Regulatory Use of Real World Evidence: Expectations, Opportunities, and Challenges

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Regulatory "objectives": what key questions do we need clinical studies to answer?

- Does the drug *work* for the proposed indication?
  - Meeting the burden of *substantial evidence of effectiveness*
- Does the drug's "benefit" (clinical relevance of efficacy in the indicated patients) *outweigh* the drug's "risks" (expected or potential safety or tolerability concerns)?

Approvability

- Can we properly describe the drug's safety profile and risks? (*Sections 5, 6: W&P, Adverse Reactions*)
- Can we reasonably describe the supporting evidence from clinical trials (*Section 14: Clinical Studies*)?

Labeling

RWE: Expectations in Law – 21st Century Cures Act

- FDA shall establish a program to evaluate the potential use of **real world evidence** (RWE) to support:
  - *Approval of new indication* for a drug approved under section 505(c)
  - Satisfy post-approval study requirements
- Program will be based on a framework that:
  - Categorizes sources of RWE and gaps in data collection activities
  - Identifies standards and methodologies for collection and analysis
  - Describes the priority areas, remaining challenges and potential pilot opportunities that the program will address
- Framework will be developed in consultation with stakeholders

Many *potential* uses of RWE beyond Regulatory

- **Hypothesis generating** retrospective or prospective observational studies (effectiveness)
- **Comparative effectiveness** research
  - Effectiveness / safety of approved drugs in broader populations in different practice settings
- **Treatment strategy** assessments
- Measure **quality of care** in health care delivery
- Assess **alternative dosing regimens** for established medications (e.g., ASA in the ADAPTABLE trial) in clinical practices
- Large pragmatic **outcome trials** in practice settings

Clinically relevant for physicians and payors

- **Landscape analyses** (e.g., drug uptake and utilization information, patterns of real world drug use)
- Post-approval **drug safety assessment**: signal detection, signal evaluation
- Detection / evaluation of **drug-drug interactions**, **medication errors**
- Prospective observational studies, including registries, used to **support registration** or **label expansion** (e.g., in cancer, rare diseases)
- Large simple, pragmatic **outcome trials** in practice settings (e.g., PMRs)

+ have utility in regulatory decisions

- **Assess alternative dosing regimens** for established medications
- RCTs with RWE supporting **label expansion –** new indications, new populations, additional endpoints (e.g., large pragmatic outcome trials)

Potential uses in regulatory decision-making

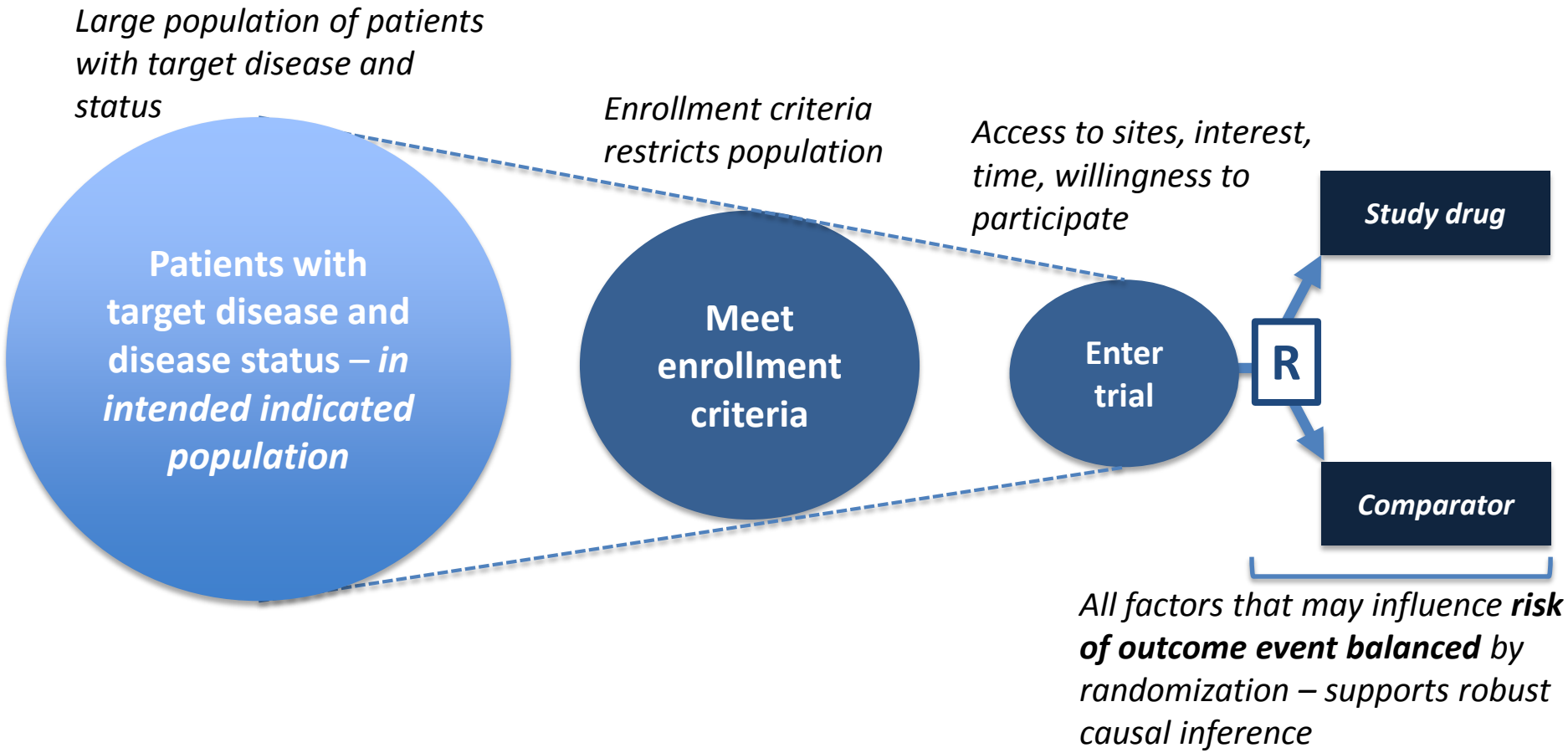
Usual Phase 3 studies: value and limitations

- RCTs can provide a *precise assessment* of efficacy and safety
  - Potential for **valid causal inferences**

    = does the drug work – strong internal validity
  - Patients with the disease / status (**defined, specific entry criteria**); well-characterized response (**established endpoints**); responsive to treatment (**enhanced adherence, exclusion criteria**)

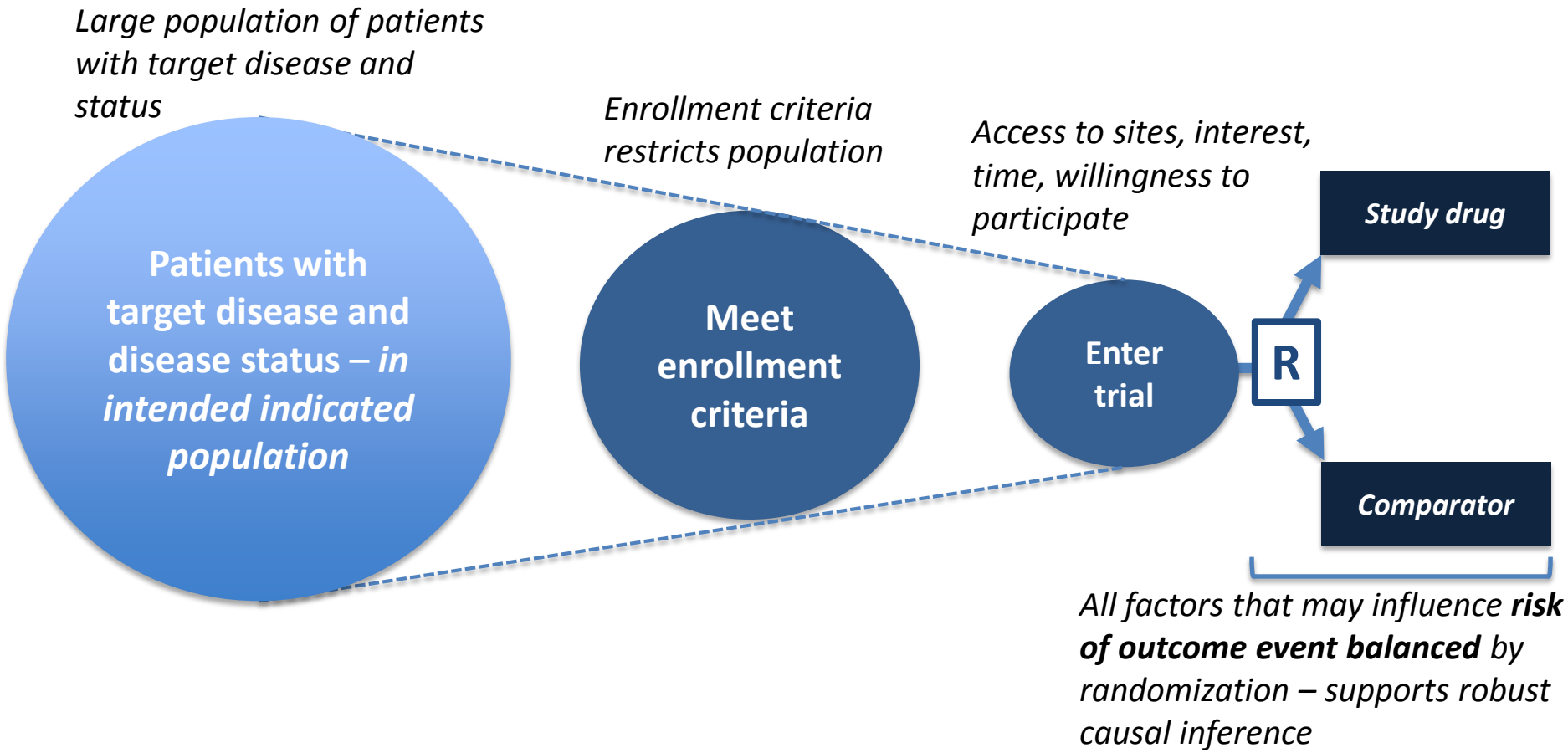
    = accurate effect size estimate in trial
  - Traceable, reliable data set upon which to base regulatory decisions
- But have limitations:
  - Resource intensive, long time to complete
  - Selected population vs post-approval use – internal validity vs *external validity/generalizability*
    - Limitations: fewer who are older, with multiple co-morbidities, on many concomitant medications

Drawing causal inferences: RCT vs Observational analyses



Greater external validity ⟷ *Greater internal validity*

Drawing causal inferences: RCT vs Observational analyses

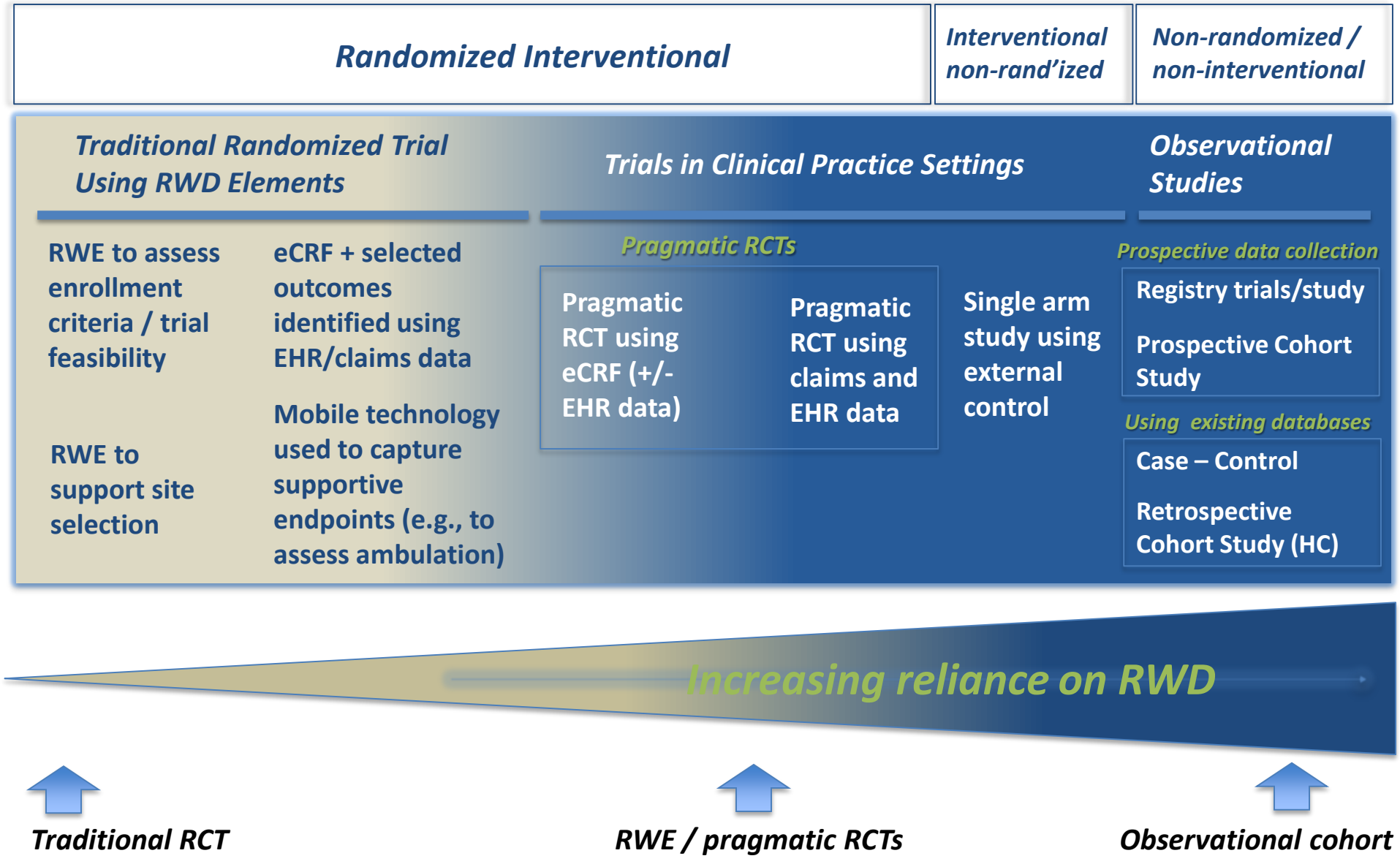


Greater external validity ⟷ Greater internal validity

Why expand use of RWD/RWE?

- **Much broader and diverse patient experience** vs traditional Phase 3 clinical studies
  - Includes settings and patients who will use drug post-approval
  - Patients with broader age, racial/ethnic, co-morbid disease, disease severity, concomitant medication
- **Very large sample sizes** – potential for detection of infrequent events, drug-drug interactions
- **Wide range of additional information that can be important in regulatory decision-making**
- **Lower resource intensity**
  - *Observational database studies*: utilizing data from routine interactions of patients with their health care system
  - *Pragmatic clinical trials*: usually non-blinded (low cost of drug supply), data emerging from patient's usual health care - data extracted from EHR/claims, more limited eCRFs

Wide spectrum of potential uses of RWD / RWE in clinical studies



RCTs vs non-interventional database studies

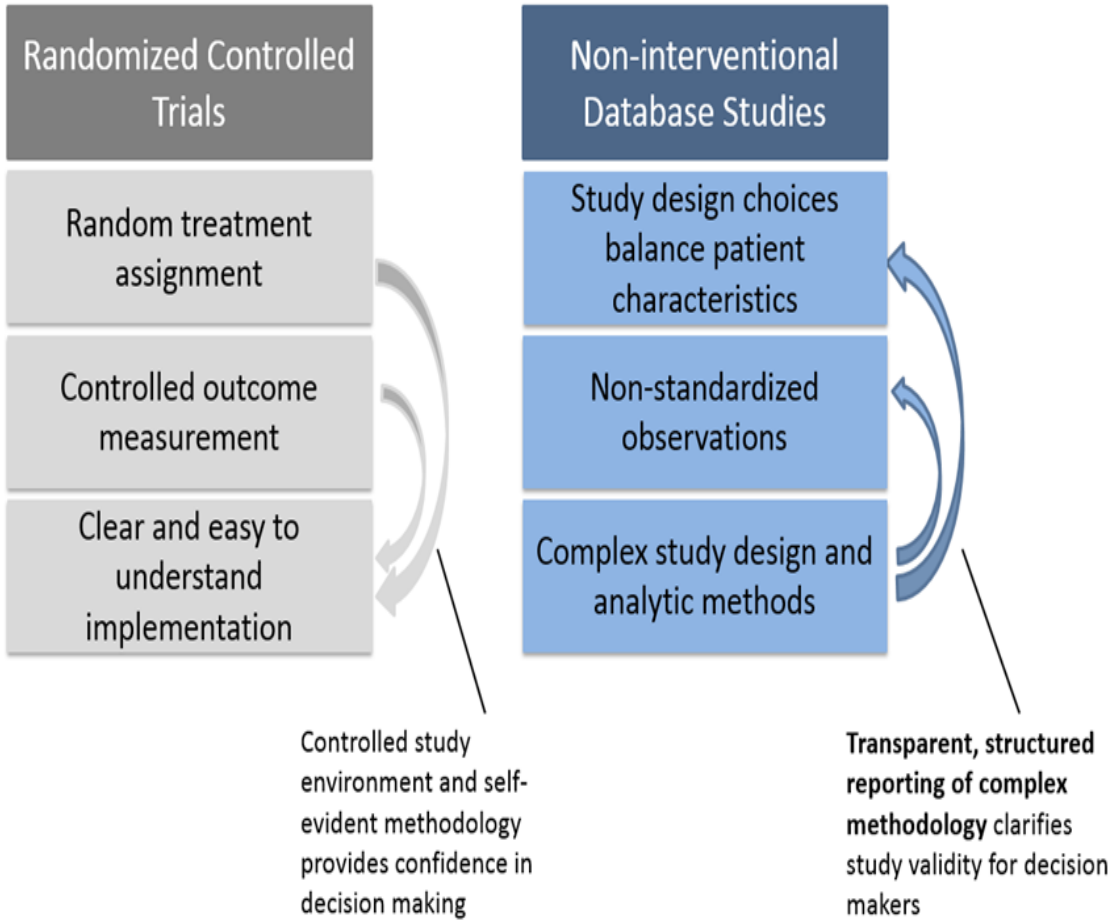


Figure courtesy of S. Schneeweiss

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But….reasons not to expand use of RWD/RWE

- Risk of *falsely concluding effectiveness* from observational dataset analyses – unclear if strong basis for causal inferences
- RCTs are "gold standard": robust determination of efficacy *and safety* of *primary importance* in regulatory decision-making
  - Broader understanding of effect estimate in indicated population highly desirable

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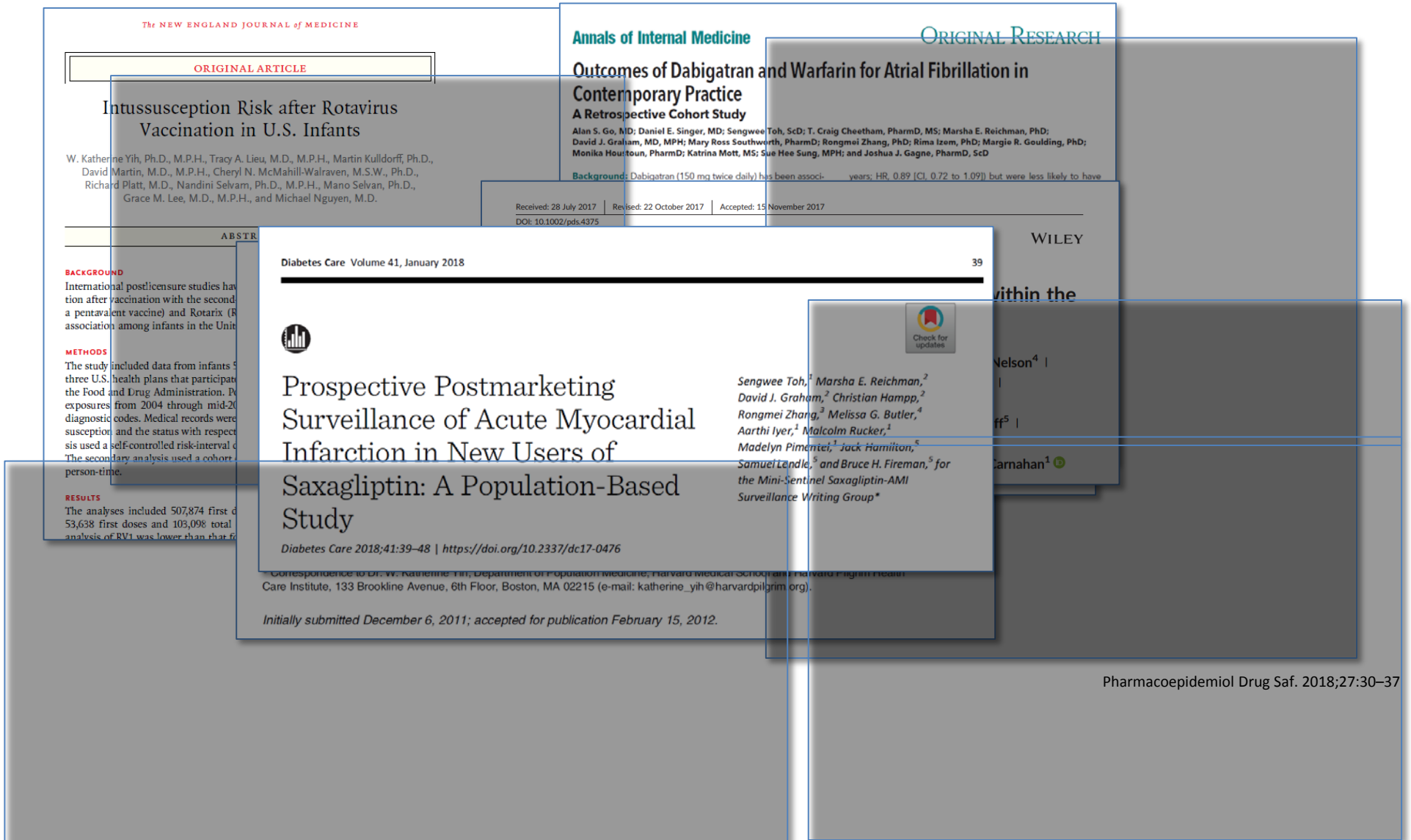
- *Improvements* in analytic and design methodologies *may* overcome limitations of observational analyses
  - New user designs
  - New methods for matching to balance outcomes risks in drug and comparator groups
  - Improving database quality (and quantity)
  - "Hardening" of EHR, and increasing claims, EHR, and pharmacy database linkages
  - Experience with pragmatic clinical trials

Extensive internal and collaborative efforts to address this question

Can these solutions now allow us to draw robust causal inferences?

Experience with RWE generation



Historical controls (RWE) often used in rare diseases

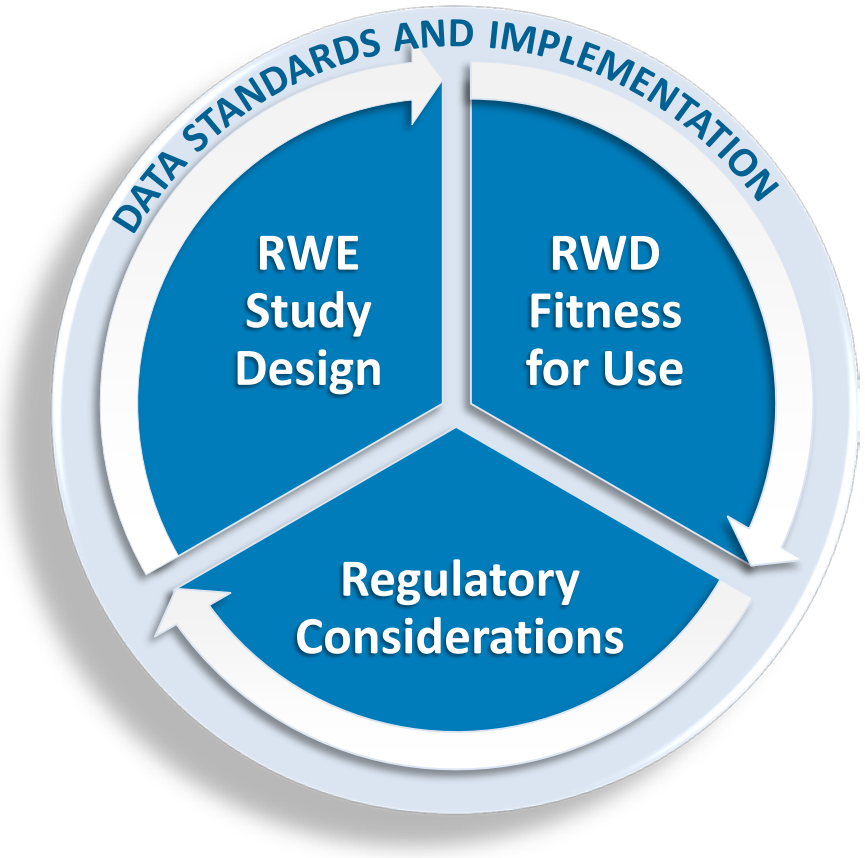
Drug	Indication	Status	Data source
Voraxaze *(glucarpidase)*	Treatment of MTX toxicity	Approved 2012	▪ Approval based on open-label, NIH **compassionate Use Protocol**
Uridine Triacetate	Treatment of 5 FU overdose	Approved 2015	▪ Two single-arm, open label expanded access trial of **135 patients compared to case history control**
Brincidofovir	Treatment of Ebola	Phase II ongoing	▪ Non-random open label single arm trial with **historical and contemporary controls** with multi-stage trial design
Carbaglu® (carglumic acid) Tablets	Treatment of NAGS deficiency	Approved 2010	▪ Retrospective, non-random, un-blinded case series of 23 patients compared to **historical control group**
Myozyme (alglucosidase alfa)	Treatment of Pompe disease	Approved 2004	▪ Open-label, non-randomized study of 18 patients compared to **historical control group of 62 untreated patients**
Refludan®	Anti-coagulation in heparin-induced thrombocytopenia	Approved 1998	▪ Two non-randomized, open-label multicenter trials using **historical control comparator group from chart review**
ANTIZOL (fomepizole) injection	Treatment of methanol or ethylene glycol poisoning	Approved 1997	▪ 2 open-label, uncontrolled studies with **historical control dating back to 1946 collected from chart reviews**
Ucephan	Treatment of urea cycle disorder	Approved 1987	▪ Multi-center open-label, non-randomized study of 56 patients compared to survival rates of **untreated historical controls**

*Blinatumomab vs historical standard therapy of adult relapsed/ refractory acute lymphoblastic leukemia https://www.nature.com/bcj/journal/v6/n9/full/bcj201684a.html

NOT EXHAUSTIVE

Bold = RWE

Framework for evaluating RWD/RWE for use in regulatory decisions

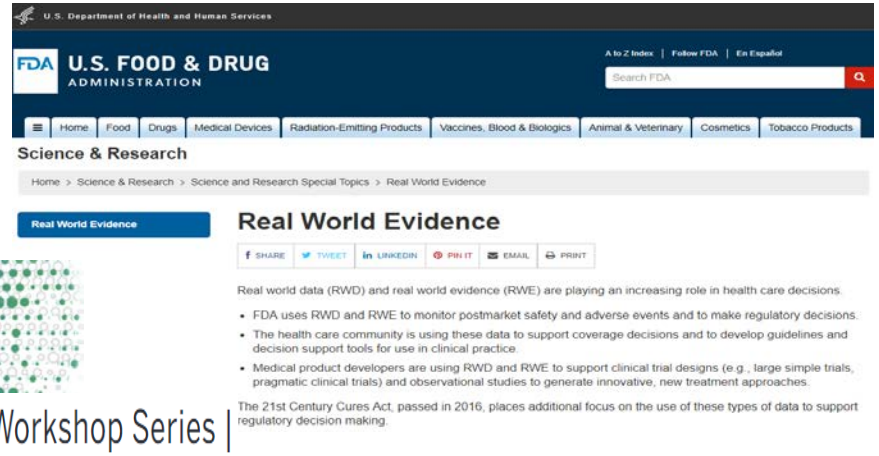


Considerations

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

FDA is actively engaging stakeholders in efforts to increase use of RWE

A Framework for Regulatory Use of Real-World Evidence
September 13, 2017



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Demonstration Project:
Assessment of Non-Interventional Designs

- **Attempted duplication of results of phase 3 & 4 RCTs over three years to provide empirical evidence base that could inform our level of confidence in high quality non-interventional designs**
- **FDA reviewers and researchers from the Brigham and Women's Hospital/Harvard Medical School Division of Pharmacoepidemiology jointly**
  - Selected trials in which claims data are sufficiently fit for purpose in a research environment
    - Oral hypoglycemic, novel oral anticoagulant, antiplatelet, antihypertensive, anti-osteoporosis, asthma, COPD, heart failure, anti-arrhythmic, and lipid lowering medications
  - Concurred with pre-specified measures of agreement
  - Reviewed an implementation process
- **Goal: 30 trials completed by March 2020**

Issues to consider: non-interventional observational studies to support regulatory decisions

Key Parameters in Feasibility and Adequacy of Non-interventional Studies			
The Research Question	**Patient and Group Selection**	**The Endpoint**	**Database Quality and Traceability**
• What "type" of research question • Can the question be answered using RWD: are there sufficient patients • Is the endpoint assessable – available in RWD	• Is patient selection appropriate • Are comparison groups balanced • Is patient management comparable	• Can the endpoint be assessed in RWD • Are the outcomes accurately evaluated • Is duration in RW database sufficient	• Database quality: accuracy, completeness • Is data traceable to source • Is source data available for inspection
And study integrity: pre-specification, posting, no data "dredging"			

The effectiveness requirement: the statutory standard for approval

- Requirement to demonstrate *substantial evidence*
- *As defined in Section 505(d), substantial evidence is*:
  - "evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by **experts qualified by scientific training and experience to evaluate the effectiveness** of the drug involved, on the basis of which it could **fairly and responsibly be concluded** by such experts that the drug will have the effect it purports or is represented to have **under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."**
- FDAMA (1997) added *flexibility*: one A&WC trial and ***confirmatory evidence***, if considered appropriate
- **21 CFR 314**: defines characteristics of an adequate and well controlled study

- The FDA *standard* requirement for *two* A&WC studies
- Reduces risk of false positive findings, bias or confounding in a single trial

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Application of the effectiveness requirement

- The statutory and regulatory framework for approval is *not* changing (FDCA 505, 21 CFR 314)
- But, application will be tailored to the characteristics of individual programs
- *One size does not fit all*
  - Common, chronic diseases vs small population programs
  - Serious and life-threatening illness with substantial unmet need vs drugs for less severe symptomatic disorders
  - Feasibility and ethics of study conduct
- The application of our frameworks will change as the types of programs change
- And, will change as the reliability of new sources of effectiveness data – e.g., RWE, mobile technology, decentralized trials – becomes clearer

But….reasons not to expand use of RWD/RWE

- Risk of *falsely concluding effectiveness* from observational dataset analyses – unclear if strong basis for causal inferences
- Double-blind RCTs "gold standard": robust determination of efficacy (drug works or doesn't) and safety of *primary importance* in regulatory decision-making
  - Broader understanding of treatment effect estimate in indicated population highly desirable – but not critical to regulatory decision

- However….many improvements in analytic and design methodologies *may* overcome limitations of observational analyses
  - New user designs and new methods for matching to balance outcomes risks in drug and comparator groups
  - Improving database quality (and quantity)
  - "Hardening" of EHR; claims, EHR, and pharmacy database linkages
  - Experience with pragmatic clinical trials and observational database analyses

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- *And*, the drug must be show to be "*safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling*" (21 CFR 314.125)

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