Why is RWE important today?

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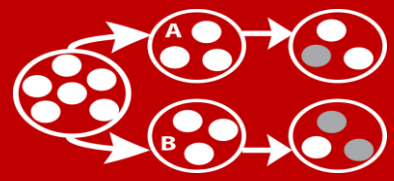
RCTs are critical, but they have limitations

- RCTs do not reflect how the product will perform in the real world
- RCTs can show whether a product is safe and efficacious, but cannot well-describe for which patient subgroups / phenotypes
- Patients in RCTs and in the real world are very different – eg age, race, ethnicity, gender, comorbidities, concomitant drugs, lifestyle variances, and varying levels of compliance. And therefore, often have different outcomes.
- Individual patient decisions are still based on inferences and intuition, rather than on precise evidence

Why do we need to consider RWE?

Most RCTs use narrow inclusion and exclusion criteria to select the participants most likely to benefit from an intervention and least likely to experience harm



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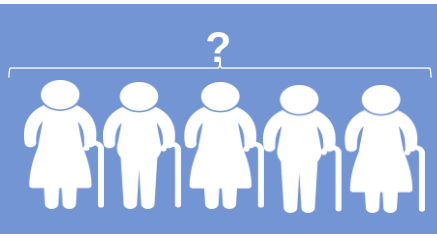

Of 20,388 US Medicare patients ≥ 65, only 1 in 5 discharged from an acute care hospital with a diagnosis of congestive heart failure (CHF) met the criteria for enrollment in 3 landmark trials that guide treatment of all CHF patients.

Masoudi FA, Havranek EP, Wolfe P, et al. Am Heart J. Aug 2003;146(2):250-257.

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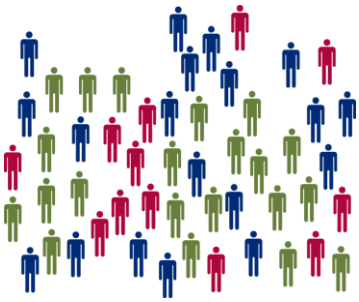
Why are subgroups so important?

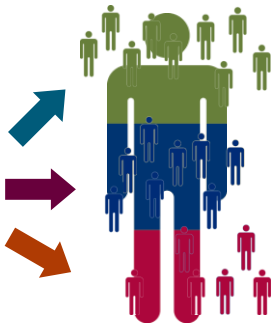
= Good outcome = Intermed outcome = Bad outcome

MEAN TREATMENT DIFFERENCE



RISK STRATIFICATION

MEAN TREATMENT DIFFERENCE



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Regulatory and market-access decisions increasingly require RWE to provide answers

- Regulators and payers are requesting RWE to support regulatory or market access decisions
- Legislators and policy-makers are actively engaging in dialogue on the value of RWD and RWE
- The U.S. Food and Drug Administration, Chinese National Medical Products Administration, and the European Medicines Agency are developing guidelines on using RWE in product reviews and approvals – but *none* are yet published
- Regulatory agencies remain hesitant to explicitly describe RWE in labelling

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FDA Draft Guidance*: EXAMPLES of SUBMISSIONS USING RWD/RWE*

FDA

- RWE submissions can be
  - Randomized clinical trials or observational studies.
  - A new protocol(s) submitted to an existing IND
  - A final study report submitted to an NDA, or BLA supplement
  - A meeting package that discusses the use of RWE
- RWE submission may be used to support varied study objectives, such as:
  - Capture clinical outcomes or safety data, including pragmatic and large simple trials
  - Single arm trials that use RWE as an external control
  - Observational studies that generate RWE intended to help to support an efficacy supplement
  - Clinical trials or observational studies using RWE to fulfill an efficacy or safety post-marketing requirement and support a regulatory decision
- NOTE: Under FDA's RWE Program, evidence from traditional clinical trials will NOT be considered RWE. The Framework Document provides some guidelines as what is considered under the Program, including hybrid designs for clinical trials.

Regulators' view of RWE: Global alignment

Key Opportunities to use RWE: Perspectives from the Chinese NMPA

- **Treatment for rare diseases**: including synthetic / external controls
- **Revised indications or drug-combination labeling**
- **Post-marketing evaluation:** more-comprehensive assessment of safety, effectiveness of approved drugs, and to refine decision making
- Guiding **clinical trial design:** I/E, endpoints
- Identify the target population: **Precision medicine and patient subgroups**

Using real-world evidence for the purpose of product registration will require adequate communication in advance with regulatory authorities to ensure alignment on the study objectives and methodology

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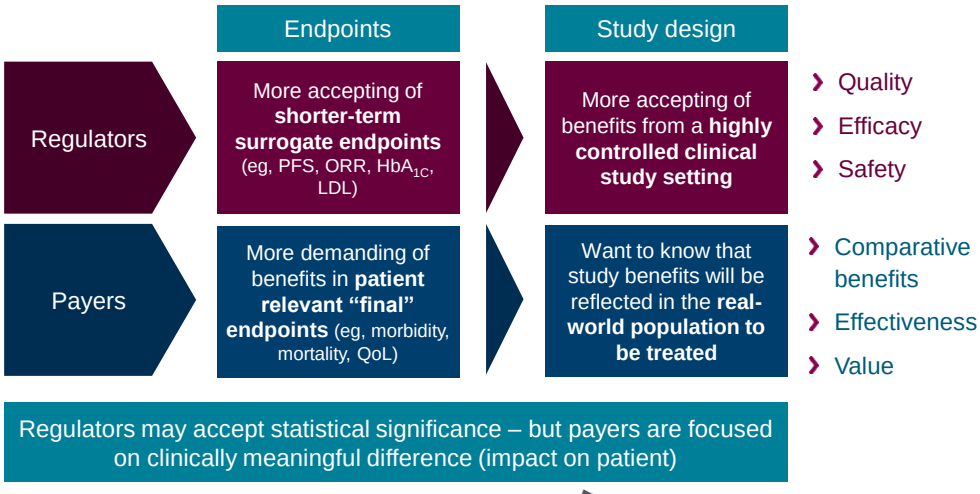
Payers challenge whether RCT findings translate into real patient benefits



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Utilizing RWE to drive product development

For Payers and Regulators

- Support formulary positioning and pricing
- Fulfill post-marketing commitments
- Support product approvals
- Substantiate reimbursement for rare-disease / accelerated-approval drugs

Demonstrate Competitive Advantage

- Differentiate from competitors
- Engage KOLs
- Maximize engagement with patients

Inform Internal Decision-Making

- Understand product usage, practice patterns, patient-selection criteria
- Drive decisions on trial design and trade-offs
- Defining unmet needs and lifecycle- management strategies

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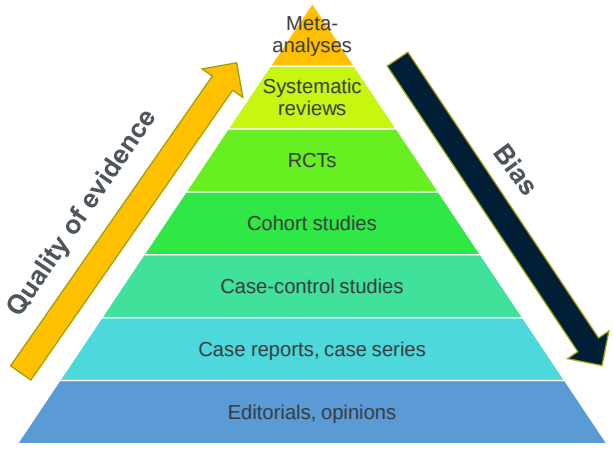
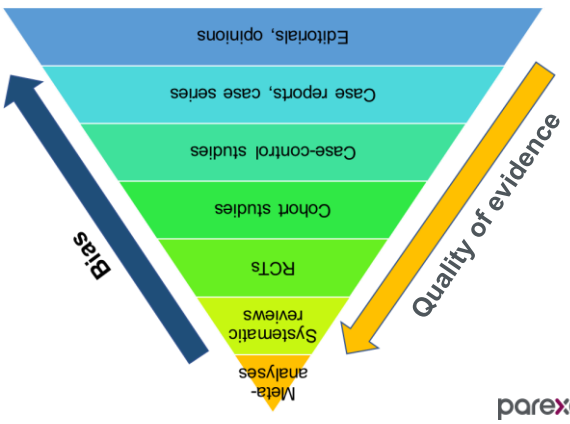
Evidence hierarchy revisited?



N. Dreyer, ISPOR

A new paradigm for evidence evaluation?



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Integrating RCT and RWE models can advance our research models to deliver meaningful insights and evidence

- RCTs and RWE are *complementary*
- RWD can help to improve the pragmatism and relevance of clinical trials by (E. Levy):
  - adding patient-reported outcomes
  - making the intervention more similar to real-life clinical interventions
  - removing unnecessary inclusion/exclusion criteria and improving generalizability
- Need to more-openly consider pragmatic trials and/or cluster-randomized models

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