OHDSI Tutorial: Design, implementation, and evaluation of cohort definitions in observational healthcare data

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Disclosures

- PBR is an employee of Janssen Research and Development, and shareholder in Johnson & Johnson
- Any opinions of the presenters expressed are their own

Agenda

1. Motivation for standardizing the cohort definition process
2. Defining a cohort in ATLAS
3. Defining a cohort in Criteria2Query
4. Hands-on experience using ATLAS and Criteria2Query
5. Evaluating cohort definitions using PheValuator
6. The journey ahead for phenotyping

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

David J. Graham, MD, MPH; Marsha E. Reichman, PhD; Michael Wernecke, BA; Rongmei Zhang, PhD; Mary Ross Southworth, PharmD; Mark Levenson, PhD; Ting-Chang Sheu, MPH; Katrina Mott, MHS; Margie R. Goulding, PhD; Monika Houstoun, PharmD, MPH; Thomas E. MaCurdy, PhD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MMSc

Background—The comparative safety of dabigatran versus warfarin for treatment of nonvalvular atrial fibrillation in general practice settings has not been established.

Methods and Results—We formed new-user cohorts of propensity score–matched elderly patients enrolled in Medicare who initiated dabigatran or warfarin for treatment of nonvalvular atrial fibrillation between October 2010 and December 2012. Among 134414 patients with 37587 person-years of follow-up, there were 2715 primary outcome events. The hazard ratios (95% confidence intervals) comparing dabigatran with warfarin (reference) were as follows: ischemic stroke, 0.80 (0.67–0.96); intracranial hemorrhage, 0.34 (0.26–0.46); major gastrointestinal bleeding, 1.28 (1.14–1.44); acute myocardial infarction, 0.92 (0.78–1.08); and death, 0.86 (0.77–0.96). In the subgroup treated with dabigatran 75 mg twice daily, there was no difference in risk compared with warfarin for any outcome except intracranial hemorrhage, in which case dabigatran risk was reduced. Most patients treated with dabigatran 75 mg twice daily appeared not to have severe renal impairment, the intended population for this dose. In the dabigatran 150-mg twice daily subgroup, the magnitude of effect for each outcome was greater than in the combined-dose analysis.

Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. (***Circulation***. **2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.**)

Key Words: anticoagulant ■ pharmacoepidemiology ■ safety ■ thrombin inhibitor ■ warfarin

- Baseline characterization of target and comparator cohort
- Descriptive summaries of:
  - Demographics
  - Medical history (prior conditions)
  - Medication use (prior drugs)
  - Prior procedures
  - Risk scores

Table 1. Sociodemographic Factors, Medical Conditions, and Medication Use at Baseline in Propensity Score–Matched Medicare Beneficiaries Initiating Dabigatran or Warfarin for Atrial Fibrillation, 2010–2012

Characteristic	Dabigatran, % (n=67 207)	Warfarin, % (n=67 207)	Standardized Mean Difference
Age group, y			
65–74	42	41	0.01
75–84	43	43	0.01
≥85	16	16	0.00
Female sex	51	52	0.01
Race/ethnicity			
White	92	92	0.00
Black	3	3	0.00
Other	5	5	0.00
Medical history			
General			
Diabetes mellitus	33	34	0.00
Hypercholesterolemia	74	74	0.00
Hypertension	87	87	0.00
Kidney failure			
Acute	5	5	0.00
Chronic	13	13	0.00
Obesity	11	11	0.00
Peptic ulcer disease	<1	<1	0.00
Prior bleeding event			
Hospitalized	1	1	0.00
Not hospitalized	3	3	0.01
Smoking	16	16	0.01
Cardiovascular disease			
Acute myocardial infarction			
Past 1–30 d	1	1	0.01
Past 31–183 d	1	1	0.00
Coronary revascularization	16	16	0.01
Heart failure			
Hospitalized	4	4	0.01
Outpatient	14	14	0.00
Other ischemic heart disease	48	49	0.01
Stroke			
Past 1–30 d	2	2	0.00
Past 31–183 d	1	2	0.00
Other cerebrovascular disease	13	13	0.00
Transient ischemic attack	7	7	0.00
Cardioablation	2	2	0.00
Cardioversion	9	9	0.02
Other medical conditions			
Falls	5	5	0.00
Fractures	2	2	0.00
Syncope	10	10	0.00
Walker use	3	3	0.00
$CHADS_2$ score*			
0–1	28	28	0.01
2	40	40	0.00
3	21	21	0.01
≥4	10	11	0.01
HAS-BLED score†			
1	9	9	0.01
2	50	50	0.01
3	32	32	0.01
≥4	9	9	0.00
Medication use			
General			
Estrogen replacement	2	3	0.00
H2 antagonists	5	5	0.00
NSAIDs	15	15	0.00
Proton pump inhibitors	26	27	0.01
SSRI antidepressants	13	13	0.01
Cardiovascular			
ACEI/ARB	59	59	0.00
Antiarrhythmics	25	25	0.01
Anticoagulants (injectable)	7	7	0.01
Antiplatelets	17	17	0.01
β-Blockers	70	71	0.00
Calcium channel blockers	42	42	0.01
Digoxin	17	16	0.00
Diuretics			
Loop	28	28	0.00
Potassium sparing	5	5	0.01
Thiazide	29	29	0.00
Nitrates	10	11	0.01
Statins	57	57	0.00
Fibrates	5	5	0.00
Diabetes related			
Insulin	6	6	0.00
Metformin	13	14	0.00
Sulfonylureas	9	10	0.00
Other	6	6	0.00
Metabolic inhibitors‡			
Amiodarone	10	10	0.00
Dronedarone	5	5	0.02
Verapamil	2	2	0.00
Azole antifungals	<1	<1	0.00

Additional factors included in the propensity score model are shown in the online-only Data Supplement. ACEI/ARB indicates angiotensin converting-enzyme inhibitor/angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; and SSRI, selective serotonin reuptake inhibitor.

*The $CHADS_2$ score assigns points for the presence of congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, stroke, or transient ischemic attack.[11]

†The HAS-BLED score assigns points for the presence of hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age ≥65 y, and antiplatelet drug or alcohol use.[12,13] Labile international normalized ratio could not be determined from claims data and was excluded from our scoring.

‡Days supply of use overlapped with the date of first prescription for warfarin

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years	
	Dabigatran	Warfarin	Dabigatran	Warfarin
Primary outcomes				
Ischemic stroke	205	270	11.3	13.9
Major hemorrhage	777	851	42.7	43.9
Gastrointestinal	623	513	34.2	26.5
Intracranial	60	186	3.3	9.6
Intracerebral	44	142	2.4	7.3
Acute myocardial infarction	285	327	15.7	16.9
Secondary outcomes				
All hospitalized bleeds	1079	1139	59.3	58.8
Mortality*	603	744	32.6	37.8

*For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% confidence interval [CI]) was 0.89 (0.79–1.00 P=0.051), whereas for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98 P=0.03).

- Incidence rate during target and comparator cohorts based on observing new events during ‘time-at-risk’ for eight selected outcome cohorts

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	[redacted]	Adjusted Hazard Ratio (95% CI)	*P* Value
Primary outcomes			
Ischemic stroke		0.80 (0.67–0.96)	0.02
Major hemorrhage		0.97 (0.88–1.07)	0.50
Gastrointestinal		1.28 (1.14–1.44)	<0.001
Intracranial		0.34 (0.26–0.46)	<0.001
Intracerebral		0.33 (0.24–0.47)	<0.001
Acute myocardial infarction		0.92 (0.78–1.08)	0.29
Secondary outcomes			
All hospitalized bleeds		1.00 (0.92–1.09)	0.97
Mortality*		0.86 (0.77–0.96)	0.006

*For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% confidence interval [CI]) was 0.89 (0.79–1.00; *P*=0.051), whereas for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98; *P*=0.03).

- Population-level effect estimation examining temporal association between target and comparator cohorts and eight selected outcome cohorts

The common building block of all observational analysis: cohorts

Required inputs:

Target cohort:
- Person
- cohort start date
- cohort end date

Comparator cohort:
- Person
- cohort start date
- cohort end date

Outcome cohort:
- Person
- cohort start date
- cohort end date

Desired outputs:

Clinical characterization
- Baseline summary of exposures (treatment utilization)

Clinical characterization
- Baseline summary of outcome (disease natural history)

Incidence summary
- Proportion/rate of outcome occurring during time-at-risk for exposure

Population-level effect estimation
- Relative risk (HR, OR, IRR) of outcome occurring during time-at-risk for exposure

Patient-level prediction
- Probability of outcome occurring during time-at-risk for each patient in population

Graham replication: Cohort characterization in ATLAS

Features are basline characteristics (e.g collected before /on cohort start)

Demographics | Conditions | **Drugs** | Procedures | Measurements | Observations | Distributions

Long Term: 365 day lookback. **Short Term:** 30d lookback. **Overlapping:** Event spans cohort start date.

Column visibility | Copy | CSV | Show 15 ▼ entries | Filter:

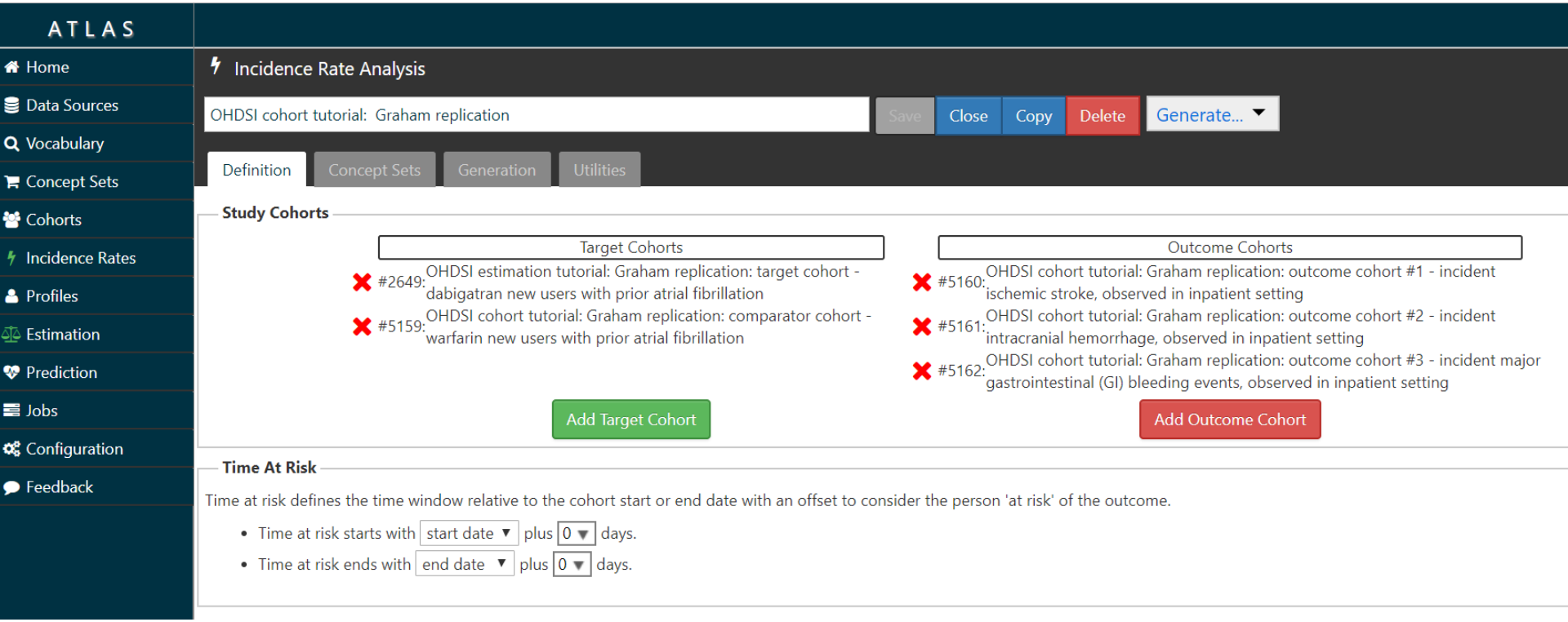
Showing 1 to 15 of 305 entries | Previous 1 2 3 4 5 … 21 Next

Analysis
- Group Era (1025)
- Era (681)

Time Window
- Long Term (708)
- Short Term (537)
- Overlapping (461)

	Concept Name	Time Window	Person Count	% of cohort
Explore	dabigatran etexilate	Long Term	19,975	100.00
Explore	Metoprolol	Long Term	8,820	44.20
Explore	Hydrochlorothiazide	Long Term	5,955	29.90
Explore	Acetaminophen	Long Term	5,739	28.80
Explore	Lisinopril	Long Term	4,935	24.80
Explore	Simvastatin	Long Term	4,851	24.30
Explore	Amlodipine	Long Term	4,808	24.10
Explore	Furosemide	Long Term	4,795	24.10
Explore	Hydrocodone	Long Term	4,590	23.00
Explore	atorvastatin	Long Term	4,422	22.20

Graham replication: Incidence summary design in ATLAS



Graham replication: Incidence summary implementation in ATLAS

ATLAS
- Home
- Data Sources
- Vocabulary
- Concept Sets
- Cohorts
- Incidence Rates
- Profiles
- Estimation
- Prediction
- Jobs
- Configuration
- Feedback

Export Analysis to CSV

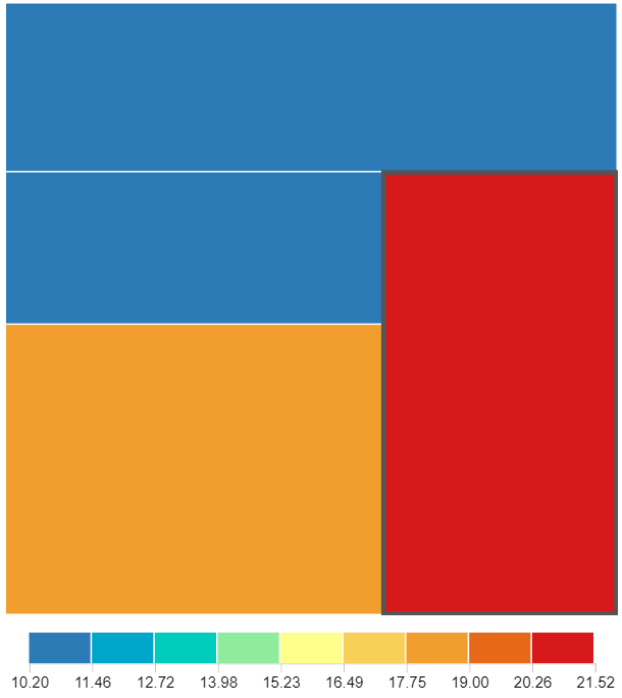
Source	Name		Persons	Cases	Proportion [+|-] per 1k persons	Time At Risk (years)	Rate [+|-] per 1k years	Started	Duration	
TRUVENMDCR_V657	Truven MDCR	Execute	18,376	93	5.06	5,852	15.89	2017-12-02, 22:46	00:00:29	Remove

Showing target cohort: OHDSI estimation tutorial: Graham replicat ▼ and outcome cohort: OHDSI cohort tutorial: Graham replication: ▼

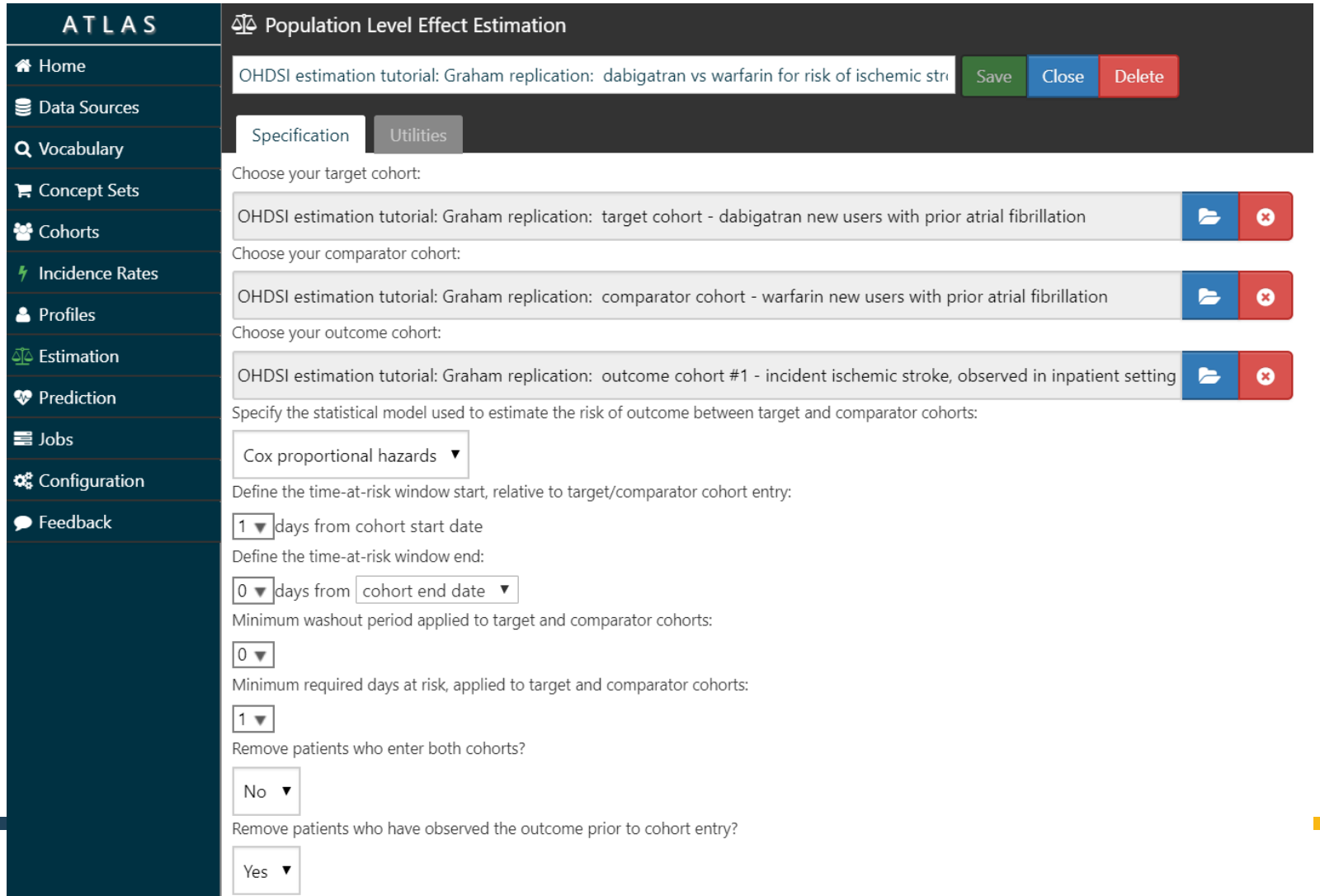
	Persons	Cases	Proportion [+|-] per 1k persons	Time At Risk (years)	Rate [+|-] per 1k years
Summary Statistics:	18,376	93	5.06	5,852	15.89

Stratify Rule	N	Cases	Proportion [+|-] per 1k persons	Time At Risk (years)	Rate [+|-] per 1k years
1. gender = MALE	10,453	50	4.78	3,391	14.74
2. age < 75	7,897	27	3.42	2,508	10.77

34 cases, 1,580 TAR, Rate: 21.52 per 1k years
5,097 (27.74%) people, 0 criteria passed, 2 criteria failed.



Graham replication: Population-level effect estimation design in ATLAS



Graham replication: Population-level effect estimation implementation using OHDSI methods

Model type: cox
Stratified: FALSE
Use covariates: FALSE
Status: OK

	Estimate	lower .95	upper .95
treatment	0.89626	0.71863	1.11829

Population counts

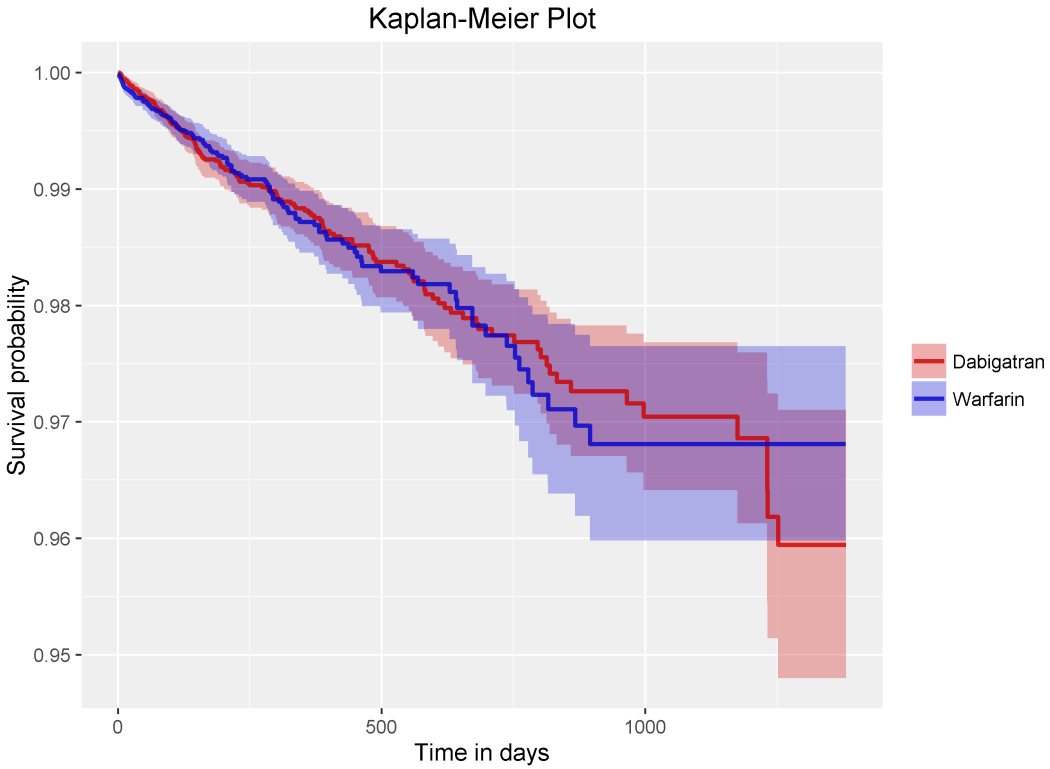
	treatedPersons	comparat
Count	17460	17460

Outcome counts

	treatedPersons	comparat
Count	164	155

Time at risk

	treatedDays	comparat
Days	4912947	3954046



Defining cohorts

Defining ‘phenotype’

Journal of the American Medical Informatics Association, 0(0), 2017, 1–6
doi: 10.1093/jamia/ocx110
Perspective

Perspective

High-fidelity phenotyping: richness and freedom from bias

George Hripcsak[1] and David J Albers[1]

- A phenotype is a specification of an observable, potentially changing state of an organism (as distinguished from the genotype, derived from genetic makeup).
- The term phenotype can be applied to patient characteristics inferred from electronic health record (EHR) data.
- The goal is to draw conclusions about a target concept based on raw EHR data, claims data, or other clinically relevant data.
- Phenotype algorithms – ie, algorithms that identify or characterize phenotypes – may be generated by domain exerts and knowledge engineers, or through diverse forms of machine learning to generate novel representations of data.

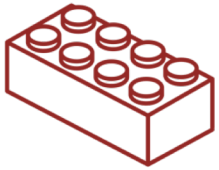
Two Approaches to Phenotyping

Rule-Based Phenotyping

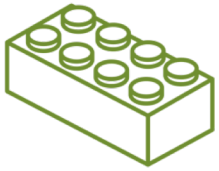
Probabilistic Phenotyping

Data are Like Lego Bricks for Phenotypng

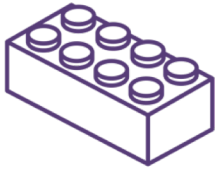
Conditions



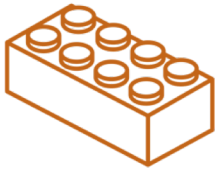
Drugs



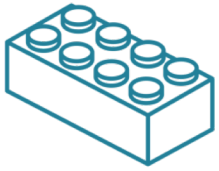
Procedures



Measurements



Observations



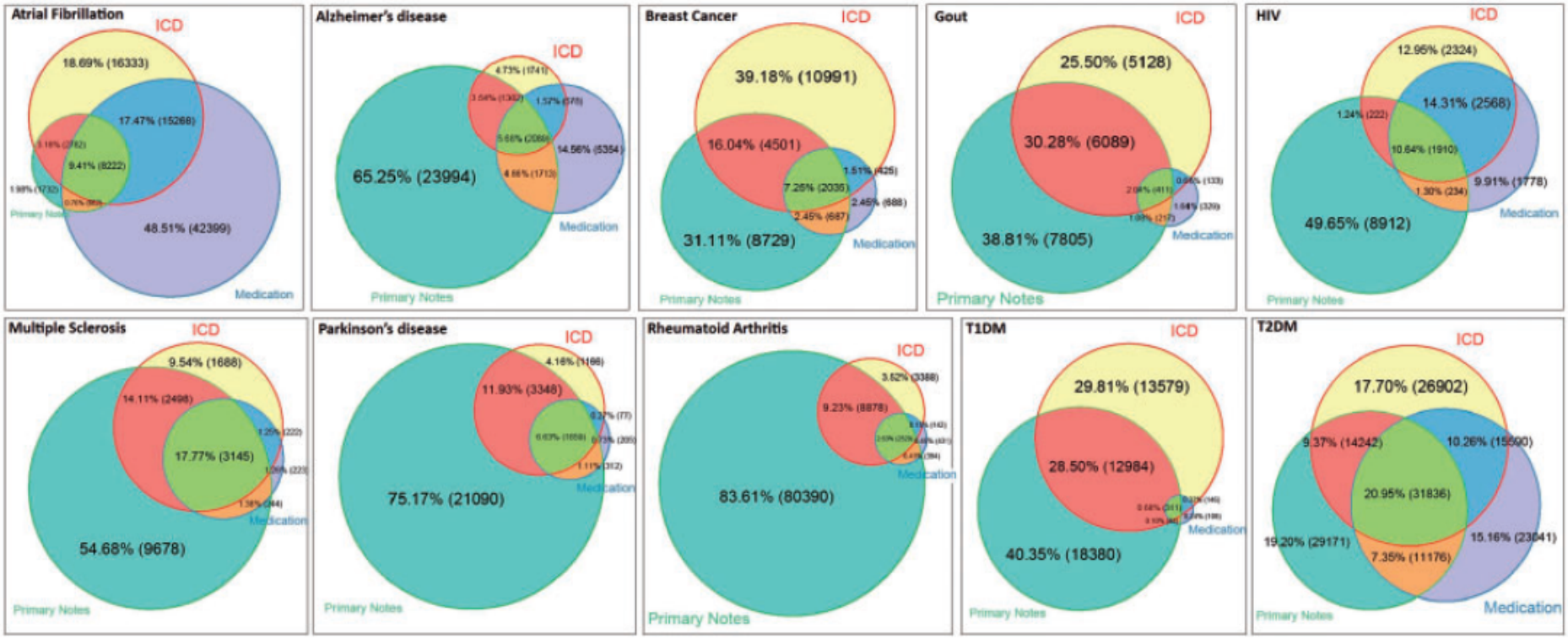
Visits

Combining billing codes, clinical notes, and medications from electronic health records provides superior phenotyping performance

RECEIVED 8 January 2015
REVISED 14 July 2015
ACCEPTED 15 July 2015
PUBLISHED ONLINE FIRST 2 September 2015

Wei-Qi Wei[1], Pedro L Teixeira[1], Huan Mo[1], Robert M Cronin[1,2], Jeremy L Warner[1,2], Joshua C Denny[1,2]

Figure 1: Weighted Venn diagrams of the distributions of patients with ICD-9, primary notes, and specific medications. Each color represents a resource. Different area colors represent the number of patients that were found within intersecting resources.



Database queries for hospitalizations for acute congestive heart failure: flexible methods and validation based on set theory

Marc Rosenman,[1,2] Jinghua He,[3] Joel Martin,[2] Kavitha Nutakki,[1] George Eckert,[4] Kathleen Lane,[4] Irmina Gradus-Pizlo,[5] Siu L Hui[2,4]

Table 3 Results for the 10 congestive heart failure (CHF) phenotype queries

Criteria to combine Venn diagram zones	N in query	Sensitivity (%)	Sensitivity, SE (%)	PPV (%)	PPV, SE (%)
Any CHF	66 942	94.3	1.3	42.8	1.5
Any dx of 428	64 832	90.9	1.3	42.5	1.5
Any dx of CHF and BNP >500 pg/mL	21 801	50.8	1.8	70.7	2.5
1^0 dx of any CHF	19 339	54.8	1.9	86.0	2.2
1^0 dx of 428	16 724	47.6	1.7	86.3	2.5
1^0 dx of any CHF and BNP >500 pg/mL	11 298	33.5	1.3	90.0	2.1
1^0 dx of 428 and BNP >500 pg/mL	9662	28.8	1.1	90.4	2.4
1^0 dx of 428 and BNP >500 pg/mL and echocardiogram	5678	16.2	0.8	86.6	3.5
1^0 dx of any CHF or BNP >500 pg/mL	29 587	71.4	2.1	73.3	2.2
1^0 dx of 428 or BNP >500 pg/mL	28 863	69.6	2.1	73.2	2.2
High BNP, no ICD-9 diagnosis for CHF					
Zone X: no ICD-9 dx of 428, but BNP >500 pg/mL	12 149	N/A	N/A	14.3	3.5

BNP, B-natriuretic peptide; PPV, positive predictive value.

OHDSI's definition of 'cohort'

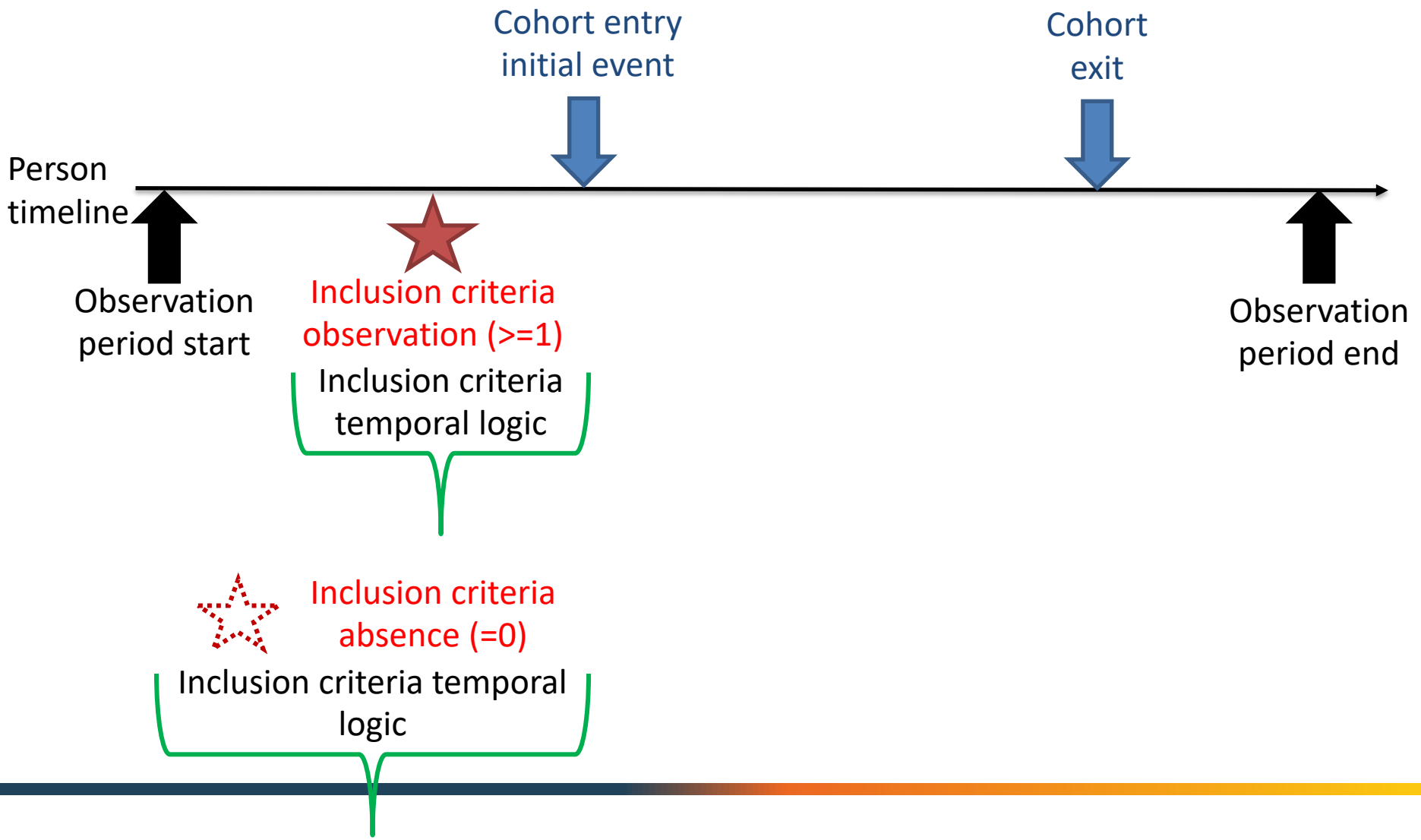
Cohort = a set of persons who satisfy one or more inclusion criteria for a duration of time

Objective consequences based on this cohort definition:

- One person may belong to multiple cohorts
- One person may belong to the same cohort at multiple different time periods
- One person may not belong to the same cohort multiple times during the same period of time
- One cohort may have zero or more members
- A codeset is NOT a cohort…

  …logic for how to use the codeset in a criteria is required

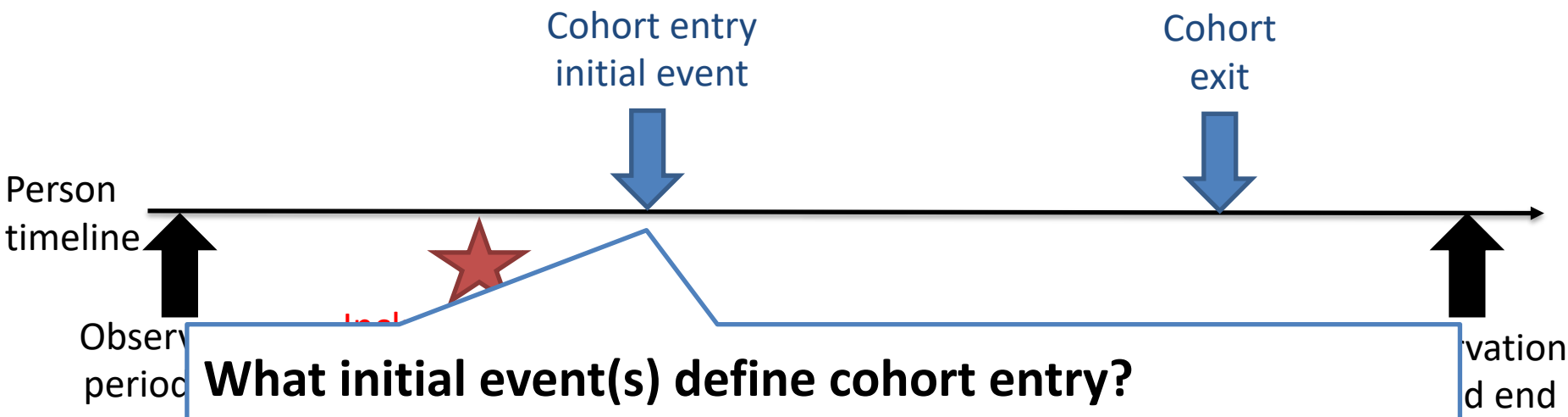
Dissecting the anatomy of a cohort definition



Questions to answer when defining a cohort

- What initial event(s) define cohort entry?
- What inclusion criteria are applied to the initial events?
- What defines a person's cohort exit?

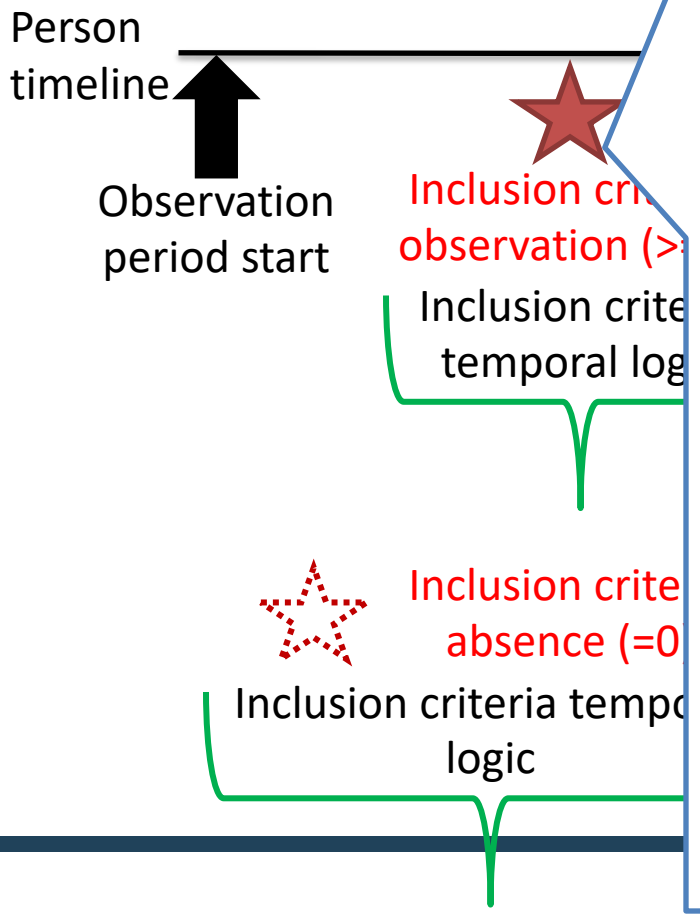
Dissecting the anatomy of a cohort definition



What initial event(s) define cohort entry?

- Events are recorded time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements and visits.
- The event index date is set to be equal to the event start date
- Initial events defined by a domain, conceptset, and any domain-specific attributes required

Dissecting the anatomy of a cohort definition



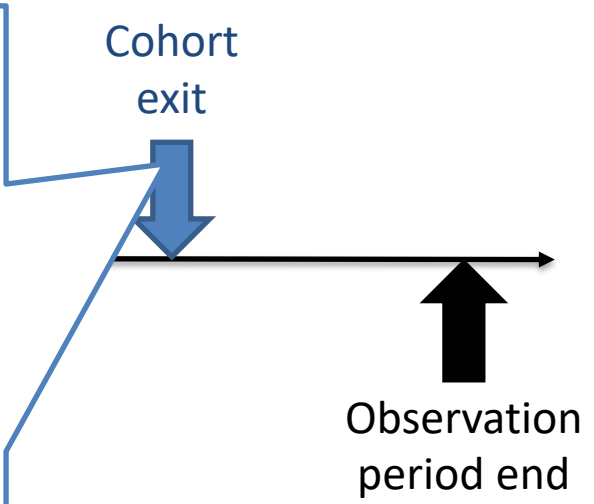
What inclusion criteria are applied to the initial events?

- The qualifying cohort will be defined as all persons who have an initial event and satisfy all qualifying inclusion criteria.
- Each inclusion criteria is defined by domain(s), conceptset(s), domain-specific attributes, and the temporal logic relative to initial events
- Each qualifying inclusion criteria can be evaluated to determine the impact of the criteria on the attrition of persons from the initial cohort (example use case: clinical trial feasibility)

Dissecting the anatomy of a cohort definition

What defines a person's cohort exit?

- Cohort exit signifies when a person no longer qualifies for cohort membership
- Cohort exit can be defined in multiple ways:
  - End of observation period
  - Fixed time interval relative to initial event
  - Last event in a sequence of related observations (ex: persistent drug exposure)
  - Censoring observations
- Cohort exit strategy will impact whether a person can belong to the cohort multiple times during different time intervals



Defining cohort components

- Domain: A Domain defines the set of allowable Concepts for the standardized fields in the CDM tables.
  - Ex: Condition, Drug, Procedure, Measurement
- Conceptset: An expression that defines one or more concepts encompassing a clinical entity of interest
  - Ex: Concepts for T2DM, concepts for antidiabetic drugs
- Domain-specific attribute:
  - Ex: DRUG_EXPOSURE: Days supply; MEASUREMENT: value_as_number, high_range
- Temporal logic: the time intervals within which the relationship between an inclusion criteria and an event is evaluated
  - Ex: Indicated condition must occur during 365d prior to or on exposure start

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

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Conclusions—In general practice settings, dabigatran was associated with reduced risk of ischemic stroke, intracranial hemorrhage, and death and increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients with nonvalvular atrial fibrillation. These associations were most pronounced in patients treated with dabigatran 150 mg twice daily, whereas the association of 75 mg twice daily with study outcomes was indistinguishable from warfarin except for a lower risk of intracranial hemorrhage with dabigatran. (***Circulation***. **2015;131:157-164. DOI: 10.1161/CIRCULATIONAHA.114.012061.**)

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Graham et al. description of the outcomes

Study Outcomes

The primary outcomes were ischemic stroke, major bleeding with specific focus on intracranial and gastrointestinal bleeding, and AMI. Secondary outcomes were all hospitalized bleeding events and mortality. The *International Classification of Diseases, Ninth Revision, Clinical Modification* codes used to define these outcomes are listed in Table II in the online-only Data Supplement. The codes defining ischemic stroke have a positive predictive value (PPV) of 88% to 95%.[18–20] Major bleeding was defined as

Table 2. International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) codes used to define study outcomes.

Outcome	ICD-9 Codes	Position	Setting
AMI	410 (all)	1st or 2nd	IP only
Ischemic stroke	433.x1, 434.x (except subcode: x0), 436	1st	IP only

Exercise: Define the outcome cohort for Graham et al.

- What initial event(s) define cohort entry?
- What inclusion criteria are applied to the initial events?
- What defines a person's cohort exit?

Graham et al. description of the cohort(s)

A new-user retrospective cohort design was used to compare patients initiating dabigatran or warfarin for the treatment of nonvalvular AF.[10] We identified all patients with any inpatient or outpatient diagnoses of AF or atrial flutter based on *International Classification of Diseases, Ninth Revision* coding who also filled at least 1 prescription for either drug from October 19, 2010 (US dabigatran approval date) through December 31, 2012, the study end date. Patients were excluded if they had <6 months of enrollment in Medicare before their index dispensing, were aged <65 years, received prior treatment with a study medication or rivaroxaban or apixaban (anticoagulants approved during the study), were in a skilled nursing facility or nursing home, or were receiving hospice care on the date of their cohort-qualifying prescription. Patients were also excluded if they had a hospitalization that extended beyond the index dispensing date. Patients discharged from the hospital on the same day as their index dispensing were included. Patients undergoing dialysis and kidney transplant recipients were also excluded. Additionally, because warfarin is approved for indications other than AF, we excluded patients with diagnoses indicating the presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement surgery in the preceding 6 months.

Exercise: Define the target exposure cohort for Graham et al.

- What initial event(s) define cohort entry?
- What inclusion criteria are applied to the initial events?
- What defines a person's cohort exit?

What initial event(s) define cohort entry?

- Do:
  - Define by existence of any observation in any domain
- Don't:
  - Define by absence of an observation - when does absence occur?
  - Define by age- year of birth is constant, but requires index date to anchor age calculation
- Caution:
  - Defining a cohort by calendar date can cause observation bias, since that date unlikely to be at point of health service utilization, ex: cases matched to controls. Consider instead defining by a visit that occurs within a calendar timeframe.

What inclusion criteria are applied to the initial events?

- Do:
  - Specify all criteria as inclusion criteria to avoid confusion of Boolean logic around inclusion vs. exclusion
  - use information on or before index event
    (think like a randomized trial: index event is study start, can't predict future)
- Don't:
  - Assume temporal logic, but always provide relative time window to evaluate criteria
- Caution:
  - There's a difference between 'first time in history with >365d prior observation' vs. 'no prior observation in last 365 days'
  - One person may have multiple initial events, criteria are applied to each event (not person)

What defines a person's cohort exit?

- Do:
  - Specify a cohort exit, even if you are not intending to use it for your analytic use case
- Don't:
  - Confuse censoring for analytical purposes with cohort definition (which can be analysis-independent)…ex: censoring at time of outcome
- Caution:
  - Time-of-cohort participation can be different from analysis time-at-risk…ex: acute effects can be studied using a fixed window post-exposure start, intent-to-treat analysis can follow person through observation period end

Defining a cohort in ATLAS

Chris Knoll

Janssen Research and Development

Defining a cohort using Criteria2Query

Cong Liu

Columbia University Medical Center

Evaluating a phenotype using PheValuator

Patrick Ryan

Janssen Research and Development

Columbia University Medical Center

Questions?

Thanks for joining
the journey!

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