Issues in the Design and Analysis of Registry-Based Studies for Regulatory and HTA Purposes

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BBS/EFSPI Meeting on "Registry Studies and Health Technology Assessment (HTA)"
Virtual Seminar, Thursday, June 23, 2022

Disclosure

- Jinma Ren and Friedhelm Leverkus are employees and stockholders of Pfizer Inc.
- This presentation reflects their personal views and not the views of Pfizer or any other organization.

Contents

- Regulatory guidance and acceptability for registry-based studies
- Considerations for the design and analysis of studies with registry-based external control
- Impact of unmeasured confounders in studies with registry-based external control
- Registry-based studies in HTA process

Regulatory guidance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on registry-based studies

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Resource: Guideline on registry-based studies (europa.eu)

FDA U.S. FOOD & DRUG ADMINISTRATION

November 2021
Real World Data/Real World Evidence (RWD/RWE)

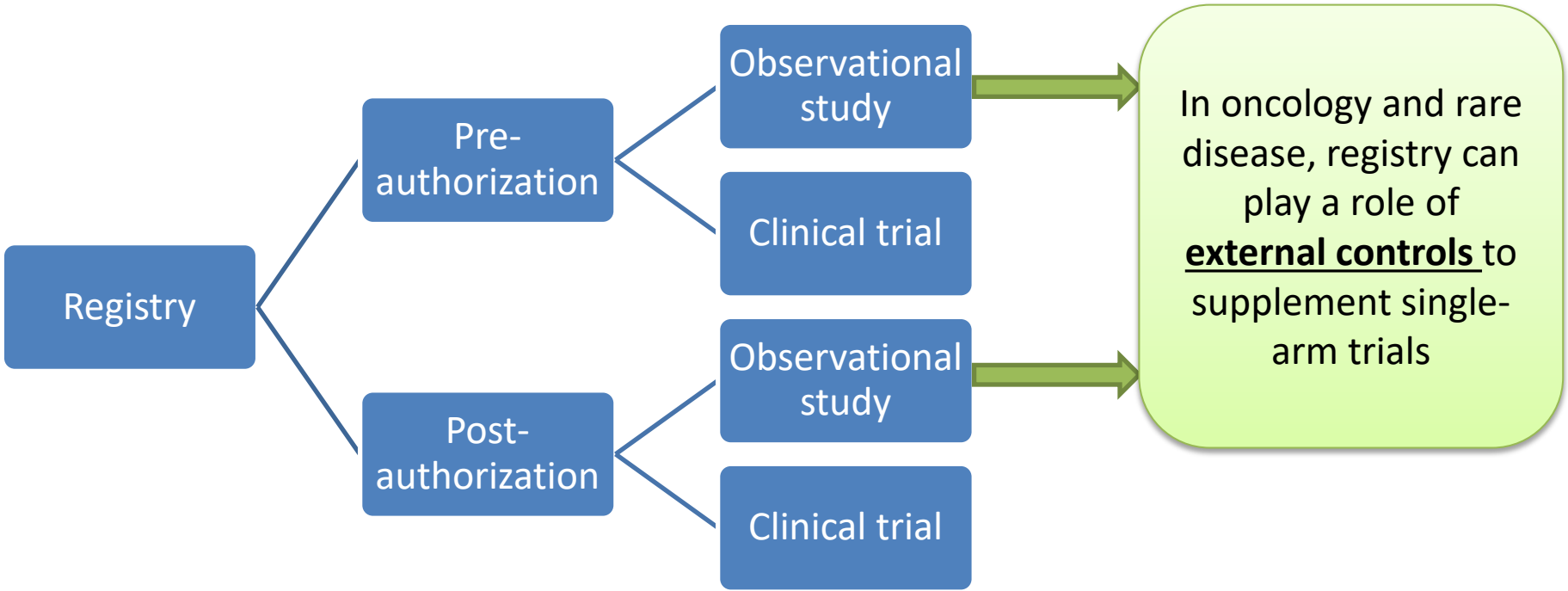
Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

Resource: https://www.fda.gov/media/154449/download

Use of registry-based studies



Regulatory guidance for using external control

The Use of External Control Design is Most Persuasive When:

(Note: In many cases not all of these themes will be met and FDA will consider the totality of evidence)

	FDA Guidance	ICH E10
• It is not possible and/or ethical to run a placebo control[1,2,4]	✓	✓
• There is no available therapy for comparison (usually the case for rare diseases)	✓	
• The disease progression is well understood or predictable[1,4,9]	✓	✓
• The outcome measure is objective[1,3,4–9,11]	✓	✓
• The treatment effect		
- is large/dramatic[1–4,9,11]	✓	✓
- is not affected by patient or investigator motivation or choice of subjects for treatment[3]	✓	
- has a strong temporal association with administration of the investigational product[3,4]	✓	
- is consistent with the expected pharmacological activity based on the target and perhaps shown in animal models[3]	✓	
- is measured in a manner that reasonably manages and minimizes bias[3]	✓	
• The control population closely resembles the treatment group including setting for and manner of treatment (i.e. standard of care)[1,2,4,8,10,11]	✓	✓
• Covariates influencing the outcomes of the disease are well characterized[1]		✓
• The control group is a well-documented population with access to individual patient records[1]		✓
• The results provide compelling evidence of a change in the established progression of disease[2]	✓	

The Use of External Control Design is Most Persuasive When:

- No feasible placebo control
- No available therapy for comparison
- Predictable disease progression
- Objective outcome measure
- Large treatment effect
- Similar population and setting

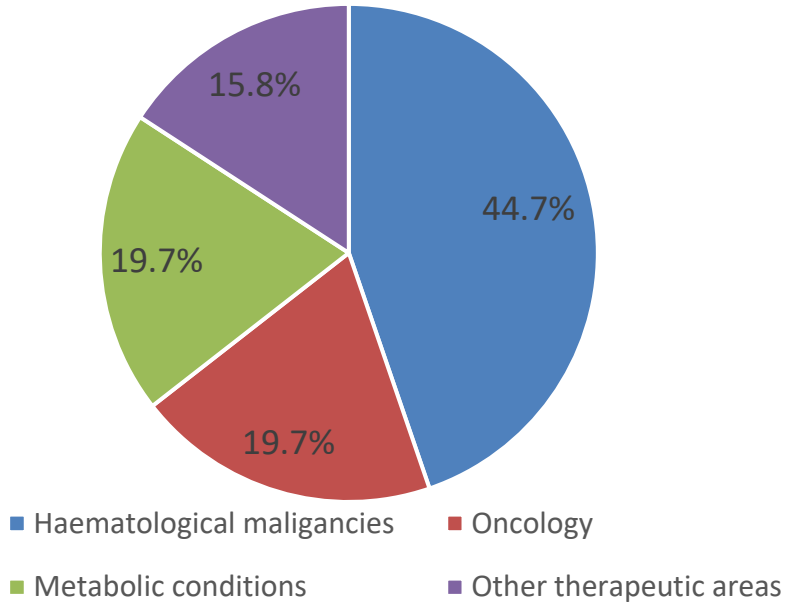
The use of an external control instead of an internal control in a complex clinical trial, if not scientifically appropriately documented as part of the clinical trial application may prevent trial authorisation.

Jahanshahi 2021. doi: 10.1007/s43441-021-00302-y

Regulatory approvals for non-RCT trials

Analysis of EMA and FDA approvals 1999-2014

- 76 unique indications were granted without RCT results



What role can a registry play in the non-RCT trials?

External control

Hatswell AJ, Baio G, Berlin JA*, et al. BMJ Open* 2016;**6:**e011666.

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A four-step approach to the design and analysis

- Registries are commonly used in the externally controlled studies
- The 4-step approach broadly covers all external control studies (e.g., supplemented SAT and augmented RCT)
- Step 4 is applicable only to augmented RCTs, not supplemented SATs
- The dotted line from Step 3 indicates that this step may be re-ordered or implemented iteratively

Gray 2020. doi: https://doi.org/10.1007/s40264-020-00944-1

Step 1a: Access feasibility

- **Do we need to use registries for an external control?**
  - Is RCT feasible and ethical?
  - Is a registry available?
  - Does the registry pass the quality check?

- **Pocock's criteria for external control**

Exchangeability criteria	Potential bias if non-exchangeable
Subject to the same eligibility criteria	Selection bias/ confounding
Distribution of important patient characteristics	Confounding, information bias
Identical treatment	Positive treatment bias
Treatment outcome(s) evaluated in the same manner	Information bias
Collected recently	Surveillance bias, unmeasured confounding
Collected in the same setting, by the same investigators	Unmeasured confounding

Ghadessi 2020. doi: 10.1186/s13023-020-1332-x
Gray 2020. doi: https://doi.org/10.1007/s40264-020-00944-1

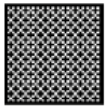
Step 1b: Identify key factors affecting bias

- Literature review, expert opinion and previous data
  - All potential confounders
- Unmeasured confounders
  - Try to include main confounders
  - Use covariates that are associated with unmeasured confounders

For each variable, it should be assessed in the RWD whether:

The variable is collected identically to the RCT and is fully available.

The variable is partially missing or prone to misclassification or measurement error; bias analysis should be considered (Step 3).



The variable is not available or collected in a way completely insufficient to the needs of the study; consider whether the study is feasible without this variable.

Gray 2020. doi: https://doi.org/10.1007/s40264-020-00944-1

Step 2: Adjust for potential confounders

	Data type	Methods	
Frequentist	**Individual data**	*G-computation*	One of Robins' g methods
		Weighting (propensity score-based)	• Inverse probability of treatment weighting (IPTW) • Overlap weighting (OW) • Standardized mortality/morbidity ratio (SMR)
		Doubly robust estimator	• Targeted Maximum Likelihood Estimation (TMLE)
		Matching/stratification	• Variable matching • Propensity score matching/stratification
	Summary data	*Network analysis, simulated treatment outcome (STC), or matching-adjusted indirect comparison (MAIC)*	
Mostly Bayesian	**Individual/summary data**	*Meta-analytic combined (MAC), meta-analytic predictive (MAP)*	

Ghadessi et al. 2020. doi: 10.1186/s13023-020-1332-x;
Naimi, Cole, and Kennedy 2017. 'An introduction to g methods', *Int J Epidemiol*, 46: 756-62.
Schuler MS, Rose S. Am J Epidemiol. 2017 Jan 1;185(1):65-73. doi:10.1093/aje/kww165.

Step 3: Assessing the threat of bias

- Quantitative Bias Analysis (QBA)

Analytical technique	Treatment of bias parameters	Number of biases analysed	Output	Combines random error?	Computationally intensive?
Simple sensitivity analysis	One fixed value assigned to each bias parameter	One at a time	Single revised estimate of association	Usually no	No
Multidimensional analysis	More than one value assigned to each bias parameter	One at a time	Range of revised estimates of association	No	No
Probabilistic analysis	Probability distributions assigned to each bias parameter	One at a time	Frequency distribution of revised estimates of association	Yes	Yes
Multiple bias modelling	Probability distributions assigned to bias parameters	Multiple biases at once	Frequency distribution of revised estimates of association	Yes	Yes

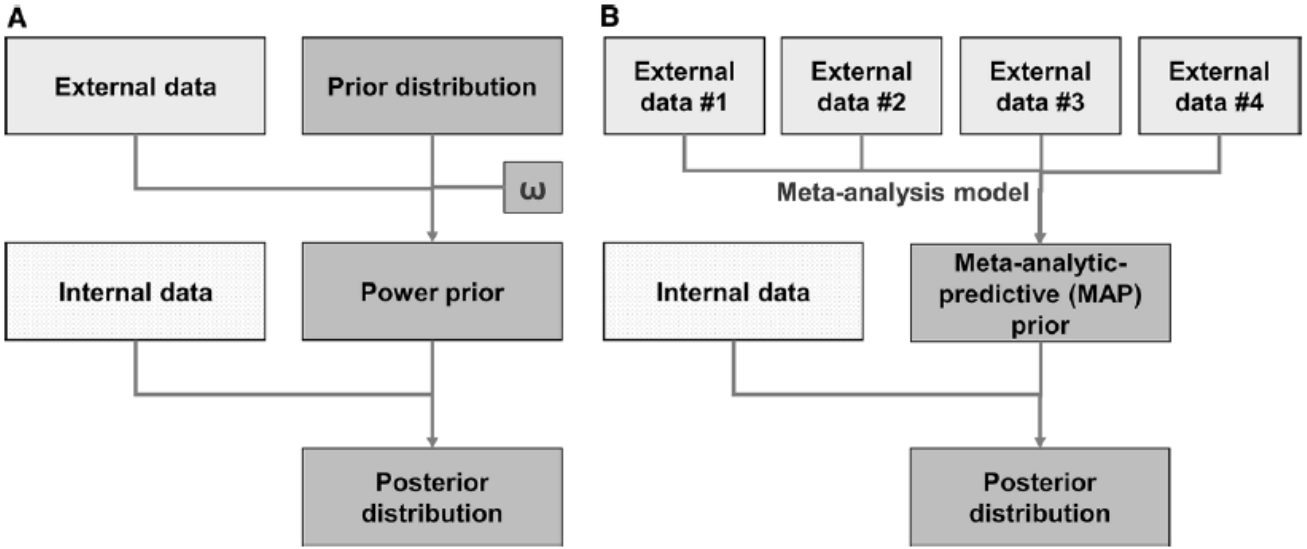
Reprinted from Lash, Fox and Fink (2009).[15]

- Report E-value: indicates how strong an unmeasured confounder is needed to fully explain away the treatment effect

Lash TL, et al. International Journal of Epidemiology. 2014, 1969-1985.
VanderWeele TJ, et al. Ann Intern Med 2017 Vol. 167 Issue 4 Pages 268-274

Step 4: Bayesian dynamic borrowing

- Create priors from external comparator data, which can then be applied to the internal control data to ***increase the total power*** of the control group
- Only be applied to augmented RCTs (e.g., N:1 design) and not to supplemented SATs.



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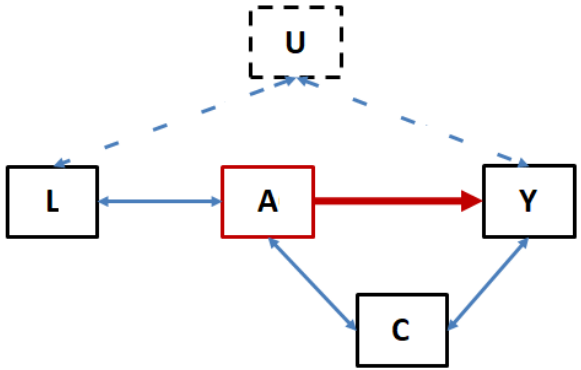
Study design (3 scenarios for unmeasured confounder)

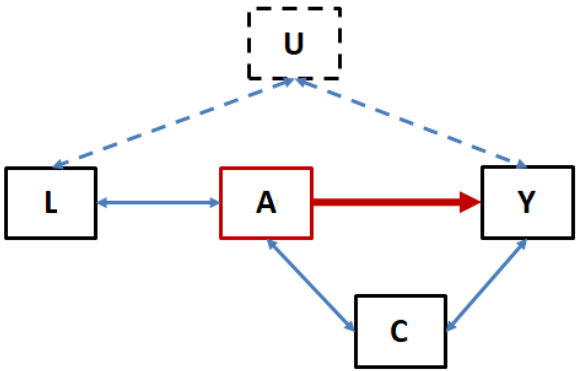
Small confounding

a) Unmeasured confounder *U* associated with *L* and *Y* (*small confounding effect*)



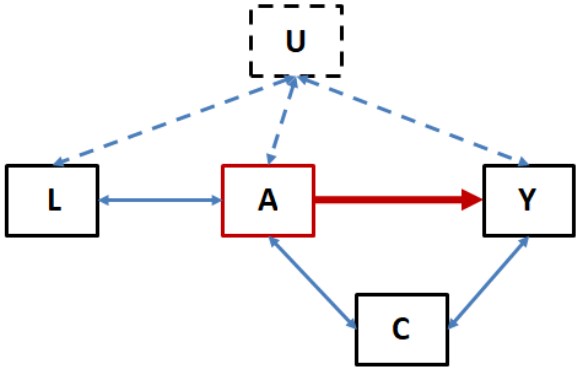
Medium confounding

b) Unmeasured confounder *U* associated with *L* and *Y* (*medium confounding effect*)



Large confounding

c) Unmeasured confounder *U* associated with *L*, *A*, and *Y* (*large confounding effect*)

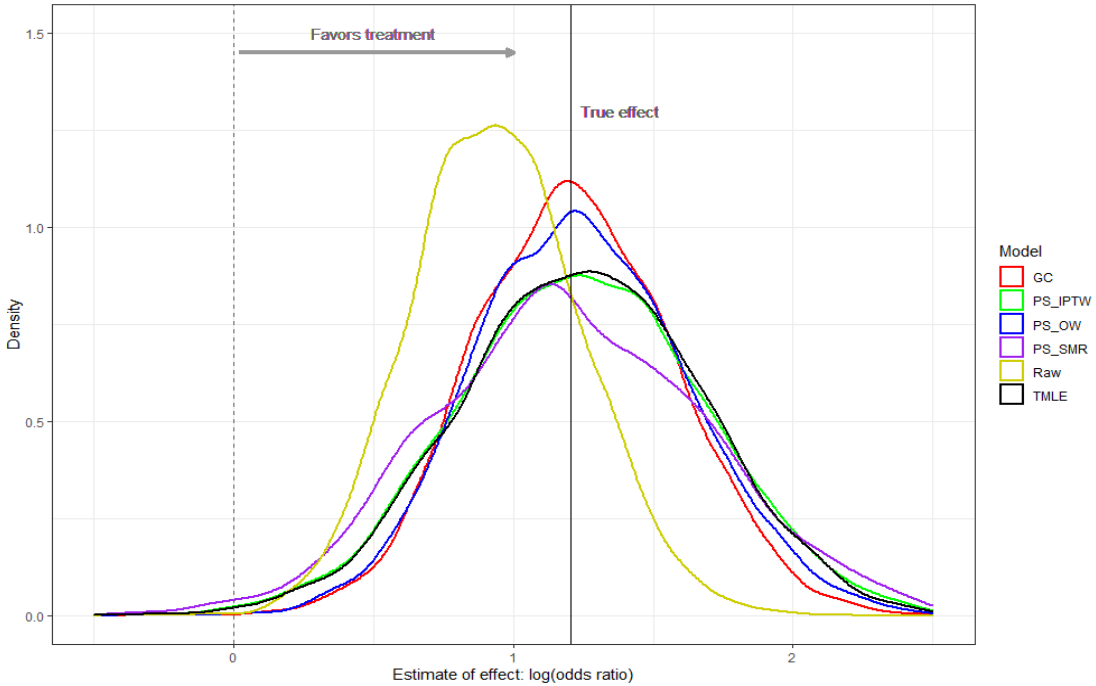


Y : Outcome
A: Treatment at baseline
L : Confounder at baseline
C: Other baseline confounders
U: Unmeasured confounder

Measured causation
Measured association
Unmeasured association

Results (N = 200, Endpoint = binary outcome, Scenario = small confounding)

- **The estimated treatment effects by selected methods were <u>approximately unbiased</u> when the unmeasured confounding was <u>small</u> *(SMD=0.08)***

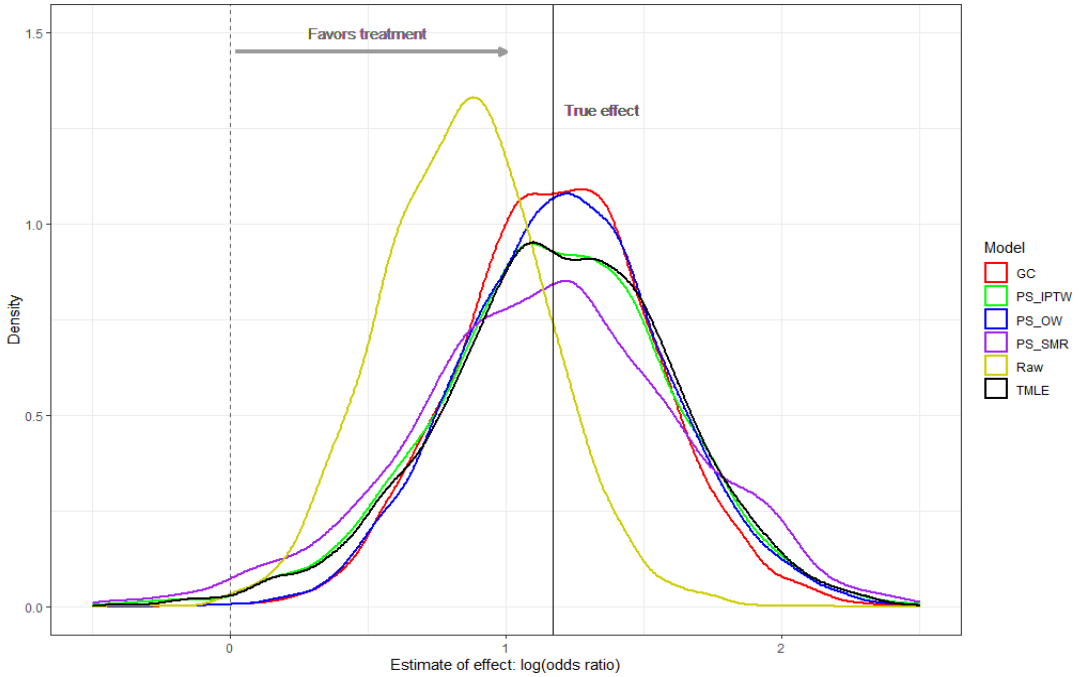


Method	RMSE	Coverage
GC	0.355	0.938
PS_IPTW	0.443	0.836
PS_OW	0.381	0.894
PS_SMR	0.500	0.777
Raw	0.405	0.854
TMLE	0.432	0.974

GC, g-computation; IPTW, inverse probability of treatment weighting; PS-, propensity score-based; RMSE, root mean squared error; SMD, standardized mean difference; SMR, standardized mortality or morbidity ratio; OW, overlap weighting; TMLE, targeted maximum likelihood estimation

Results (N = 200, Endpoint = binary outcome, Scenario = medium confounding)

- **The estimated treatment effects by selected methods were <u>relatively unbiased</u> when the unmeasured confounding was <u>medium</u>** *(SMD=0.16)*

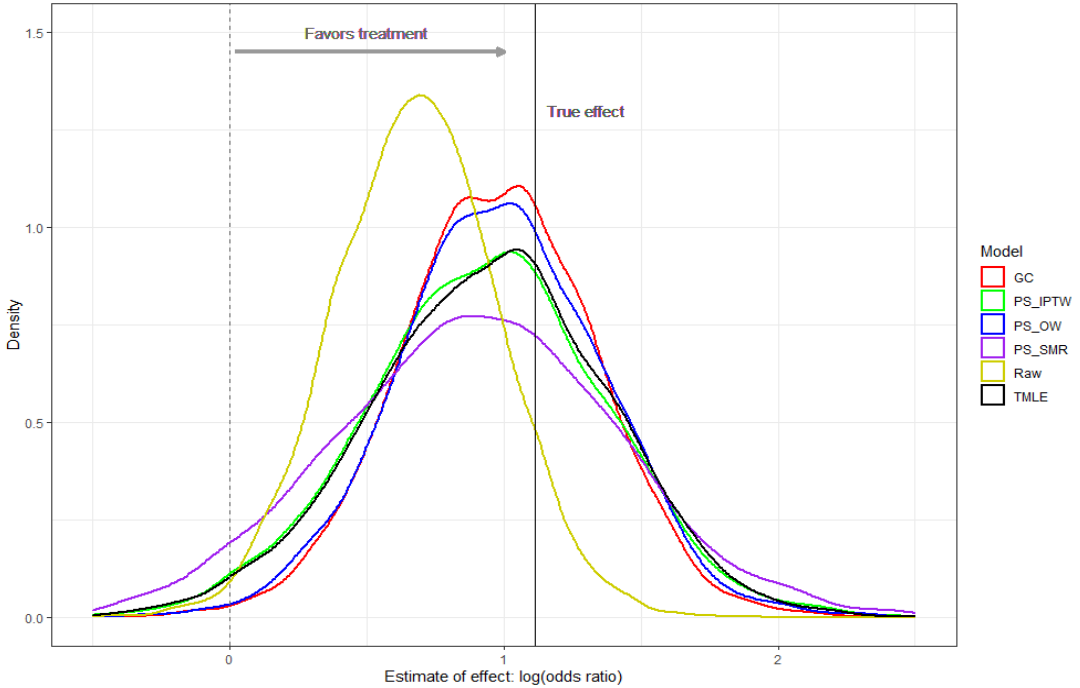


Method	RMSE	Coverage
GC	0.349	0.934
PS_IPTW	0.430	0.848
PS_OW	0.372	0.891
PS_SMR	0.497	0.773
Raw	0.443	0.796
TMLE	0.423	0.974

GC, g-computation; IPTW, inverse probability of treatment weighting; PS-, propensity score-based; RMSE, root mean squared error; SMD, standardized mean difference; SMR, standardized mortality or morbidity ratio; OW, overlap weighting; TMLE, targeted maximum likelihood estimation

Results (N = 200, Endpoint = binary outcome, Scenario = large confounding)

- **The estimated treatment effects by selected methods became <u>biased</u> when the unmeasured confounding was <u>large</u> *(SMD=0.36)***



Method	RMSE	Coverage
GC	0.376	0.917
PS_IPTW	0.470	0.794
PS_OW	0.394	0.867
PS_SMR	0.573	0.703
Raw	0.524	0.687
TMLE	0.462	0.958

GC, g-computation; IPTW, inverse probability of treatment weighting; PS-, propensity score-based; RMSE, root mean squared error; SMD, standardized mean difference; SMR, standardized mortality or morbidity ratio; OW, overlap weighting; TMLE, targeted maximum likelihood estimation

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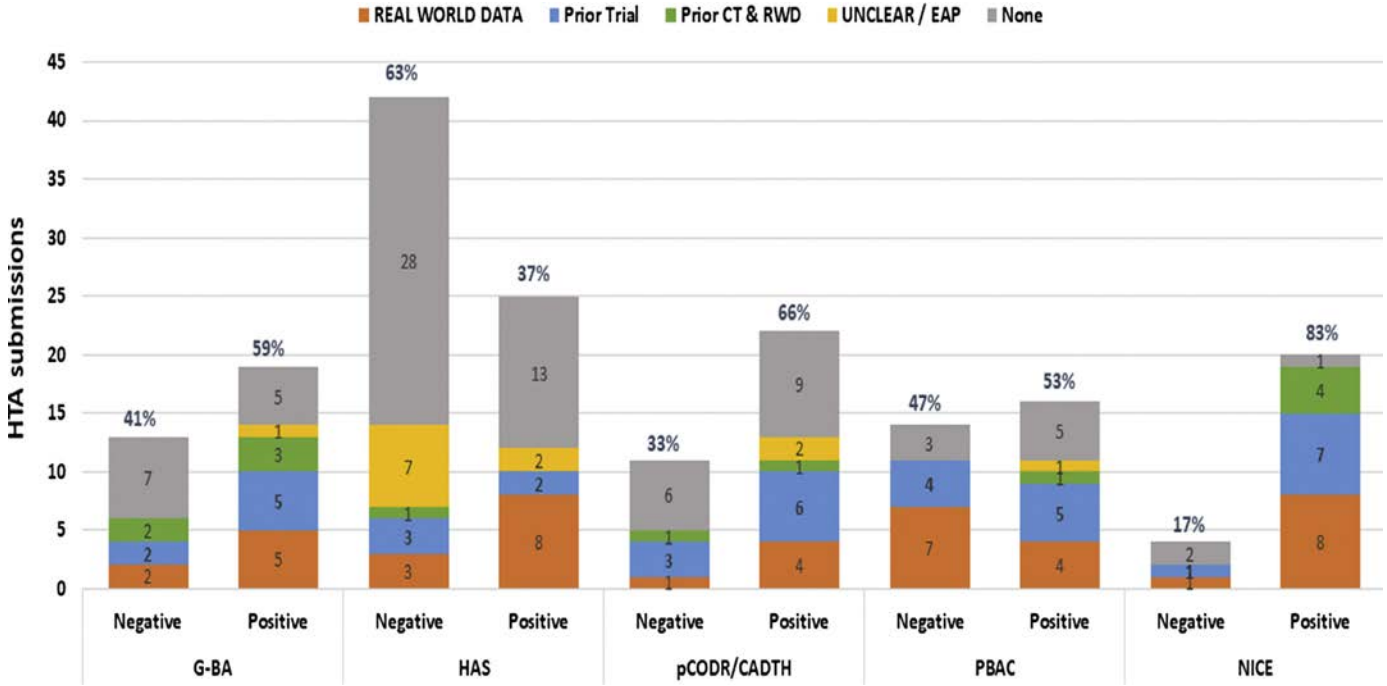
Registry-based studies in HTA process

External Comparator Submissions and Outcomes for Top 5 HTA Bodies by Volume, 2011-2019 (Based on SATs)



- **% positive and negative outcomes for SAT-based HTA submissions within the period 01/2011 to 12/2019**

If appropriate, **submissions with RWD external comparator might be more likely to have positive outcomes for SAT based-HTA submissions**

HAS, France
PBAC, Australia
G-BA, Germany
NICE, England
pCODR/CADTH, Canada

SAT, single-arm trial
HTA, health technology assessment

Patel 2021. Health Policy Analysis. https://doi.org/10.1016/j.jval.2021.01.015

Registry-based studies in German HTA process

- Challenges in practice using registry-based studies in HTA process

Compound	Indication	G-BA decision	ECA	Rationale for non-acceptance
Amivantamab	NSCLC	July 2022	Data from two registries	Missing data on patient selection and risk adjustment
Nivolumab	CRC	No added benefit	Routine data from the U.S. Flatiron Health database	Relevant risk difference in the populations (higher mortality in the USA than in Europe)
Lanadelumab	Hereditary angioedema	No added benefit	Retrospective comparison with data from studies of comparator therapy	Populations to be compared were too different

Reasons for non-acceptance by German HTA

- No extensively documented and systematic literature research and **consideration of all relevant confounders**
- **Missing data** on patient selection and risk adjustment
- **Relevant risk difference** in the populations (region, patient characteristics)
- Biomarker as **prognostic factors not included**
- **Populations** to be compared were **too different** (could not be meaningfully balanced out with statistical methods)
  - Crucial information is often missing from the data sets used, and the patient groups to be compared sometimes differ significantly
  - An appropriate benefit assessment is hardly possible with real-world data sets

Versorgungsnahe Daten in Herstellerdossiers: Es läuft noch nicht rund (iqwig.de)

Summary

- Regulatory guidance has covered the use of registry-based studies (e.g., EMA, FDA)
- Registry data are commonly used to establish an external control arm for a single-arm trial, especially in oncology and rare disease
- Registry-based studies have also been widely used in HTA process, but the challenges in practice should be recognized
- An appropriate approach needs to be considered in the design and analyze studies with registry-based external control

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