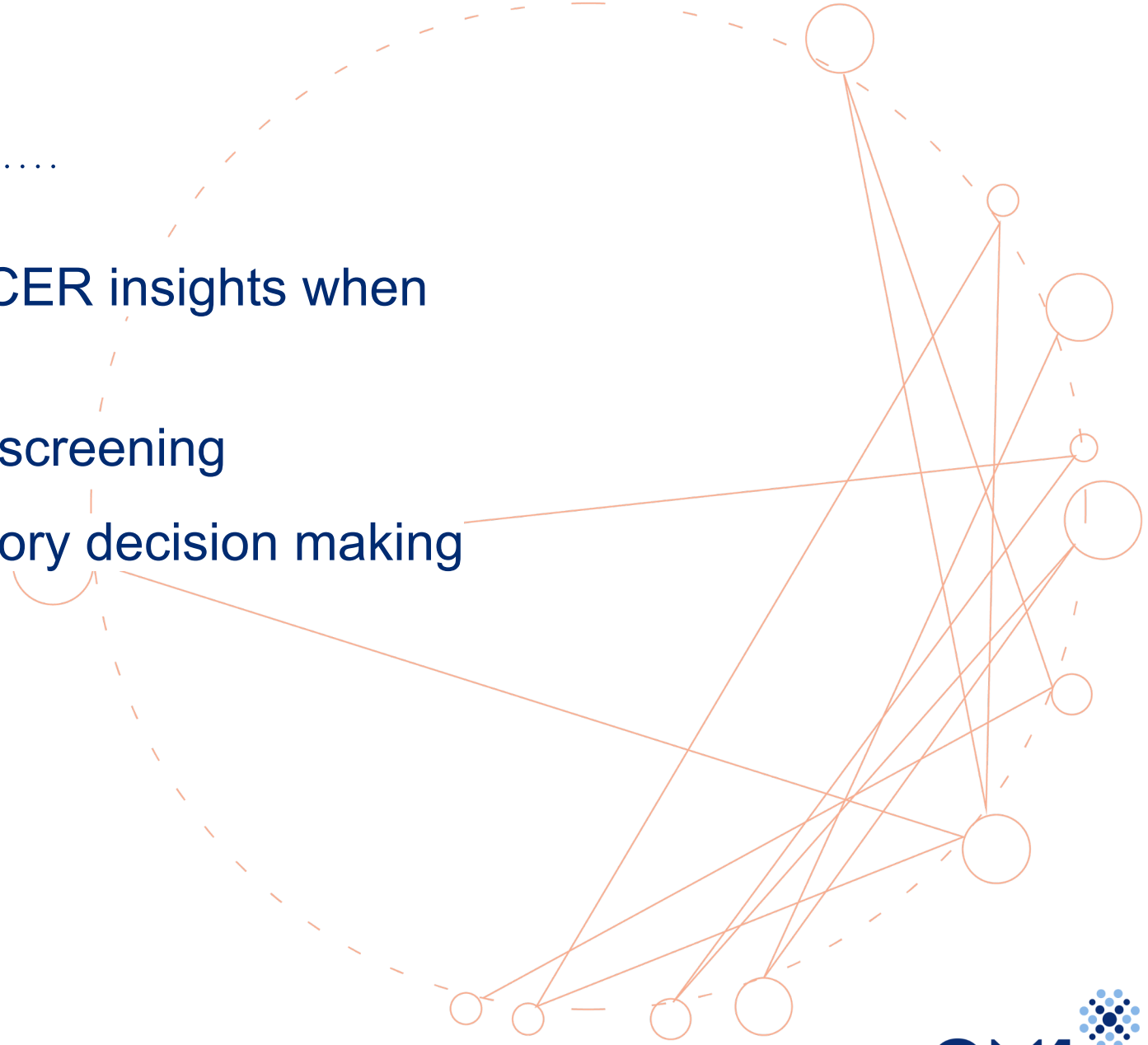
Using Real-World Data for Comparative Effectiveness

Jessica Paulus, ScD
Senior Director, Epidemiology, OM1

ISPOR Annual Meeting: May 16, 2022

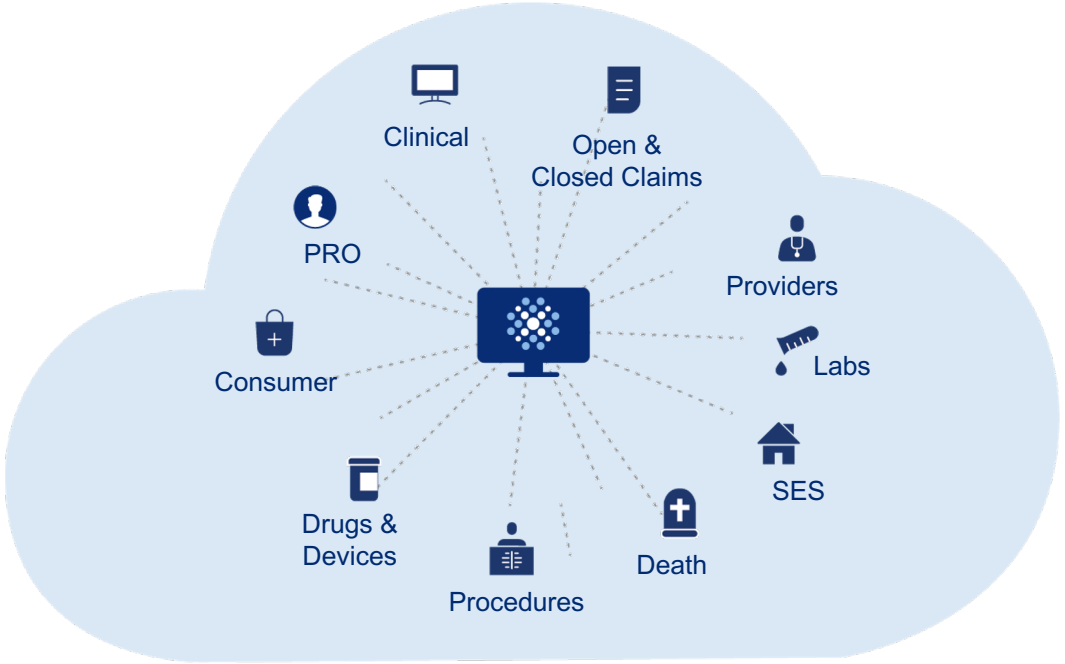
Topics

- Opportunities (& caveats) for CER insights when leveraging real-world data
- Case example: breast cancer screening
- Using RWD to support regulatory decision making



Real-world data (RWD)

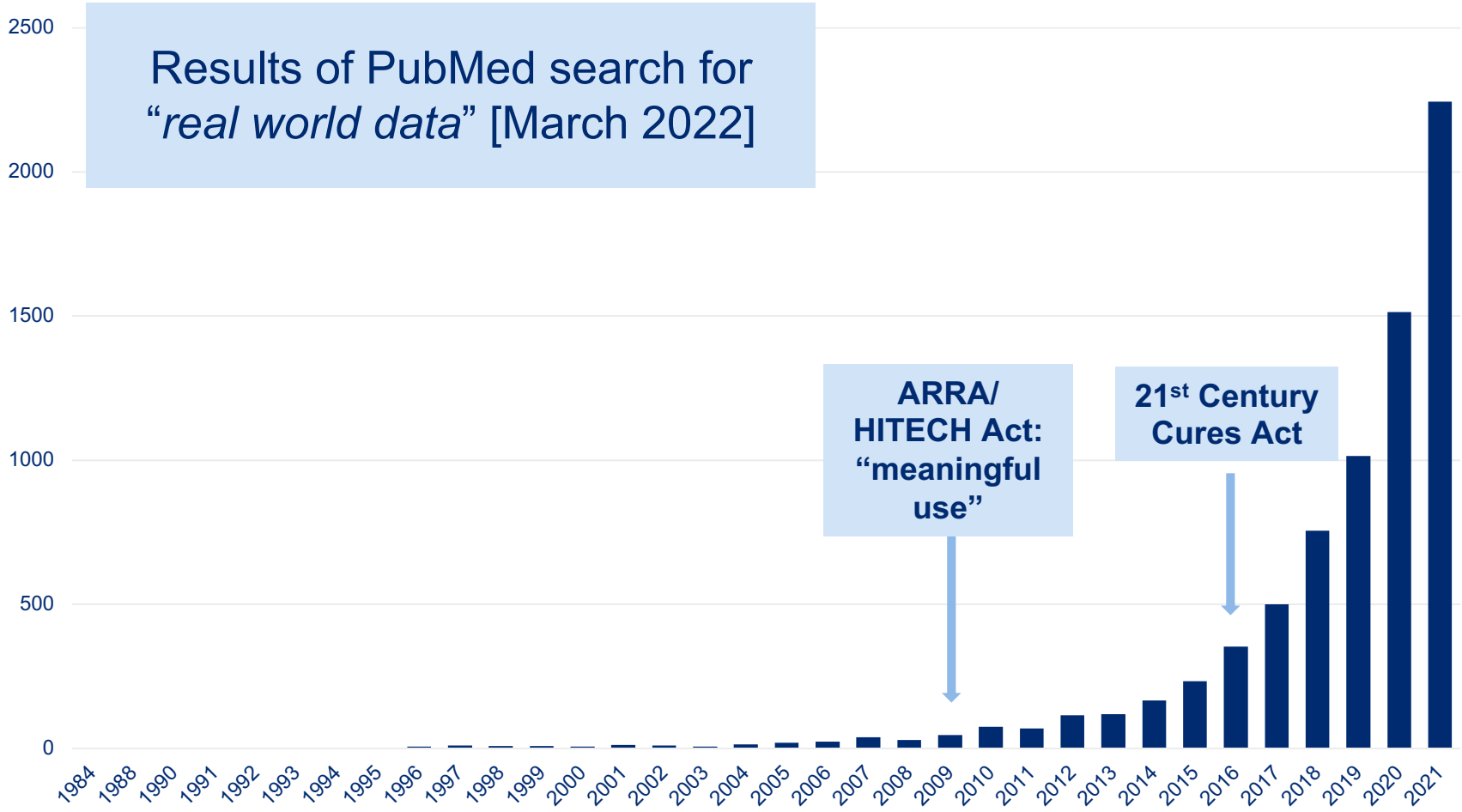
- RWD are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources
- A wide variety of RWD sources– EHR records, medical & pharmacy claims, disease registries, patient-reported data
- Significant longitudinality
- Includes patients more representative of clinical practice than RCTs; more heterogeneity in case mix



Why this matters

RWD can provide deep insight, across broad populations and over longer periods of time. Heterogeneity reveals safety and efficacy effects that may not be apparent in randomized trial environments.

RWD is a rapidly growing source of evidence



https://pubmed.ncbi.nlm.nih.gov/

A common goal of CER:

Real-world data (RWD) studies

Right treatment
Right patient
Right time

Clinical trial design and execution

OM1

Opportunities for CER insights using RWE

1

Patient Representativeness and Heterogeneity

Can examine treatment effects in populations typically excluded from trials; treatment and safety effects unveiled in subgroups with greater “case-mix”

2

Efficiency

Larger sample sizes, with greater power to ascertain more data elements

3

Longitudinality

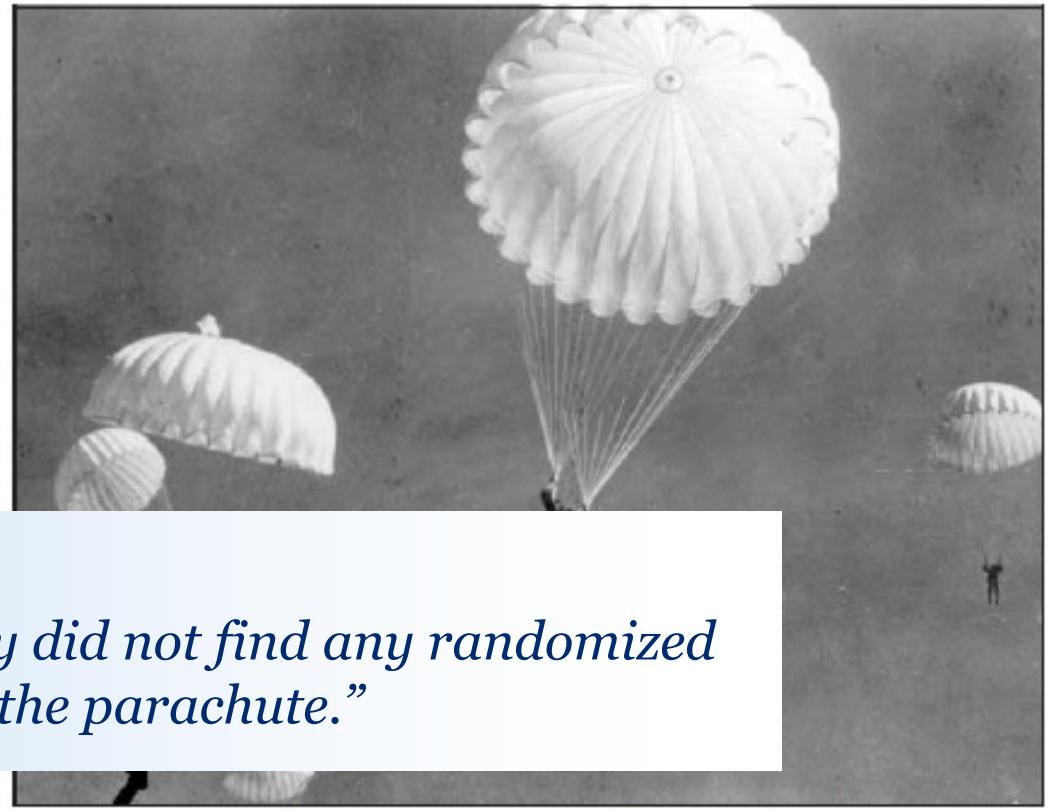
Longer follow-up to examine long-term outcomes and safety events

A key RWE advantage

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

"Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomized controlled trials"



"Results:
Our search strategy did not find any randomized controlled trials of the parachute."

BMJ 2003;327:1459–61

Addressing Bias

- Confounding, selection bias, information bias
- Explosion of advanced tools for confounding control (e.g., propensity scores, instrumental variables)
- Yet “basic” study design - harmonization of questions and populations - is of critical importance (e.g., restricted cohort or new user designs, examining heterogeneity of treatment effects)

ORIGINAL ARTICLE

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] Alvaro Alonso,[c] Roger Logan,[a] Francine Grodstein,[a,d] Karin B. Michels,[a,d,e] Walter C. Willett,[a,d,f] JoAnn E. Manson,[a,d,g] and James M. Robins[a,h]

American Journal of Epidemiology

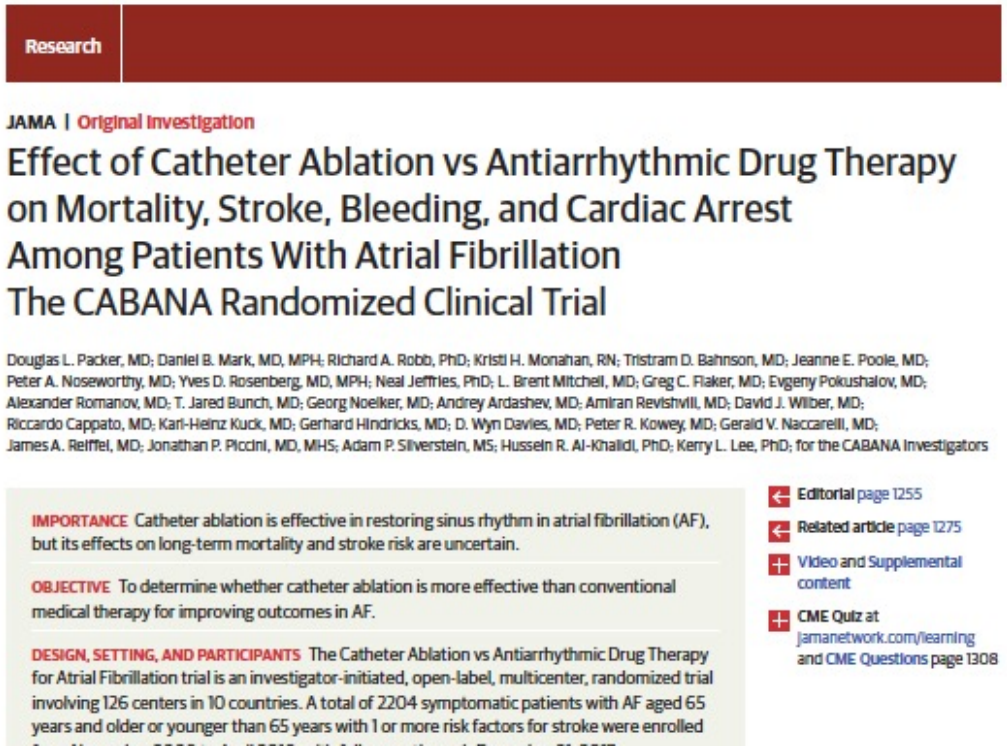
Vol. 183, No. 8
DOI: 10.1093/aje/kwv254
Advance Access publication: March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

Ablation for AF: RCT and RWE experiments in parallel



Research

JAMA | Original Investigation

Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation The CABANA Randomized Clinical Trial

Douglas L. Packer, MD; Daniel B. Mark, MD, MPH; Richard A. Robb, PhD; Kristi H. Monahan, RN; Tristram D. Bahnson, MD; Jeanne E. Poole, MD; Peter A. Noseworthy, MD; Yves D. Rosenberg, MD, MPH; Neal Jeffries, PhD; L. Brent Mitchell, MD; Greg C. Flaker, MD; Evgeny Pokushalov, MD; Alexander Romanov, MD; T. Jared Bunch, MD; Georg Noelker, MD; Andrey Ardashev, MD; Amiran Revishvili, MD; David J. Wilber, MD; Riccardo Cappato, MD; Karl-Heinz Kuck, MD; Gerhard Hindricks, MD; D. Wyn Davies, MD; Peter R. Kowey, MD; Gerald V. Naccarelli, MD; James A. Reiffel, MD; Jonathan P. Piccini, MD, MHS; Adam P. Silverstein, MS; Hussein R. Al-Khalidi, PhD; Kerry L. Lee, PhD; for the CABANA Investigators

Editorial page 1255

Related article page 1275

Video and Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1308

IMPORTANCE Catheter ablation is effective in restoring sinus rhythm in atrial fibrillation (AF), but its effects on long-term mortality and stroke risk are uncertain.

OBJECTIVE To determine whether catheter ablation is more effective than conventional medical therapy for improving outcomes in AF.

DESIGN, SETTING, AND PARTICIPANTS The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation trial is an investigator-initiated, open-label, multicenter, randomized trial involving 126 centers in 10 countries. A total of 2204 symptomatic patients with AF aged 65 years and older or younger than 65 years with 1 or more risk factors for stroke were enrolled

2,204 symptomatic patients with AF randomized

ESC European Society of Cardiology

European Heart Journal (2019) 40, 1257–1264 doi:10.1093/eurheartj/ehz085

FASTTRACK CLINICAL RESEARCH

Atrial fibrillation

Atrial fibrillation ablation in practice: assessing CABANA generalizability

Peter A. Noseworthy[1,2]*, Bernard J. Gersh[2], David M. Kent[3,4], Jonathan P. Piccini[5], Douglas L. Packer[2], Nilay D. Shah[1,6,7], and Xiaoxi Yao[1,6]

[1]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, 200 1st St SW, Rochester, MN, USA; [2]Department of Cardiovascular Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN, USA; [3]Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Boston, MA 02111, USA; [4]Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Boston, MA 02111, USA; [5]Duke Center for Atrial Fibrillation, Duke Clinical Research Institute, Duke University Medical Center, 2400 Pratt St, Durham, NC 27705, USA; [6]Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, 205 3rd Ave SW, Rochester, MN 55905, USA; and [7]OptumLabs, One Main Street, 10th Floor, Cambridge, MA 02142, USA

Received 17 April 2018; revised 16 May 2018; editorial decision 9 February 2019; accepted 11 February 2019; online publish-ahead-of-print 15 March 2019

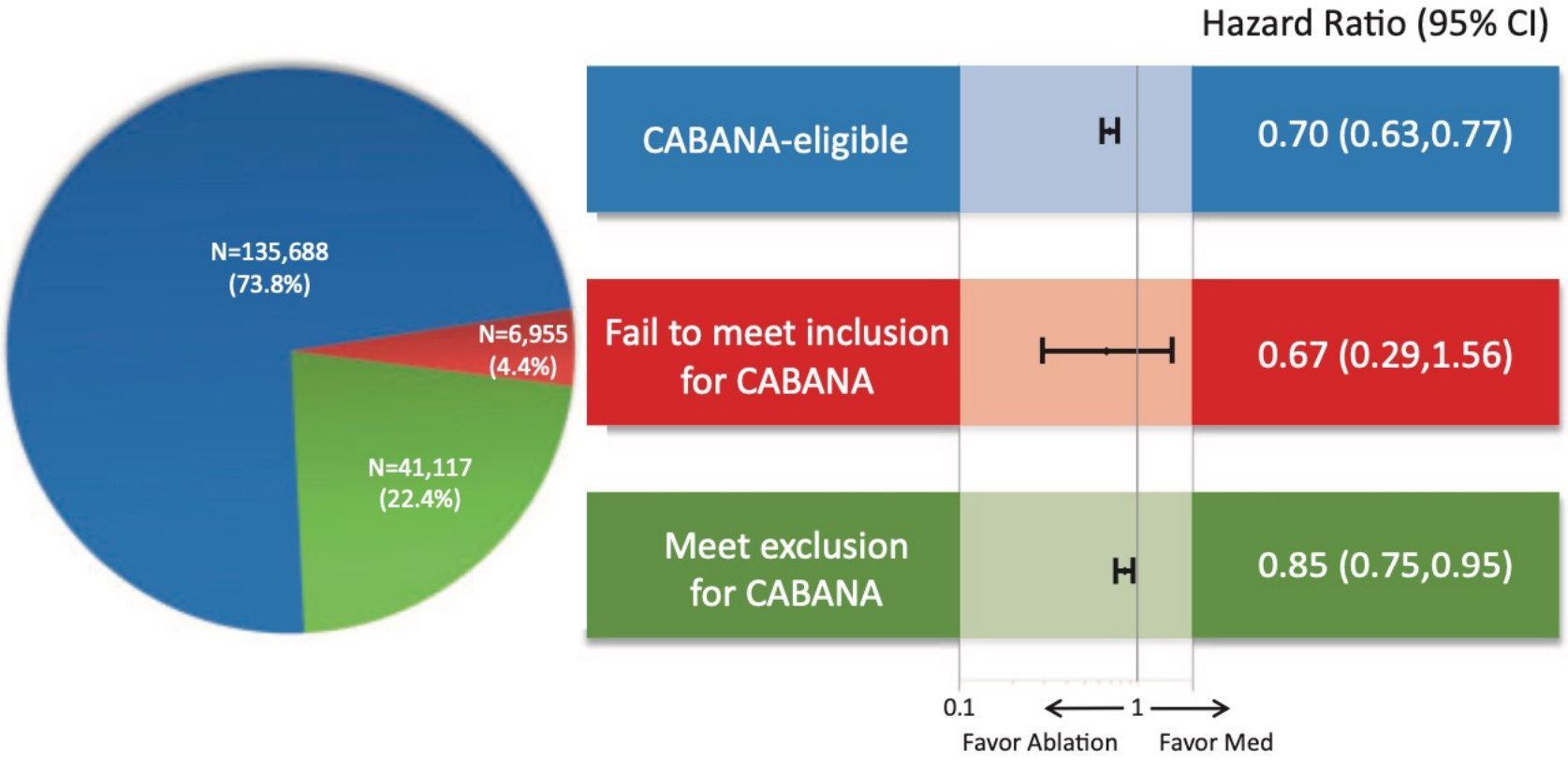
See page 1265 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz168)

183,760 patients with AF treated with ablation or medical therapy in routine practice

Packer DL, et al. Effect of catheter ablation vs. antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation. *JAMA*. 2019. March 15.

Noseworthy PA et al. Atrial fibrillation ablation in practice: Assessing CABANA generalizability. *Eur Heart J*. 2019. March 15

Design Matters for CER using RWD



Noseworthy et al. Eur Heart J. 2019 Apr 21;40(16):1257-1264.

RWE Case Study: Breast cancer screening comparative effectiveness study

Project rationale

How Can A Leading 3D Mammography Device Company Partner with Leading KOLs to

- Rapidly identify and drive adoption of best practices in breast cancer screening
- Influence clinical practice guidelines, such as USPSTF
- Enable rapid claims expansion
- Provide direction for a product roadmap

Opportunity

- Leverage the adoption of electronic medical records and advances in data analytics to utilize real world evidence to answer key questions regarding the comparative effectiveness of 3D vs. 2D mammography for breast cancer screening

Evidence gaps for 3D mammography

Longitudinality: A need to observe improvement in longer-term outcomes, such as stage shift

"Before introducing DBT [3D]] … we should wait for … clinically relevant reduction in the interval cancer rate, hopefully associated with a **reduction in the advanced cancer rate**."

Bernardi et al 2017 (SIRM- Italian Society of Medical Radiology)

"There is a pressing need for rigorous US-based studies … that report ***on longer-term outcomes***, including … the **stage distribution of detected cancers**."

Melnikow et al 2016 (USPSTF Evidence Review – Screening for Breast Cancer with Digital Breast Tomosynthesis)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Are Small Breast Cancers Good because They Are Small or Small because They Are Good?

Donald R. Lannin, M.D., and Shiyi Wang, M.D., Ph.D.

The recent article by Welch et al.[1] in the *Journal* showed clearly that since the adoption of widespread screening mammography, small breast cancers have increased in incidence over three times more than large cancers have decreased. This implies that many small cancers are not destined to progress to large cancers; instead, their detection results in overdiagnosis. The purpose of our study was to characterize groups of tumors that are likely to contain a large portion of overdiagnosed cancers and to explain the mechanism that may have led to their overdiagnosis.

metastases, and distant metastases in these groups is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

We adopted the approach by Etzioni et al.[3] to evaluate the mean lead time (the length of time between when a cancer can be detected by screening and when it would have become clinically apparent without screening) across the three prognostic groups. We first applied the estimate of Welch et al.[1] that the overall rate of overdiagnosis for invasive tumors was 22%. We assumed that the favorable group had the highest rate of

Corresponding Phase 3 Trial: *Results in 2030*

TMIST

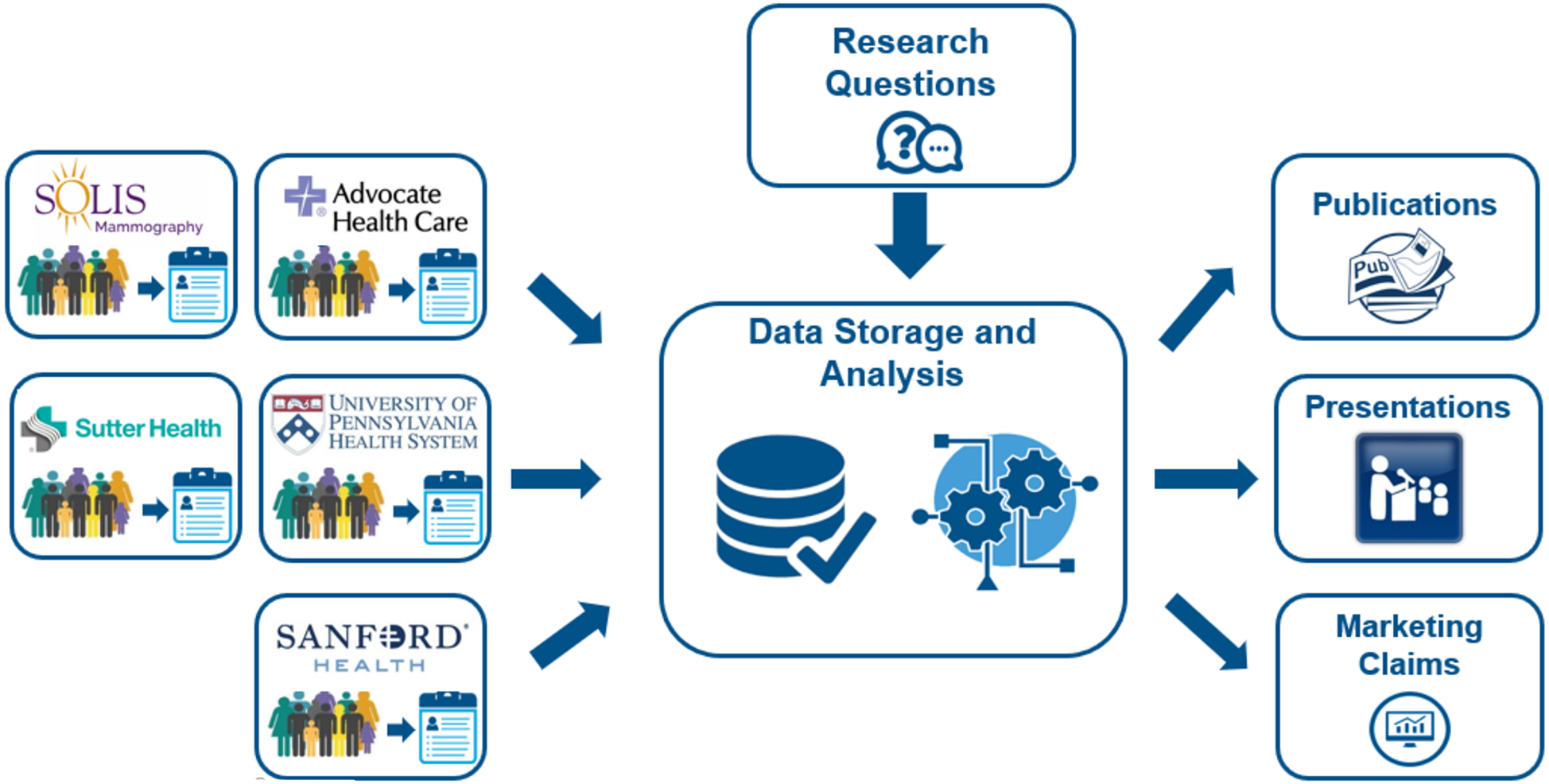
Take part in this breast cancer screening trial that will help lead to **personalized screening**

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

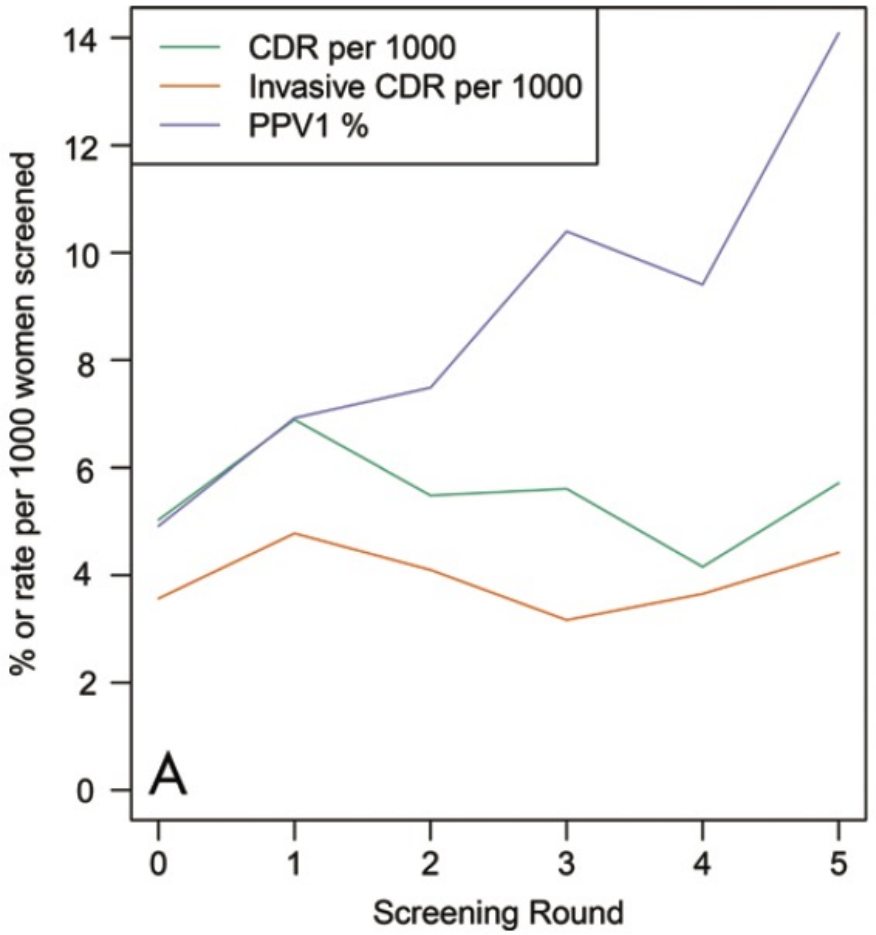
OM1

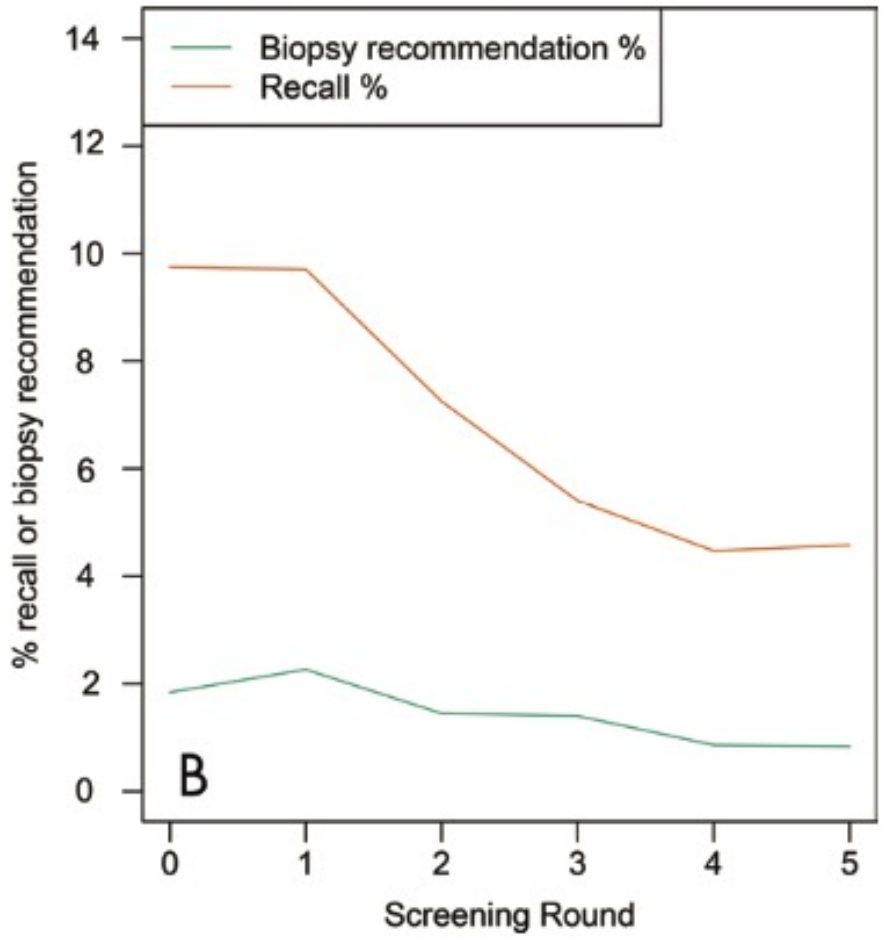
Breast Cancer Screening RWE CER Study

Efficiency: Target sample size of **>1,000,000 women** undergoing screening mammography



Improved screening outcomes sustained



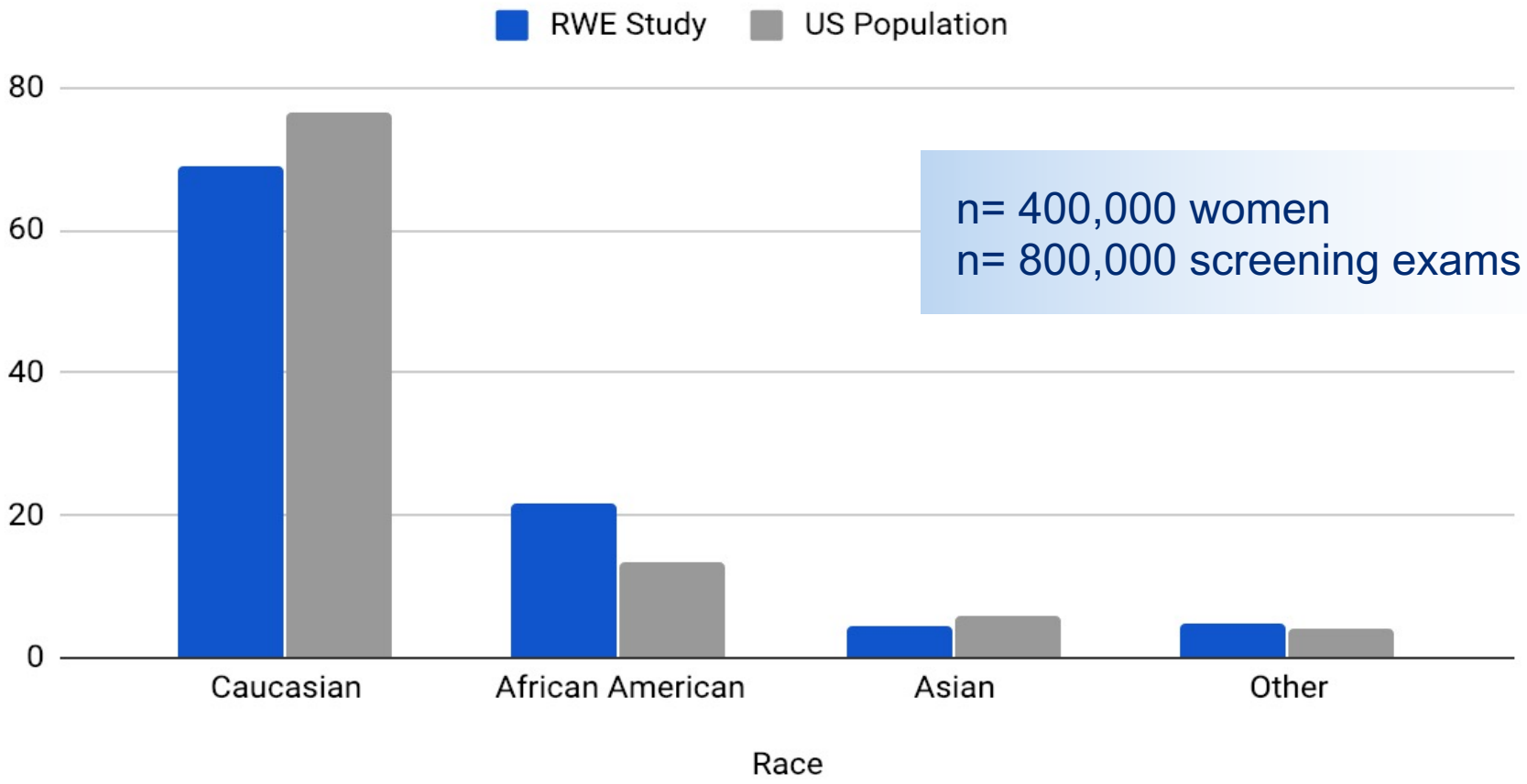


n= 30,000 women, n= 70,000 screening exams

Conant et al, Radiology 2020; 295:285–293

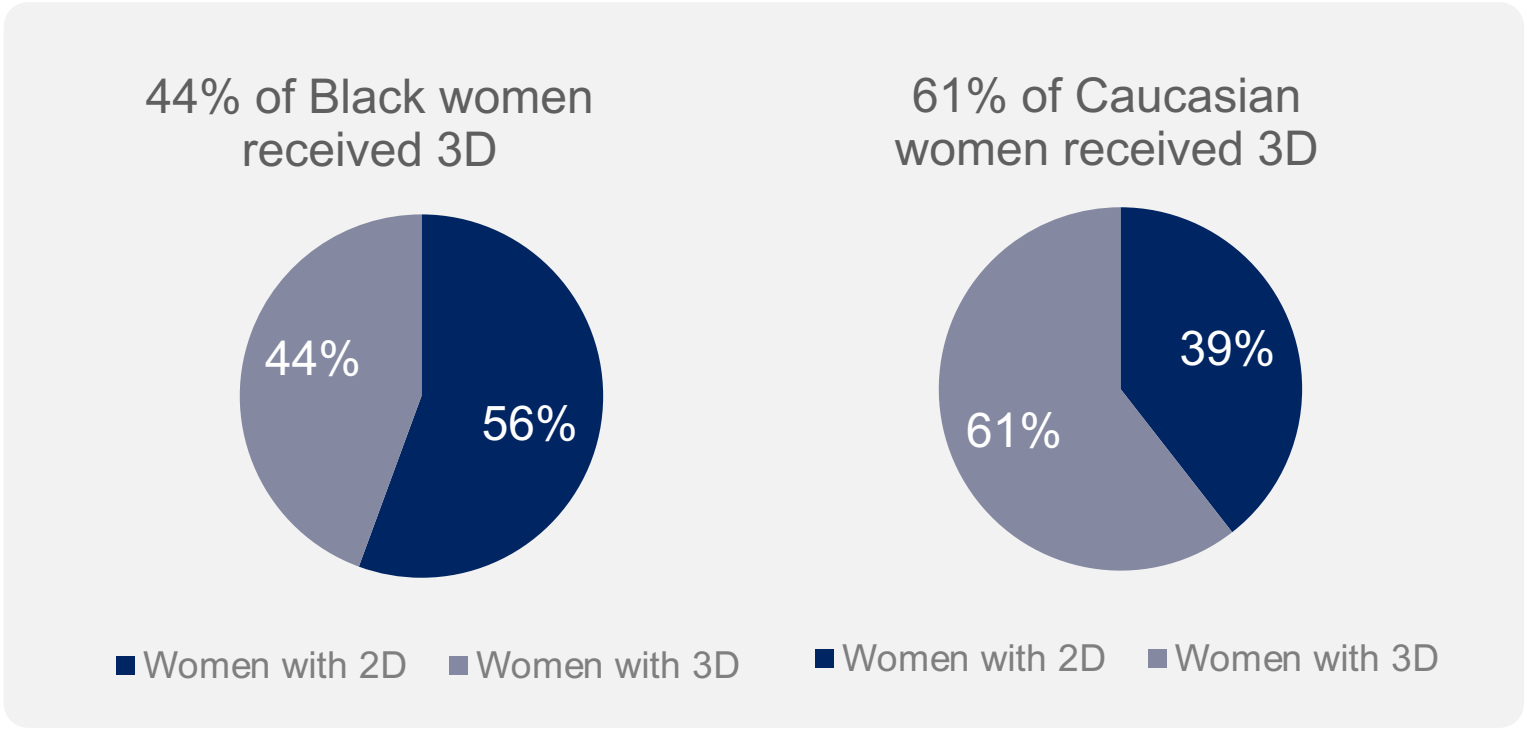
RWE design enables a more racially diverse cohort

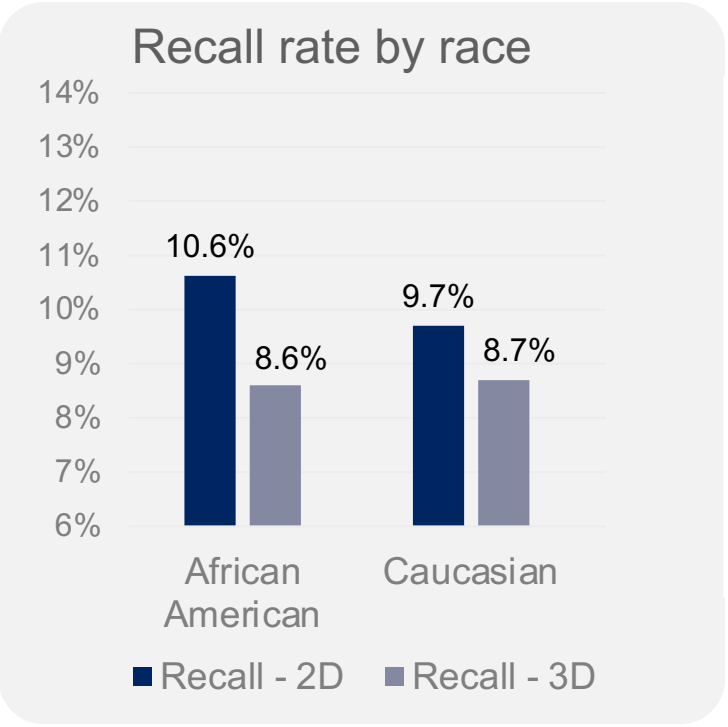
Patient Representativeness: Breast cancer carries one of the highest observed racial disparities in mortality – barriers in access to technology



US population source: US Census data, 2018

Reduced access to 3D for black women – 3D benefits all





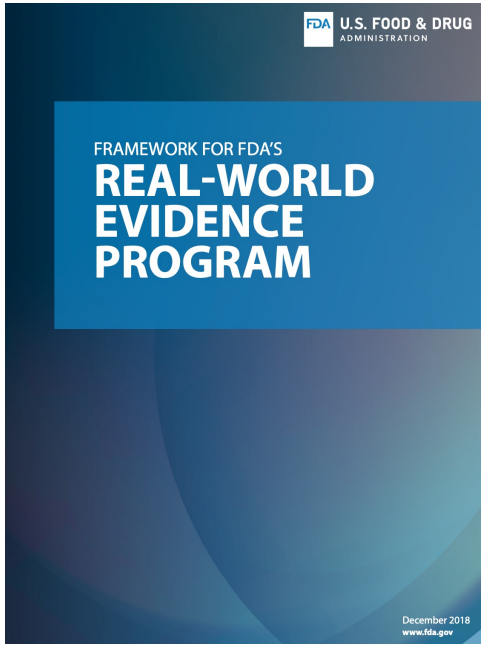
n= 400,000 women, n= 800,000 screening exams

Journal of the American College of Radiology 2021 18906-918DOI: (10.1016/j.jacr.2020.12.033)

RWE for Regulatory Decision Making

2021 FDA Guidance for Industry for RWE

2018



2021

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the Real-World Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2021
Real-World Data/Real-World Evidence (RWD/RWE)

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2021
Real World Data/Real World Evidence (RWD/RWE)

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

mments and suggestions regarding this draft document should be submitted within 90 days of blication in the *Federal Register* of the notice announcing the availability of the draft idance. Submit electronic comments to https://www.regulations.gov. Submit written mments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 hers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the cket number listed in the notice of availability that publishes in the *Federal Register*.

r questions regarding this draft document, contact (CDER) Ansalan Stewart, 240-402-6631, or BER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

November 2021
Real World Data/Real World Evidence (RWD/RWE)

https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

RWE for Regulatory Decision Making

- Submit protocols and statistical analysis plans to FDA for review, ***a priori***

- Are the appropriate patients included?
- Are the necessary data elements available?

- Are the data accurate, complete, and traceable?
- ***Validation*** of all key data elements

Conclusions

1. RWD approaches can ***catalyze insights*** in comparative effectiveness by including a broader range of patients, larger sample sizes, and extended follow-up. Studies can be executed quickly.

2. Critical to ***address the biases*** arising from real-world practice and real-world data sources. Modern analytical tools are advancing quickly, but good study design is paramount.

3. The landscape for use of ***RWD for regulatory decision making*** is advancing rapidly, along with benchmarks and methods for maximizing data “fitness for use.”

Thank you

Jess Paulus, ScD

Senior Director, Epidemiology

jpaulus@om1.com

EXTRA SLIDES

	Interventional	Observational
Primary data collection for research	• Traditional RCTs	Cohort, case control studies
		Real-world data
	• Pragmatic RCTs	Registry-based studies
Secondary use of clinical data	• Cluster RCTs	Health or claims-based analyses

Adapted from: Pharmacoepidemiol Drug Saf. 2020;29:1514–1517.

Opportunities for CER Insights Using RWE

Real-world Evidence	*Randomized Evidence*
• Examine treatment effects in populations typically excluded from trials • Detect heterogeneity of treatment effects • Larger sample sizes • Longer follow-up to examine long term outcome and safety events	• Maximize treatment contrast (structured and supported environment) • Control of bias, especially confounding • “Gold standard” for clinical and regulatory decision making

RESEARCH

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,[1] Linda R Valsdottir,[1] Michael W Yeh,[2] Changyu Shen,[1] Daniel B Kramer,[1] Jordan B Strom,[1] Eric A Secemsky,[1] Joanne L Healy,[1] Robert M Domeier,[3] Dhruv S Kazi,[1] Brahmajee K Nallamothu[4] On behalf of the PARACHUTE Investigators

ABSTRACT

OBJECTIVE

To determine if using a parachute prevents death or major traumatic injury whe

DESIGN

Randomized controlled tri

SETTING

Private or commercial airc
2017 and August 2018.

PARTICIPANTS

92 aircraft passengers age
screened for participation
and were randomized.

INTERVENTION

Jumping from an aircraft (a
parachute versus an empt

regarding the effectiveness of an intervention exist in the community, randomized trials might selectively enroll individuals with a lower perceived likelihood

"Parachute use did not reduce death or major traumatic injury when jumping from aircraft in the first randomized evaluation of this intervention."

"However, the trial was only able to enroll participants on small stationary aircraft on the ground, suggesting cautious extrapolation to high altitude jumps."

ant jumping from aircraft with an empty backpack.
major injury upon impact with the ground

OM1®

BMJ 2018;363:k5094