JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Principles of Drug Effectiveness Research

Jodi Segal, MD, MPH
Johns Hopkins University

Course Overview

- Principles of drug effectiveness research
- Methods in drug effectiveness research: Part 1
- Methods in drug effectiveness research: Part 2
- Applied examples of drug effectiveness research

Lecture Contents

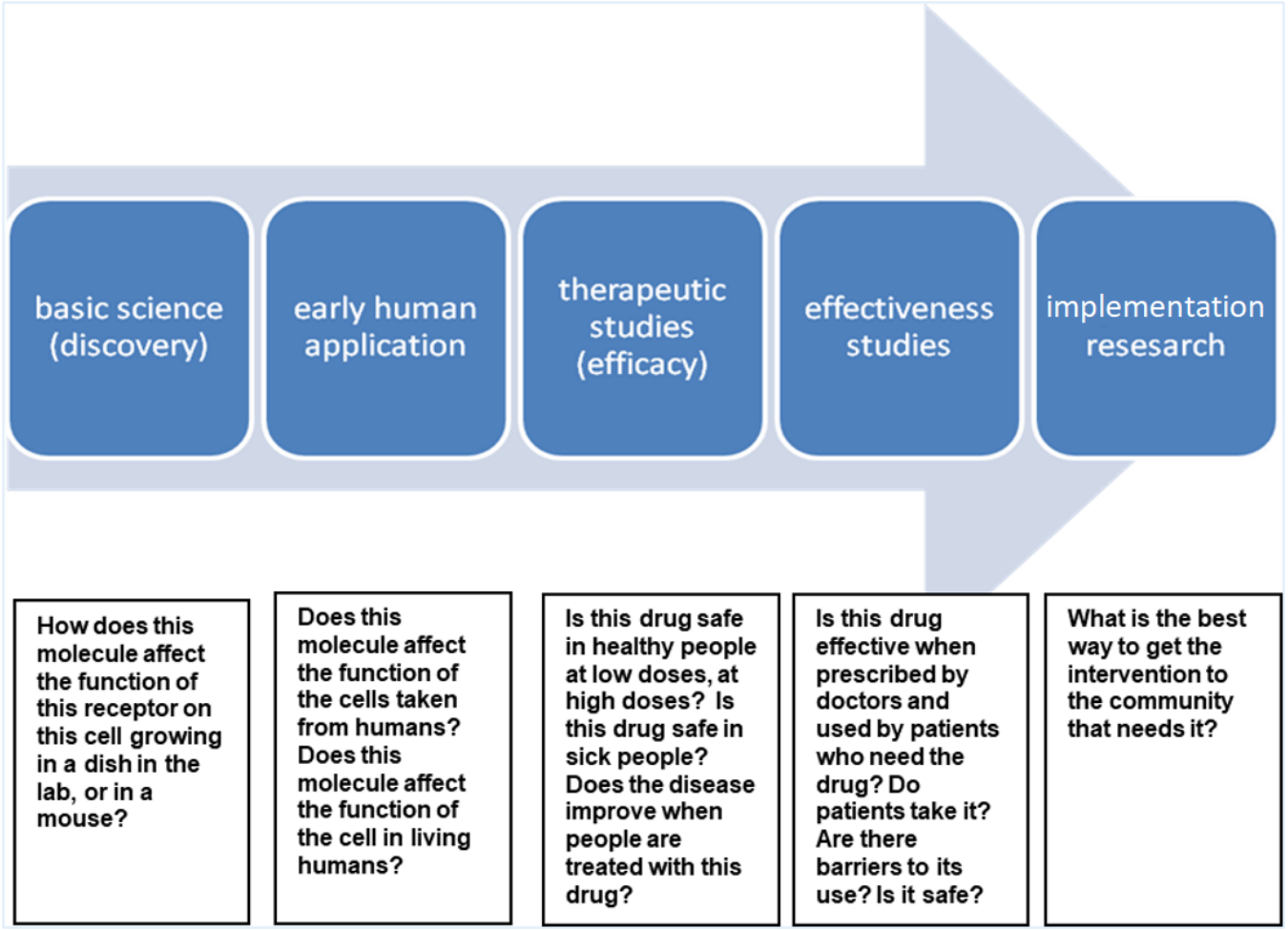
1. Goals of effectiveness research
2. Efficacy vs. effectiveness evidence
3. Stakeholders who need evidence
4. Real-world evidence for decision-making
5. Framing a research question
6. Choosing important outcomes

Goals of Effectiveness Research

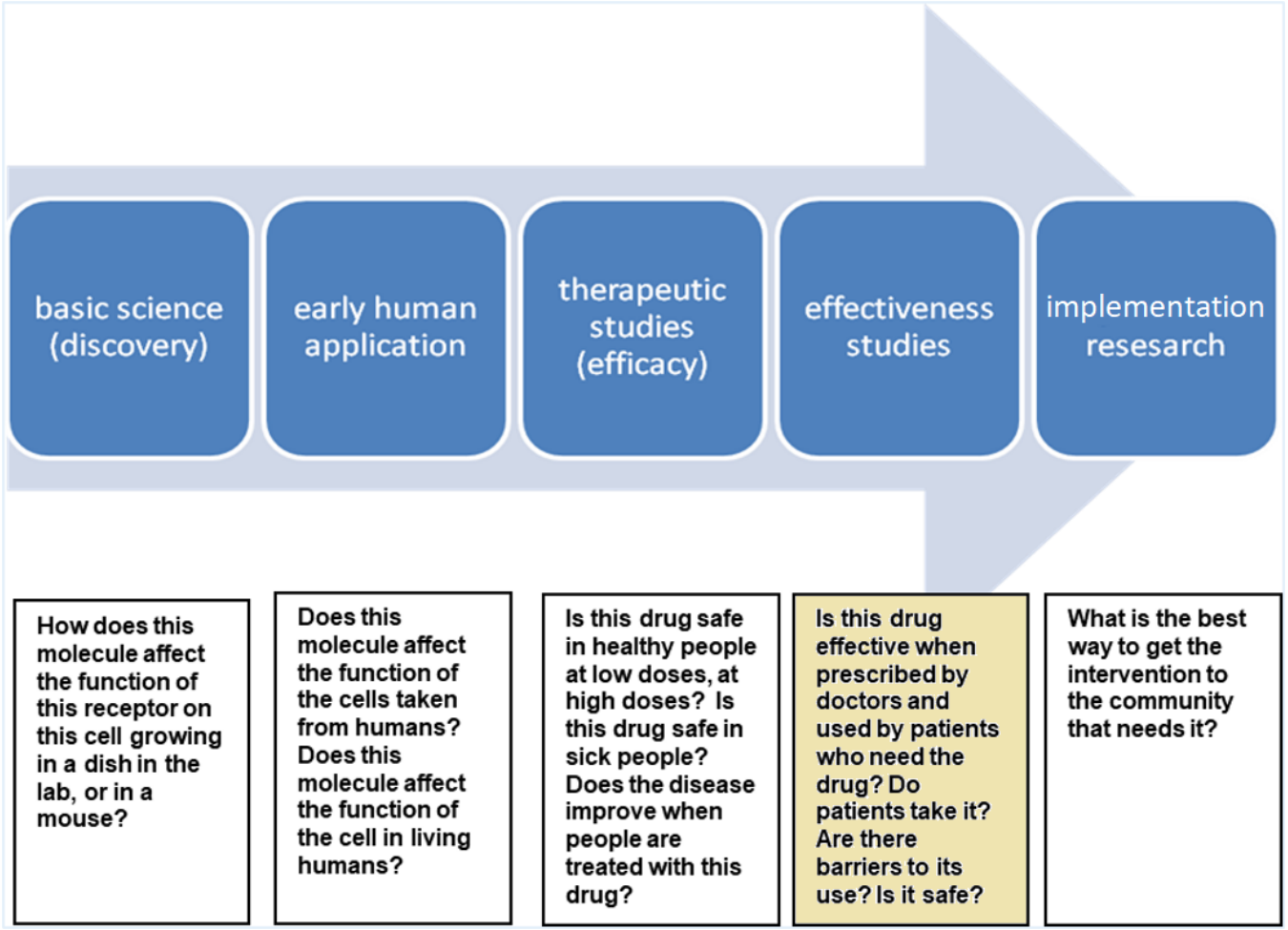
Goal of Improving Human Health

- The “problem” that we solve is lack of evidence about what works best
- We seek to learn which therapies work best for patients—which are most effective, safe, affordable, and tolerable
- We generate evidence about the benefits and harms and costs of different treatment options
- This evidence can then be translated into interventions that improve patient outcomes, or it can inform regulatory decisions or coverage decisions or formulary decisions

A Translational Science Pathway—1



A Translational Science Pathway—2



Efficacy vs. Effectiveness

Why This Distinction?

- Pharmaceutical industry invests the majority of its time and financial resources into premarket clinical research, answering first the “safety” question and then the “efficacy” question
- They are indeed interested in their drugs through their whole “life cycle,” but postmarketing evaluation of effectiveness is not a priority

Phase I	Phase II	Phase III	Phase IV
20-80 participants	**100-300 participants**	**1,000-3,000 participants**	**Thousands of participants**
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

Source: https://ihshealths.com/phases-i-iv/

Efficacy Studies and Effectiveness Studies

- ***Efficacy studies*** aim to investigate whether an intervention works under optimal circumstances
  - Answer the question “Can it work?”

- ***Effectiveness studies*** aim to evaluate whether an intervention works under usual circumstances
  - Answer the question “Does it work?”

Comparing Efficacy Studies and Effectiveness Studies

	Efficacy studies	Effectiveness studies
Objective	Does it work under optimal circumstances?	Does it work under usual circumstances?
Motivation	Regulatory approval	Practice guidelines, formulary approval
Intervention	Fixed regimen	Flexible regimen like used in practice
Comparator	Placebo, often; sometime standard of care	Usual care or other active comparator
Design	Randomized controlled trials, most often	Observational designs or pragmatic trials
Subjects	Highly selected or “eligible” subjects	Usual users of the product
Outcomes	Condition-specific (sometime biomarkers or surrogate outcomes); strong link to mechanism; short-term horizon	Comprehensive (for example, quality of life, patient-centered outcomes), perhaps weak link to mechanism of action; short- and long-term horizon

Source: Bombardier C, Maetzel A Pharmacoeconomic evaluation of new treatments: efficacy versus effectiveness studies? *Annals of the Rheumatic Diseases* 1999;58:I82-I85.

Effectiveness Research Goals

- Design should be motivated by the informational needs
  - What evidence do we need?
  - Who will use the results of this research?
  - What do they need for decision making?

Who Needs Evidence? Stakeholders

What Is a Stakeholder?

- What is a stakeholder?
  - People or groups that have an interest in a particular decision and the evidence that supports a decision
  - Communities that might be affected by or use the results of research
  - The people who need to be “around the table” asking the questions and informing the research
- Stakeholders provide unique and valuable perspectives, beyond those of the researcher, and should be involved in the design of research
- Stakeholder involvement can ultimately lead to greater use and uptake of research results by patients, regulators, and the broader health care community

Defining Stakeholders: “Seven P’s”

Category	Description
Patients and the public	Current and potential consumers of patient-centered health care and population-focused public health, their caregivers, families, and patient and consumer advocacy organizations
Providers	Individuals (e.g., nurses, physicians, pharmacists, and other providers of care) and organizations (e.g., hospitals, clinics, community health centers, community-based organizations, pharmacies, skilled nursing facilities, schools) that provide care to patients and populations
Purchasers	Employers, the self-insured, government, and other entities responsible for underwriting the costs of health care
Payers	Insurers, Medicare and Medicaid, state insurance exchanges, individuals with deductibles, and others responsible for reimbursement for interventions and episodes of care
Policymakers	Department of Health and Human Services, Ministries of Health, Congress, States, professional associations, hospitals, health systems
Product makers	Drug and device manufacturers
Principal investigators	Other researchers and their funders

Source: Concannon, T. W., Meissner, P., Grunbaum, J. A., et al. (2012). A new taxonomy for stakeholder engagement in patient-centered outcomes research. Journal of General Internal Medicine, 27(8), 985–991; http://doi.org/10.1007/s11606-012-2037-1

What Do the Seven P's Need From Pharmacoepidemiologic Research?

Stakeholder	Needs
Patients	Want to know what drug is most effective and safest (and most affordable)
Clinicians	Want to know what drug is most effective and safest, most tolerable, fewest drug–drug interactions
Researchers	Want to generate high-quality evidence
Purchasers	Want cost-effectiveness information (includes effectiveness information)
Payers	Want cost-effectiveness information (includes effectiveness information)
Industry	Wants information about postmarketing safety
Hospitals and health systems	Want information about effectiveness and safety to make a formulary
Policymakers (regulators)	Want information about safety to act if harms are discovered

Why Do Stakeholders Need Evidence? Real-World Decision-Making

Real-World Evidence Definition

- **Real-world *evidence (RWE)*** is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data

- **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
  - Examples:
    - Data derived from electronic health records
    - Administrative claims data
    - Data from product or disease registries
    - Data gathered from other sources (such as digital health technologies) that can inform on health status

Source: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence as of February 2023.

Use of RWE by U.S. Food and Drug Administration (FDA)

- The 21st Century Cures Act of 2016 in the United States was designed to accelerate medical product development and bring new innovations and advances faster and more efficiently to the patients who need them
- FDA created a framework in 2018 to help them evaluate potential uses of RWE for regulation; this has continued to evolve over time, and guidance documents are periodically released on the topic
- FDA's RWE Program was designed to consider how RWD could generate RWE about product effectiveness to **help support approval of new indications** for approved drugs or to **help to support or satisfy post-approval study requirements**

1. New indications
2. Postmarketing requirements

Source: 21st Century Cures Act of 2016 https://www.congress.gov/bill/114th-congress/house-bill/34

FDA's Initial Framework for Using RWE

- FDA assesses (paraphrased):
  - Whether the RWD are fit for use
  - Whether the trial or observational study to generate RWE will provide adequate scientific evidence to answer the regulatory question
  - Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

Source: Framework for FDA's Real World Evidence Program 2018. https://www.fda.gov/media/120060/download?attachment

More Specifically for Retrospective Observational Studies

- FDA focuses on critical questions (paraphrased):
  - What are the characteristics of the **data** (e.g., contain data on a relevant endpoint, consistency in documentation, lack of missing data) that improve the likelihood of valid results?
  - What are the characteristics of the **study design and analysis** (e.g., use of active comparators, considerations about unmeasured confounders, use of non-inferiority designs) that improve the likelihood of a valid result?
  - What **sensitivity analyses and statistical diagnostics** should be prespecified for observational studies using RWD to generate RWE for effectiveness?

Source: Framework for FDA's Real World Evidence Program 2018. https://www.fda.gov/media/120060/download?attachment

FDA Framework (Also) Describes Use of Trials That Generate RWE

"FDA generally considers a traditional clinical trial to be one that is usually supported by a research infrastructure that is largely separate from routine clinical practice and is designed to control variability and maximize data quality."

…

"Some clinical trials may use hybrid design. For example, certain elements of a clinical trial could rely on the collection and analysis of RWD extracted from medical claims, EHRs, or laboratory and pharmacy databases."

…

"Clinical trial designs can also include some elements that more closely resemble routine clinical practice, which are sometimes described as 'pragmatic' elements. These pragmatic clinical trials often rely on RWD and have the potential to generate RWE."

EHR = electronic health record.
Source: Framework for FDA's Real World Evidence Program 2018. https://www.fda.gov/media/120060/download?attachment

RWE Clinical Trial That Used RWD—1

ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; start date April 2016) (NCT02697916)

- This pragmatic clinical trial compares two commonly used aspirin doses, 81 mg and 325 mg, by randomizing patients with a history of myocardial infarction or known atherosclerotic cardiovascular heart disease to one of the two doses
- Used EHRs and claims data to capture primary endpoints of death, hospitalization for nonfatal myocardial infarction or nonfatal stroke

Source: Jones, W. S., Mulder, H., Wruck, L. M., Pencina, M. J., Kripalani, S., Muñoz, D., Crenshaw, D. L., Effron, M. B., Re, R. N., Gupta, K., Anderson, R. D., Pepine, C. J., Handberg, E. M., Manning, B. R., Jain, S. K., Girotra, S., Riley, D., DeWalt, D. A., Whittle, J., … Hernandez, A. F. (2021). Comparative effectiveness of aspirin dosing in cardiovascular disease. *The New England Journal of Medicine*, *384*(21), 1981–1990. https://doi.org/10.1056/NEJMoa2102137

RWE Clinical Trial That Used RWD—2

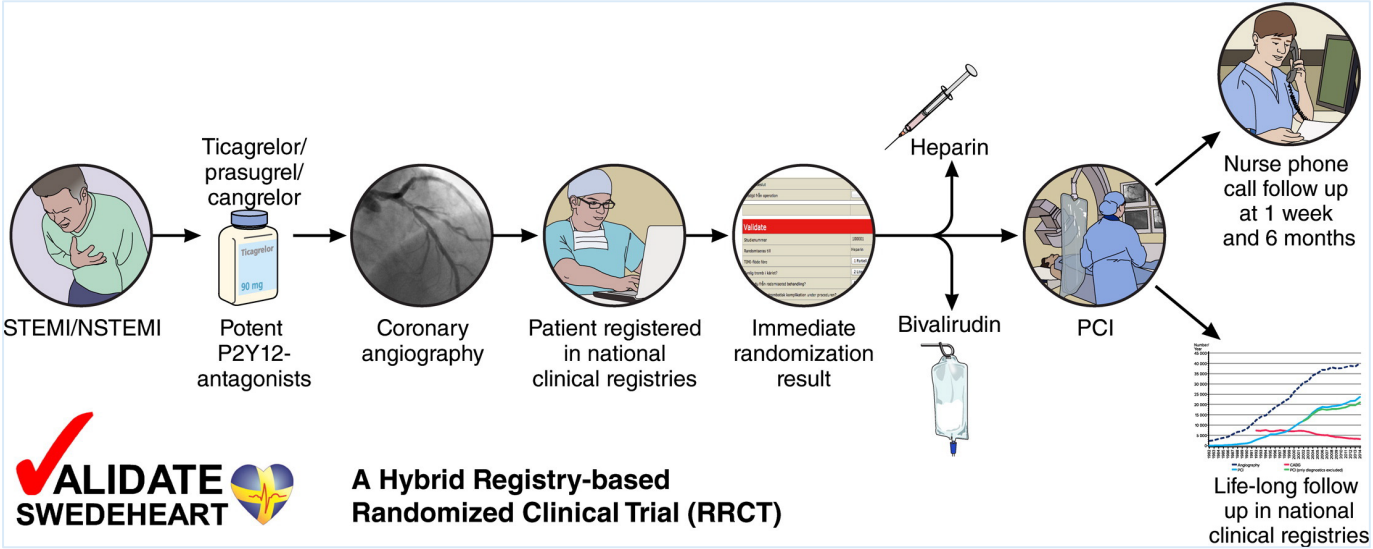
ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness; start date April 2016) (NCT02697916)

- The trial uses electronic algorithms to identify potential participants from the National Patient-Centered Clinical Research Network (PCORnet) health system partners
- The trial is integrated into routine clinical care with minimal inclusion/exclusion criteria and no treatment protocol requirement beyond the assignment to one of the two doses of aspirin
- CONCLUSIONS: Effectiveness and safety outcomes did not differ significantly with daily use of 81 mg as compared with 325 mg of aspirin in patients with established atherosclerotic cardiovascular disease, and adherence was better with the 81-mg dose

Source: Jones, W. S., Mulder, H., Wruck, L. M., Pencina, M. J., Kripalani, S., Muñoz, D., Crenshaw, D. L., Effron, M. B., Re, R. N., Gupta, K., Anderson, R. D., Pepine, C. J., Handberg, E. M., Manning, B. R., Jain, S. K., Girotra, S., Riley, D., DeWalt, D. A., Whittle, J., … Hernandez, A. F. (2021). Comparative effectiveness of aspirin dosing in cardiovascular disease. *The New England Journal of Medicine*, *384*(21), 1981–1990. https://doi.org/10.1056/NEJMoa2102137

Another Example of RWE Clinical Trial that Used RWD—1

VALIDATE-SWEDEHEART (The Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial)(NCT02311231)



Source: Erlinge, D., Omerovic, E., Fröbert, O., et al. (2017). Bivalirudin versus heparin monotherapy in myocardial infarction. *The New England Journal of Medicine*, *377*(12), 1132–1142. https://doi.org/10.1056/NEJMoa1706443

Another Example of RWE Clinical Trial that Used RWD—2

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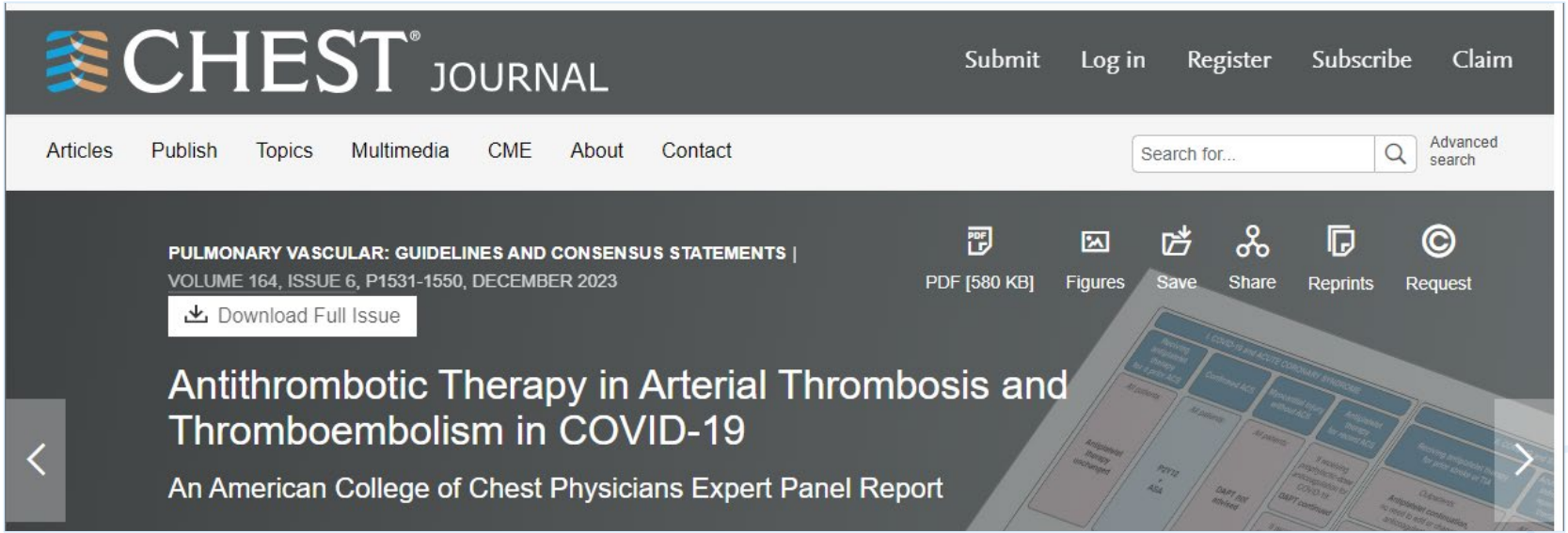
- CONCLUSIONS: Among patients undergoing PCI for myocardial infarction, the rate of the composite of death from any cause, myocardial infarction, or major bleeding was not lower among those who received bivalirudin than among those who received heparin monotherapy

Source: Erlinge, D., Omerovic, E., Fröbert, O., et al. (2017). Bivalirudin versus heparin monotherapy in myocardial infarction. *The New England Journal of Medicine*, *377*(12), 1132–1142. https://doi.org/10.1056/NEJMoa1706443

Other Decision Makers Use RWE

- Clinical Practice Guidelines are meant to inform the practice of medicine
  - Example: “CHEST Guidelines”

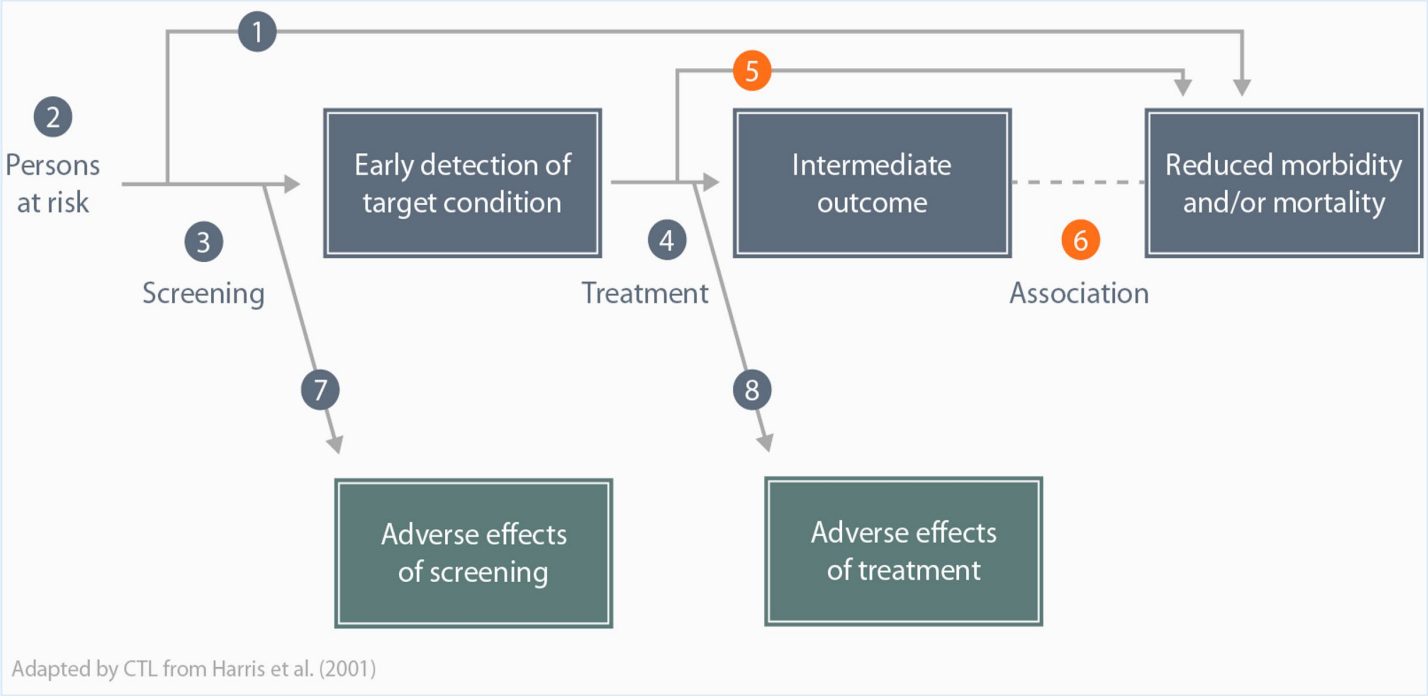


Clinical Practice Guidelines

- Some are strictly based on evidence, and some are not (based more on expert opinion)
- Some make recommendations only on the basis of evidence from randomized controlled trials, and some use evidence from observational studies
- Our work can importantly inform clinical practice guidelines as we generate RWE that demonstrates what works in practice

Framing a Research Question About Effectiveness

Create an Analytic Framework



Adapted by the Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health, from: Figure 1, "Generic a nalytic framework for screening topics," in: Harris, R. P., Helfand, M., Woolf, S. H., et al. (2001). Current methods of the US Preventive Services Task Force: A review of the process. *American Journal of Preventive Medicine*, *20*(3 Suppl), 21–35. https://doi.org/10.1016/s0749-3797(01)00261-6

PICOTS Formulation

- **P**opulation
- **I**ntervention
- **C**omparator
- **O**utcomes
- **T**iming
- **S**etting

- PICOTS
  - Most helpful for comparative effectiveness or safety questions
  - Often, the comparator is “usual care” or how things are currently being done
  - Certainly not the only way to frame a question

Clinical Question

- Clinicians want to know what oral medicines are most effective second-line treatments for adults with type 2 diabetes mellitus

PICOTS to Frame the Question

PICOTS Category	Detail
P	Adults with type 2 diabetes mellitus taking metformin
I	Second-line oral hypoglycemic medications
C	Other second-line oral hypoglycemic medications
O	Mortality, retinopathy, nephropathy, glycemic control, hypoglycemic events
T	2-year outcomes
S	Outpatient setting

Answerable Question About Effectiveness

- What is the **effectiveness** of SGLT2 inhibitors with metformin compared to GLP-1 receptor agonists with metformin in adults with type 2 diabetes on the outcomes of progression of kidney disease 2 years after initiation of therapy?

Answerable Question About Safety

- What is the **safety** of SGLT2 inhibitors with metformin compared to GLP-1 receptor agonists with metformin in adults with type 2 diabetes on the outcome of hypoglycemia with the first three months after initiation of therapy?

Outcomes

Effective and Safe

Investigations of safety and effectiveness require that we specify **outcomes** that are important to one or more stakeholders

- Do patients care whether a newly approved medication **lowers LDL** by 3%?
- Does the FDA care whether a newly approved medication has a 40% greater risk of **death** than the medications that are standardly used for this condition?
- Do clinicians care whether a newly approved medication has 20% lower likelihood of treatment **discontinuation** than the older medication?

Therapeutic Studies Outcomes

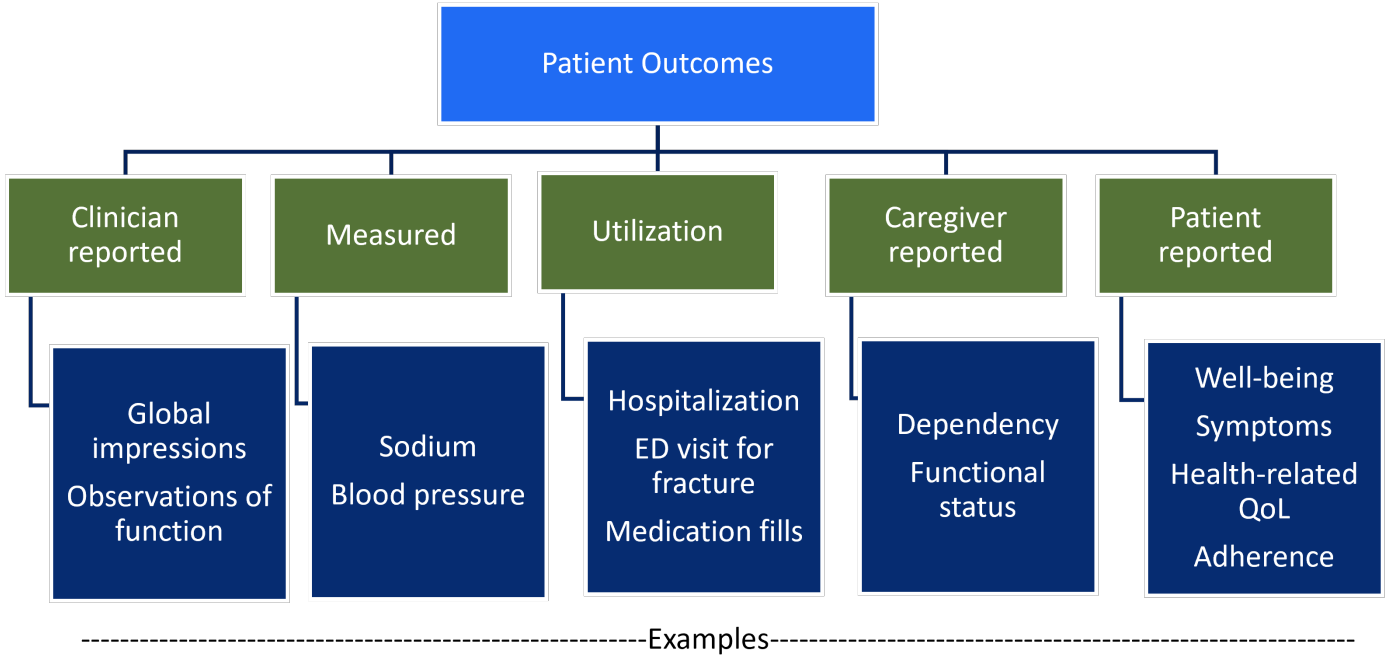
Outcome	Example
Effectiveness	First-line SGLT2 inhibitors are associated with **lower lifetime rates of congestive heart failure, ischemic heart disease, myocardial infarction, and stroke** compared with metformin
Safety	First-line use of SGLT2 **increases genitourinary infections** relative to first-line use of metformin
Economic	First-line SGLT2 inhibitors **cost $43 000 more** than first-line metformin over lifetime use

Source: Choi JG, Winn AN, Skandari MR, Franco MI, Staab EM, Alexander J, Wan W, Zhu M, Huang ES, Philipson L, Laiteerapong N. First-Line Therapy for Type 2 Diabetes With Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists : A Cost-Effectiveness Study. Ann Intern Med. 2022 Oct;175(10):1392-1400

Other Therapeutic Outcomes

- Other relevant outcomes when evaluating a treatment might include:
  - **Patient-relevant outcomes:** acceptability of treatment, satisfaction, need for treatment intensification, side effects, adverse events, days missed from work
  - **Health system–relevant outcomes:** patterns of health care usage after treatment, total costs of care, patient-reported satisfaction, diabetes quality metrics
  - **Regulatory-relevant outcomes:** adverse events, deaths, product confusion, quality deficits

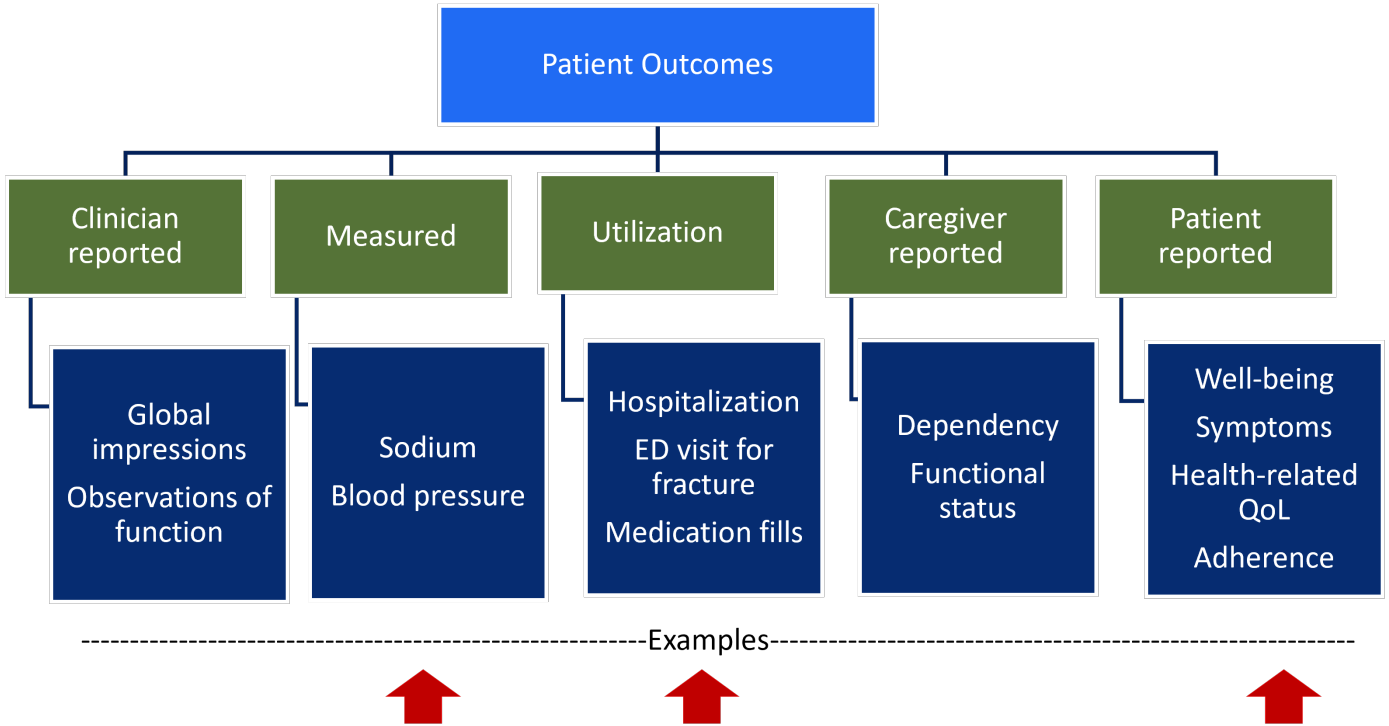
Breadth of Patient Outcomes



ED = emergency department, QoL = quality of life.

Adapted from: Acquadro, C., Berzon, R., Dubois, D., et al. (2003). Incorporating the patient's perspective into drug development and communication: An ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. *Value in Health*, *6*(5), 522–531. https://doi.org/10.1046/j.1524-4733.2003.65309.x

Most Accessible in Real-World Data



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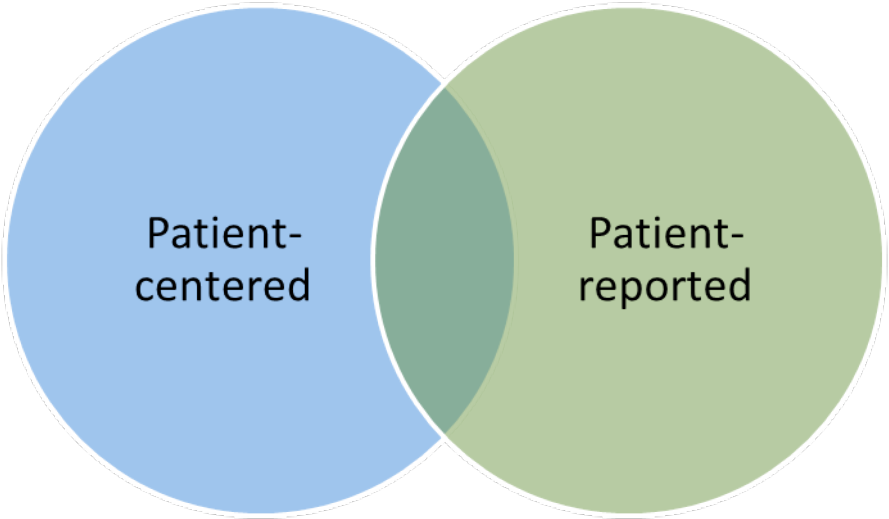
Some Outcomes Are Patient-Centered and Important (but Are Not Patient-Reported)

- ✓ **Death**
- ✓ Pain
- ✓ Health-related quality of life (HrQoL)
- ✓ Palpitations
- ✓ **Liver fibrosis score**
- ✓ Out-of-pocket (OoP) costs
- ✓ **Viral clearance at 12 weeks**
- ✓ Time to return to work



Summary of Module

- Why we do effectiveness research?
- What is evidence?
- Who cares about effectiveness and safety evidence?
- What is the difference between efficacy and effectiveness evidence?
- How might you begin framing a meaningful question including a focus on important outcomes?