	Calibration approach incorporating balancing weights and sampling weights	The transported treatment effect of sulfonylurea and metformin in terms of risk differences in all-cause mortality suggested that metformin was associated with lower mortality than sulfonylurea treatment, which was consistent with the original findings from study sample and target population (e.g. risk differences in 5-year mortality between sulfonylurea and metformin: 4.0%, 95%CI: 3.4%, 4.6%). The transported estimate indicated a 2.4% (95%CI: -4.1%, 8.8%) increase in mortality risk among patients receiving insulin provision therapy compared to those who receiving insulin sensitization therapy, which was aligned with the observations in the VA cohort.
5. Ling et al., 2022, US	**Study sample:** 752 patients with estrogen receptor positive (ER (+)), human epidermal growth factor receptor negative (HER2 (-)) metastatic breast cancer receiving second-line therapy identified from the Flatiron Health database **Target population:** 3,109 patients who were eligible to receive first-line treatment in the same database	**Exposure:** Fulvestrant-palbociclib relative to letrozole-palbociclib **Outcome:** Progression free survival within 3 years of follow-up after start of therapy **Transported outcome:** Relative treatment effect: hazard ratio (HR)	Inverse probability of selection weighting	The transported HR for the effect of fulvestrant-palbociclib relative to letrozole-palbociclib in the target first-line population was consistent to the HR estimated in the original second-line population: 1.12 (95% CI 0.90, 1.39) vs. 1.11 (95% CI 0.93, 1.32).
6. Mollan et al., 2021, US	**Study sample:** 3,949 randomised participants from 4 AIDS Clinical Trials Group (ACTG) RCTs living with HIV and initiating first-line antiretroviral therapy (ART) **Target population:** 8,291 trials-eligible US adults initiating ART identified in RWD	**Exposure:** Efavirenz-containing ART regimen relative to efavirenz-free regimens **Outcome:** Incidence of and time to suicidal thoughts/behaviours during study follow-up as identified from adverse event reports and death data **Transported outcomes:** Absolute (non-comparative) outcome: incidence rates (IRs) in each treatment group Relative treatment effect: HRs Absolute treatment effect: incidence rate differences (IRDs)	Inverse odds of participation weighting	Transported IRs of suicidal thoughts/behaviours in the target population were higher for both treatment groups than the rates in the RCT sample.** The transported IRD for efavirenz-containing regimen vs. efavirenz-free regimens in the target population was similar to the one in the RCT sample: IRD of 5.4 (95% CI -0.4, 11.4) per 1,000 person-years vs. 5.1 (95% 1.6, 8.7). The transported HR in the target population was attenuated compared to the HR in the RCT sample: 1.8 (95% CI 0.9, 4.4) vs. 2.3 (95% CI 1.2, 4.4).
7. Ramagopalan et al., 2022, Switzerland	**Study samples:** 1. 8,447 patients receiving first-line chemotherapy for advanced non-small cell lung cancer (NSCLC) identified from the Flatiron Health (FH) database 2. 1,653 patients receiving first-line pembrolizumab from the same NSCLC cohort identified from the FH database **Target populations:** 1. 1,476 patients who initiated first-line chemotherapy for advanced NSCLC identified using population-based data in Canada 2. 287 patients who initiated first-line pembrolizumab for advanced NSCLC identified using population-based data in Canada	**Exposures:** Two treatment strategies: first-line chemotherapy and first-line pembrolizumab **Outcome:** Overall survival (OS) over 60 months of follow-up for first-line chemotherapy and over 30 months for first-line pembrolizumab **Transported outcome:** Absolute (non-comparative) outcome: OS in each treatment group	Outcome regression approach	For first-line chemotherapy, transported OS closely approximated the unadjusted Kaplan-Meier estimates in the target population (mean absolute difference of 0.56% over 60 months of follow-up). For first-line pembrolizumab, the transported OS was initially higher but eventually converged with the Kaplan-Meier curve (mean absolute difference of 4.54% over 30 months of follow-up). The unadjusted Kaplan-Meier estimates for each treatment group in the original study sample and target population were similar, especially for first-line pembrolizumab.

Note: *Article included two other case studies applying similar transportability methods. **IRs not reproduced here due to space constraints

Figure 2: Distribution of included studies across disease areas

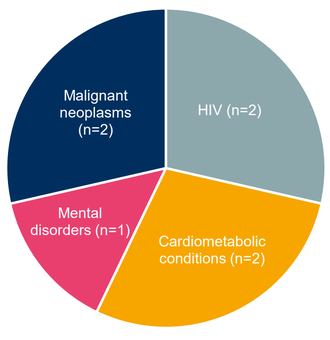
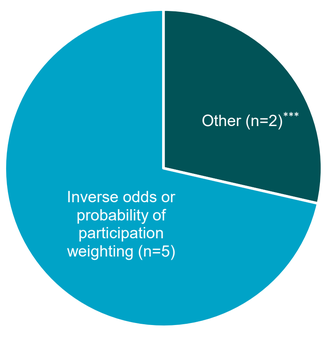


Figure 3: Transportability methods utilised in the included studies



***Other category included pooled logistic outcome model and data-fusion approach using calibration weights

- The included articles span various clinical areas, encompassing HIV, malignant neoplasms, and mental disorders (**Figure 2**). The predominant method employed to transport an estimate from a source population to the target population was inverse odds of probability weighting, which was utilised in 5 out of the 7 studies (**Figure 3**).
- Across the included studies, the transported results tended to be very similar in terms of magnitude and direction to the results in the original study sample and/or observed results in the target population (if available). However, in some cases, statistically significant estimates became non-significant when transported to the target population. Only one study[7] validated the transported estimates by comparing them to the observed estimates in the target population.

Conclusions

- The evidence base on real-world applications of transportability methods is limited. More examples of transporting results from RWD studies are required to support the use of these methods for decision making in HTA.
- In the meantime, HTA agencies require guidance to assess and manage submissions that utilise RWD from outside of their country to prevent unnecessary delay in decisions and, ultimately, treatment access.

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