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Pharmacoepidemiology and Its Role in the Drug Approval Process

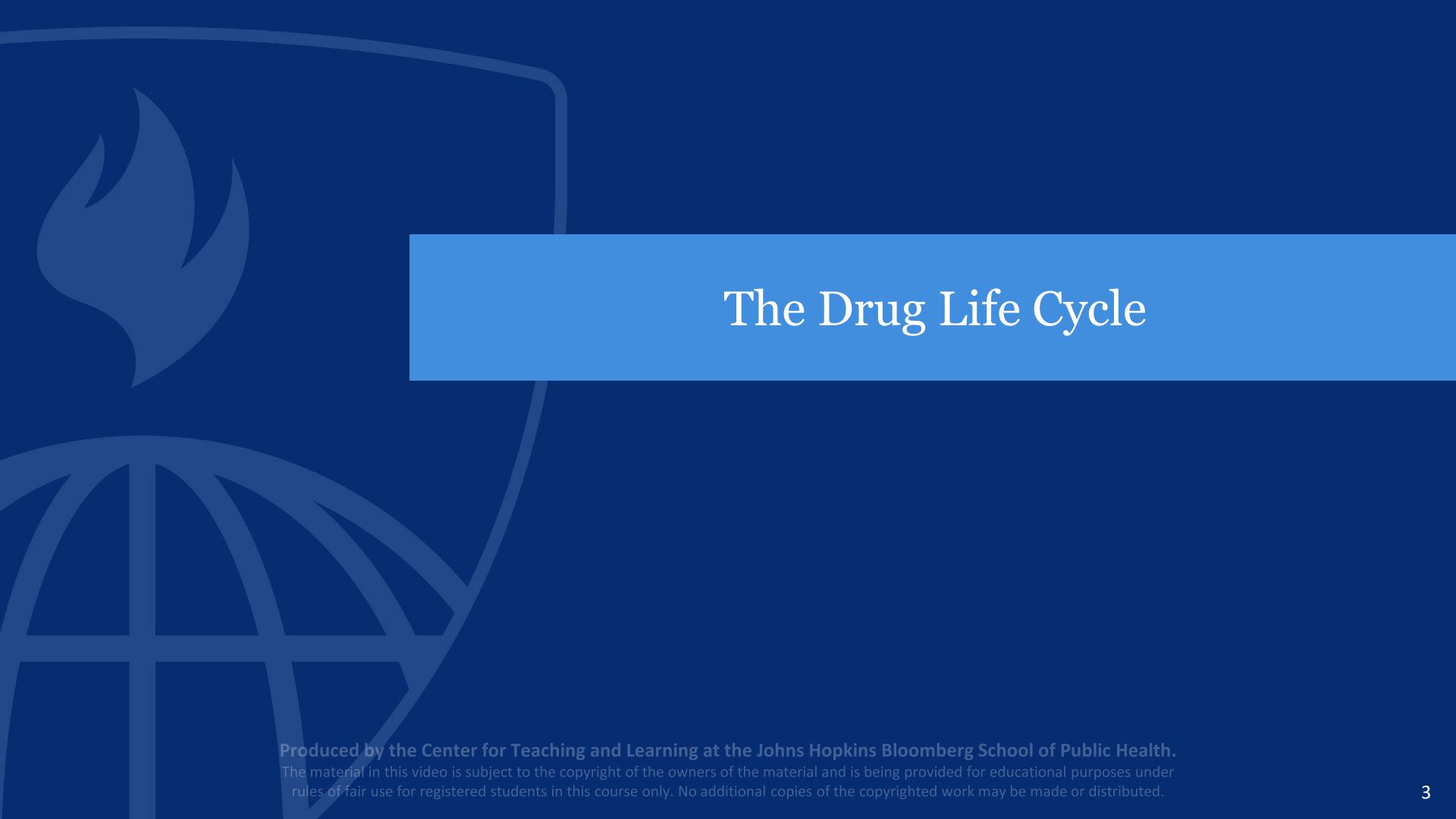
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- ▶ Drug life cycle
- ▶ What is pharmacoepidemiology (p'epi)?
- ▶ Role of p'epi in drug discovery and phase 1 to 3 trials
- ▶ Role of p'epi in postmarketing studies
- ▶ Role of p'epi and real-world evidence to inform regulatory, policy, and clinical decisions
- ▶ Future of p'epi



The Drug Life Cycle

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Stages of the Drug Life Cycle

- ▶ Describes market behavior of drug products
- ▶ Four stages:
 1. Testing and approval trajectory
 2. Market growth
 3. Drug maturity
 4. Drug decline

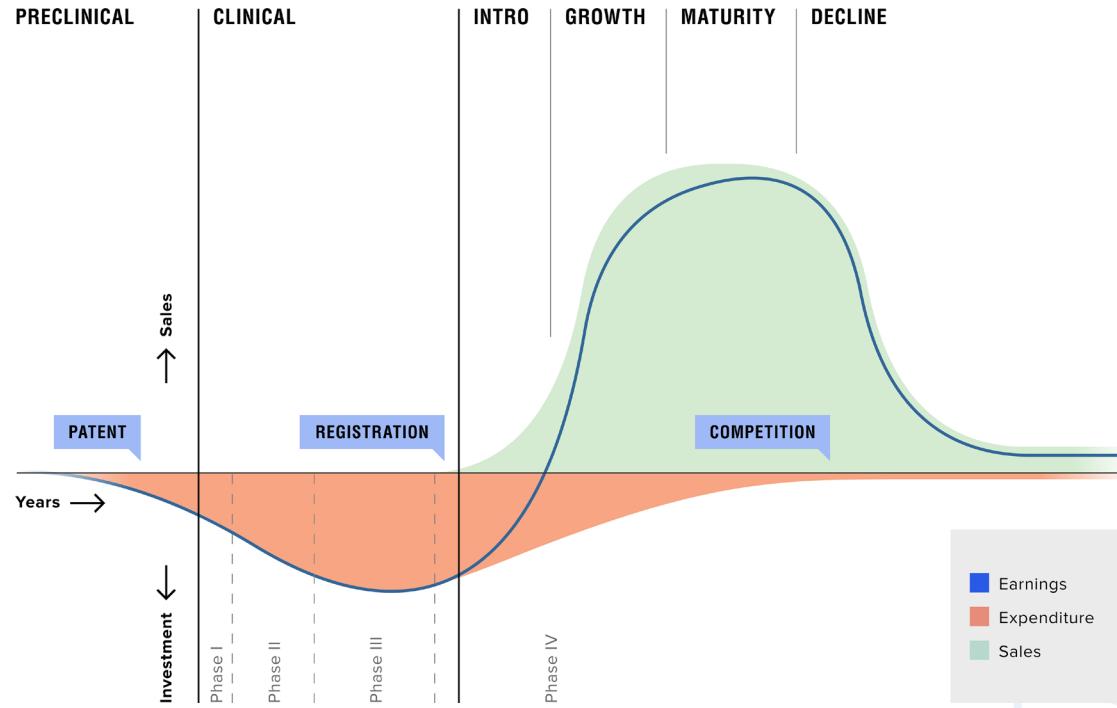


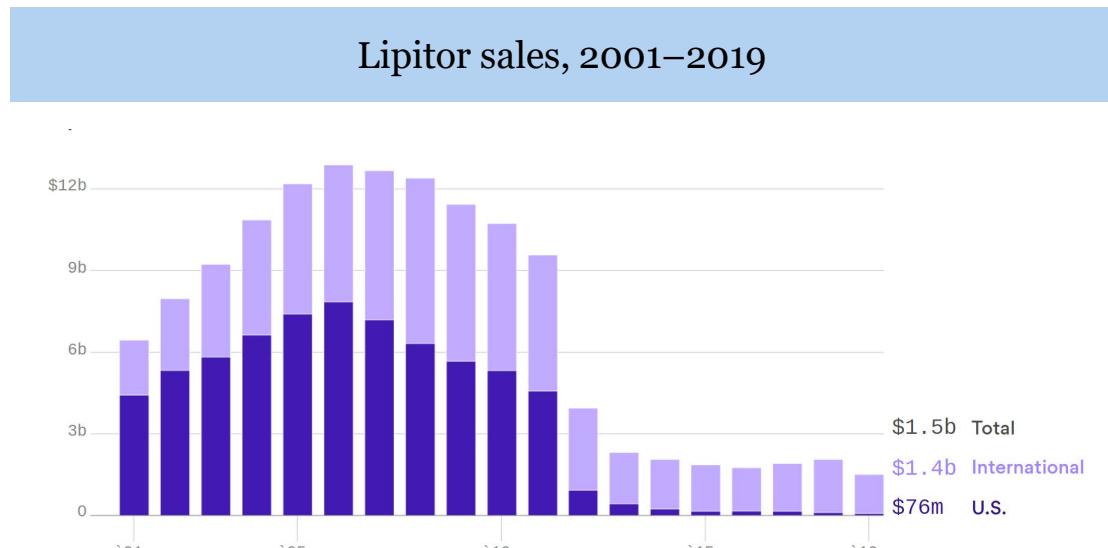
Image source: Figure 2, "Drug life cycle curve," in: Gronde, T. van der, Uyl-de Groot, C. A., & Pieters, T. (2017). Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. *PloS One*, 12(8), e0182613. <https://doi.org/10.1371/journal.pone.0182613>

Patent and Exclusivity

- ▶ **Patents** are a property right granted by the United States Patent and Trademark Office (USPTO) anytime during the development of a drug and can encompass a wide range of claims
 - ▶ 20 years from the patent filing date
- ▶ **Exclusivity** is exclusive marketing rights granted by the FDA
 - ▶ It is a period of time during which a brand-name drug is protected from generic drug competition
 - 5 years—new chemical entity
 - 7 years—orphan drug exclusivity
 - 3 years—new clinical investigation exclusivity
- ▶ Most drugs receive 12 to 16 years of monopoly through both types of protection after the drug is approved
- ▶ Once market exclusivity expires, generic drugs can enter the market

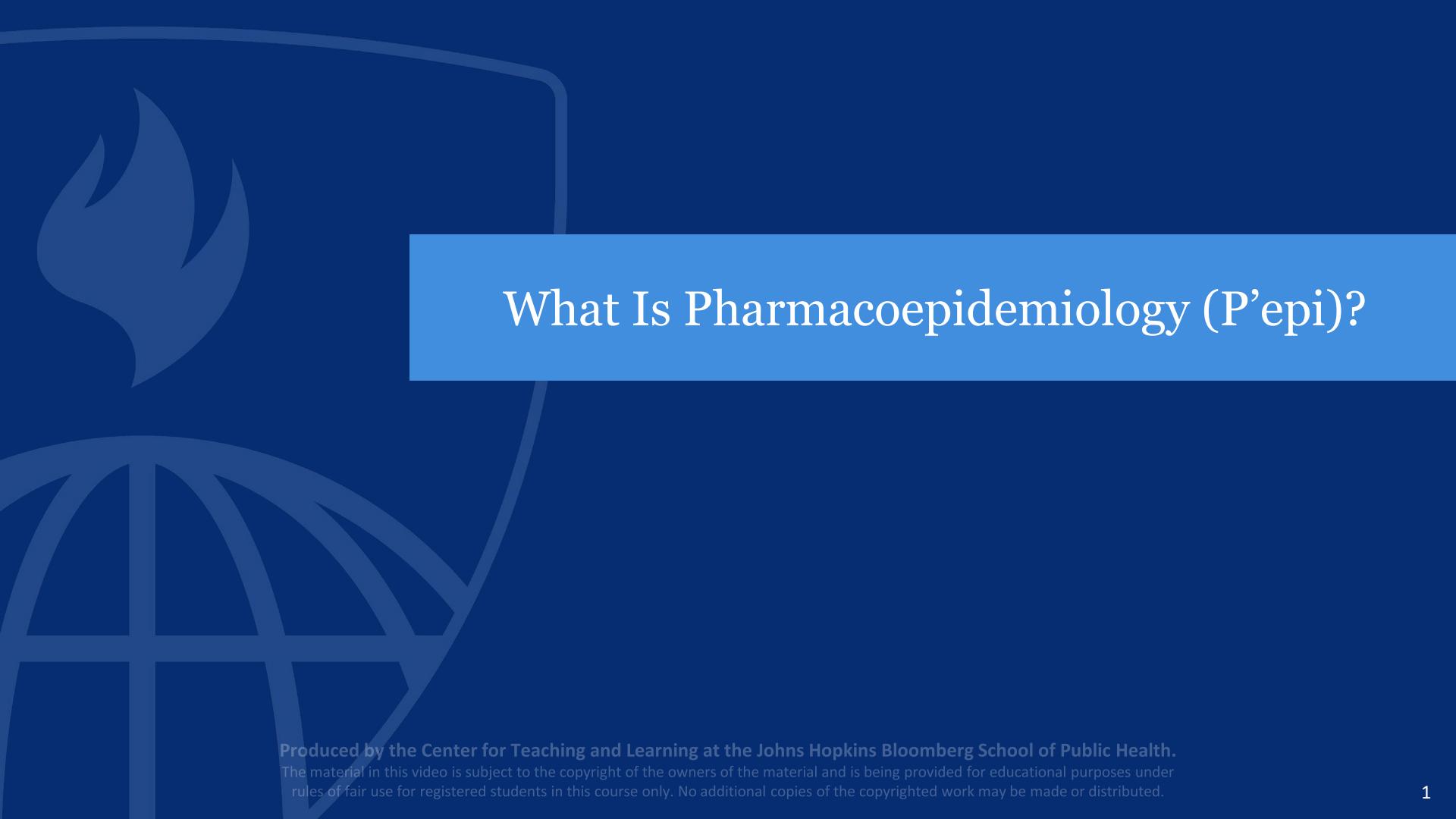
Case Study of Lipitor (Atorvastatin)

- ▶ **Lipitor**—cholesterol-lowering medicine
 - ▶ Blockbuster drug for Pfizer
 - ▶ Market approval in 1996
- ▶ Lipitor patent expired in 2011
- ▶ Lifetime sales of \$149 billion
 - ▶ Peak sales of \$13 billion in 2006
 - ▶ \$9.57 billion in 2011
 - ▶ \$3.94 billion in 2012
 - ▶ Continue to decline



Source: Sagonowsky, E. (2017, August 17). The decade's top 10 patent losses, worth a whopping \$915B in lifetime sales. Fierce Pharma. <https://www.fiercepharma.com/pharma/decade-s-top-10-patent-losses-featuring-seismic-sales-shifts>

Image source: Naema Ahmed / Axios. Chart, "Lipitor sales, 2001–19," in: Herman, B. (2019, October 30). Cholesterol drug Lipitor is still generating billions for Pfizer. Axios. <https://wwwaxios.com/2019/10/30/lipitor-pfizer-drug-patent-sales-2019>



What Is Pharmacoepidemiology (P'epi)?

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Pharmacoepidemiology

Pharmacoepidemiology = pharmacology + epidemiology

► **Pharmacology**

- Study of the effects of drugs

► **Clinical pharmacology**

- Study of the effects of drugs in humans
- Individualization of therapy by determining risk and benefits specific to the patient

► **Epidemiology**

- Study of the distribution and determinants of diseases in populations
- Methods

Pharmacoepidemiology is an applied field that borrows focus on inquiry from clinical pharmacology and methods of inquiry from epidemiology

Pharmacoepidemiology (P'epi) Definition

Traditional definition

- ▶ An applied science that uses epidemiological techniques to study **drug** effects
- ▶ Pharmacoepidemiology is the study of the use of and the effects of **drugs** in large numbers of people

New definition (2024)

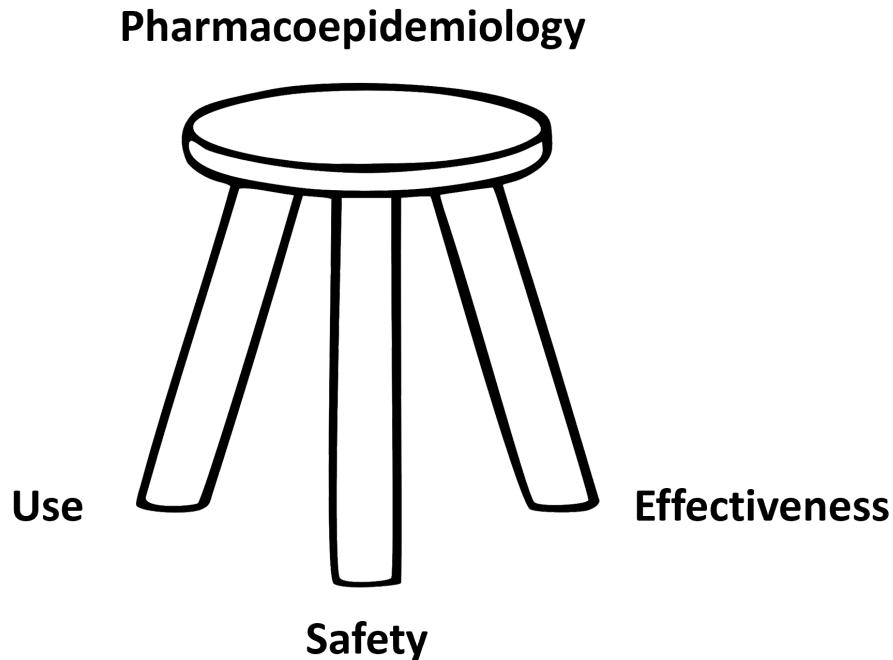
- ▶ A scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of **medical products and interventions** in human populations
 - ▶ Broadens the scope by including drugs, vaccines, devices, biologics, and other health care interventions
 - ▶ Endorsed by the International Society for Pharmacoepidemiology (ISPE)

Sources:

Edlavitch, S. A., & Tilson, H. H. (2021). For consideration by pharmacoepidemiologists. *Pharmacoepidemiology and Drug Safety*, 30(12), 1619–1620. <https://doi.org/10.1002/pds.5365>

Osborne, V., Goodin, A., Brown, J., et al. (2024). Updated core competencies in pharmacoepidemiology to inform contemporary curricula and training for academia, government, and industry. *Pharmacoepidemiology and Drug Safety*, 33(4), e5789. <https://doi.org/10.1002/pds.5789>

Pharmacoepidemiology: Three Pillars



Real-World Evidence (RWE) and Real-World Data (RWD)

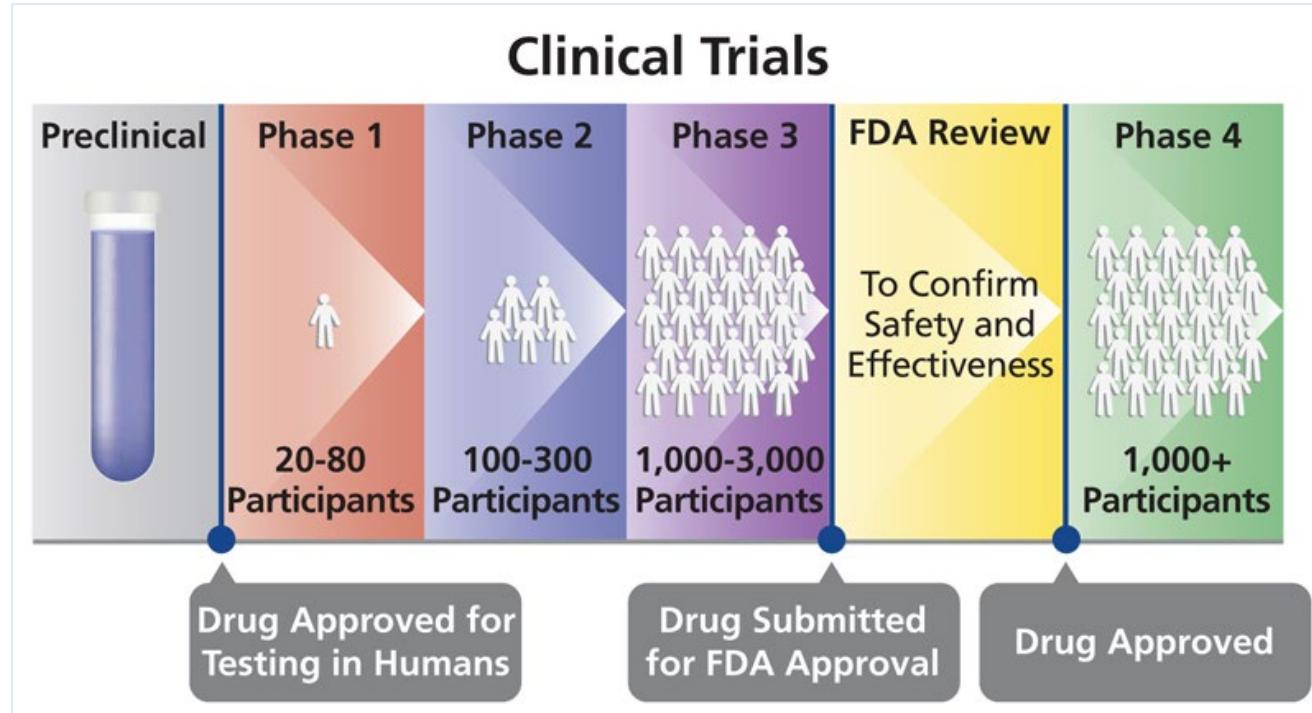
- ▶ The terms ***real-world evidence*** (RWE) and ***real-world data*** (RWD) have emerged in the recent years
- ▶ RWD
 - ▶ Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (FDA)
 - ▶ Routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials (EMA)
- ▶ RWE
 - ▶ Clinical evidence regarding a medical product's use and potential benefits or risks derived from the analysis of RWD (FDA)
 - ▶ Evidence derived from the analysis of RWD (EMA)

Sources:

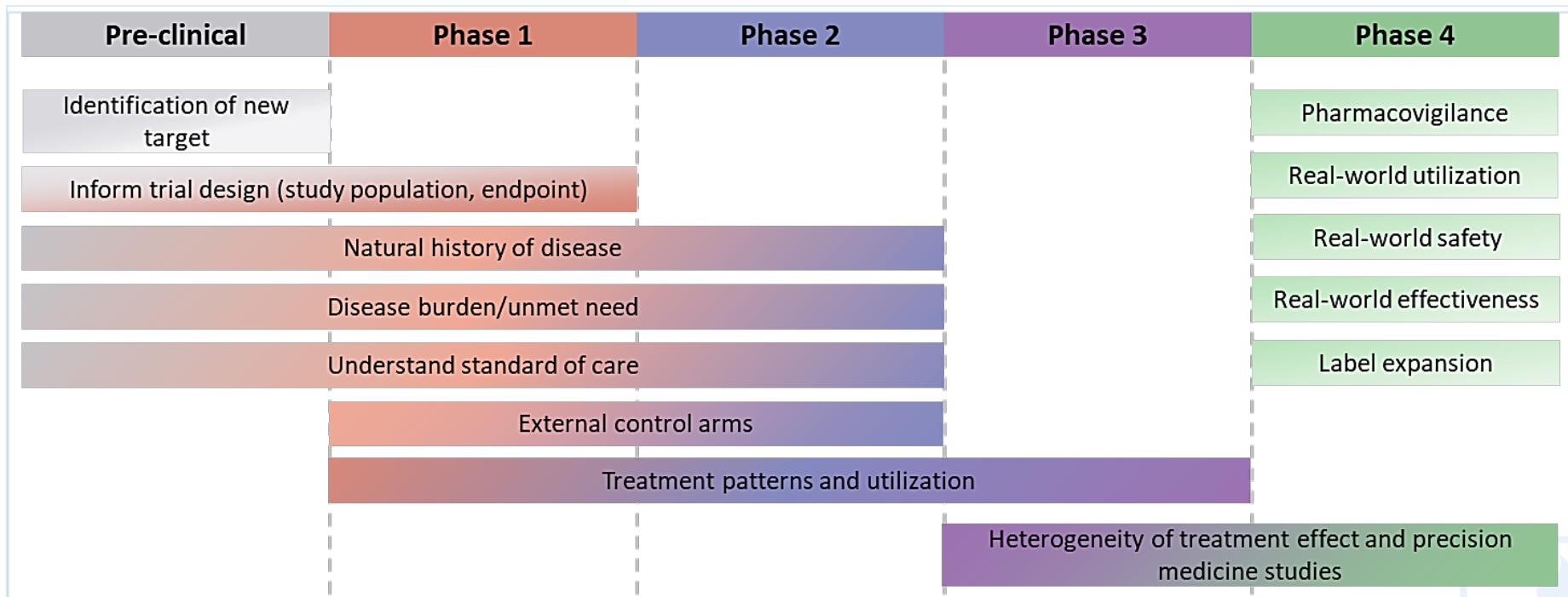
Hernandez, R. K., Critchlow, C. W., Dreyer, N., et al. (2025). Advancing principled pharmacoepidemiologic research to support regulatory and healthcare decision making: the era of real-world evidence. *Clinical Pharmacology and Therapeutics*, 117(4), 927–937. <https://doi.org/10.1002/cpt.3563>

Toh, S. (2017). Pharmacoepidemiology in the era of real-world evidence. *Current Epidemiology Reports*, 4(4), 262–265. <https://doi.org/10.1007/s40471-017-0123-y>

Recap: Drug Approval Process



Role of Pharmacoepidemiology in the Drug Approval Process

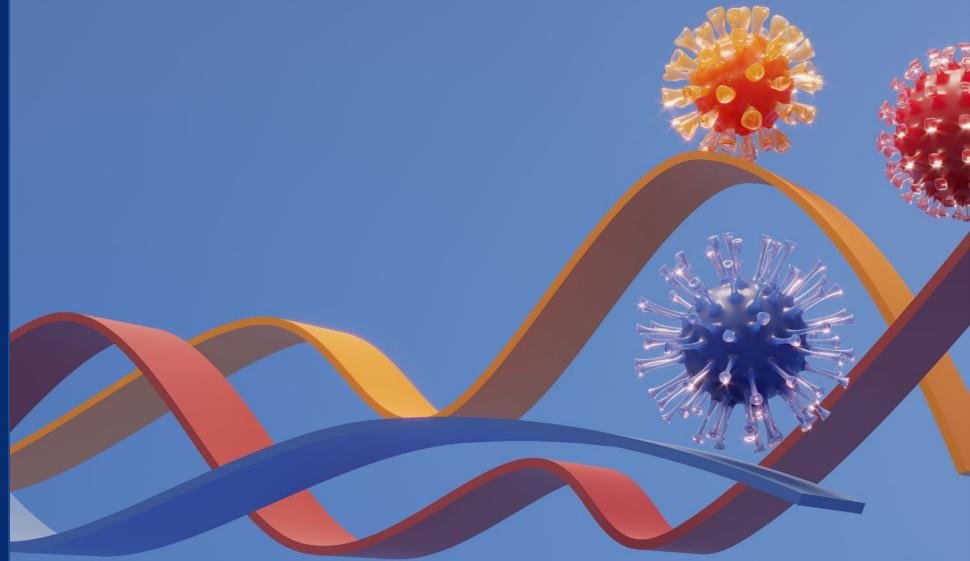




Role of P'epi in Drug Discovery and Phase 1 to 3 Trials

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Natural History of Disease



What Is the Natural History of a Disease?

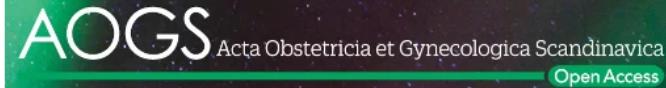
- ▶ “Defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease’s onset until either the disease’s resolution or the individual’s death”
- ▶ Pre-planned real-world study to aid drug development process
 - ▶ Identify patient population for clinical trials
 - Characterize study population for demographics and clinical characteristics
 - Inform potential inclusion and exclusion criteria
 - ▶ Understanding evolution of disease
 - ▶ Identification of risk factors for developing disease
 - ▶ Identification of biomarkers
 - ▶ Evaluation of clinical outcome or endpoint selection for trials
- ▶ Particularly useful for rare diseases but can also be used for non-rare diseases

Sources:

Bratton, E., Holt, C., Kromrey, S., & Keefer, J. (n.d.). *Natural History Studies for Rare Diseases: Development Strategies for External Comparator Arms Leveraging Real World Insights*. IQVIA.
<https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/natural-history-studies-for-rare-diseases.pdf>

FDA/CDER, Hills, I. (2019). Rare Diseases: Natural History Studies for Drug Development Guidance for Industry: Draft Guidance. <https://www.fda.gov/media/122425/download>

Natural History of Disease: Case Study—1



Free Access

Natural history of endometrial cancer: report of one woman who did not accept treatment

Anders Norström, Seth Granberg

First published: 01 April 2004 | <https://doi.org/10.1111/j.0001-6349.2004.00092c.x>

- ▶ One woman diagnosed at the age of 47
- ▶ Followed without treatment for 9 years



Endometrial cancer risk factors & biomarkers for natural history & early detection: The Mayo Study

- ▶ Large study to collect information on
 - ▶ Novel biospecimen
 - ▶ Clinical and epidemiological risk factors
 - ▶ Biomarker measures
 - ▶ Cancer risk assessment

Sources:

Norström, A., & Granberg, S. (2004). Natural history of endometrial cancer: Report of one woman who did not accept treatment. *Acta Obstetricia Et Gynecologica Scandinavica*, 83(5), 506–507. <https://doi.org/10.1111/j.0001-6349.2004.00092c.x>

US National Cancer Institute. (2019, November 12). Endometrial cancer risk factors & biomarkers for natural history & early detection: The Mayo Study. <https://dceg.cancer.gov/research/cancer-types/endometrium-uterus/mayo-study>

Natural History of Disease: Case Study—2

Research Question	Results
<ul style="list-style-type: none">▶ Evaluate endometrial cancer risk assessment and early detection strategies in high-risk populations ▶ Women from one health system	<ul style="list-style-type: none">▶ Characterizes demographic and clinical characteristics of 1,205 women—49 with endometrial cancer ▶ Risk factors:<ul style="list-style-type: none">▶ Age▶ Body mass index▶ Smoking▶ Hormone therapy use

Unmet Need and Treatment Patterns

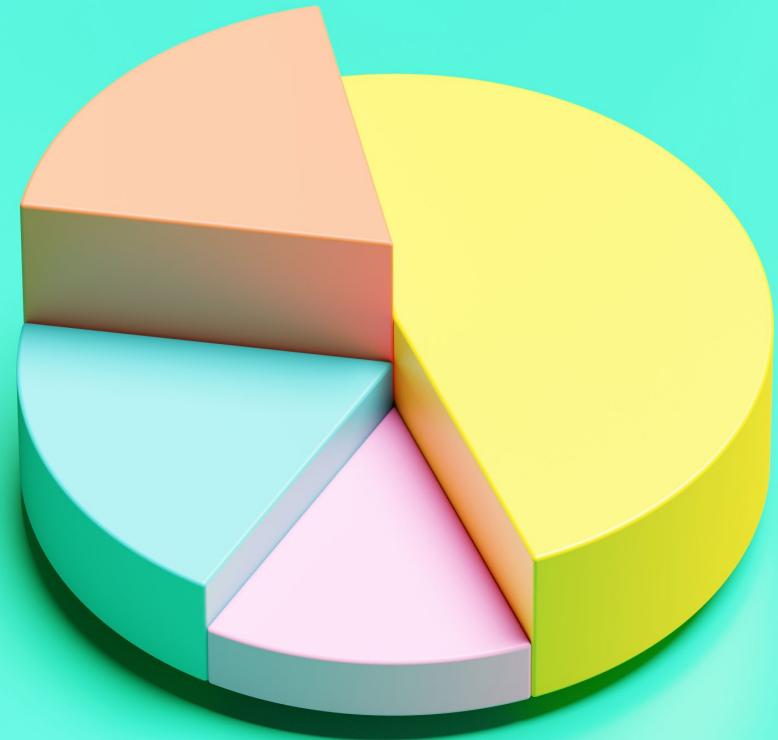


Image: Microsoft Corp. stock image.

What Are Unmet Need and Treatment Patterns?

Unmet Need	Treatment Patterns
<ul style="list-style-type: none">▶ FDA definition▶ An unmet medical need is a condition the treatment or diagnosis of which is not addressed adequately by available therapy	<ul style="list-style-type: none">▶ How are patients treated with existing treatments?▶ Identify trends and patterns in treatment use▶ Characterize clinical outcomes among patients treated with existing treatments

Unmet Need and Treatment Patterns: Case Study

Research Question	Results
<ul style="list-style-type: none">► Defining areas of high unmet need can fuel development and provide guidance for clinical trials► To describe patient characteristics, treatment patterns, and clinical outcomes in women with advanced endometrial cancer► Oncology electronic health records from the United States	<ul style="list-style-type: none">► Characterized patient population► Described contemporary treatment with different types of anticancer drugs► Noted poor survival outcomes among patients with advanced endometrial cancer<ul style="list-style-type: none">► Need for new treatment options

Drug Approval Based on Real-World Evidence



Image adapted by the Center for Teaching and Learning, Johns Hopkins Bloomberg School of Public Health, from Starline on www.freepik.com.

“FDA Approves New Use of Transplant Drug Based on Real-World Evidence,” 2021

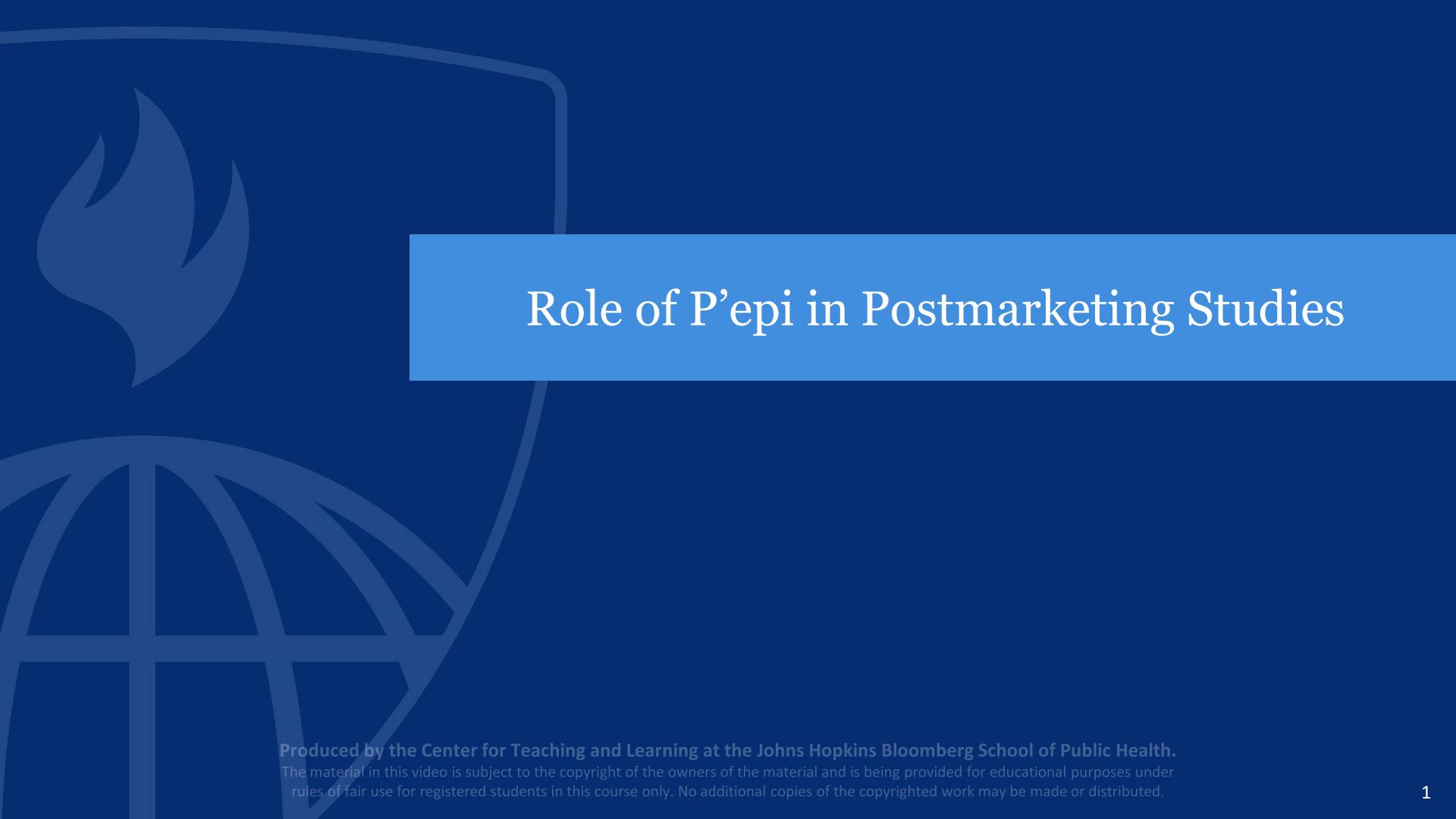
FDA approves new use of transplant drug based on real-world evidence



Today, the U.S. Food and Drug Administration approved a new use for [Prograf](#) ([tacrolimus](#)) based on a non-interventional (observational) study providing [real-world evidence \(RWE\)](#) of effectiveness. FDA approved Prograf for use in combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation.

Content current as of:
07/16/2021

Regulated Product(s)
Drugs



Role of P'epi in Postmarketing Studies

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Pharmacoepidemiological Studies: Setting the Stage

- ▶ High-level overview of 4 studies
 - ▶ For simplicity and clarity, I focused on drugs approved for obesity in the United States
 - ▶ No details on methods
- ▶ Obesity
 - ▶ Higher than normal or healthy weight
- ▶ Drugs—glucagon-like peptide 1 (GLP1) receptor agonists:
 - ▶ Semaglutide
 - ▶ Tirzepatide
 - ▶ Liraglutide

Effectiveness in the Real World



Image: Microsoft Corp. stock image.

Effectiveness in the Real World—Example

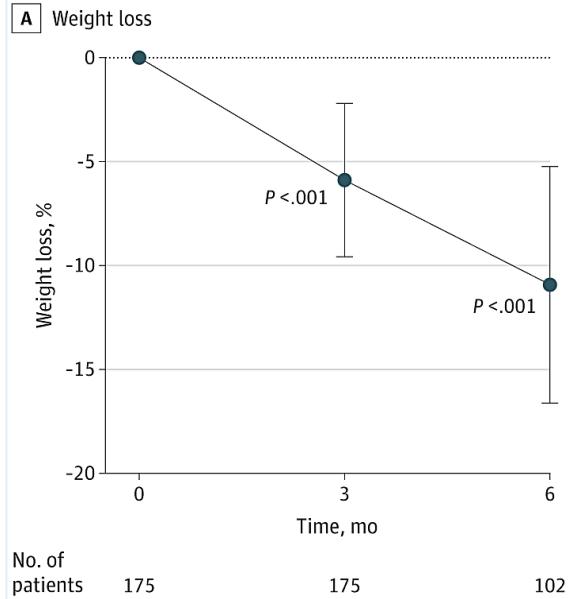
Background

- ▶ Drug approved for weight loss
 - ▶ Semaglutide
- ▶ What is the effectiveness of semaglutide in reducing weight in the real world?

Research Question

- ▶ Estimate weight loss associated with semaglutide at doses used in randomized clinical trials for patients with overweight or obesity
- ▶ Electronic health records from one health system
- ▶ Weight loss at 3 and 6 months

Results



Source: Figure 2A, "Percentage weight loss at 3 and 6 months," in: Ghusn, W., De la Rosa, A., Sacoto, D., et al. (2022). Weight loss outcomes associated with semaglutide treatment for patients with overweight or obesity. *JAMA Network Open*, 5(9), e2231982. <https://doi.org/10.1001/jamanetworkopen.2022.31982>

Real-World Utilization and Adherence



Image: Microsoft Corp. stock image.

Real-World Utilization—Example

Background

- ▶ In clinical trials, people continue taking drugs as per the trial protocol
- ▶ In the real world, people stop taking drugs for a number of reasons

Research Question

- ▶ Estimated the prevalence of GLP-1 agonist discontinuation among individuals with diabetes or obesity
- ▶ US Healthcare claims data
- ▶ Estimate proportion of people who stop taking GLP-1 at 3, 6, and 12 months

Results

% discontinuing GLP-1

Month	Diabetes only	Obesity only
3	26%	36%
6	30%	45%
12	36%	50%

Comparative Effectiveness Study



Image: Microsoft Corp. stock image.

Comparative Effectiveness Study—Example

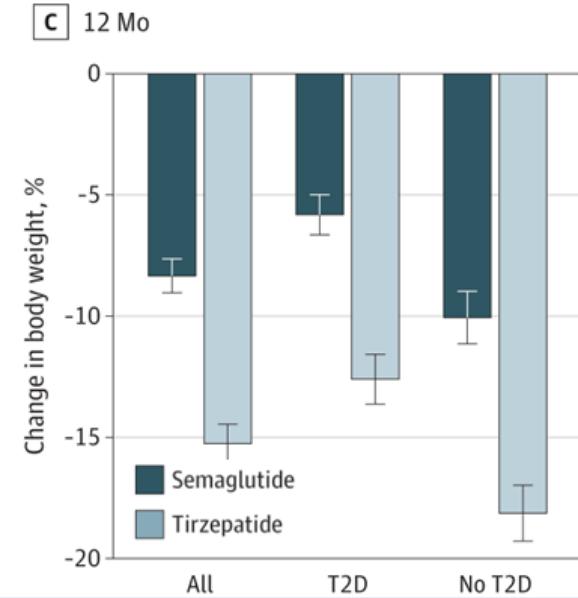
Background

- ▶ Two drugs approved for weight loss:
 - ▶ Semaglutide
 - ▶ Tirzepatide
- ▶ Is one drug better than the other in the real world?

Research Question

- ▶ Head-to-head comparison of semaglutide and tirzepatide for weight loss
- ▶ Electronic health records data
- ▶ Compared weight loss among individuals at 3, 6, and 12 months

Results



Source: Figure 3C, "Mean percentage change in body weight at 12 months receiving treatment for the overall population, those with type 2 diabetes (T2D), and those without T2D," in: Rodriguez, P. J., Goodwin Cartwright, B. M., Gratzl, S., et al. (2024). Semaglutide vs tirzepatide for weight loss in adults with overweight or obesity. *JAMA Internal Medicine*, 184(9), 1056–1064.
<https://doi.org/10.1001/jamainternmed.2024.2525>

Real-World Safety



Image: Microsoft Corp. stock image.

Real-World Safety—Example

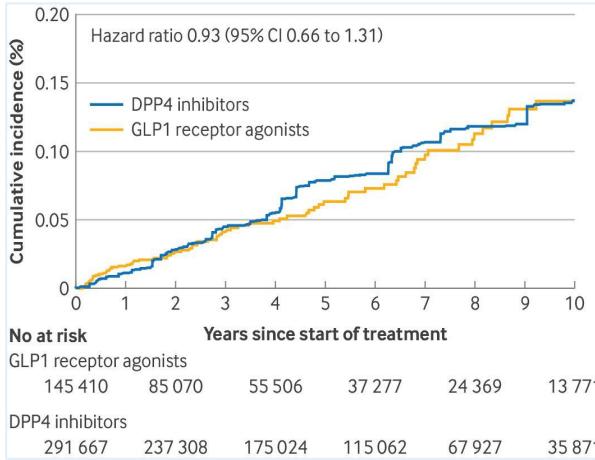
Background

- ▶ Glucagon-like peptide 1 (GLP1) receptor agonist
 - ▶ Semaglutide, liraglutide
- ▶ Some concerns about increased risk of thyroid cancer—studies in rodents
- ▶ Is the increased risk the same among humans?

Research Question

- ▶ To investigate whether GLP-1 use is associated with increased risk of thyroid cancer
- ▶ Health care and administrative registers from Denmark, Norway, and Sweden
- ▶ Compared risk of thyroid cancer among people who used GLP-1 vs. other drugs

Results





Role of P'epi and Real-World Evidence to Inform Regulatory, Policy, and Clinical Decisions

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Regulatory Decisions

FDA approves new use of transplant drug based on real-world evidence

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Today, the U.S. Food and Drug Administration approved a new use for [Prograf \(tacrolimus\)](#) based on a non-interventional (observational) study providing [real-world evidence \(RWE\)](#) of effectiveness. FDA approved Prograf for use in combination with other immunosuppressant drugs to prevent organ rejection in adult and pediatric patients receiving lung transplantation.

- ▶ Systematic review of FDA approvals from 2019 to 2021 to understand the use of real-world evidence (RWE) in regulatory decision-making
 - ▶ 116 approvals used RWE
 - ▶ 88 used RWE to provide evidence of safety or effectiveness
 - 8—substantial or primary evidence
 - 57—supporting evidence
 - 38—product labels

Sources:

US Food and Drug Administration. (2021). FDA approves new use of transplant drug based on real-world evidence. FDA. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence>

Purpura, C. A., Garry, E. M., Honig, N., Case, A., & Rassen, J. A. (2022). The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clinical Pharmacology and Therapeutics*, 111(1), 135–144. <https://doi.org/10.1002/cpt.2474>

Policy Decisions

Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines

Christopher M. Jones, PharmD, MPH,¹ Jana K. McAninch, MD, MPH, MS²

Conclusions: ED visits and drug overdose deaths involving both opioid analgesics and benzodiazepines increased significantly between 2004 and 2011. Interventions to improve the appropriate prescribing and use of these medications are needed.

(Am J Prev Med 2015;49(4):493–501) Published by Elsevier Inc. on behalf of American Journal of Preventive Medicine

FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning

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The FDA has issued new information about the combined use of medication-assisted treatment (MAT) drugs with benzodiazepines or other central nervous system depressants. See the [FDA Drug Safety Communication](#) issued on 9-20-2017.

Sources:

Jones, C. M., & McAninch, J. K. (2015). Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *American Journal of Preventive Medicine*, 49(4), 493–501. <https://doi.org/10.1016/j.amepre.2015.03.040>

US Food and Drug Administration. (2024). FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. FDA. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-risks-and-death-when-combining-opioid-pain-or>

Hwang, C. S., Kang, E. M., Kornegay, C. J., Staffa, J. A., Jones, C. M., & McAninch, J. K. (2016). Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. *American Journal of Preventive Medicine*, 51(2), 151–160. <https://doi.org/10.1016/j.amepre.2016.02.014>

Clinical Decisions

Drug Safety Communications

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Español

药物安全通讯

Drug Safety Podcasts

The FDA Drug Safety Communications posted on this web page are intended to provide important information to patients and health care professionals about new safety issues with the medicines they are taking or prescribing so they can make more informed decisions about treatment.

Widespread or long-term use of drugs by patients may uncover side effects not discovered during the clinical trials a drug company did to get FDA approval of the medicine. As a result, FDA physicians and scientists continue to monitor the safety of drugs after they are approved. When we learn information about a potential new safety issue, we review the data from available clinical trials or other studies, case reports, and medical literature. Based on what we find, we may require changes to the prescribing information or the patient Medication Guide. We may also release a Drug Safety Communication to alert patients and health care professionals about the issue. [Read more.](#)

► Two examples:

1. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients
2. Serious liver injury being observed in patients without cirrhosis taking Ocaliva (obeticholic acid) to treat primary biliary cholangitis
 - Monitor liver tests often for early identification of worsening liver function



Future of P'epi

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Past Trends in Pharmacoepidemiology

- ▶ Increase in in the number of individuals attending the annual conference on pharmacoepidemiology
- ▶ Increase in the number of academic programs to study pharmacoepidemiology
- ▶ Growth in data sources—health care claims and electronic health records
- ▶ Development of innovative methods in pharmacoepidemiology
- ▶ Greater use by pharmaceutical companies to drive drug development
 - ▶ Departments: pharmacoepidemiology, real-world evidence, or health economics and outcomes research
- ▶ Increase in acceptability by regulatory agencies
 - ▶ Assess medication safety
 - ▶ Approval of some drugs using real-world data

Future of Pharmacoepidemiology—1

1. Data

- ▶ Linking data from several sources—claims, electronic health records, wearables, genomics
- ▶ Rise of common data models—FDA Sentinel, PCORnet, OMOP (Observational Medical Outcomes Partnership), N3C (National Clinical Cohort Collaborative)

2. Study design and methods

- ▶ Greater adoption of newer methods—reporting guidelines and checklist, target trial emulation, graphical depiction of study design

3. Statistical analysis

- ▶ Increasing use of advanced statistical and causal inference methods

Future of Pharmacoepidemiology—2

4. Artificial intelligence (AI) and machine learning (ML)

- ▶ Use of AI/ML for safety signal detection
- ▶ Use of natural language processing to capture information from clinical notes
- ▶ Use of large language models for post-marketing surveillance

5. Data visualization and dashboards

- ▶ Use of dashboards for data visualization and faster analysis

6. Precision medicine

- ▶ Leverage pharmacogenomic data to tailor treatments based on individual's genetic profile

Summary

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Summary—1

- ▶ Drug life cycle:
 - ▶ Describes market behavior of drug through 4 stages
 - ▶ Discussed patent and exclusivity
- ▶ Pharmacoepidemiology (p'epi):
 - ▶ Pharmacology + epidemiology
 - ▶ Three pillars: use, safety, and effectiveness
- ▶ P'epi in drug discovery and phase 1 to 3:
 - ▶ Inform trial design, natural history of disease, disease burden and unmet need, treatment patterns, and utilization

Summary—2

- ▶ P'epi in postmarketing studies:
 - ▶ Pharmacovigilance, real-world use, safety and effectiveness
- ▶ Role of p'epi and real-world evidence:
 - ▶ Case studies to inform regulatory, policy, and clinical decisions
- ▶ Future of p'epi:
 - ▶ Future is bright with innovation in data linkage, artificial intelligence / machine learning