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Improving healthcare decisions

Transparency in RWE – Can We Navigate the Key Challenges?

Issue Panel, 5 Nov 2109
ISPOR Europe 2019, Copenhagen

ISPOR/ISPE Joint Special Task Force on Real World Evidence in Health Care Decision Making

Objective: To provide a clear set of good practices for enhancing the transparency, credibility, and reproducibility of real world database studies in healthcare, with the aim of improving the confidence of decision-makers in utilizing such evidence.

STF work initiated late 2016, published Sept 2017

Transparency Paper Co-Chairs

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Read the freely available Good Practices Reports
ispor.org/RWEinHealthcareDecisions

4

Transparency of study processes

5

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Transparency of Process - Primary Recommendations

1. A priori, determine and declare that study is a “HETE” or “exploratory” study
2. Post a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis.
3. Publish HETE study results with attestation to conformance and/ or deviation from original analysis plan.
4. Enable opportunities for replication of HETE studies whenever feasible (ie, for other researchers to be able to reproduce the same findings using the same data set and analytic approach).
5. Perform HETE studies on a different data source and population than the one used to generate the hypotheses to be tested, unless it is not feasible.
6. Authors of the original study should work to publicly address methodological criticisms of their study once it is published.
7. Include key stakeholders (eg, patients, caregivers, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers) in designing, conducting, and disseminating the research.

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Real-World Evidence Transparency Partnership

ispe International Society for Pharmacoepidemiology
ISPOR
Duke MARGOLIS CENTER for Health Policy
National Pharmaceutical Council
U.S. National Library of Medicine ClinicalTrials.gov
INAHTA
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
FDA
CADTH
AHRQ Agency for Healthcare Research and Quality Advancing Excellence in Health Care
NATIONAL HEALTH COUNCIL
Zorginstituut Nederland
AMCP Academy of Managed Care Pharmacy
Representatives from 7 pharma companies
Anthem
Syneos Health
flatiron
OPTUMLabs
NICE National Institute for Health and Care Excellence
patientslikeme

Draft White Paper Released on Sept. 18th – Open for Public Comment

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Improving Transparency in Non-Interventional Research for Hypothesis Testing—WHY, WHAT, and HOW: Considerations from The Real-World Evidence Transparency Initiative

Draft White Paper

September 18, 2019

This White Paper was authored by the Steering Committee of the Real-World Evidence Transparency Initiative Partnership. The Initiative is led by ISPOR, the International Society for Pharmacoepidemiology, Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council, with involvement of a number of other organizations and stakeholders. A list of all authors can be found in the appendix.

The white paper comment period remains open through Nov. 15: https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative

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ispe
National Pharmaceutical Council
Duke MARGOLIS CENTER for Health Policy

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ISPOR Summit 2019

Real-World Evidence Transparency Initiative

October 11, 2019 | Baltimore, MD, USA

www.ispor.org/Summit2019

Agenda

1. Transparency in RWE - Time for a Unified Approach
2. Registration site(s) - Opportunities to Optimize
3. Nuts and Bolts of Fit-for-Purpose
4. Behavior Modification - Boosting and Nudging
5. Transparency in RWE - Moving Forward

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Shirley Wang, PhD, MSc
Harvard Medical School,
Boston, MA, USA

Parallel efforts in progress…

Guiding principle: Don't let perfect be the enemy of good

Registration of Hypothesis Evaluating RWE
Multi-stakeholder Steering Group

Goals:

Increase transparency of research process

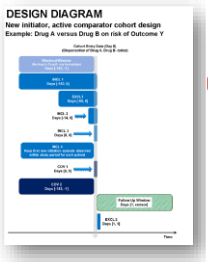
1. **Short term:** Identify central location for pre-registration
2. **Medium term:** Determine what registration will entail (progressive effort)
3. **Long term:** Aim for a (near) to complete denominator

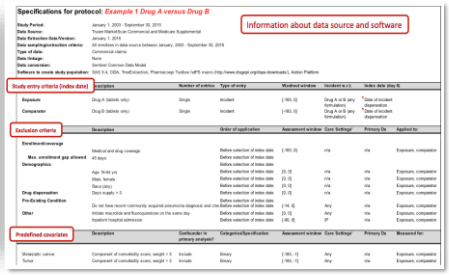
Structured reporting template with design visualization
Public/private project including FDA + consortium of sponsors

Goals:

Increase clarity in reporting of study implementation

1. Reduce misinterpretation
2. Simplify reporting
3. Maximize efficiency (for researchers and reviewers)





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Study registration: Why, what, how?

Why?

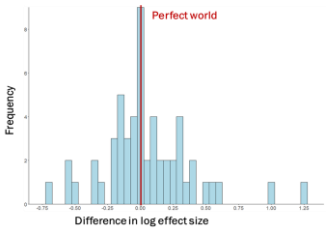
Study registration is about clear communication

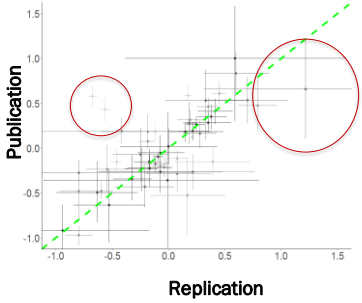
Study registration: Why, what, how?

What?

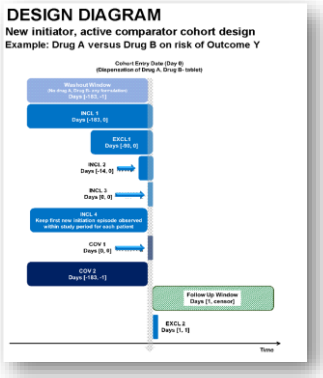
Need to include core elements to make it useful

Also want to maximize efficiency

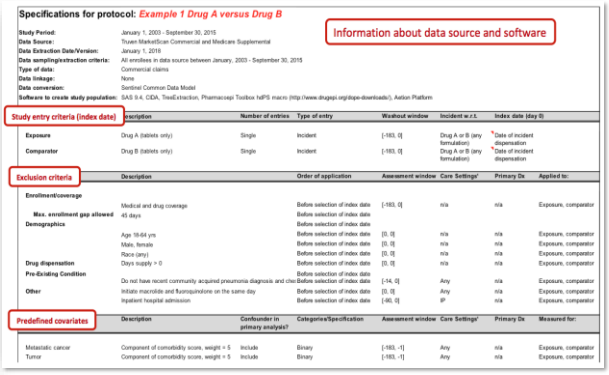




What core elements to include in hypothesis evaluating RWE registration?



Visual representation of key temporal anchors



Study parameter table: details of data, study design, and analysis

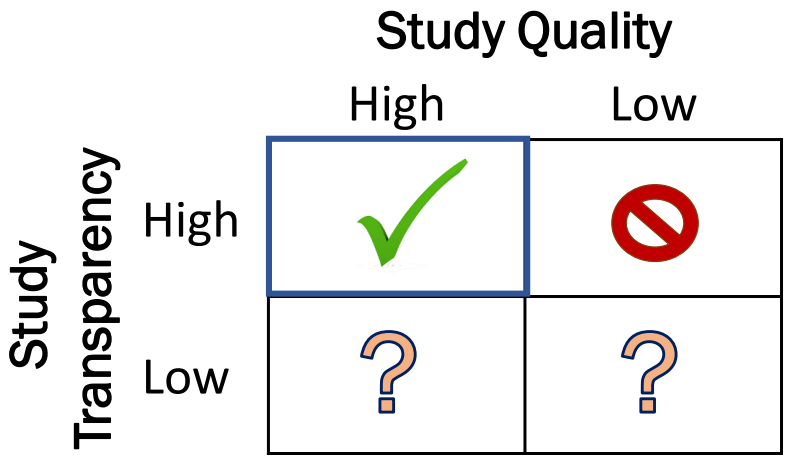
- Administrative information (who, IRB, DUA)
- Attestation regarding level of exploration of data
- Version control (when, why)
- Appendices with code algorithms
- …

Study registration: Why, what, how?

How?

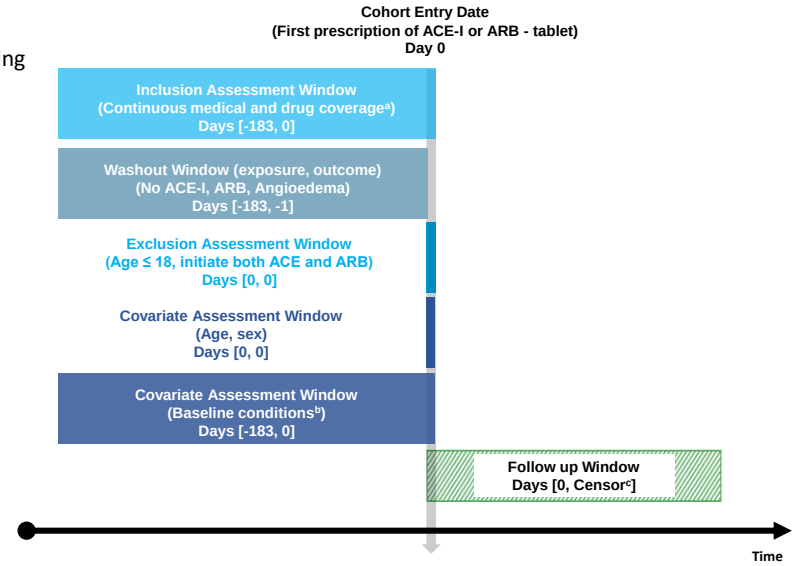
Standardize how we communicate about the science, not how we do the science

Study Transparency ≠ Study Quality



Example of simple design diagram

A cohort study to evaluate the risk of angioedema with angiotensin converting enzyme inhibitors (ACE-I) versus angiotensin II receptor blockers (ARB)

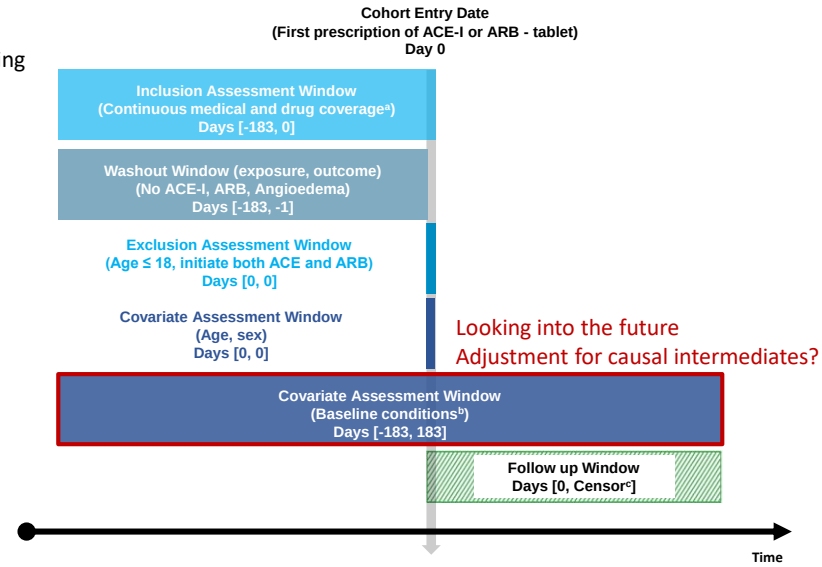


a. Up to 45 day gaps in medical or pharmacy enrollment allowed
b. Baseline conditions included: allergic reactions, diabetes, heart failure, ischemic heart disease, non-steroidal anti-inflammatory drugs
c. Earliest of: outcome of interest (angioedema), switching or discontinuation of study drugs, death, disenrollment, 365 days of follow-up, end of the study period

17 Toh S, et al *Arch Intern Med.* 2012

Adjustment for causal intermediates?

A cohort study to evaluate the risk of angioedema with angiotensin converting enzyme inhibitors (ACE-I) versus angiotensin II receptor blockers (ARB)



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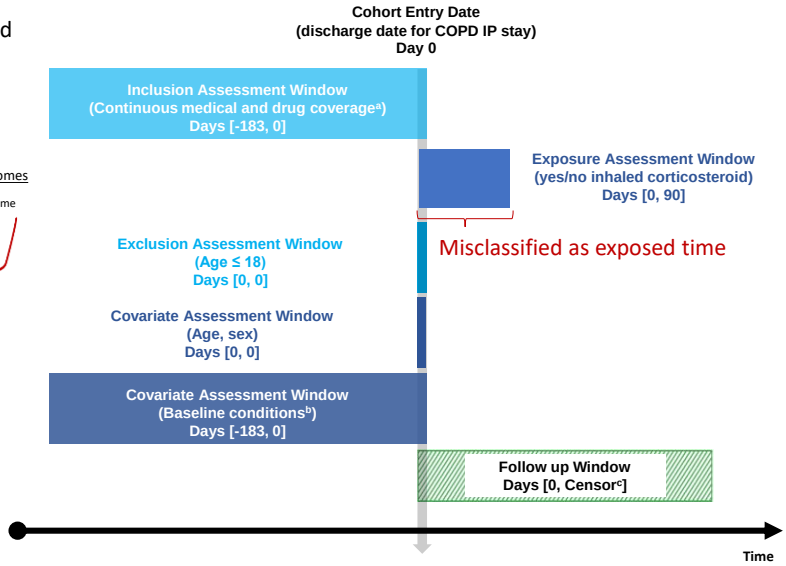
Immortal time bias?

Risk of death with inhaled corticosteroid after hospitalization for chronic obstructive pulmonary disease

Exposed Outcomes vs Unexposed Outcomes

Exposed time + immortal time Unexposed time



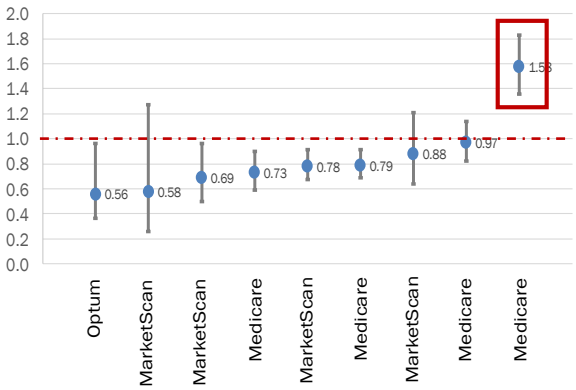
a. Up to 45 day gaps in medical or pharmacy enrollment allowed
b. Baseline conditions included: Charlson, healthcare utilization, other bronchodilator
c. Earliest of: outcome of interest (death), switching or discontinuation of study drugs, death, disenrollment, 365 days of follow-up, end of the study period

19 Suissa, 2012 RMMJ

With greater clarity about study implementation comes increased ability to evaluate validity

From the REPEAT replication sample

Dabigatran vs. Warfarin on risk of major bleeding in patients with atrial fibrillation



Example from JAMA Internal Medicine

Abstract:

We identified participants as those newly diagnosed as having atrial fibrillation from October 1, 2010, through October 31, 2011, and who **initiated dabigatran or warfarin** treatment within 60 days of initial diagnosis.

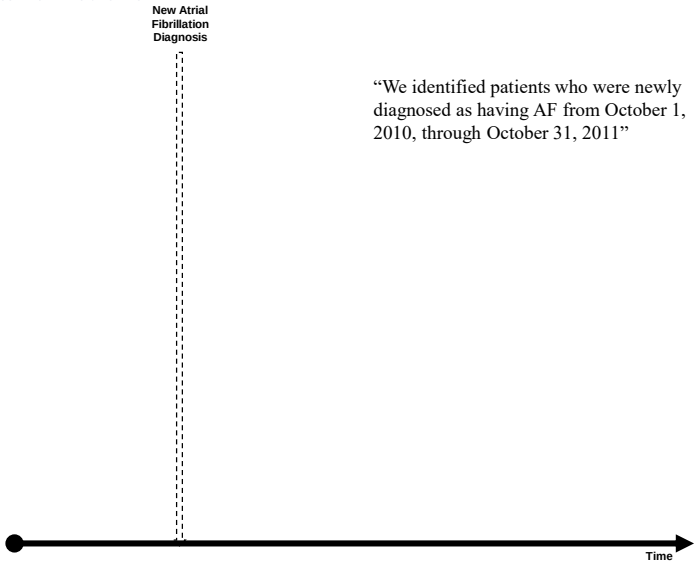
Methods:

We identified patients who were **newly diagnosed as having AF** from October 1, 2010, through October 31, 2011, by using the CMS Chronic Condition Warehouse indicator that traced the first diagnosis date back to January 1, 1999. The diagnosis of AF was defined as having 1 inpatient or 2 outpatient claims with primary or secondary International Classification of Diseases, Ninth Revision (ICD-9), code 427.31. We also required that individuals in our study sample had **filled an outpatient prescription for either dabigatran or warfarin within 2 months** of the first diagnosis (N = 9562). Those who **filled prescriptions for dabigatran and warfarin during the first 2 months after diagnosis** were excluded (N = 158). We followed up each individual from the first prescription of dabigatran or warfarin until discontinuation of use for more than 60 days, switch of anticoagulants, death, or December31, 2011. Our final overall study sample included 1302 dabigatran users and 8102 warfarin users.

…

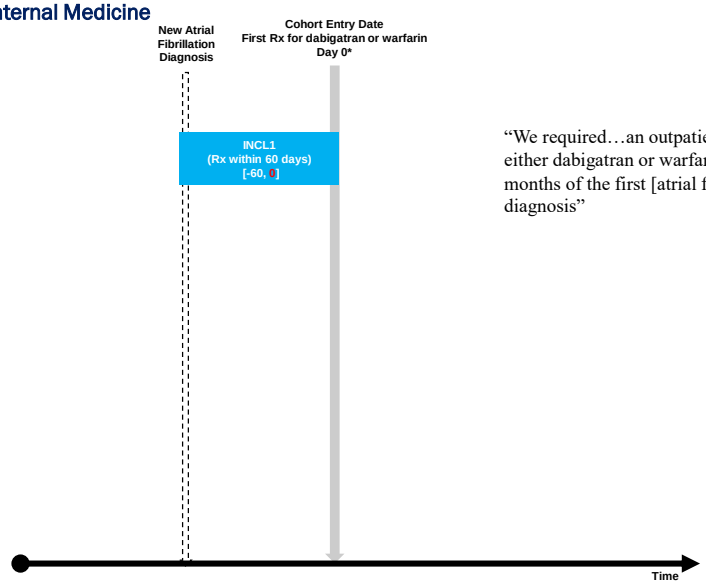
No attrition table or design diagram was provided.

Example from JAMA Internal Medicine



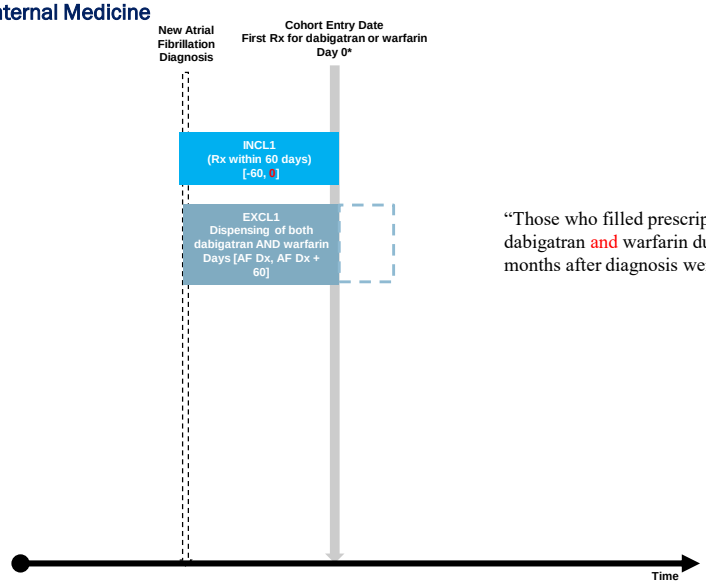
Harvard / Brigham Division of Pharmacoepidemiology and Pharmacoeconomics

Example from JAMA Internal Medicine



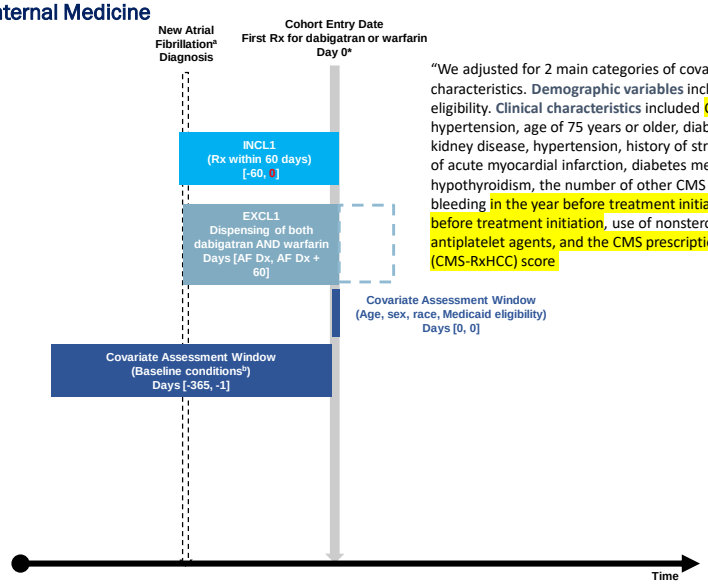
"We required…an outpatient prescription for either dabigatran or warfarin within 2 months of the first [atrial fibrillation] diagnosis"

Example from JAMA Internal Medicine



"Those who filled prescriptions for dabigatran and warfarin during the first 2 months after diagnosis were excluded"

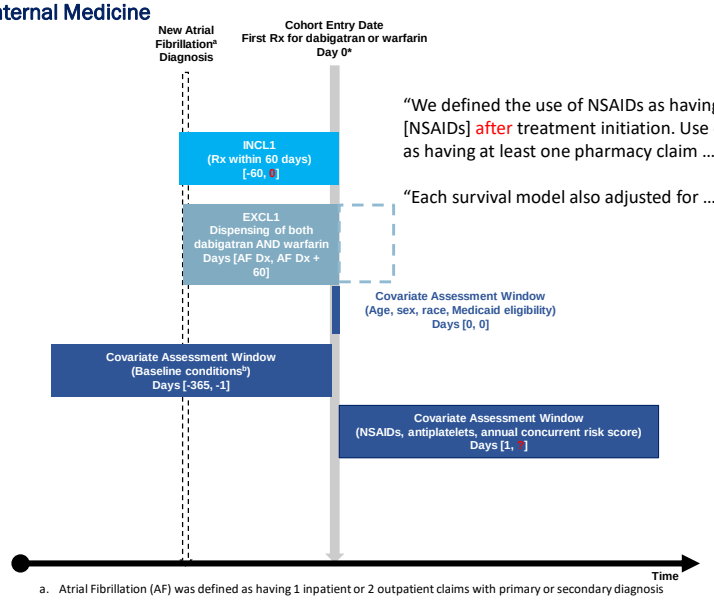
Example from JAMA Internal Medicine



"We adjusted for 2 main categories of covariates: demographic variables and clinical characteristics. **Demographic variables** included age, sex, race, and Medicaid eligibility. **Clinical characteristics** included CHADS2 (congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus, and stroke) score, chronic kidney disease, hypertension, history of stroke or transient ischemic attack, history of acute myocardial infarction, diabetes mellitus, congestive heart failure, acquired hypothyroidism, the number of other CMS priority comorbidities…, history of bleeding in the year before treatment initiation, history of hospitalization in the year before treatment initiation, use of nonsteroidal inflammatory drugs (NSAIDs), use of antiplatelet agents, and the CMS prescription drug hierarchical condition category (CMS-RxHCC) score

a. Atrial Fibrillation (AF) was defined as having 1 inpatient or 2 outpatient claims with primary or secondary diagnosis position of ICD-9 code 427.31
b. Baseline conditions included: CHADS2 score, Chronic kidney disease, Hypertension, Previous stroke or TIA, Acute MI, Diabetes, Congestive heart failure, Acquired hypothyroidism, History of bleeding, History of hospitalization, # of CMS priority comorbidities categorical, CMS-RxHCC score

Example from JAMA Internal Medicine

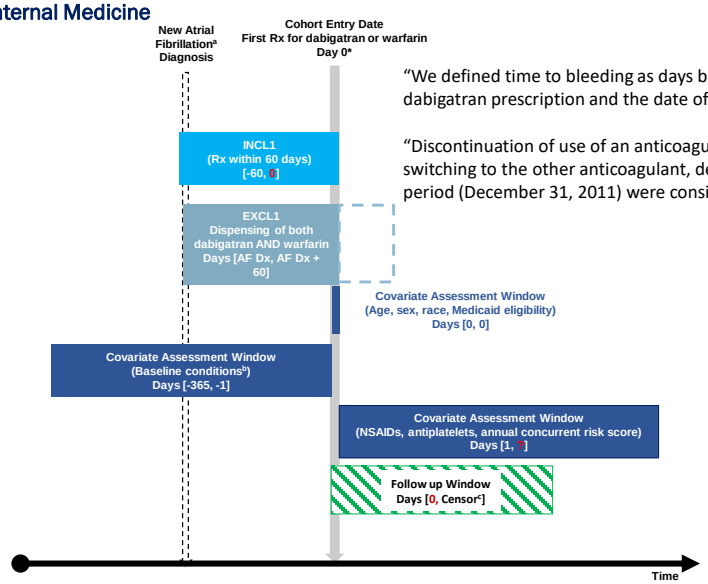


"We defined the use of NSAIDs as having at least one prescription for [NSAIDs] after treatment initiation. Use of antiplatelet agents was defined as having at least one pharmacy claim … after treatment initiation."

"Each survival model also adjusted for … annual concurrent risk score"

a. Atrial Fibrillation (AF) was defined as having 1 inpatient or 2 outpatient claims with primary or secondary diagnosis position of ICD-9 code 427.31
b. Baseline conditions included: CHADS2 score, Chronic kidney disease, Hypertension, Previous stroke or TIA, Acute MI, Diabetes, Congestive heart failure, Acquired hypothyroidism, History of bleeding, History of hospitalization, # of CMS priority comorbidities categorical, CMS-RxHCC score

Example from JAMA Internal Medicine

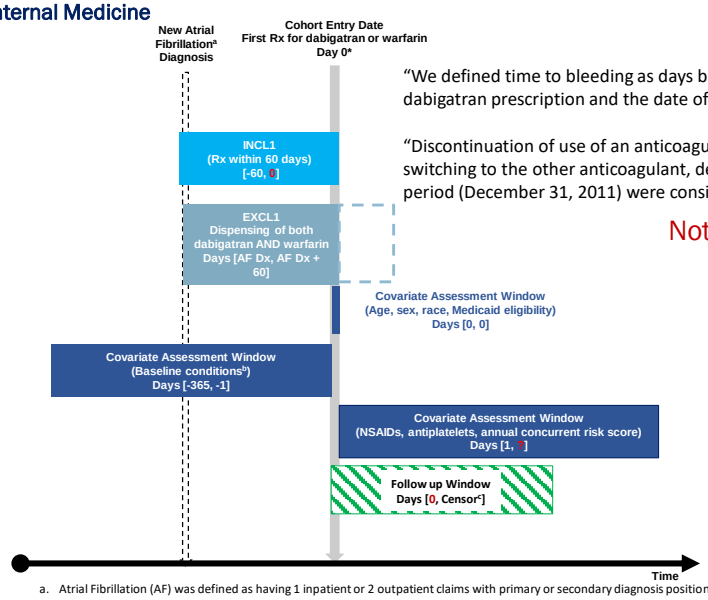


"We defined time to bleeding as days between the first warfarin or dabigatran prescription and the date of the bleeding event"

"Discontinuation of use of an anticoagulant (defined as a gap ≥60 days), switching to the other anticoagulant, death, and the end of the study period (December 31, 2011) were considered censoring events"

a. Atrial Fibrillation (AF) was defined as having 1 inpatient or 2 outpatient claims with primary or secondary diagnosis position of ICD-9 code 427.31
b. Baseline conditions included: CHADS2 score, Chronic kidney disease, Hypertension, Previous stroke or TIA, Acute MI, Diabetes, Congestive heart failure, Acquired hypothyroidism, History of bleeding, History of hospitalization, # of CMS priority comorbidities categorical, CMS-RxHCC score
c. Earliest of: discontinuation of initial drug (gap ≥ 60 days), switching of study drugs, death, end of study period (12/31/11)

Example from JAMA Internal Medicine



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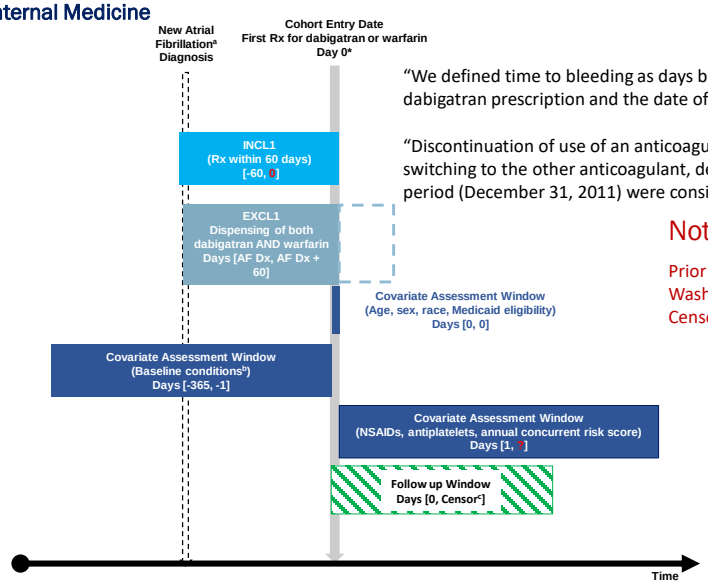
Notice anything missing?

a. Atrial Fibrillation (AF) was defined as having 1 inpatient or 2 outpatient claims with primary or secondary diagnosis position of ICD-9 code 427.31
b. Baseline conditions included: CHADS2 score, Chronic kidney disease, Hypertension, Previous stroke or TIA, Acute MI, Diabetes, Congestive heart failure, Acquired hypothyroidism, History of bleeding, History of hospitalization, # of CMS priority comorbidities categorical, CMS-RxHCC score
c. Earliest of: discontinuation of initial drug (gap ≥ 60 days), switching of study drugs, death, end of study period (12/31/11)

Harvard / Brigham Division of Pharmacoepidemiology and Pharmacoeconomics

Example from JAMA Internal Medicine



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"Discontinuation of use of an anticoagulant (defined as a gap ≥60 days), switching to the other anticoagulant, death, and the end of the study period (December 31, 2011) were considered censoring events"

Notice anything missing?

Prior enrollment requirement?
Washout for identifying initiators?
Censoring on disenrollment?

a. Atrial Fibrillation (AF) was defined as having 1 inpatient or 2 outpatient claims with primary or secondary diagnosis position of ICD-9 code 427.31
b. Baseline conditions included: CHADS2 score, Chronic kidney disease, Hypertension, Previous stroke or TIA, Acute MI, Diabetes, Congestive heart failure, Acquired hypothyroidism, History of bleeding, History of hospitalization, # of CMS priority comorbidities categorical, CMS-RxHCC score
c. Earliest of: discontinuation of initial drug (gap ≥ 60 days), switching of study drugs, death, end of study period (12/31/11)

Example from JAMA Internal Medicine

SUMMARY SPECIFICATION FOR ANALYTIC STUDY POPULATION

Example Drug A versus Drug B on risk of Outcome Y

A. Meta-data about data source and software

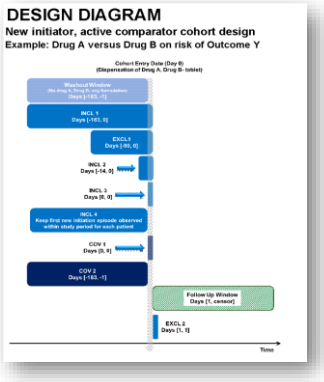
Study Period:	10/1/2009 - 12/31/2011
Eligible Cohort Entry Period:	10/1/2010 - 10/31/2011
Data Source:	Medicare
Data Extraction Date/Version:	
Data sampling/extraction criteria:	5% random sample of enrollees in data source between January 1, 2010 - Decemeber 31, 2011
Type of data:	Administrative claims
Data linkage:	None
Data conversion:	None
Software to create study population:	

B. Index Date (day 0) defining criterion	Description	Number of entries	Type of entry	Washout window	Incident w.r.t.	Index date (day 0)
Exposure	Dabigatran	Single	Prevalent			Date of incident dispensation
Comparator	Warfarin	Single	Prevalent			Date of incident dispensation

C. Inclusion Criteria	Description	Order of application	Assessment window	Care Settings[1]	Primary Dx	Applied to:
Enrollment/coverage	Medical and drug coverage			n/a	n/a	Exposure, comparator
Max. enrollment gap allowed	N/A					Exposure, comparator
Atrial Fibrillation (AF)	1 inpatient OR 2 outpatient diagnoses	Before selection of index date	[-60, 0]	IP, OP	No	Exposure, comparator

D. Exclusion Criteria	Description	Order of application	Assessment window	Care Settings[1]	Primary Dx	Applied to:
Atrial Fibrillation (AF)	Atrial Fibrillation (AF)	Before selection of index date	[Jan 1 1999, -60]	Any	No	Exposure, comparator
Days supply on index date (Dabigatran/Warfarin)	Days supply > 0 for Dabigatran OR Warfarin	Before selection of index date	[0, 0]	n/a	n/a	Exposure, comparator
Dabigatran AND Warfarin User	Both dispensed within 60 days of new AF diagnosis	After selection of index date	[AF Dx, AF Dx +60]	n/a	n/a	Exposure, comparator

What core elements to include in hypothesis evaluating RWE registration?



Visual representation of key temporal anchors

Study parameter table: details of data, study design, and analysis

(who, IRB, DUA)

- Attestation regarding level of exploration of data
- Version control (when, why)
- Appendices with code algorithms
- …

"Lockbox" capacity

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RWE Transparency and the Peer-Review Process

C. Daniel Mullins, PhD

Professor and Chair, Pharmaceutical Health Service Research Dept
University of Maryland Baltimore

Editor-in Chief (along with Mike Drummond)
Value in Health

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RWE Transparency and the Peer-Review Process

- Many journal reviewers (and editors!) still are not comfortable with studies that include data on individuals with non-random assignment
- Even those reviewers (and editors!) who are comfortable with non-random assignment find many methods sections to be a black box
- Some reviewers (and editors!) go so far as to promote complete transparency with open access models and data
  - HIPAA concerns
  - Intellectual property concerns

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RWE Transparency and the Peer-Review Process

- Was the research question and study hypothesis pre-specified?
  - Or was the analysis a fishing exploration?
  - Does the study reflect HEOR or a marketing campaign?
- Are the methods appropriate and replicable?
- Are the data and their limitations adequately described?
  - Are the data fit for purpose?
  - Is the data generation process introducing bias (e.g. coding for billing in US)?
  - How are missing data handled?
- Is there "fair balance" in study outcomes?
  - Or do the analyses seem to "cherry pick" more favorable results?
  - Are Conclusions derived directly from Results?
  - Are Conclusions "reasonable" v. an extrapolation beyond the Results?

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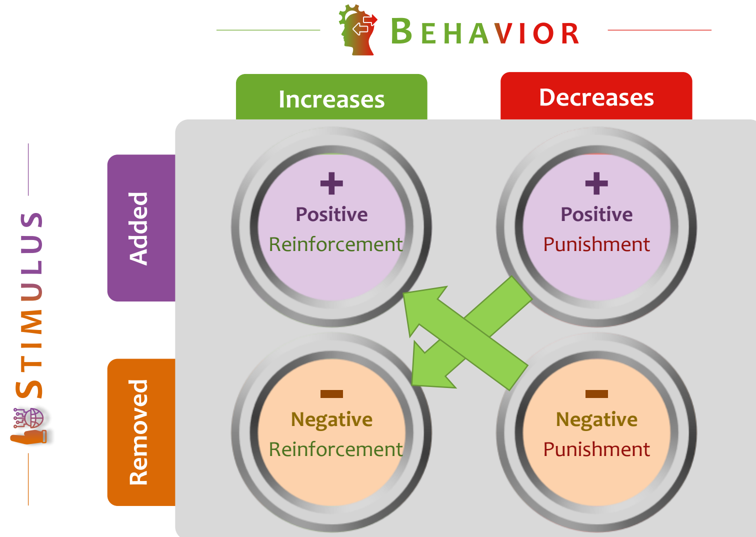
Contingencies: Behavioral Principles



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Behavioral factors relevant to study registration

Mentimeter

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Discussion

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