Assessing and minimizing bias in observational comparisons

What is known and what questions remain?

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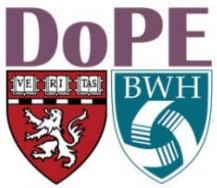

When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?

Jessica M. Franklin[1] and Sebastian Schneeweiss[1]

Regulators consider randomized controlled trials (RCTs) as the gold standard for evaluating the safety and effectiveness of medications, but their costs, duration, and limited generalizability have caused some to look for alternatives. Real world evidence based on data collected outside of RCTs, such as registries and longitudinal healthcare databases, can sometimes substitute for RCTs, but concerns about validity have limited their impact. Greater reliance on such real world data (RWD) in regulatory decision making requires understanding why some studies fail while others succeed in producing results similar to RCTs. Key questions when considering whether RWD analyses can substitute for RCTs for regulatory decision making are WHEN one can study drug effects without randomization and HOW to implement a valid RWD analysis if one has decided to pursue that option. The WHEN is primarily driven by externalities not controlled by investigators, whereas the HOW is focused on avoiding known mistakes in RWD analyses.

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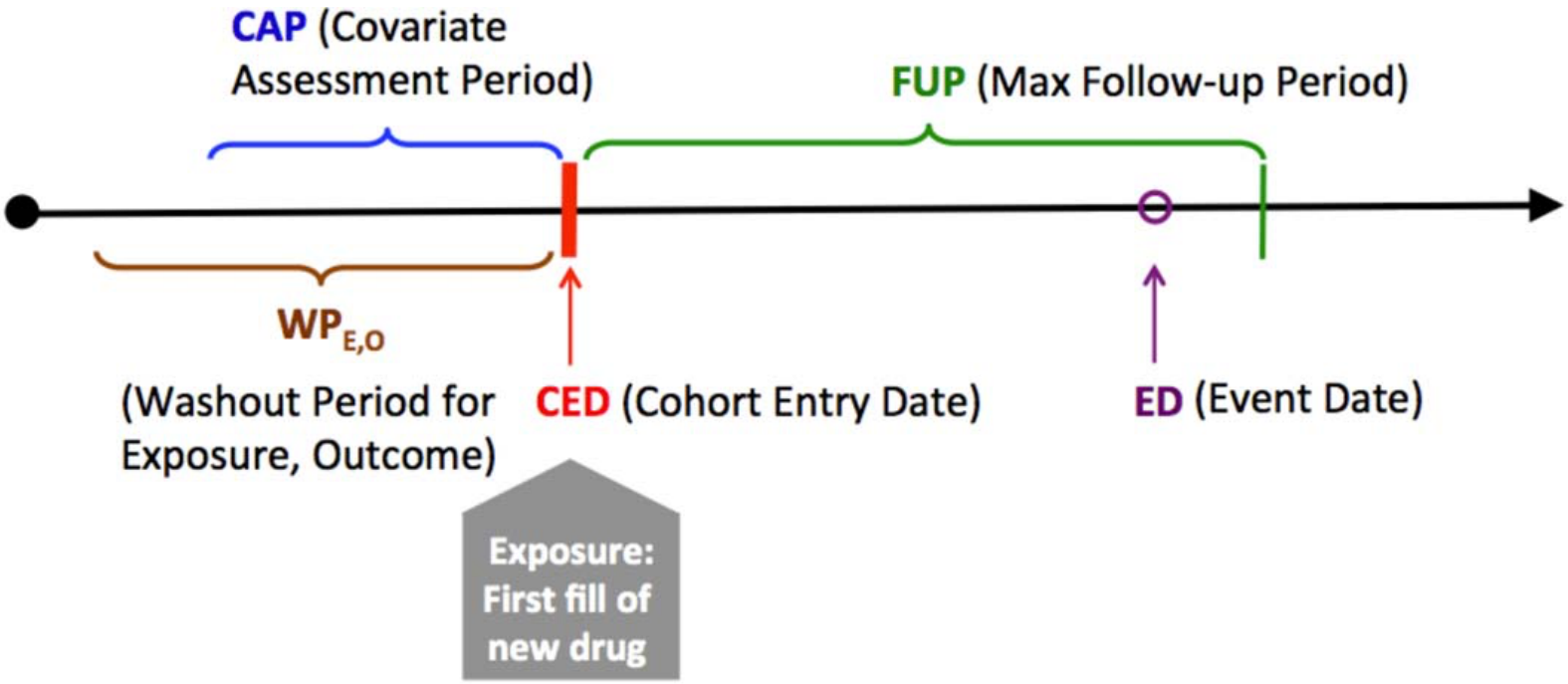
New user design



* Like in RCTs, a new-user design ensures that all patient characteristics are measured (and balanced) before the drug exposure starts. A washout period ensures no use of the study drug and outcomes before cohort entry. The clearly defined inception point of the new use of a drug makes it possible to study drug effects dependent on duration of use and reduces the risk of immortal time bias.

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ORIGINAL ARTICLE

Claims-based studies of oral glucose-lowering medications can achieve balance in critical clinical variables only observed in electronic health records

Elisabetta Patorno MD[1] | Chandrasekar Gopalakrishnan MD[1] |
Jessica M. Franklin PhD[1] | Kimberly G. Brodovicz DrPH[2] | Elvira Masso-Gonzalez PhD[3] |
Dorothee B. Bartels PhD[3,4] | Jun Liu MD[1] | Sebastian Schneeweiss MD[1]

Covariate (%)	Lina	DPP-4	Lina	Sulf	Lina	Pio
HbA1c	7.8	7.9	7.8	8.1	8.0	8.2
BMI						
Overweight	11.3	10.7	10.8	12.6	12.5	16.4
Obese	35.8	37.3	36.5	40.3	34.1	35.2
Duration of diabetes < 3 years	23.8	25.1	29	30.2	23.9	29.7
Current smoker	8.8	8.9	10.8	10.1	9.7	7.9

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Avoidable methodological mistakes are common

Methodological issue	Cohort studies (N=100)	Case-control (N=55)
Immortal Person-Time	66%	58%
Over-Adjustment	37%	87%
Inappropriate comparator		
1. Compared with non-diabetic patients	13%	11%
2. Compared with non-treated diabetic patients	7%	7%
3. Compared with any combination group that includes either 1 or 2.	44%	78%

* Patorno E, et al. Patterns of methodological issues arising in the observational literature evaluating glucose-lowering medications and cancer risk. 2017; in progress.

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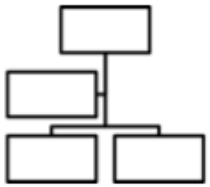
Process

Products

Candidate RCTs

List of RCTs to be reproduced with RWD

Select target RCTs



Document exclusions:

Limited RWD, Key measurements missing, Extremely strong confounding
etc. …

Set up scalable RWD analytics platform

RWD study infrastructure:

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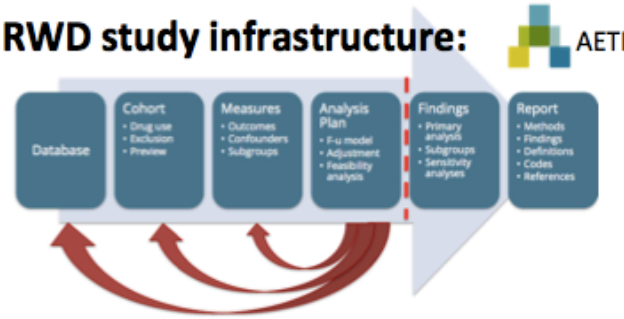
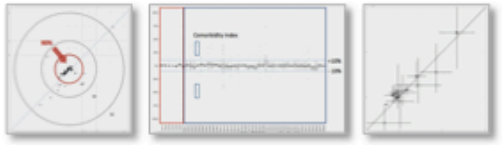


Scalable RWD infrastructure

Reproduce RCTs with RWD

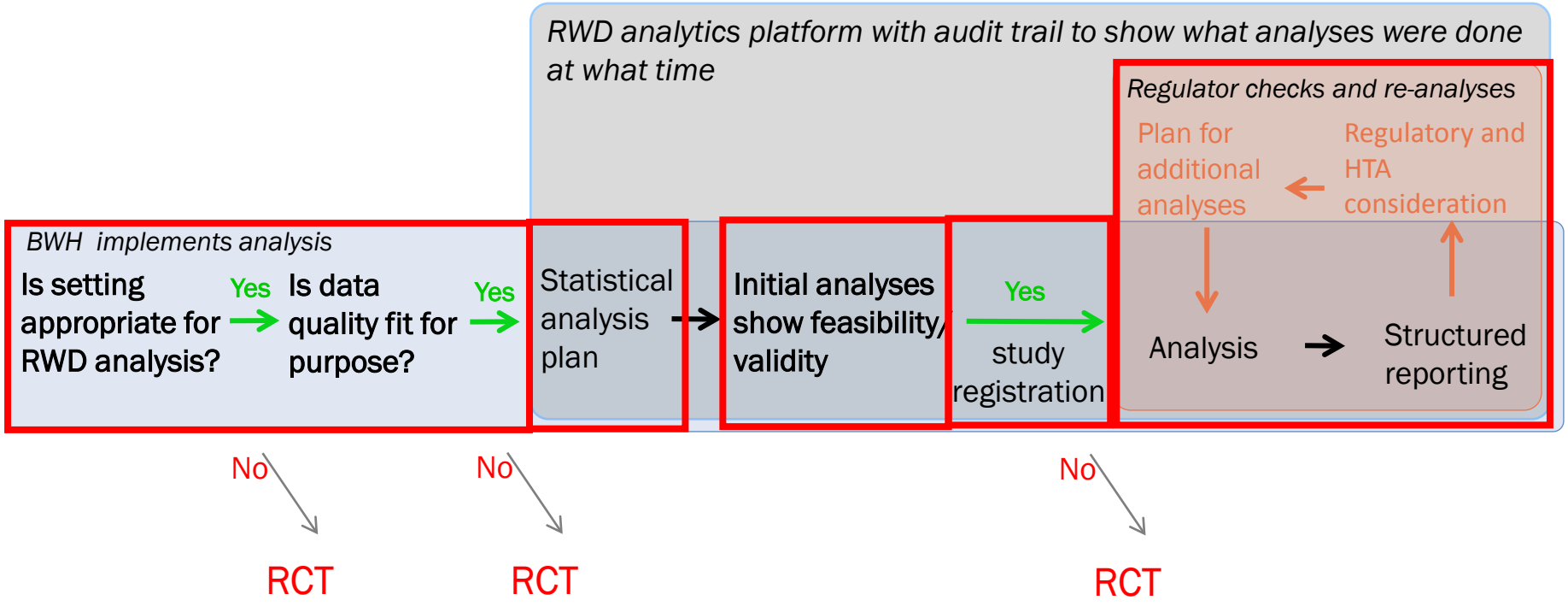
Quantify accuracy of RWD studies



Expert group guidance

FDA

RWD Implementation Process



Thanks!

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