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Nonrandomized Real-World Evidence on Medications and the RCT DUPLICATE Project

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National Academies' Standing Committee on Evidence Synthesis and Communications in Diet and Chronic Disease Relationships

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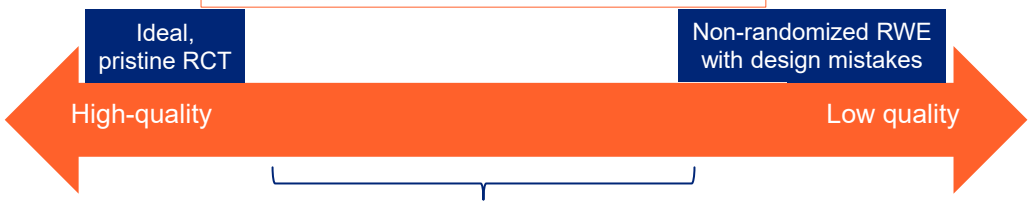
RWE and the Quality Spectrum

Real-World Data (RWD): data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE): clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.



- No loss to follow-up
- Perfect measurements
- Perfect adherence to randomized therapy

Most randomized and higher quality nonrandomized studies live in this range.

- Major confounding
- Immortal time bias
- Reverse causality
- Detection bias

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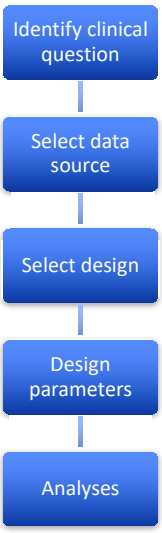
Comparing RCT and RWE results

- Improved understanding of methodology for nonrandomized RWE studies in recent years
- Major concerns about the validity of nonrandomized RWE remain.
  - How do we evaluate the credibility of nonrandomized RWE?
- Emulate RCTs in RWD. If nonrandomized RWE findings can match RCT findings, then we gain confidence in RWE studies.
  - Which methods perform better in real data and real clinical questions
  - Which questions can be answered with RWE



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RCT DUPLICATE

- Led by Mass General Brigham and Harvard Medical School
- Focused first on healthcare claims data

Nonrandomized Real-World Evidence to Support Regulatory Decision Making: Process for a Randomized Trial Replication Project

Jessica M. Franklin[1]*, Ajinkya Pawar[1], David Martin[2], Robert J. Glynn[1], Mark Levenson[3], Robert Temple[4] and Sebastian Schneeweiss[1]

Research

JAMA | Original Investigation

Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses Results of 32 Clinical Trials

Shirley V. Wang, PhD, ScM; Sebastian Schneeweiss, MD, ScD; and the RCT-DUPLICATE Initiative

Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies

First Results From the RCT DUPLICATE Initiative

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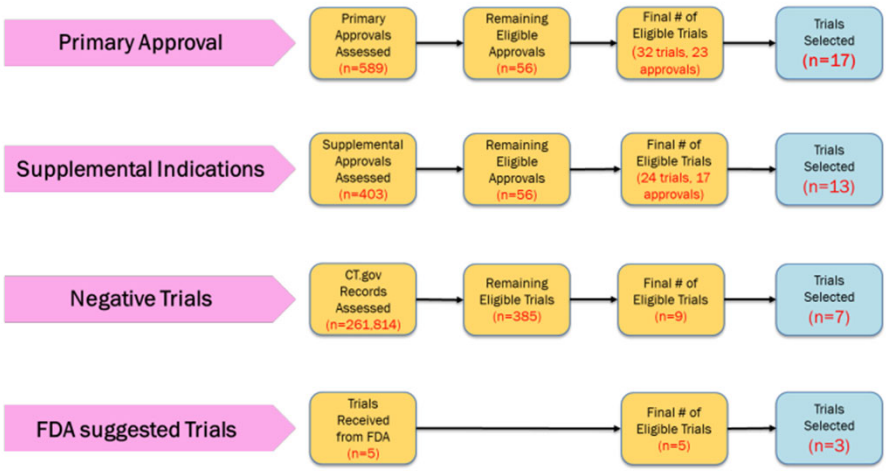
Initial search strategy



Three claims data sources:
- Optum Clinformatics
- IBM Marketscan
- Medicare

Exclude:
- Endpoints not captured
- Exposure not captured
- Major inclusion/ exclusion criteria not captured
- Major confounders not captured

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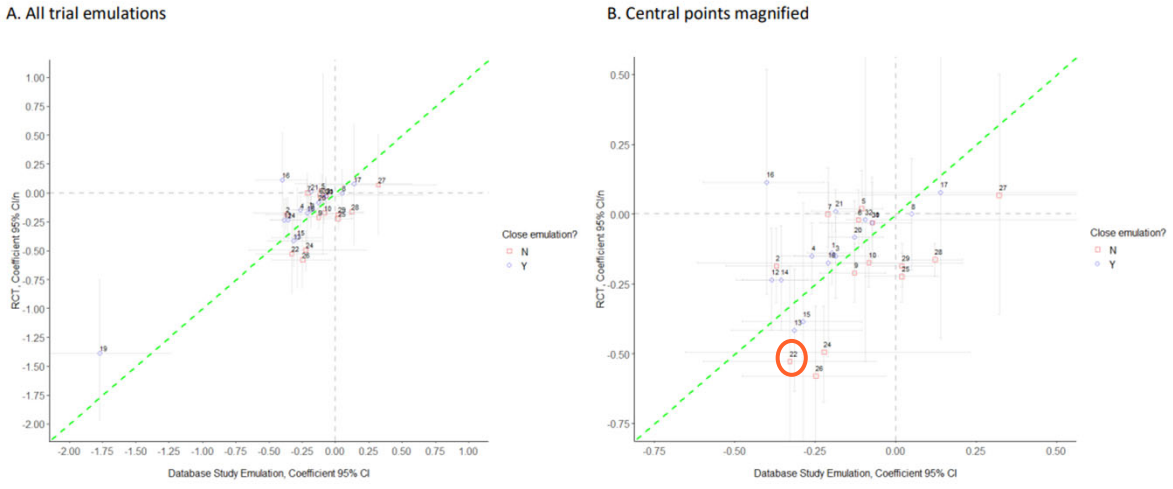
Calibration plots



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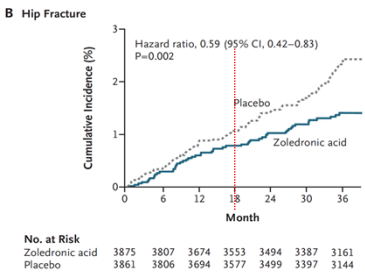
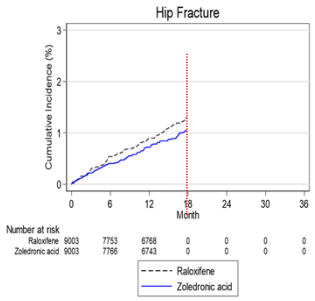
HORIZON: Hip fracture on zoledronic acid vs placebo

	RCT	RWE
Reported results	HR = 0.59	HR = 0.75
36 months FU	HR = 0.59	HR = ??
18 months FU	HR = 0.75	HR = 0.75

KM from Horizon-pivotal trial



KM - Optum+Marketscan



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RCT DUPLICATE learnings (so far)

- Emulating a trial design in RWD is hard.
  - If you were answering the question with RWD, you wouldn't design your study in the same way.
- Nonetheless, RWD can in certain circumstances come to similar conclusions as the randomized trial.

- If we want to use RWD to supplement RCT data, we need to know in this specific setting whether RWD will be comparable to the trial.
  - Relying on RWD/RWE for second study showing effectiveness
  - Relying on RWD/RWE to support supplemental indications, expanded populations, etc.
  - Hybrid RCTs that supplement the control arm with patients from RWD
  - External control arms derived from RWD
  - RCT patients linked to RWD sources

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