

Randomized/interventional

Non-randomized/ interventional

Non-randomized/ non-interventional

Traditional randomized trial, using elements of RWD

Trials in clinical practice settings (with pragmatic elements)

Observational studies

RWD to assess
enrollment criteria
& trial feasibility

Selected outcomes
identified using
EHR/claims data, etc.

RCT using electronic case
report forms or EHR or claims
data (or combination)

Single-arm study
with external
control arm

Observational cohort
study

RWD to support
site selection

Mobile technology
used to capture
supportive endpoints

Case-control study

RWD Challenges

- ❑ Selection bias
- ❑ Intercurrent events
- ❑ Informative missingness
- ❑ Treatment by indication
- ❑ High dimensional covariates
- ❑ Outcome measurement error
- ❑ Statistical model misspecification
- ❑ Differences between external control and RCT

*Targeted Learning
path supports regulatory
decision making*

Targeted Learning

- ✓ Roadmap for causal and statistical inference
- ✓ Realistic statistical model
- ✓ Statistical estimand approximates answer to causal question
- ✓ Flexible estimation and dimension reduction with Super Learner
- ✓ Model-free sensitivity analysis
- ✓ TMLE targets statistical question