Ethics
in Real World Studies

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Level	Example of Evidence
Level 1	Meta-analysis of Homogenous RCTs Randomized Control Trial
Level 2	Meta-analysis of Level 2 or Heterogenous Level 1 Evidence Prospective Comparative Study
Level 3	Review of Level 3 Evidence Case-control Study Retrospective Cohort Study
Level 4	Uncontrolled Cohort Studies Case Series
Level 5	Expert Opinion Case Report Personal Observation
Foundational Evidence	Animal Research *In Vitro* Research Ideas, Speculation

Higher

Lower

"Most Published Research Findings are False"

- Simulations show that for most study designs and settings, **it is more likely for a research claim to be <u>false than true</u>**.
- Several methodologists have pointed out that the **<u>high rate</u>** of **non-replication** of research discoveries is a consequence of the
  - convenient of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, i.e., *p*-value < 0.05.

Ioannidis JPA. PLoS Med. 2005;2(8): e124.

Factors influencing the credibility of research findings

The smaller the studies conducted

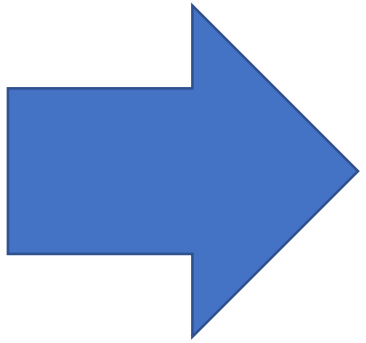
The smaller the effect sizes

The greater the number and the lesser the selection of tested relationships

The greater the flexibility in designs, definitions, outcomes, and analytical modes

The greater the financial and other interests and prejudices

The hotter a scientific field (with more scientific teams involved)

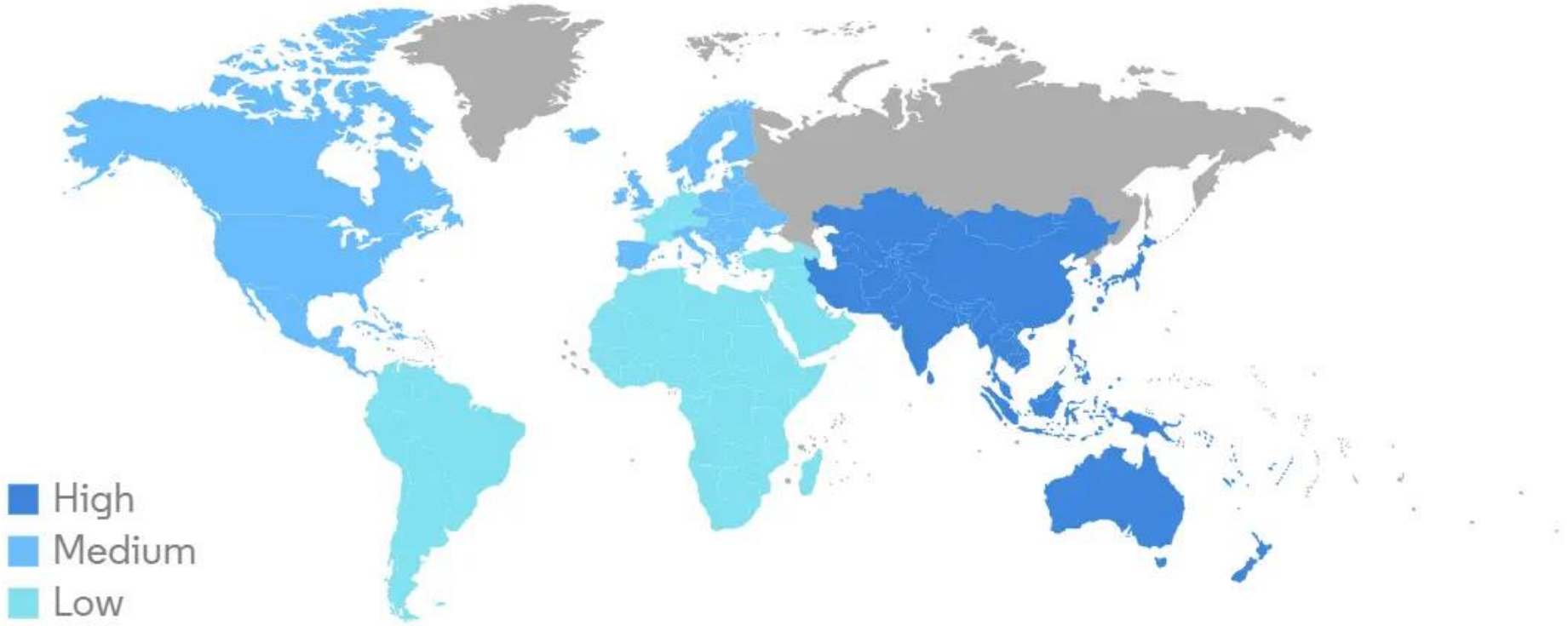


… the less likely the research findings are to be true.

The rise of Real World Studies

- Although the first article introducing the concept of **Real World Studies** was published **in 1967** (Schwartz D., Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis.*1967; 20:637–648),
  - the scientific community has **only recently** started to be aware of the issue.
    - Terms like ***pragmatic*** and its synonyms, ***practical*** and ***naturalistic***, have been used at an increasing rate to express the need for more evidence that is applicable in routine clinical settings.

Real-World Evidence Solutions Market - Growth Rate by Region



Source: Mordor Intelligence

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

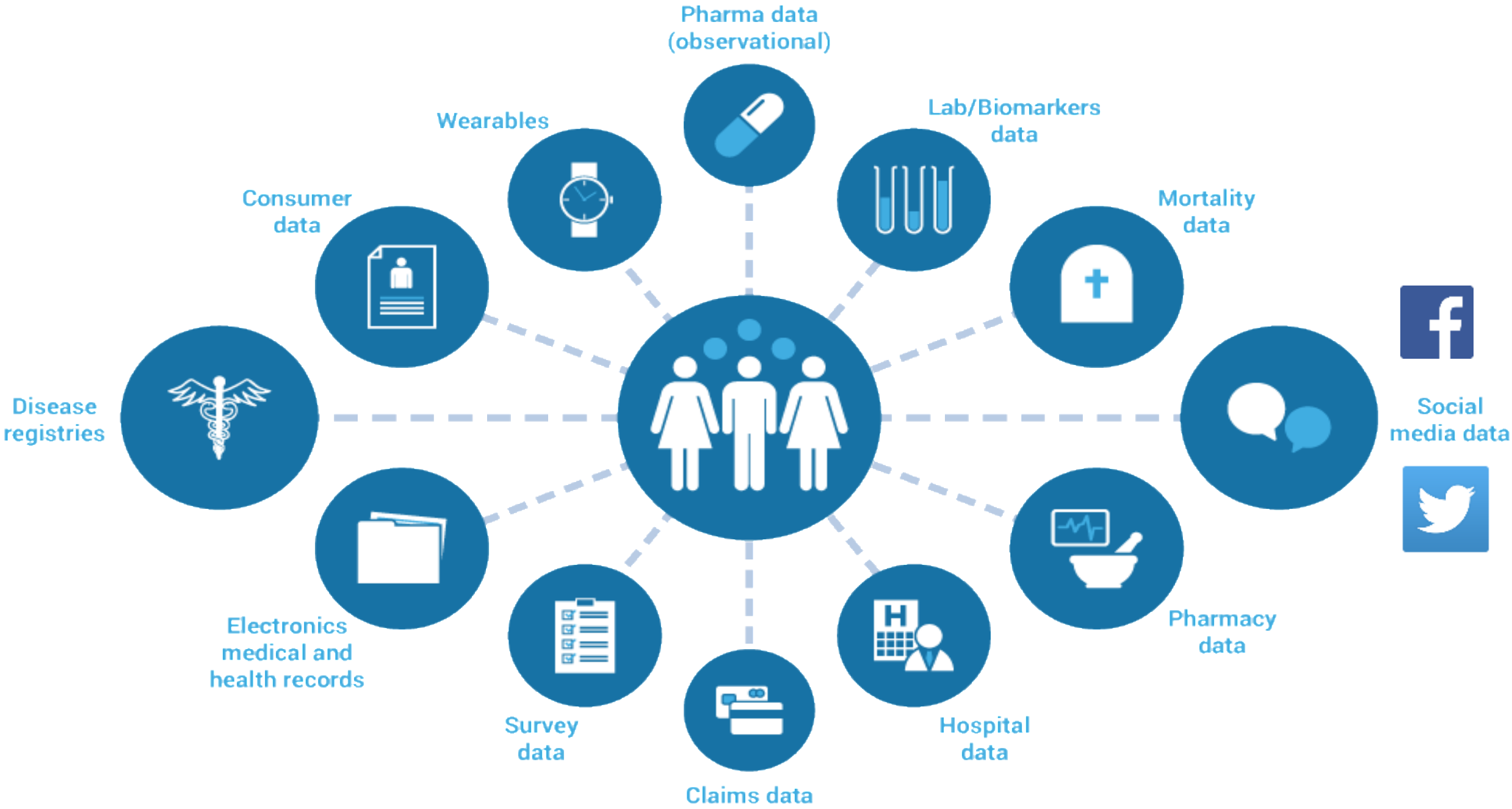
Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

N Engl J Med 2016; 375:2293-2297 | December 8, 2016 | DOI: 10.1056/NEJMsb1609216

… one of the most important advances in clinical trial methodology ***may be the broadening of the application of randomization outside more typical venues for clinical trials*** *…*

Real World Data & Evidence

- **Real-world data** (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- RWD can be generated from:
  - Electronic health records (EHRs)
  - Medical claims, billing data, and insurance data
  - Data from product and disease registries
  - Patient-generated data, including from in-home-use settings
  - Data gathered from other sources that can inform on health status, such as mobile devices
- **Real-world evidence** (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

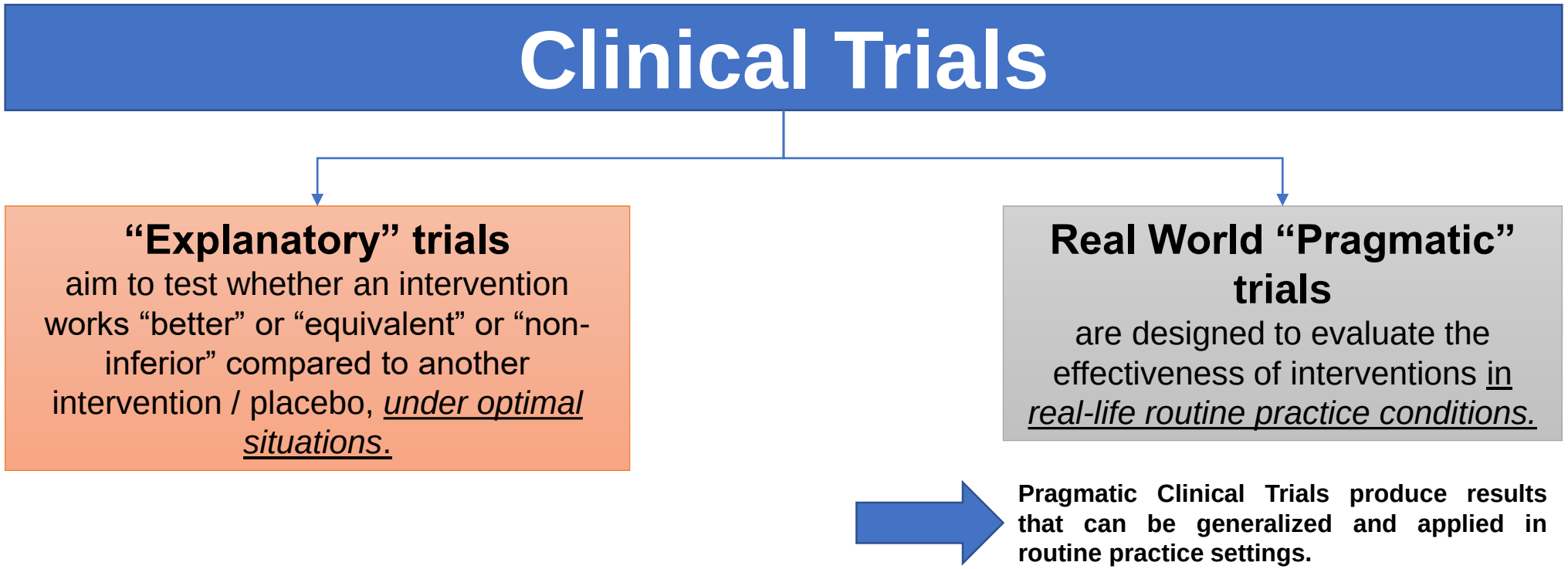

Pharma data (observational)
Wearables
Lab/Biomarkers data
Consumer data
Mortality data
Disease registries
Social media data
Electronics medical and health records
Pharmacy data
Survey data
Hospital data
Claims data


Real World Studies
Real World Data
Real World Evidence

Real World Studies

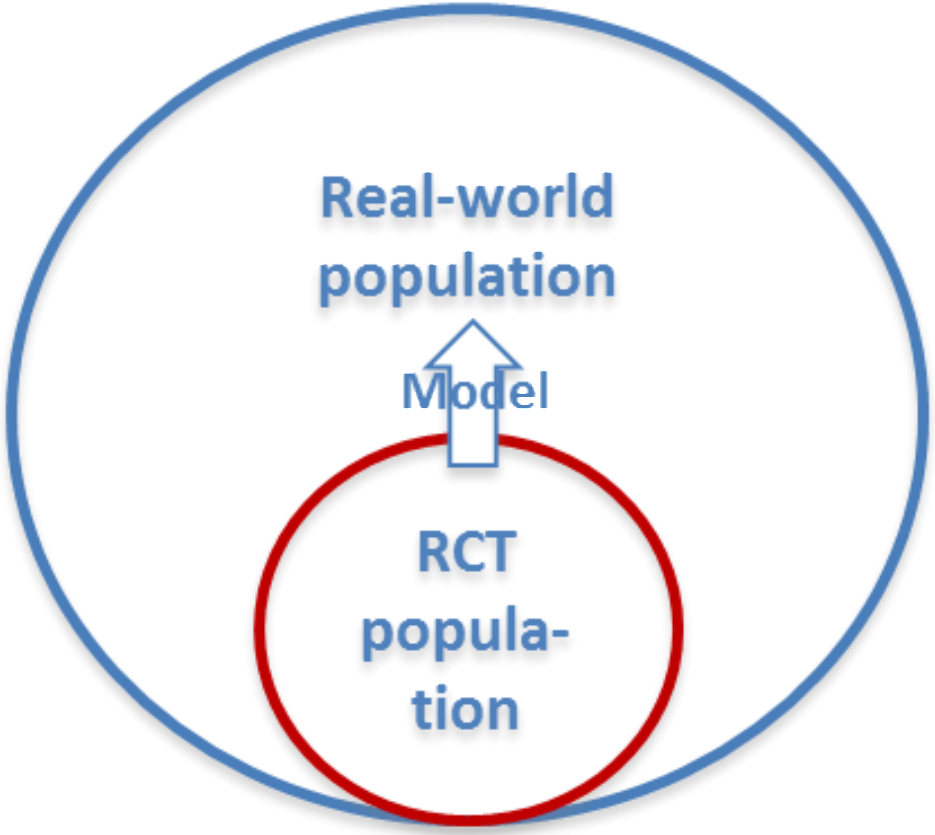
Pragmatic Trials

Randomised Clinical Trials (RCT) have been the main tool used by the health sciences community to test and evaluate interventions.

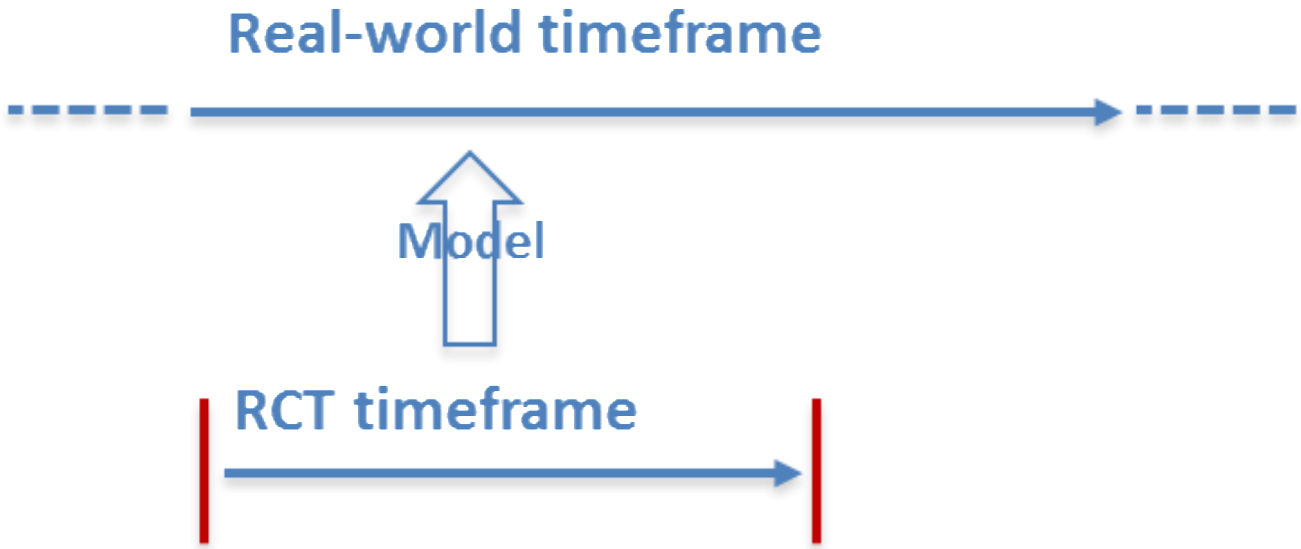


Real World Studies are Playing an Important Role in Health Care Decisions.

- Include a patient population that is **far more representative** of unselected patient populations than those of RCTs.
- Can have **very large sample sizes.**
- Can provide information on treatments in **patient groups that are usually excluded from RCTs**.
- Are generally **less expensive** and **quicker** than RCTs.
- Can assess a **broad range of outcomes**.



Prediction for new population



Prediction over time

Features	RCTs	RWD
Purpose	Efficacy	Effectiveness
Setting	Experimental setting	Real-world setting
Follow up	Designed	In actual practice
Treatment	Fixed pattern	Variable pattern
Study group	Homogenous	Heterogeneous
Attending physician	Investigator	Many practitioners
Comparator	Placebo/selective alternative interventions	Many alternative interventions
Patient monitoring	Continuous, per protocol	Changeable

RCT VS. RWS

Limitations of Real World Studies

Real World Studies have

- low internal validity,
- lack of quality control regarding data collection and
- susceptibility to multiple sources of bias for comparing outcomes.
- Ethical issues

Ethics in Real World Studies

- The history of research ethics can be divided into a number of periods of time:
  - Pre-1800
  - 1800–1939
  - 1939–1947
  - 1947–1964
  - 1964–present
  - the future

Research Ethics Principles

- Social and clinical value.
- Scientific validity.
- Fair subject selection.
- Favorable risk-benefit ratio.
- Independent review.
- Informed consent.
- Respect for potential and enrolled subjects.

Gelling L. J Clin Nurs. 2020

Do we still need Research Ethics in the current world of “real world studies”?

Research ethics in the conduct of the real-world research is extremely complex and has got no less complex since RECs were introduced.

Ethical issues and research regulations are widely perceived as obstacles to the design, review and conduct of RWS.

Ethical issues in Real World Studies:
a review of the recent literature identifies gaps in ethical argumentation

Table 1 Sumary of major themes

Main Themes	Associated Question	Majority View
Research-Practice Distinction	Is research morally distinct from clinical practice?	• Rejects the distinction between research and practice • Rests on an empirical claim that research often introduces risks that are unrelated to a patient's clinical care • Problematic assumption that research automatically involves higher risks than clinical practice.
Consent	Is consent required, and if so how extensive must the consent process be for low-risk pragmatic RCTs?	• Low-risk pragmatic RCTs may proceed without consent (i.e., waiver of consent) • Limited to cases in which risk of participation is low and other consent options are unworkable • Altered informed consent models may strike a balance between autonomy and burden for researchers.
Disclosure	What aspects of research must be disclosed to research participants of low-risk pragmatic RCTs?	• Information should only be disclosed if research participation adds risks over and above clinical practice • Disagreement whether to disclose randomization • No disclosure required in an ethically robust learning health care system.
Oversight	What level of oversight is required for low-risk pragmatic RCTs?	• Oversight is time consuming, costly and complex • Burdens stem from the faulty research-practice distinction and the lack of inter-institutional standardization • Review process for low-risk pragmatic RCTs should be streamlined.

Goldstein et al. BMC Medical Ethics, 2018

Ethical issues in Real World Studies

- **Disclosing research purpose** … there is agreement that the purpose of the research ought to be disclosed to prospective participants in RWS.
- **Disclosing risks and benefits** … there is also agreement that the risks and benefits of participation in a RWS must be disclosed.
- **Disclosing randomization** … there is no consensus as to whether randomization needs to be disclosed (i.e., randomization focuses on its impact on the physician-patient relationship).
- **Oversight** … there is no consensus on monitoring. Some focus on steps to improve the current review process, including transparent policies, safeguards and stakeholder participation; some suggest the need for a case-by-case approach to determine when streamlined review is both needed and appropriate, depending on the level of risk posed.

Conclusions

- Research Ethics Committees are, mainly, to protect studies participants from harm.
  - As RWS commonly involve usual care interventions, the risks may be minimal.
    - **This leads many to reject the research-practice distinction and question the need for informed consent.**
- The function of monitoring should be understood broadly, as protecting the liberty and welfare interest of participants and promoting public trust in research, remains essential, even in RWS.
  - Appropriate Ethics Review Committees may needed for RWS.

Conclusive Remarks
The Rise of “Pragmatism”

- The cornerstone of a **RWS** is **the ability to evaluate an intervention's effectiveness in real life** and achieve maximum external validity,
  - i.e., to be able to generalize results to many settings.
  - **But what is the definition of “real life” when it comes to health sciences?**
- **Policy approaches** for the generation and interpretation of Real-World Evidence and data are urgently needed,
  - to identify best practices for the ethical usage of real-world evidence by industry, regulatory bodies, and payers, with a specific focus on data from non-trial preapproval access to investigational interventions.