The Use of Real-World Data and Real-World Evidence at the US FDA

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Disclaimer

- This talk reflects the views of the author and should not be construed to represent FDA's views or policies.

FDA Definitions

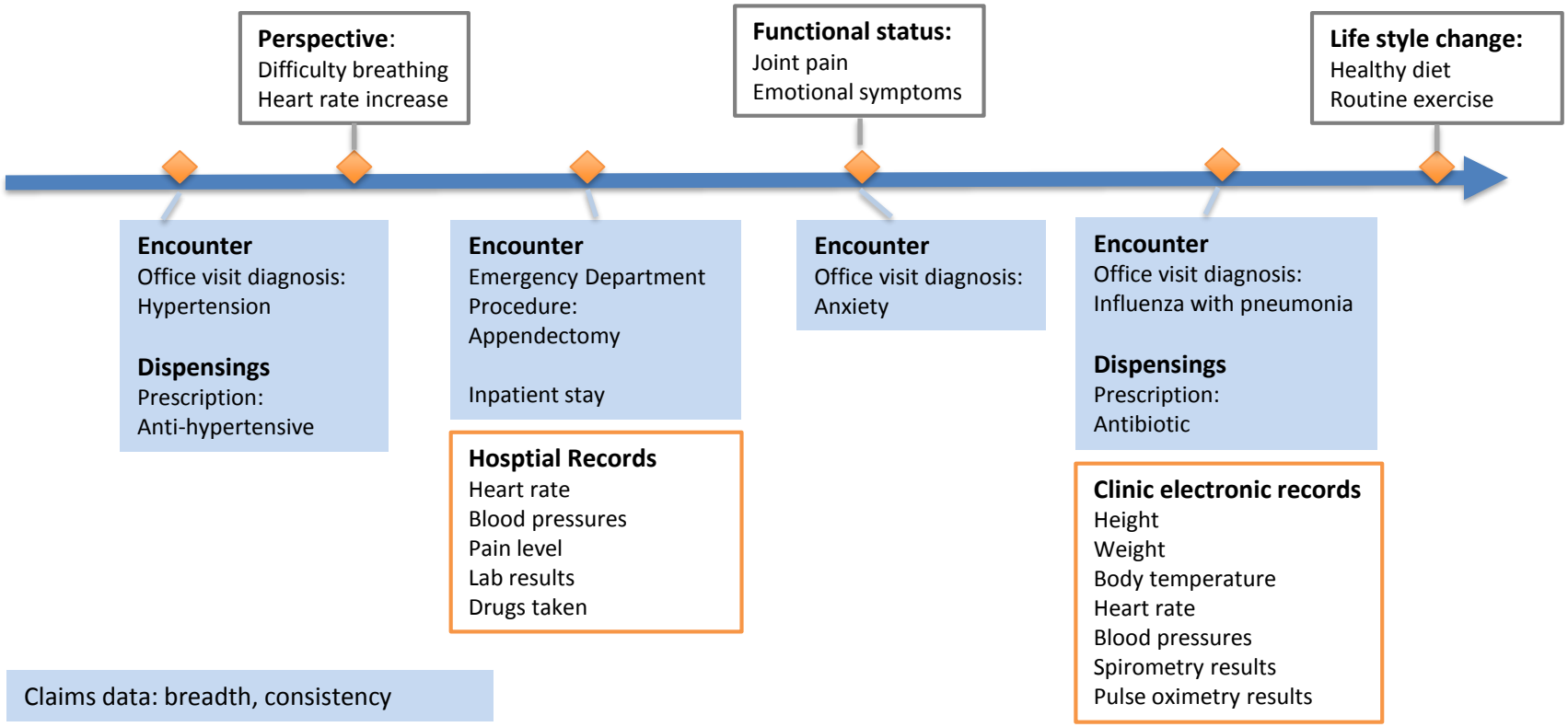
Real World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

- electronic health records (EHRs)
- claims and billing data
- data from product and disease registries
- patient-generated data including 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 regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Generated using many different study designs, including but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies.

Real-World Data



Claims data: breadth, consistency

Electronic Health Records: depth, only certain occasions

Data not captured: how to fill the gap?

RWD/RWE: What Are the Goals?

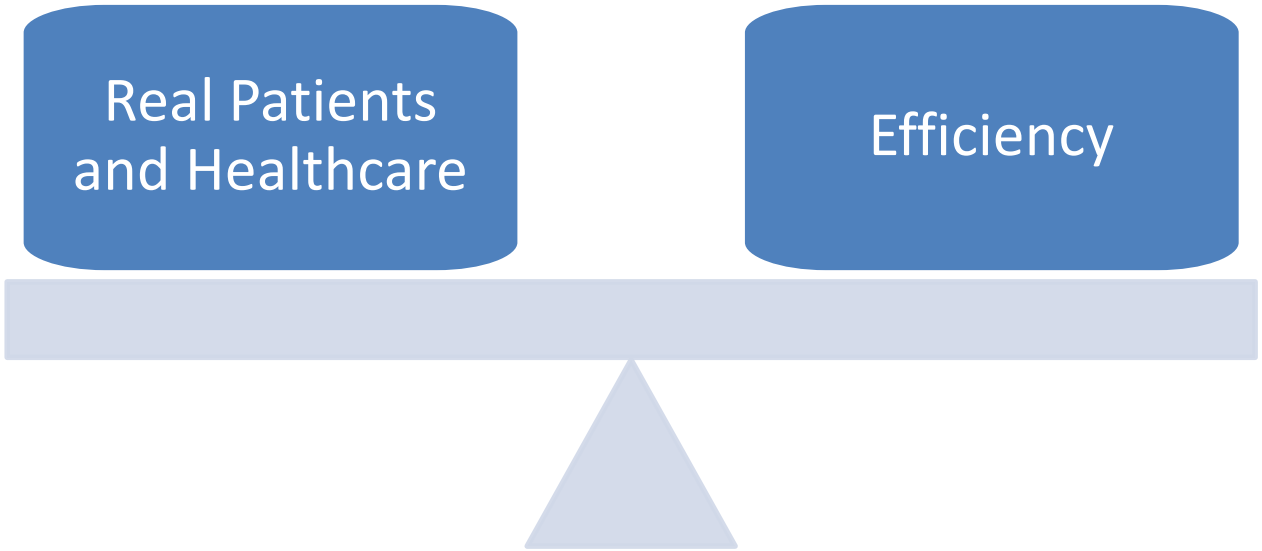
Traditional RCTs typically

- Occur outside standard medical practice and procedures
- Use select groups of patients
- Involve special infrastructure and data collection

RWE/RWD Goals

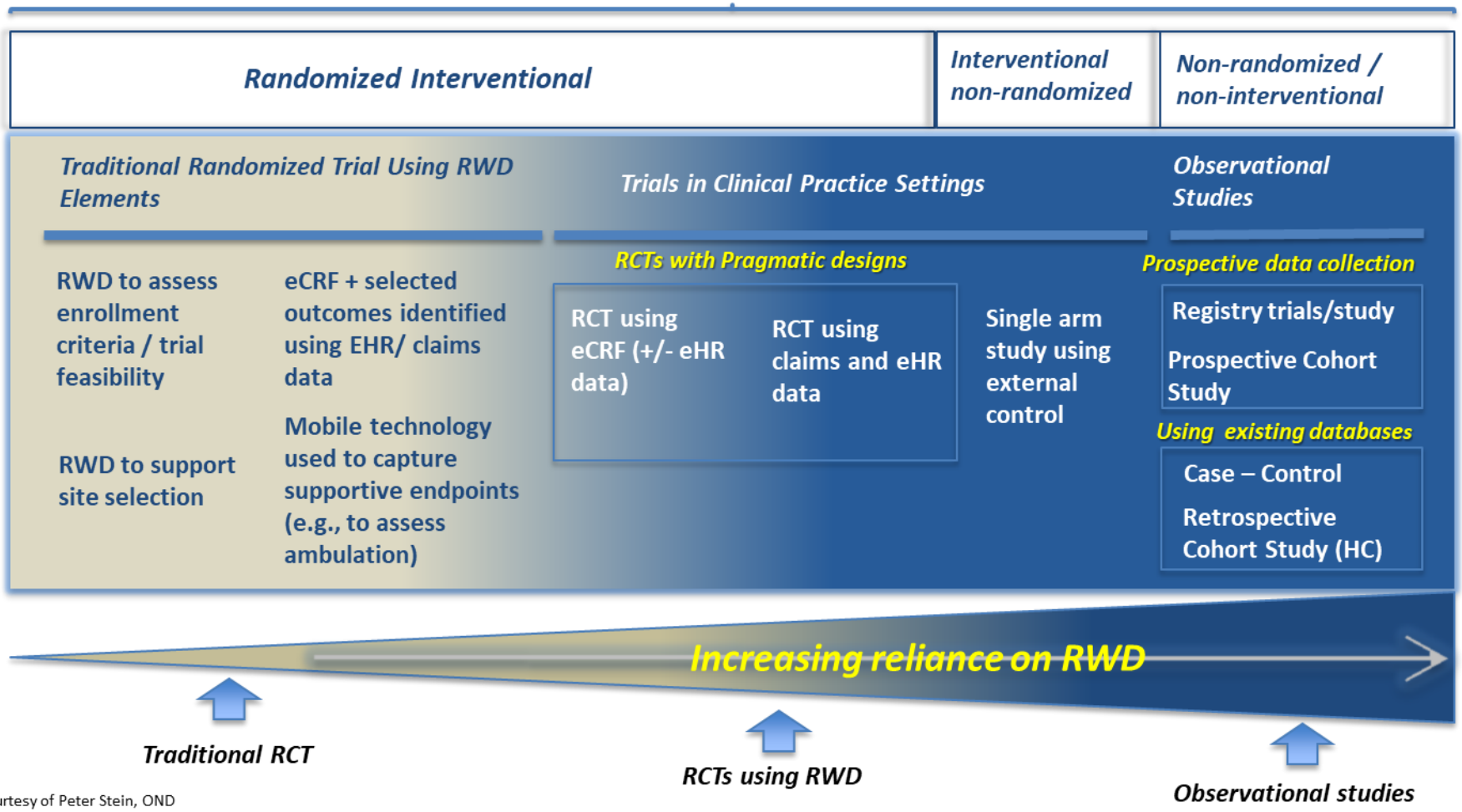
- Reflect the diversity of patients and actual health-care practices
- Improve efficiency by making use of existing data and infrastructure
- Maintain evidentiary standards

RWE Give and Take



Wide Spectrum of Potential Uses of RWD / RWE in Clinical Studies

Different challenges and opportunities for each approach



Courtesy of Peter Stein, OND

Substantial Evidence Efficacy

"**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 involve 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."

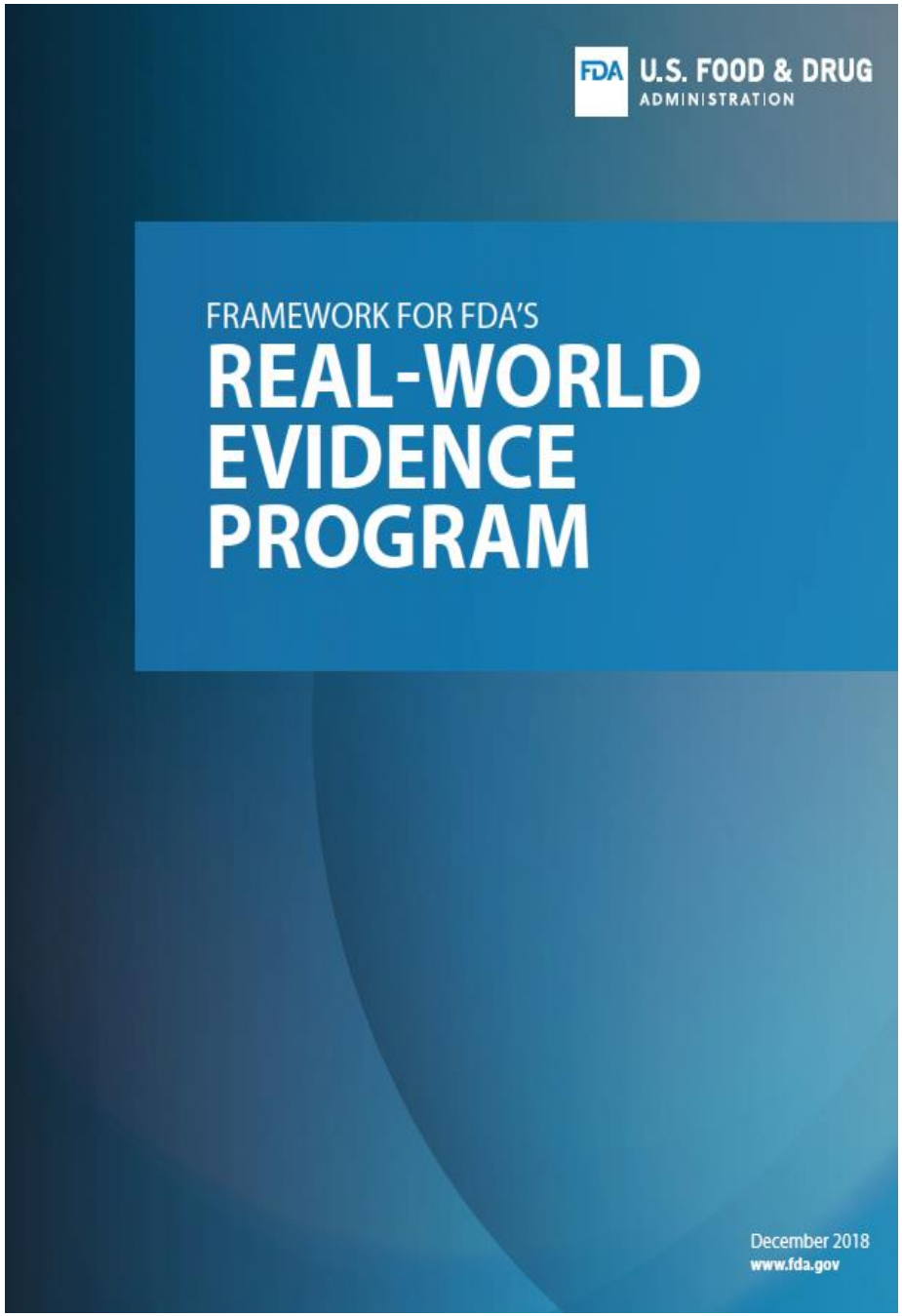
Federal Food, Drug, and Cosmetic Act 1962

Drug Regulation History:
https://www.fda.gov/AboutFDA/History/ProductRegulation/ucm593465.htm

21st Century Cures Act (2016)

- establish a program to evaluate the potential use of real world evidence-
  - to help to support the approval of a new indication for a drug approved under section 355(c) of this title; and
  - to help to support or satisfy postapproval study requirements.
- "real world evidence" means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials.

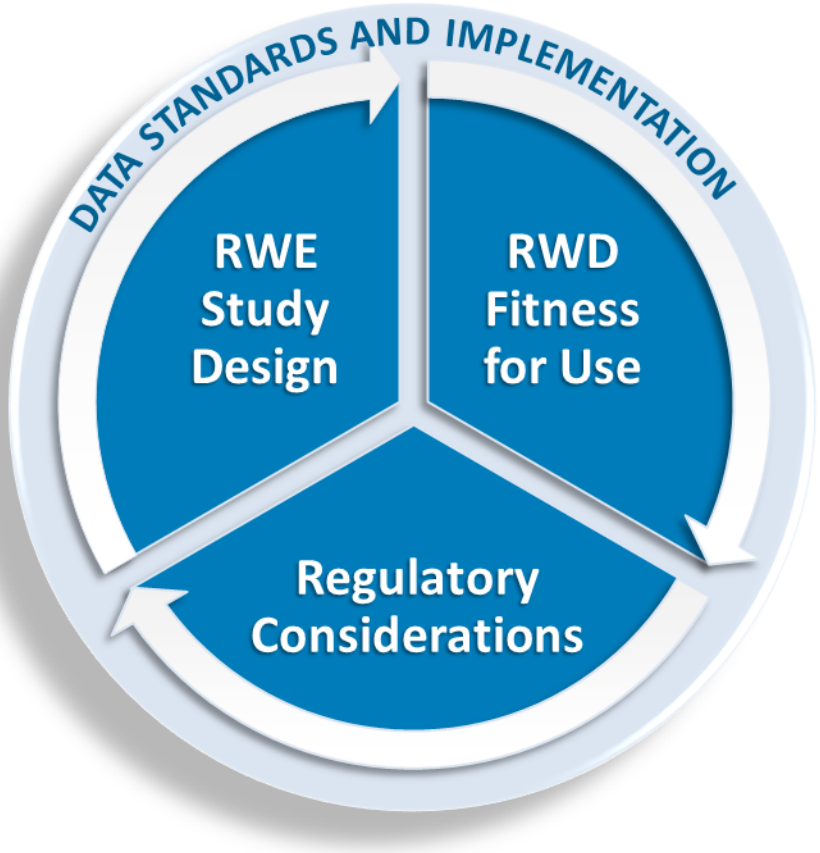
SEC. 505F. UTILIZING REAL WORLD EVIDENCE. Amended by Food and Drug Administration Reauthorization Act 2017



- **Intended for drug and biological products**
- **Outlines FDA's plan to implement the RWE program**
- **Multifaceted program**
  - **Internal processes**
  - **Guidance development**
  - **Stakeholder engagement**
  - **Demonstration projects**
- **Comment period closes April 16, 2019**

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

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**

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CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND: Nonvitamin K antagonist oral anticoagulants (NOACs) are alternatives to warfarin in patients with nonvalvular atrial fibrillation. Randomized trials compared NOACs with warfarin, but none have compared individual NOACs against each other for safety and effectiveness.

METHODS: We performed a retrospective new-user cohort study of patients with nonvalvular atrial fibrillation enrolled in US Medicare who initiated warfarin (n = 183,318), or a standard dose of dabigatran (150 mg twice daily; n = 86,198), rivaroxaban (20 mg once daily; n = 106,389), or apixaban (5 mg twice

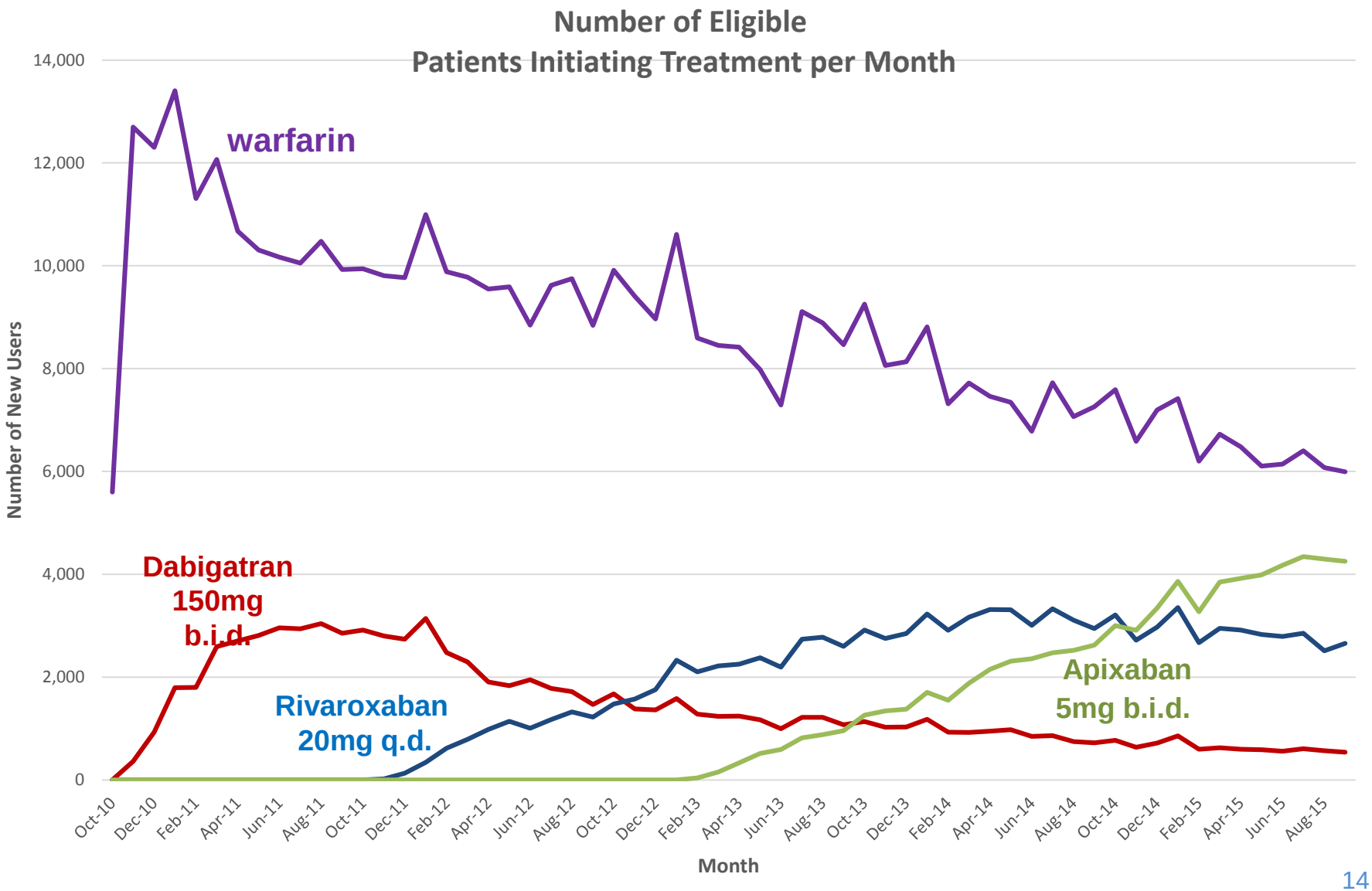
Anticoagulants

- Indication: reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

- Warfarin (1954)
- Non-vitamin K Oral Anticoagulants (NOAC)
  - Dabigatran (2010)
  - Rivaroxaban (2011)
  - Apixaban (2012)
  - Edoxaban (2015)

- Approvals based on RCT trials, individual NOAC vs. warfarin

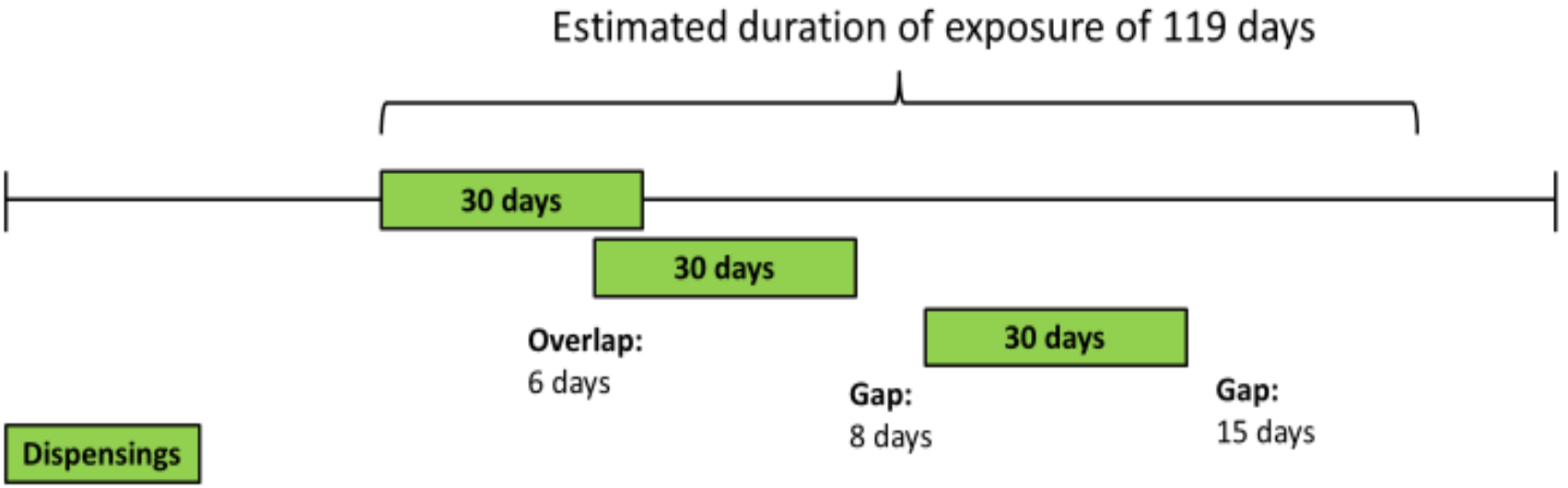
Pattern of Use in Medicare



Study Motivation

- Are there clinically meaningful differences between NOACs in stroke, bleeding, and mortality risks?
- How do NOACs compare with warfarin in “real world”?
- Data Source: Medicare Claims

Episodes of Drug Use, Stockpiling Algorithms



Toy Example, algorithm accruing overlap (up to 7 days), allowing gaps in therapy up to 15 days

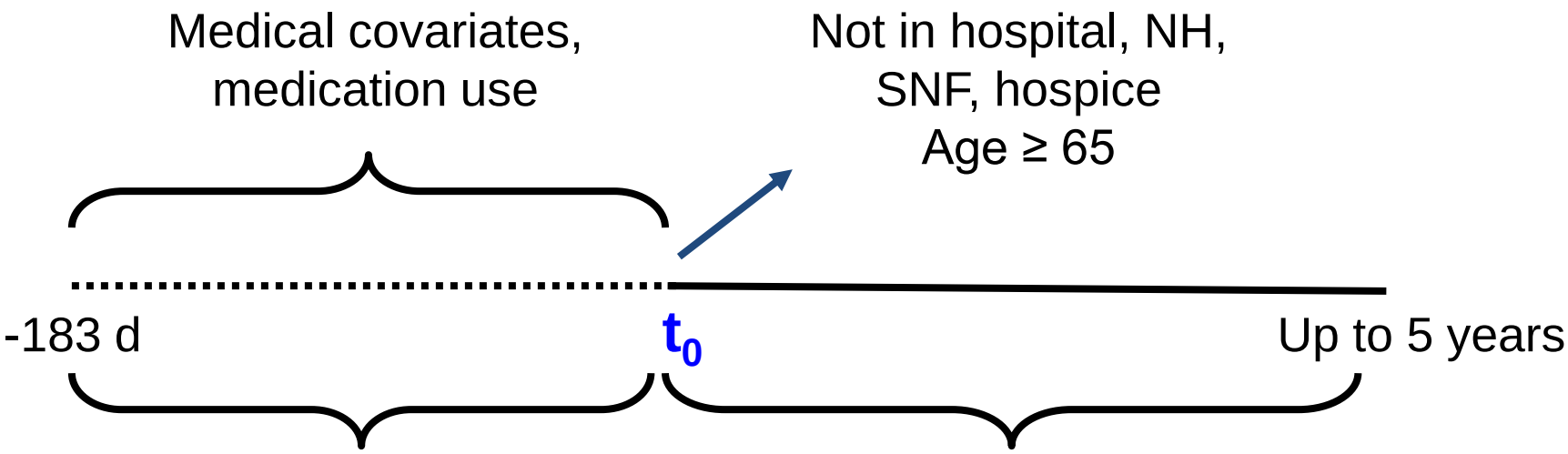
- Exposure was defined based on:
  - Pharmacy dispensed prescriptions (Rx).
  - National Drug Codes used to identify study drugs

Outcomes

Primary outcomes defined based on ICD9 codes from previously validated outcome algorithms:

- Thromboembolic stroke: PPV of 88-95%
- Intracranial hemorrhage: PPV of 89-97%
- Major extracranial bleeding: PPV of 87%
- Death: 95% of deaths captured by linkage to Social Security Data Files

New-User Cohort, Time-to-Event Study

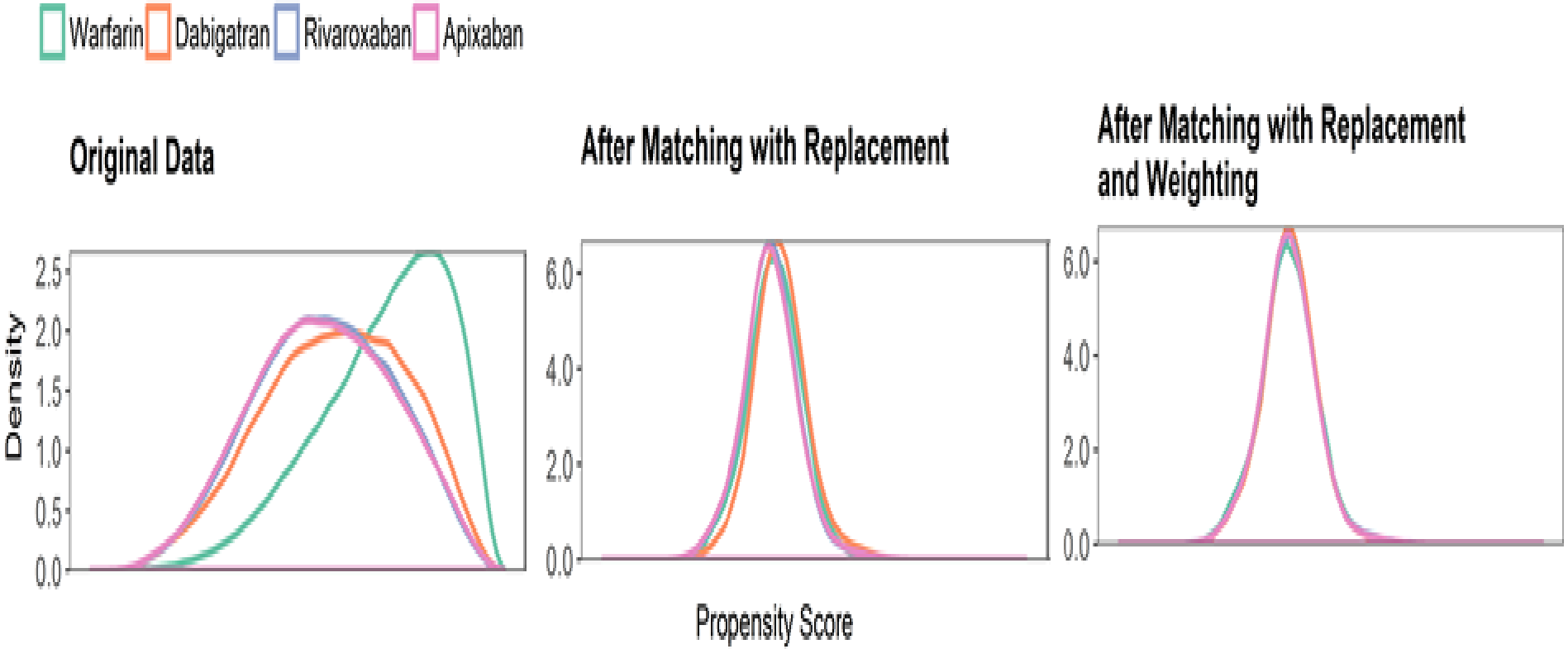


No oral anticoagulants
No valvular heart disease
No VTE, joint replacement

Censor: Switch, therapy gap, NH, hospice, SNF, dialysis/transplant, outcome, study end

Outcomes: Ischemic stroke, intracranial hemorrhage, major extracranial bleeding, death

Propensity score distributions



Hazard ratios & relative risks from the current Medicare study and the pivotal randomized trials

Outcome	Medicare (3-NOACs-warfarin study). Adj HR (95% CI)	RE-LY (dabigatran-warfarin) Trial. RR (95% CI)	ROCKET-AF (rivaroxaban-warfarin) Trial. HR (95% CI)	ARISTOTLE (apixaban-warfarin) Trial HR (95% CI)
Ischemic stroke				
Dabigatran: Warfarin	0.80 (0.70-0.93)	0.76 (0.60-0.98)		
Rivaroxaban: Warfarin	0.72 (0.63-0.83)		0.94 (0.75-1.17)	
Apixaban: Warfarin	0.71 (0.60-0.83)			0.92 (0.74-1.13)
Intracranial hemorrhage				
Dabigatran: Warfarin	0.38 (0.31-0.47)	0.40 (0.27-0.60)		
Rivaroxaban: Warfarin	0.65 (0.56-0.77)		0.67 (0.47-0.93)	
Apixaban: Warfarin	0.54 (0.43-0.68)			0.42 (0.30-0.58)

Relative risks & hazard ratios from the current Medicare study and the pivotal randomized trials

Outcome	Medicare (3 NOACs-warfarin study. Adj HR (95% CI)	RE-LY (dabigatran-warfarin) Trial. RR (95% CI)	ROCKET-AF (rivaroxaban-warfarin) Trial. HR (95% CI)	ARISTOTLE (apixaban-warfarin) Trial HR (95% CI)
Major extracranial bleed				
Dabigatran: Warfarin	1.04 (0.96-1.14)	1.07 (0.92-1.25)		
Rivaroxaban: Warfarin	1.38 (1.29-1.49)		Not reported*	
Apixaban: Warfarin	0.51 (0.45-0.58)			0.79 (0.68-0.93)
All-cause mortality				
Dabigatran: Warfarin	0.73 (0.67-0.80)	0.88 (0.77-1.00)		
Rivaroxaban: Warfarin	0.81 (0.75-0.88)		0.85 (0.70-1.02)	
Apixaban: Warfarin	0.66 (0.60-0.74)			0.89 (0.80-0.998)

* Major GI bleed: Medicare: HR=1.48 (1.36-1.60); ROCKET-AF (estimated): RR=1.47 (1.19-1.81)

Final Thoughts

- There is a wealth of RWD
- Clearly RWD can been used to answer important medical questions
- How and when to use it to provide strong evidence is under development

Acknowledgements

- Rongmei Zhang
- Elande Baro
- David Graham
- Jacqueline Corrigan-Curay

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you

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