Harnessing Real-World Data for Enhanced Drug Development in the Pharmaceutical Industry

Presenter: Greg Ginn
Date: November 4, 2024

Confessions of a Real-World Data (RWD) Denier

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Confessions of a Real-World Data (RWD) Denier

I never believed in using RWD for Drug/Device development…

- **I've Supported RCTs for 35+ Years**
- **Issues with RWD:**
  - **Concerns Over Data Quality:**
    RCTs - data collection tightly controlled and verified while **RWD** sources may lack rigor
  - **Bias and Confounding Variables:**
    RCTs - designed to minimize bias (rand. and blinding) which **RWD** often lack
  - **Lack of Standardization: RCTs** - use strict protocols while **RWD** may have no uniform approach
  - **Regulatory Hesitation: RCTs** - typically required by Regulatory agencies who were cautious about **RWD**
  - **Complexity in Interpretation: RCTs** - clear outcomes, controlled environments while RWD has complexities and unstructured phenomena - difficult to interpret

… Until I met a RWD believer…

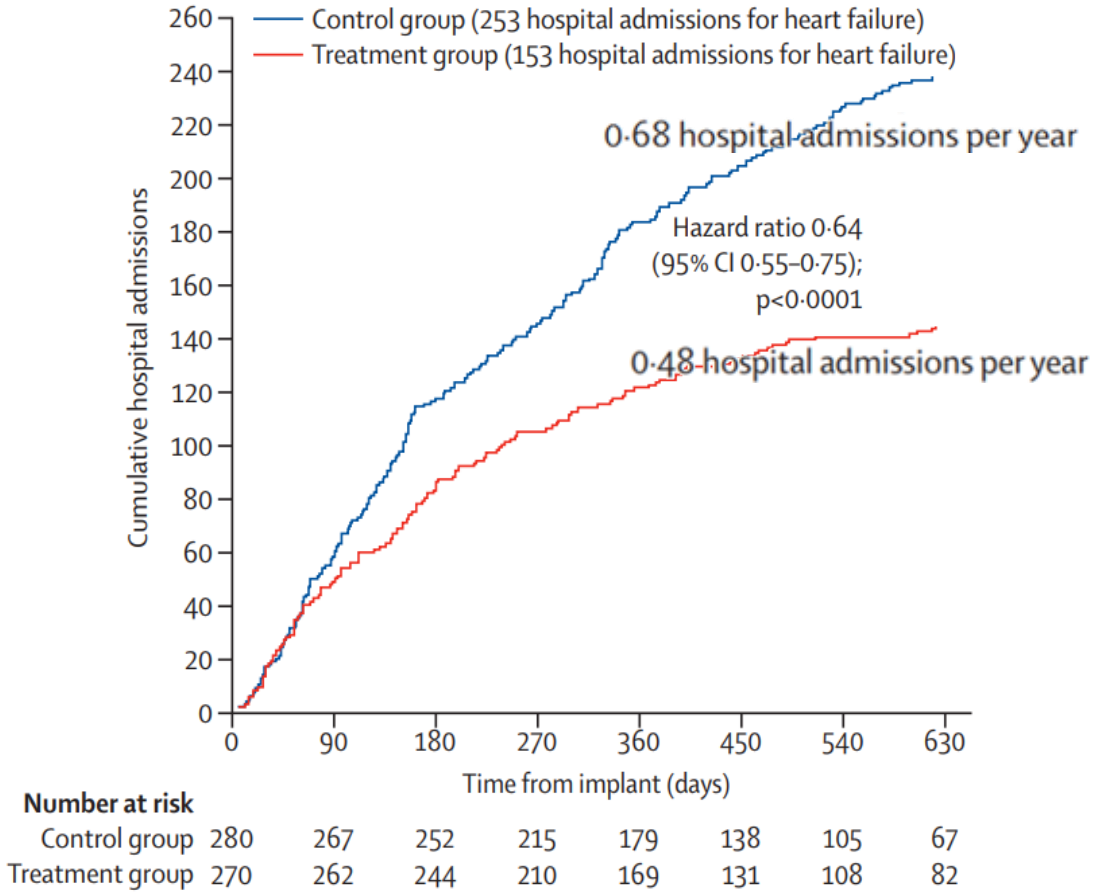
and FDA told me …

Your RCT Trial is not Real-World Enough

Results from CHAMPION RCT Trial

CHAMPION RCT Trial Analysis

Abraham, W. T., et al. (2011). "*The Lancet*, 377(9766), 658-666

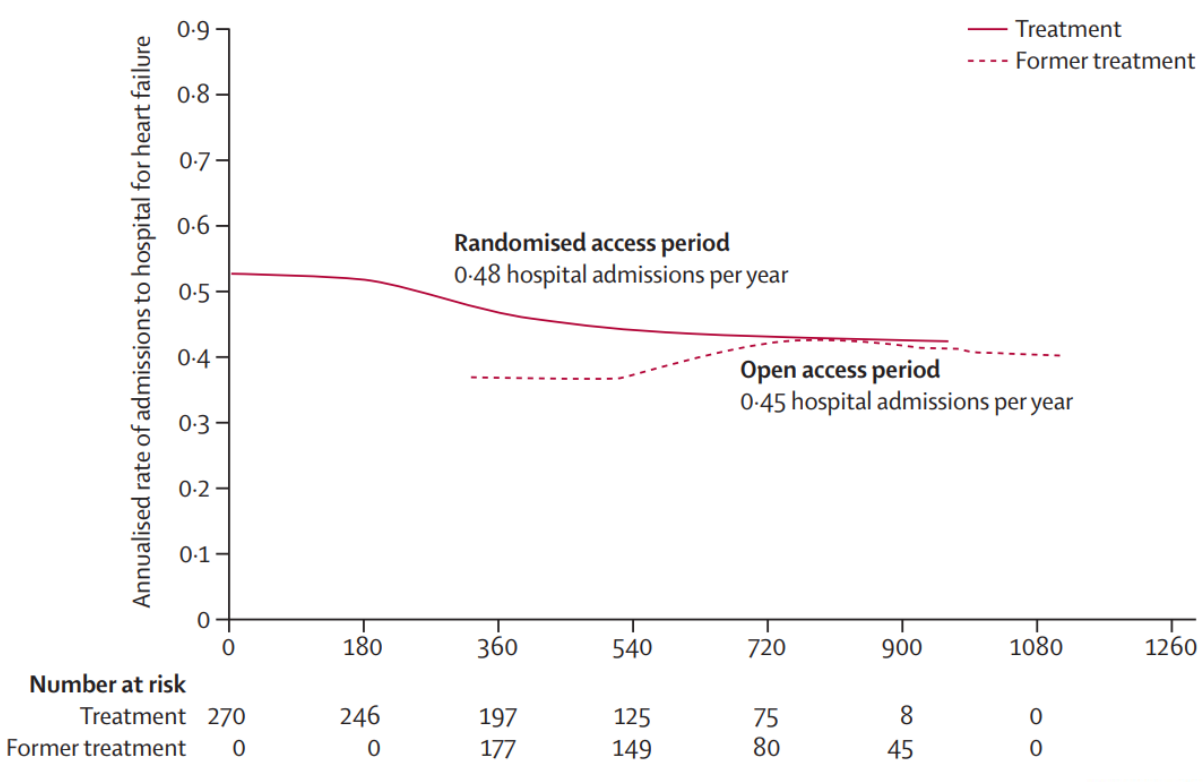


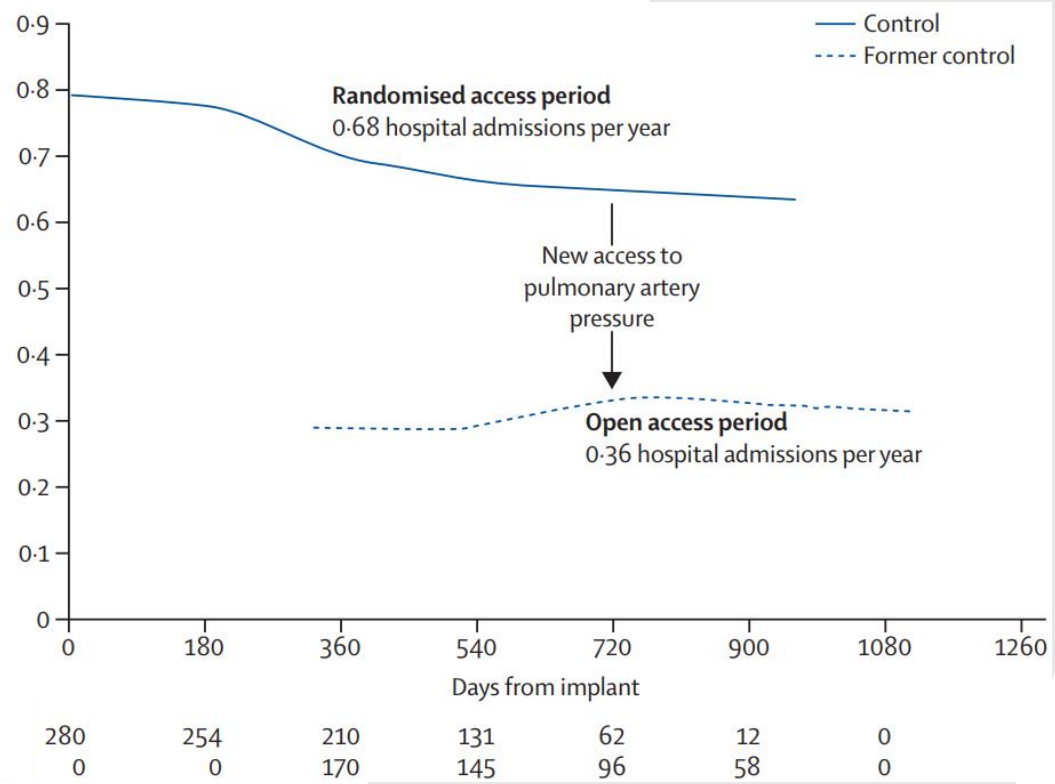
What was I to do?

Your RCT is not Real-World Enough

Results from CHAMPION RCT Trial

- **Randomized access period**
- **Open access period (Real World Data)**





Agenda

OUTLINE OF PRESENTATION

I. Introduction to RWD
II. Data Integration and Quality
III. Drug Development and Adaptive Clinical Trials
IV. Pharmacovigilance and Post-Market Surveillance
V. Patient-Centric Approaches
VI. Regulatory Considerations
VII. Case Studies
VIII. Future Directions

I. Introduction to Real-World Data (RWD)

- FDA defined Real World Evidence (RWE) and RWD as:

> "data regarding the usage, or the potential benefits or risks, of a drug derived from sources **other than traditional clinical trials**" [505F(b) of the FD&C Act]

- Comes from wide range of sources, including:
  - Electronic health records (EHRS)
  - Insurance Claims data
  - Patient registries
  - Health insurance databases
  - Pharmacy Data
  - Wearable Devices and Health Apps
- Diverse set of data types: Demographics, MHx, Labs, Rx records, Diagnoses, and Outcomes.
- Unlike data in controlled clinical trials, RWD is generated during routine patient care

I. Introduction to Real-World Data (RWD)

RWD is Important for several reasons:

Drug Development: Can be used to **Identify** unmet medical needs, **Design** more patient-centric clinical trials, and **Evaluate** safety & effectiveness of new therapies in RW settings.

Comparative Effectiveness Research:
Compares performance of Therapies against Competitors to determine market position.

Safety Surveillance:
Detecting and monitoring AEs and safety concerns in Post-Market phases is essential to identify any safety signals

Health Economics and Outcomes Research (HEOR):
Evaluating cost-effectiveness and longer-term outcomes for reimbursement and market access decisions.

Regulatory Decision-Making:
Health authorities like the FDA and EMA are increasingly recognizing the value of RWD in regulatory decision-making processes.

II. Data integration and quality

1. Challenges of Data Integration:

Data Heterogeneity: RWD comes from various sources, different structures, format, and coding systems.

Data Volume: Massive datasets can be overwhelming, and Integration can be difficult

Data Privacy and Compliance: Patient data in RWD sources often subject to strict privacy regulations and security. Health Insurance Portability and Accountability Act (HIPAA) in the US, adds complexity to the process.

Temporal Misalignment: RWD is collected at different times, which may not align perfectly - challenging to track patients' treatment journeys accurately and impacts of time-to-event analyses.

II. Data integration and quality

2. Ensuring Data Quality:

Data Cleaning: removing errors, inconsistencies, and dealing with missing values.

Standardization: Standardizing data elements, e.g., medical terminologies, coding systems (e.g., ICD-10), and units of measurement for consistency and comparability.

Data Validation: Algorithms and validation checks to identify outliers and errors to ensure accuracy and reliability

Data Linkage: Data from multiple sources must be linked to ensure patient records are correctly matched..

IV. Pharmacovigilance and post-market surveillance

1. Continuous Monitoring for Drug Safety:

Signal Detection: RWD sources (e.g., electronic health records (EHRs), insurance claims, and patient registries), allow continuous monitoring of patient outcomes and safety events.

AE Identification: RWD can help identify rare AEs or long-term side effects not apparent in the controlled environment of RCTs.

Comparative Safety Studies: RWD enables comparison of different drugs within same therapeutic class or evaluation of new drugs against existing treatments, helping identify potential safety concerns.

IV. Pharmacovigilance and post-market surveillance

2. Signal Detection and Risk Assessment:

Pharmacovigilance Algorithms: Develop algorithms to detect statistical signals including

- **Disproportionality analyses** – are occurrence of a AEs disproportionate to what would be anticipated based on background data
- **Bayesian data mining** - incorporating prior knowledge and enhancing detection of rare events
- **Machine learning techniques** – automation of analyses that can learn from previous data and make predictions

Risk Assessment:

- RWD provides broader and more diverse patient population for risk assessment
- Allows regulators and companies to make decisions about drug labeling and risk mitigation

IV. Pharmacovigilance and post-market surveillance

3. Regulatory Reporting:

Regulatory Requirements: Agencies (e.g., FDA in US, EMA in Europe), mandate reporting of AEs and safety data which can be fulfilled by RWD

Benefit-Risk Assessment: RWD assists in assessing overall benefit-risk profile of a drug - crucial for regulatory authorities to determine labeling changes or whether post-market studies, are needed

Labeling Updates: RWD can lead to updates in drug labels with new safety information or contraindications, ensuring that healthcare providers and patients are aware of potential risks.

Risk Minimization: RWD can inform risk minimization strategies, such as Risk Evaluation and Mitigation Strategies (REMS), ensuring that benefit to risk profile remains adequte

V. Patient-centric approaches

Patient-centric approaches in drug development increasingly recognized as essential to meet needs and **preferences** of patients. RWD plays a pivotal role in this transformation:

1. PATIENT-REPORTED OUTCOMES (PROS):

- **Definition:** PROs - measures of patient's health status, symptoms, and overall well-being **reported directly by the patient** – may include quality of life, pain, physical function, and other patient-relevant outcomes.
- **RWD Sources**: from patient registries, electronic health records (EHRs), and health apps often include PROs collected during routine clinical care.
- **Role in Drug Development:** Incorporating PROs into drug/device development allows companies to assess treatment effectiveness from **patient's perspective and experience**.

V. Patient-centric approaches

2. PATIENT PREFERENCES:

Definition:

- Reflect individual **attitudes**, **values**, and **priorities** regarding treatment options.
- Include their willingness to **accept potential risks** in exchange for **specific benefits**.
- Important to understand what matters most to patients regarding treatment decisions

RWD Sources: Surveys, interviews, and patient registries

Role in Drug Development:

- RWD on patient preferences inform decisions about Tx design, labeling, and marketing.
- Understanding patient preferences guides development of therapies aligning with patients' values.

V. Patient-centric approaches

3. REAL-WORLD TREATMENT PATTERNS:

Definition: Real-world treatment patterns refer to actual usage of drugs or therapies by patients in clinical practice outside the controlled environment of clinical trials.

RWD Sources: Claims data, EHRs, and pharmacy records provide insight into how drugs are prescribed, administered, and adhered to in real-world clinical settings.

Role in Drug Development:

- RWD on real-world treatment patterns can inform the design of clinical trials to better mimic how treatments are used in practice.
- Understanding real-world usage helps refine dosing regimens, treatment adherence strategies, and patient support programs.

V. Patient-centric approaches

4. ADVANTAGES OF PATIENT-CENTRIC APPROACHES WITH RWD:

Personalized Medicine: By incorporating patient perspectives and real-world data, companies can develop therapies more aligned with an individual patients' needs.

Better Treatment Outcomes: RWD-driven patient-centric approaches can lead to development of treatments with greater impact on patient outcomes, as they address what matters most to patients.

Improved Treatment Adherence: Understanding real-world treatment patterns can help design interventions and support systems that improve patient adherence to prescribed therapies, leading to better health outcomes.

Enhanced Regulatory Decision-Making: Regulatory agencies increasingly consider patient-reported data and preferences when making approval and labeling decisions, ensuring that drugs meet patient needs and align with their preferences.

VI. Regulatory Considerations

1. FDA'S FRAMEWORK FOR REAL-WORLD EVIDENCE (RWE):

Understanding the **evolving regulatory environment** is crucial in using Real-World Data (RWD) and Real-World Evidence (RWE) in the pharmaceutical and device industry.

Framework Overview: In December 2018, the FDA released its framework for RWE, outlining its approach to using RWD to support regulatory decision-making. The framework emphasizes the importance of RWE in various stages of drug development, from pre-market to post-market. Selected Guidance Documents include:

- Framework for FDA's Real-World Evidence Program
- Use of Electronic Health Records in Clinical Investigations
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
- Data Standards for Drug and Biological Production Submissions Containing Real-World Data
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
- Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
- Use of Real-World Data and Real-World Evidence to Support Effectiveness of New Animal Drugs

VI. Regulatory Considerations

2. EMA'S STANCE ON REAL-WORLD DATA (RWD):

European Perspective: EMA has also recognized the value of RWD is actively exploring ways to incorporate RWD into regulatory decision-making launching initiatives and pilot projects to assess the utility of RWD in regulatory processes.

The European Medicines Agency (EMA) has released new guidance detailing the types of studies that can be performed for RWE generation and how they can support RWD studies in the context of regulatory decision-making. (22 April 2024)

VI. Regulatory Considerations

3. DATA QUALITY AND VALIDITY:

Ensuring Data Quality: Statisticians have responsibility for data quality and validity in RWD studies including data cleaning, validation, and addressing potential biases in the data.

Compliance with Regulatory Guidelines: Statisticians responsible for ensuring that RWD studies meet regulatory guidelines for data quality, which can vary between the FDA and EMA. They also ensure that data sources and methods align with Good Clinical Practice (GCP) and Good Epidemiological Practice (GEP) standards.

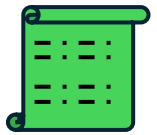
4. COLLABORATION AND COMMUNICATION:

Interactions with Regulatory Agencies: Statisticians engage in regulatory interactions to present the results of RWD studies and answer questions from regulatory agencies - demonstrate the validity and relevance of RWD in supporting regulatory decisions.

Cross-Functional Collaboration: Statisticians collaborate with cross-functional teams, including data scientists, epidemiologists, and medical experts, to ensure that RWD studies are well-designed and adequately powered to answer specific regulatory questions.

Transparency and Documentation: Statisticians are responsible for providing clear, transparent, and well-documented analyses of RWD studies, making it easier for regulatory agencies to evaluate and validate the findings.

VII. Case Studies



1. Desai et al., HFH Reductions w/ PAP Monitoring, *JACC* Vol. 69, NO.19, 2017, MAY 16, 2017:2357–65.

- **BACKGROUND:** In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association [NYHA] Functional Class III Heart Failure Patients) trial, heart failure hospitalization (HFH) rates were lower in patients managed with guidance from an implantable pulmonary artery pressure sensor compared with usual care.

- **DATA SOURCE AND IDENTIFICATION OF THE COHORT:** Retrospective cohort study using CMS administrative claims data from the Standard Analytic File to evaluate health care utilization in U.S. Fee-for-service Medicare beneficiaries receiving a CardioMEMS PAP sensor implant during the period following FDA approval for commercial use (from June 1, 2014, onward).

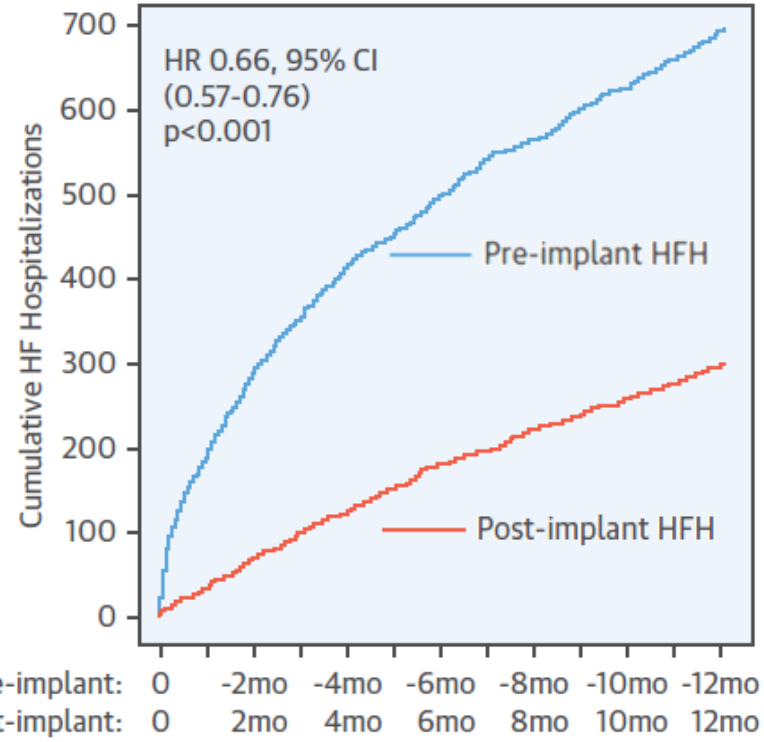
- **ANALYSIS OF EFFECTIVENESS:** We compared rates of HFH (defined using the published CMS methodology) and all-cause hospitalization during the 6 months before and following device implantation using the Andersen-Gill model for recurrent events, with censoring at the time of death, ventricular assist device (VAD) implantation, or cardiac transplantation.

VII. Case Studies

- 1. Desai et al., HFH Reductions With PAP Monitoring, *JACC* Vol. 69 , NO.19, 2017, MAY 16 , 2017:2357–65

RWD Study Analysis

Desai, A.S. et al. J Am Coll Cardiol. 2017;69(19):2357-65.

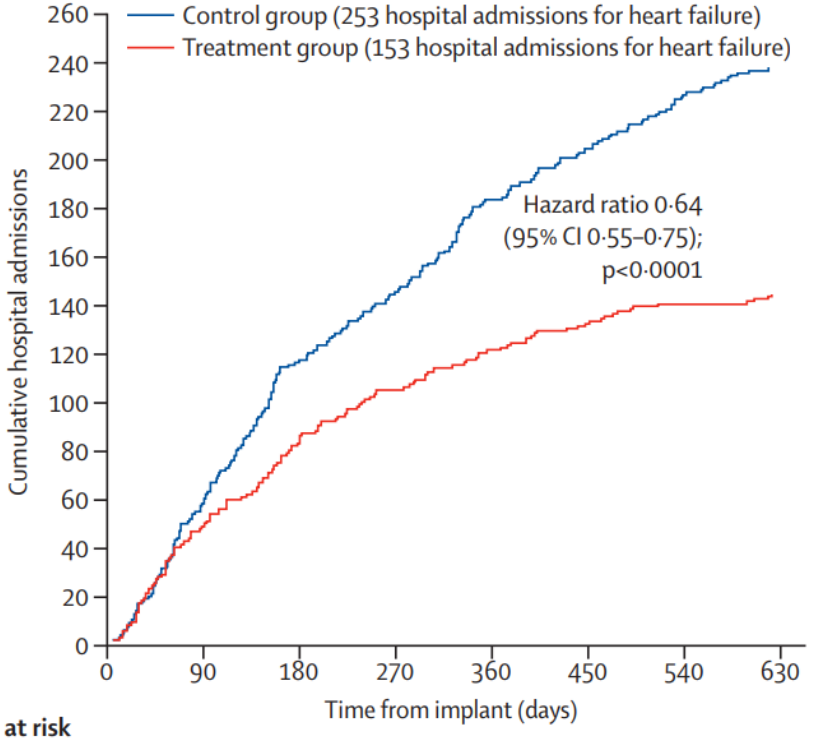


Number at risk

Pre-implant	*480*	*480*	*480*	*480*	*480*	*480*	*480*
Post-implant	*480*	*450*	*435*	*409*	*394*	*373*	*357*

CHAMPION RCT Trial Analysis

Abraham, W. T., et al. (2011). "*The Lancet*, 377(9766), 658-666



Number at risk

Control group	280	267	252	215	179	138	105	67
Treatment group	270	262	244	210	169	131	108	82

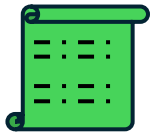
VII. Case Studies

2. Abraham et al., Association of Ambulatory Hemodynamic Monitoring of Heart Failure With Clinical Outcomes in a Concurrent Matched Cohort Analysis, *JAMA Cardiol*. 2019;4(6):556-563

- **BACKGROUND:** In a randomized clinical trial, heart failure (HF) hospitalizations were lower in patients managed with guidance from an implantable pulmonary artery pressure sensor compared with usual care. It remains unclear if ambulatory monitoring could also improve long-term clinical outcomes in real-world practice.

- **DESIGN, SETTING, AND PARTICIPANTS:** This matched cohort study of Medicare beneficiaries used claims data collected between June 1, 2014, and March 31, 2016. Medicare patients who received implants of a pulmonary artery pressure sensor were identified from the 100% Medicare claims database. Each patient who received an implant was **matched** to a control patient by demographic features, history of HF hospitalization, and number of all-cause hospitalizations. **Propensity scoring** based on comorbidities (arrhythmia, hypertension, diabetes, pulmonary disease, and renal disease) was used for **additional matching**. Data analysis was completed from July 2017 through January 2019. The study cohort consisted of 1087 patients who received an implantable pulmonary artery pressure sensors and 1087 matched control patients

VII. Case Studies



2. Abraham et al., Association of Ambulatory Hemodynamic Monitoring of Heart Failure With Clinical Outcomes in a Concurrent Matched Cohort Analysis, *JAMA Cardiol*. 2019;4(6):556-563

- **MATCHING:** An identical match was defined in each iterative run based on sequential matching of demographic attributes (sex, race, history of implantable cardioverter defibrillator or cardiac resynchronization therapy implant, end stage renal disease status, and age within 5 years), then comorbidities (diabetes, hypertension, renal disorders, pulmonary disorders, and arrhythmia), followed by the closest propensity score (derived using logistic regression). Additionally, patients were matched if they incurred an identical number of HF and non-HF hospitalizations and if the timing of each HF hospitalization was within 4 months. This method was used to provide a close approximation of HF severity between patients who received implants and control patients. Finally, after the matching procedure, we compared the severity of HF hospitalization using length of stay for each HF hospitalization and cumulative number of hospitalized days per patient.

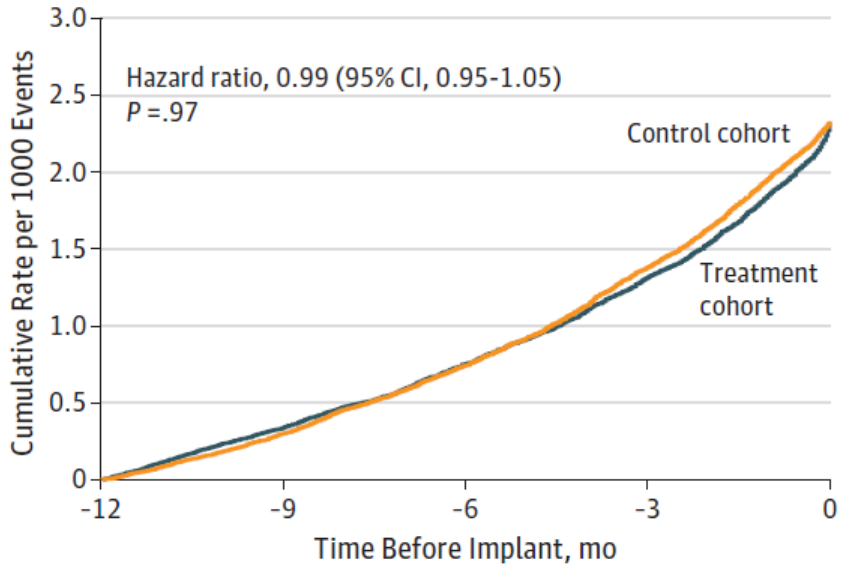
- **MAIN OUTCOMES AND MEASURES:** The rates of HF hospitalization were compared using the Andersen-Gill method. Days lost owing to events were compared using a nonparametric bootstrap method.

VII. Case Studies

- 1. Desai et al., HFH Reductions With PAP Monitoring, *JACC* Vol. 69 , NO.19, 2017, MAY 16 , 2017:2357–65

RWD HF Hospitalizations Before Sensor Implant

Figure 1. Time Series of Heart Failure Hospitalizations in the 12 Months Before Pulmonary Artery Pressure Sensor Implant

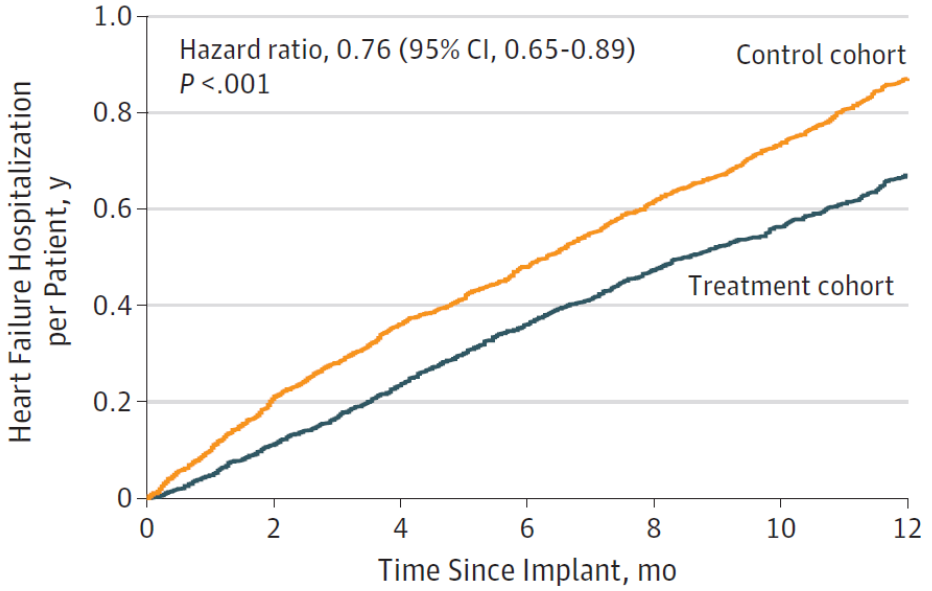


No. at risk

Treatment cohort	1087	1087	1087	1087	1087
Control cohort	1087	1087	1087	1087	1087

RWD HF Hospitalizations After Sensor Implant

A Cumulative HF hospitalizations after PAP sensor implantation



No. at risk

Treatment cohort	1087	1037	991	944	908	862	830
Control cohort	1087	1000	931	891	850	805	764

VIII. Future Directions:

1. ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING IN RWD ANALYSIS:

Advanced Data Processing:

- Can be leveraged to process and analyze large volumes of complex RWD.
- Can assist in data cleaning, normalization, and feature engineering.

Predictive Modeling:

- Can build predictive models that identify patterns, relationships, and trends within RWD.
- For example, predictive modeling can help forecast disease progression, treatment response, or the likelihood of adverse events.

Natural Language Processing (NLP):

- Can extract valuable insights from unstructured RWD sources, such as clinical notes and text-based patient records.
- Can be used to identify patient-reported outcomes, sentiment analysis, and even adverse event reporting from social media data.

VIII. Future Directions:

2. DATA SHARING COLLABORATIONS:

Collaboration is essential for harmonizing and integrating diverse RWD sources.

- Efforts are ongoing to ensure that data from **different healthcare systems** and organizations can be **combined effectively** for broader analyses.

Patient Data Access:

- Giving patients **greater control** over their health data, enabling them to share their RWD with researchers or for clinical trial participation.
- Data sharing collaborations involve patient consent and data governance.

Global Data Networks:

- Observational Health Data Sciences and Informatics (OHDSI) network - results informed clinical guidelines and **influenced Tx treatment decisions globally.**
- International data sharing collaboration that facilitates large-scale RWD research.

Cross-Industry Partnerships:

- **Collaborations** between pharmaceutical companies, healthcare providers, tech companies, and research institutions
- Example: Pharmaceutical company **partnering** with tech company to access patient-generated health data from wearable device.

Regulatory Involvement: Increasingly **promoting data sharing collaborations**. FDA's **Sentinel System** in the U.S. - prime example of a **public-private collaboration** for monitoring drug safety using diverse RWD sources.

VIII. Future Directions:

EXAMPLES

AI for Predictive Analytics: In a case study, AI and machine learning were used to predict disease progression in patients with a rare condition using a combination of structured and unstructured RWD sources. This enabled early intervention and personalized treatment approaches, improving patient outcomes.

Natural Language Processing (NLP) for AE Detection: NLP was applied to analyze patient narratives in clinical notes within EHRs to detect adverse events. The automated system found previously unknown safety signals, leading to further investigation and regulatory action.

Data Sharing for Drug Repurposing: A collaborative effort involving multiple pharmaceutical companies and research institutions shared de-identified patient data to identify potential new applications for existing drugs. This led to the discovery of a promising candidate for a rare disease, significantly accelerating the development process.

IX. Conclusion

In the evolving landscape of pharmaceutical research and healthcare decision-making, Real-World Data (RWD) has emerged as a valuable asset, offering insights that inform drug development, enhance patient outcomes, and guide regulatory decisions.

Statisticians and data scientists play pivotal roles in harnessing the power of RWD to address various critical aspects of the pharmaceutical industry. Key highlights from the topics discussed include:

RWD in the Pharmaceutical Context: RWD, drawn from sources like electronic health records, claims data, and patient registries, is invaluable for providing a real-world perspective on healthcare outcomes and treatment efficacy.

Data Integration and Quality: Statisticians are instrumental in overcoming challenges related to data integration and ensuring data quality, enabling the reliable analysis of RWD.

Thank you!

Questions??