Principles of Conducting Pharmacoepidemiologic Studies in the context of Disease-Modifying Therapies

Daniela Moga, MD PhD
Associate Professor
University of Kentucky

College of Pharmacy

Disclosure

With respect to the content of the following presentation, I have no actual or potential conflicts of interest and have no financial relationships to disclose.

Outline

1. General pharmacoepidemiologic considerations
2. The trial emulation framework to study effectiveness of therapies
3. Key considerations for generating RWE on disease-modifying therapies

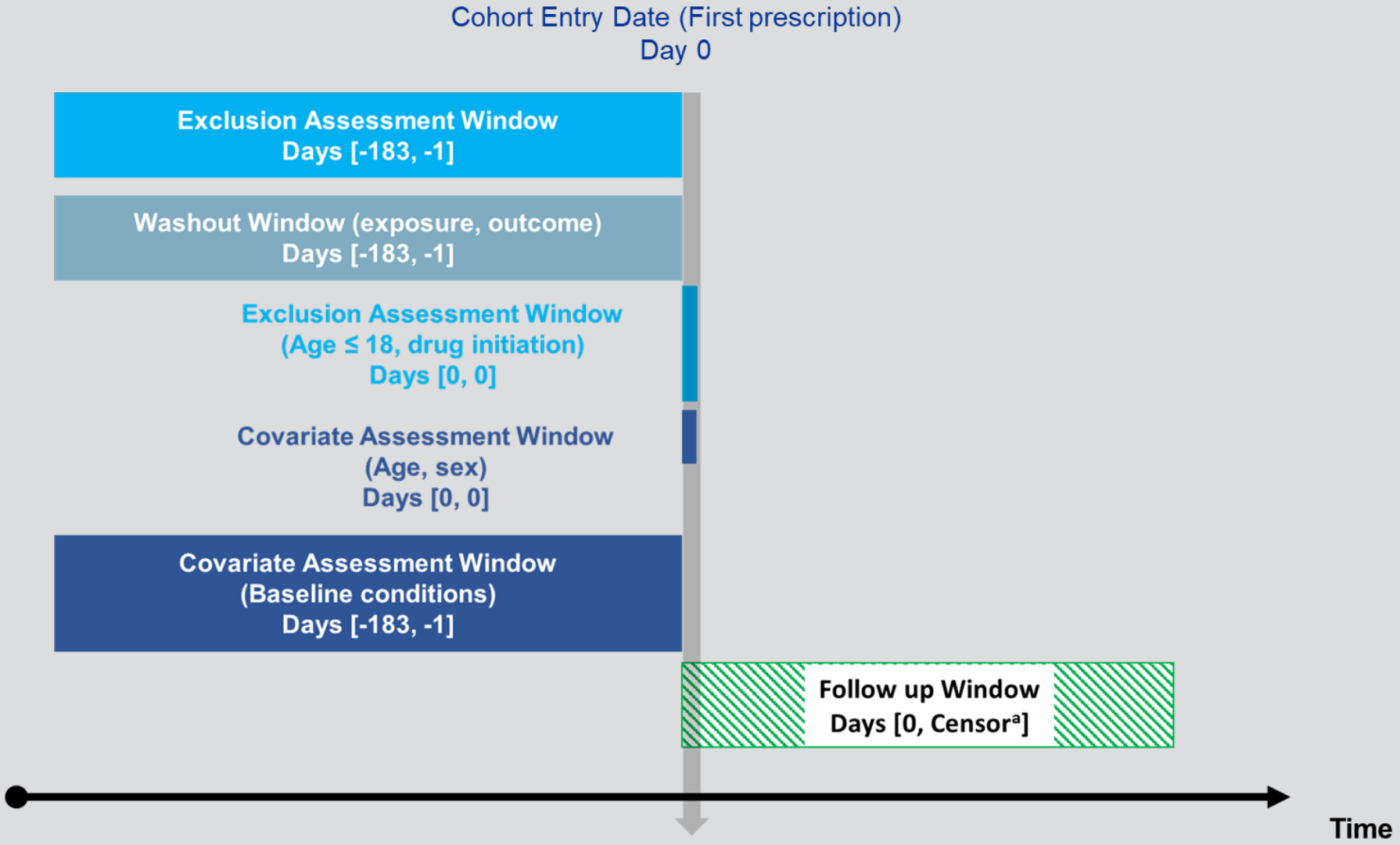
Some General Pharmacoepidemiologic Considerations

Study design and analysis considerations:

1. New user vs prevalent user
2. Counterfactual selection
3. Time zero and immortal time bias
4. Confounding control
5. Follow-up and censoring
6. Heterogeneity of treatment effect

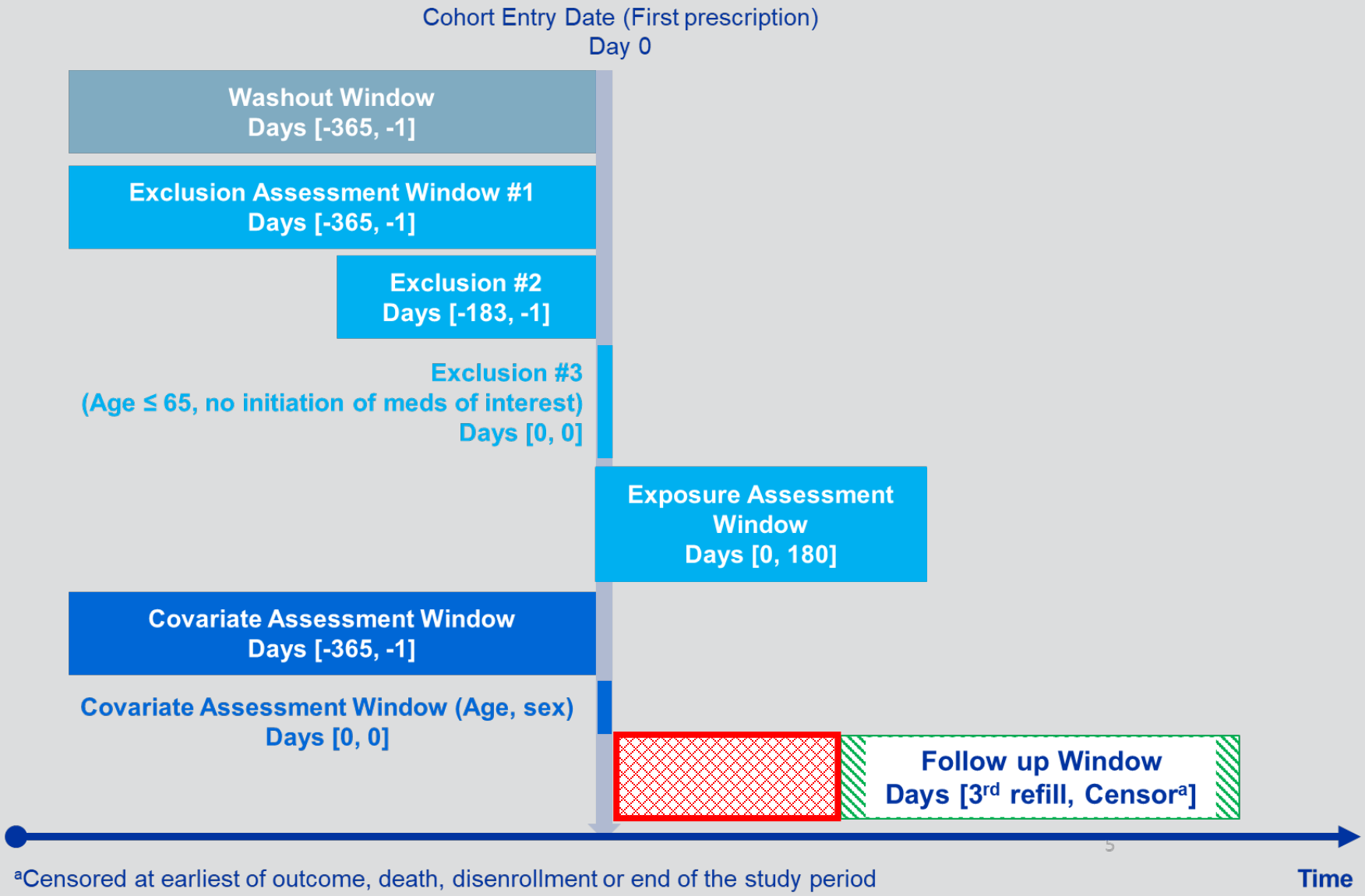
Data availability/quality considerations:

1. Information bias
2. Available sample size/power



[a]Earliest of: outcome of interest, switching or discontinuation of study drugs, death, disenrollment, 365 days of follow-up, end of the study period

Schneeweiss S., et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398-406. doi: 10.7326/M18-3079



Schneeweiss S., et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398-406. doi: 10.7326/M18-3079

The ***Trial Emulation*** Framework

Step 1: Articulate the ***causal question-*** define the protocol of a hypothetical randomized trial that would provide the answer

Step 2: Emulate the components of the protocol using observational data

Hernán MA, et al. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014
Hernán MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med. 2021 Oct 7;385(15):1345-1348. doi: 10.1056/NEJMp2113319.
García-Albéniz X, et al. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. Eur J Epidemiol. 2017 Jun;32(6):495-500. doi: 10.1007/s10654-017-0287-2.

The ***Trial Emulation*** Framework

Step 1: Articulate the ***causal question***

i. Specify the components of the causal estimands
   a. Eligibility criteria
   b. Treatment strategies
   c. Treatment assignment
   d. The start and end of follow-up
   e. Outcomes
   f. Causal contrasts: intention-to-treat vs per protocol
ii. Data analysis plan

Step 2: Emulate the trial protocol using RWD

Important considerations:

- Fit for purpose data availability
- Emulation of randomization
- Alignment of eligibility (immortal time bias)
- Treatment assignment/ placebo vs no treatment
- The start of follow-up (i.e., time zero)

The *Trial Emulation* Framework

Causal estimand

Protocol component	Target trial specification	Target trial emulation
Eligibility criteria	Who will be included in the study?	
Treatment strategies	What interventions will eligible persons receive?	
Treatment assignment	How will eligible persons be assigned to interventions?	
Outcomes	What outcomes in eligible persons will be compared among intervention groups?	
Follow-up	During which period will eligible persons be followed in the study?	
Causal contrast	Which counterfactual contrast will be estimated using the above data?	
Statistical analysis	How will the counterfactual contrasts be estimated?	

Hernán MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med. 2021 Oct 7;385(15):1345-1348. doi: 10.1056/NEJMp2113319.
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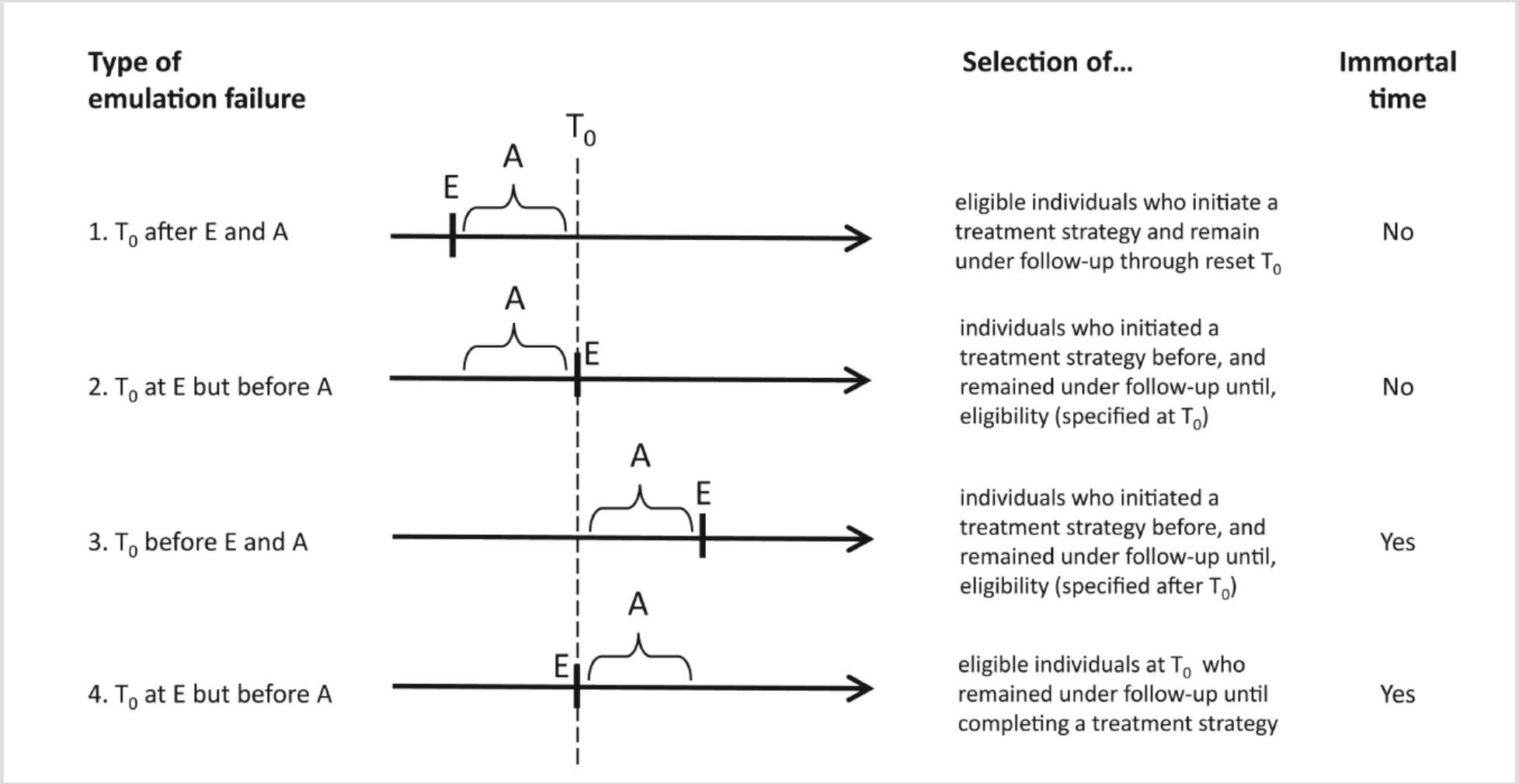

Examples of failures of emulation of a target trial using observational data.
T0= time zero; E= eligibility; A= period during which treatment strategies are assigned.

Hernán MA, et al. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70-75. doi:10.1016/j.jclinepi.2016.04.014

Key Considerations in Studying Disease-Modifying Therapies

1. **Eligibility criteria**: RCT vs CMS
2. **Treatment strategy**: one point exposure vs time-varying recommendations

   "participants received … donanemab (700 mg for the first 3 doses and 1400 mg thereafter) … administered intravenously every 4 weeks for up to 72 weeks. If amyloid plaque level (assessed at 24 weeks and 52 weeks) was less than 11 Centiloids on any single PET scan or less than 25 but greater than or equal to 11 Centiloids on 2 consecutive PET scans…, donanemab was switched to placebo in a blinded procedure"

3. **Exposure identification and measurement**: EHR data, part B claims data, CMS registry data, patient reporting
4. **Comparison group and immortal time bias** (time zero)
5. **Appropriate outcome measurement**: diagnosis codes (EHR, claims) vs cognitive and functional assessment (EHR, cohort data, CMS registry?)
6. **Emulating randomization and confounding control**
7. **Follow-up** (selection bias, competing events)

Sims JR, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA.* 2023;330(6):512–527. doi:10.1001/jama.2023.13239

A Need for Rigorous Studies using RWD

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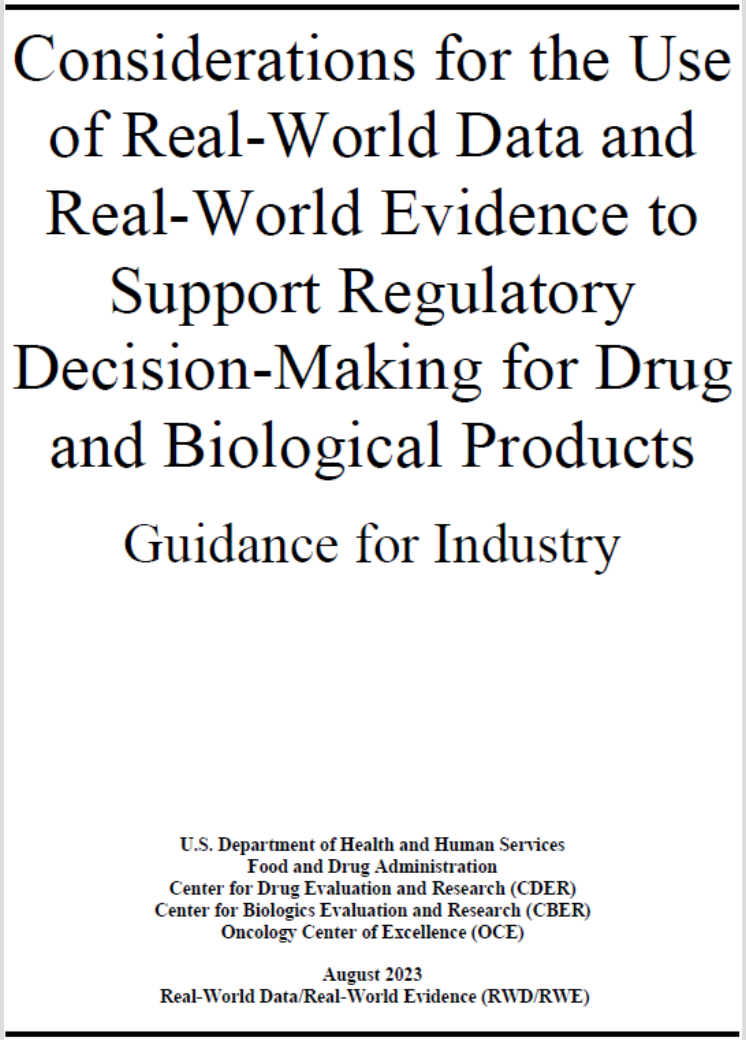
DOI: 10.1002/pds.5507

ORIGINAL ARTICLE

WILEY

HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force

Wang et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. Pharmacoepidemiol Drug Saf. 2023 Jan;32(1):44-55. doi: 10.1002/pds.5507.


Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2023
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/media/171667/download

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Thank you!