



# Walkthrough of implementing a cohort study using OHDSI tools



# 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



# What is the design used by Graham et al?

Input parameter	Design choice
Target cohort (T)	dabigatran new users with prior atrial fibrillation
Comparator cohort (C)	warfarin new users with prior atrial fibrillation
Outcome cohort (O)	Ischemic stroke
Time-at-risk	1 day after cohort start → cohort end
Model specification	1:1 propensity score-matched univariable conditional Cox proportional hazards



# 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.<sup>10</sup> 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.



# Graham et al. replication: Designing the target cohort in ATLAS

ATLAS

Home  
Data Sources  
Search  
Concept Sets  
**Cohort Definitions**  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs  
Configuration  
Feedback

Cohort #5346

mschuemi graham dabigatran

Definition **Concept Sets** Generation Reporting Export Messages

enter a cohort definition description here

Cohort Entry Events

Events having any of the following criteria:

+ Add Initial Event

a drug era of **dabigatran**

+ Add attribute...

Delete Criteria

✗ for the first time in the person's history

✗ era start is: On or After 2010-10-19

✗ with age in years at era start Greater or Equal To 65

with continuous observation of at least 183 days before and 0 days after event index date

Limit initial events to: earliest event per person.

Restrict initial events

Inclusion Criteria

New inclusion criteria

1. Has prior atrial fibrillation or atrial flutter diagnosis
2. Has no prior treatment with comparator drug (warfarin)
3. Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)
4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
5. Not undergoing dialysis or kidney transplant recipient
6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months
7. No deep vein thrombosis or



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ATLAS

Home  
Data Sources  
Search  
Concept Sets  
Cohort Definitions  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs  
Configuration  
Feedback

Cohort #5346

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Definition **Concept Sets** **Characterization** **Reporting** **Export** **Messages**

enter a cohort definition description here

**Cohort Entry Events**

Events having any of the following criteria:

- a drug era of **dabigatran**
- for the first time in the person's history
- era start is: **On or After** **2010-10-19**
- with age in years at era start **Greater or Equal To** **65**

with continuous observation of at least **183** days before and **0** days after

Limit initial events to: **earliest event** per person.

**Restrict initial events**

**Include Criteria**

New inclusion criteria

- Has prior atrial fibrillation or atrial flutter diagnosis
- Has no prior treatment with comparator drug (warfarin)
- Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)
- Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
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- No mitral valve disease, heart valve repair, or replacement in the prior 6 months
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ATLAS

Home  
Data Sources  
Search  
Concept Sets  
Cohort Definitions  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs  
Configuration  
Feedback

Cohort #5346

mschuemi graham dabigatran

Definition **Concept Sets** Generation Report

enter a cohort definition description here

Cohort Entry Events

Events having any of the following criteria:

a drug era of **dabigatran**

for the first time in the person's history

era start is **on or After** 2010-10-19

with at least **in years at era start** Greater or Equal To 6

with continuous observation of at least **183** days before a

Initial events to: **earliest event** per person.

Restrict initial events

**Inclusion Criteria**

New inclusion criteria

1. Has prior atrial fibrillation or atrial flutter diagnosis
2. Has no prior treatment with comparator drug (warfarin)
3. Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)
4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
5. Not undergoing dialysis or kidney transplant recipient
6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months
7. No deep vein thrombosis or pulmonary embolism in the prior 6 months
8. No joint replacement surgery in

+ Add Initial Event  
+ Add attribute...  
Delete Criteria





# Graham et al. replication: Designing the target cohort in ATLAS

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Home | Data Source | Search | Concept Set | **Cohort Design** | Characterization | Cohort Panel | Incidence | Profiles | Estimation | Prediction | Jobs | Configuration | Feedback

**Has prior atrial fibrillation or atrial flutter diagnosis** [Copy] [Delete]

enter an inclusion rule description

having **any** of the following criteria: [Add criteria to group...]

**Criteria 1:**

- with **at least 1** using all occurrences of:
- a condition occurrence of **Atrial fibrillation** [Add attribute...]
- where **event starts** between **All** days **Before** and **0** days **After** **index start date** [Add additional constraint]
- ☐ restrict to the same visit occurrence

**Criteria 2:**

- or with **at least 1** using all occurrences of:
- a condition occurrence of **Atrial flutter** [Add attribute...]
- where **event starts** between **All** days **Before** and **0** days **After** **index start date** [Add additional constraint]
- ☐ restrict to the same visit occurrence

**Exclusion Criteria:**

- (rivaroxaban or apixaban)
- 4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
- 5. Not undergoing dialysis or kidney transplant recipient
- 6. No mitral valve disease, heart valve repair or replacement in the prior 6 months
- 7. No deep vein thrombosis or pulmonary embolism in the prior 6 months
- 8. No joint replacement surgery in the prior 6 months

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Home  
Data Sources  
Search

**Inclusion Criteria**  

New inclusion criteria

1. Has prior atrial fibrillation or atrial flutter diagnosis

2. Has no prior treatment with comparator drug (warfarin)

Has prior atrial fibrillation or atrial flutter diagnosis

enter an inclusion rule description

having any of the following criteria:

+ Add criteria to group...

Copy Delete

## Cohort Exit

### Event Persistence:

Event will persist until: end of a continuous drug exposure

### Continuous Exposure Persistence:

Specify a concept set that contains one or more drugs. A drug era will be derived from all drug exposure events for any of the drugs within the concept set, using the specified persistence window as a maximum allowable gap in days between successive exposure events and adding a specified surveillance window to the final exposure event. If no exposure event end date is provided, then an exposure event end date is inferred to be event start date + days supply in cases when days supply is available or event start date + 1 day otherwise. This event persistence assures that the cohort end date will be no greater than the drug era end date.

Concept set containing the drug(s) of interest: dabigatran

- Persistence window: allow for a maximum of 3 days between exposure records when inferring the era of persistence exposure
- Surveillance window: add 0 days to the end of the era of persistence exposure as an additional period of surveillance prior to cohort exit.

Feedback

Event will persist until: end of a continuous drug exposure

### Continuous Exposure Persistence:

Specify a concept set that contains one or more drugs. A drug era will be derived from all drug exposure events for any of the drugs within the concept set, using the specified persistence window as a maximum allowable gap in days between successive exposure events and adding a specified surveillance window to the final exposure event. If no exposure event end date is provided, then an exposure event end date is inferred to be event start date + days supply in cases when days supply is available or event start date + 1 day otherwise. This event persistence assures that the cohort end date will be no greater than the drug era end date.

Concept set containing the drug(s) of interest: dabigatran

- Persistence window: allow for a maximum of 3 days between exposure records when inferring the era of persistence exposure
- Surveillance window: add 0 days to the end of the era of persistence exposure as an additional period of surveillance prior to cohort exit.

### Censoring Events:

Exit Cohort based on the following criteria:

No censoring events selected.

+ Add Censoring Event

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Home  
Data Sources  
Search  
Concept Sets  
Cohort Definitions  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs  
Configuration  
Feedback

Cohort #5346

mschuemi graham dabigatran

Definition Concept Sets Generation Reporting Export Messages 9

New Concept Set Import Export All Concept Sets To CSV

Show 10 entries Filter Cohort Concept Sets:

Id	Title
0	dabigatran
1	Atrial fibrillation
2	Atrial flutter
3	rivaroxaban
4	apixaban
5	long term care visit
6	Hospice observations
7	Heart valve disease, repair or replacement
8	warfarin
9	Hip/knee joint replacement or revision

Showing 1 to 10 of 13 entries

Previous 1 2 Next

Concept Set Expression Included Concepts 160 Included Source Codes Export Import

Name: dabigatran

Show 25 entries Search:

Showing 1 to 1 of 1 entries

Concept Id	Concept Code	Concept Name	Domain	Standard Concept Caption	Exclude	Descendants	Mapped
40228152	1037042	dabigatran etexilate	Drug	Standard	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

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Classification Non-Standard Standard

Delete Concept Set Copy To Concept Set Repository Close Concept Set

Every entity referenced the cohort definition needs to a complete definition of concepts and associated source codes



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**ATLAS**

Home  
Data Sources  
Search  
Concept Sets  
**Cohort Definitions**  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs  
Configuration  
Feedback

**Cohort #5347**

mschuemi graham warfarin

Definition **Concept Sets**

enter cohort definition description

**Cohort Entry Events**

Events having any of the following criteria:

- a drug era of **warfarin**
- ✗ for the first time in the person's history
- ✗ era start is: **On or After** **2010-10-19**
- ✗ with age in years at era start **Greater or Equal To** **65**

with continuous observation of at least **183** days before and **0** days after event index date

Limit initial events to: **earliest event** per person.

**Restrict initial events**

**New inclusion criteria**

1. Has prior atrial fibrillation or atrial flutter diagnosis
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4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date
5. Not undergoing dialysis or kidney transplant recipient
6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months

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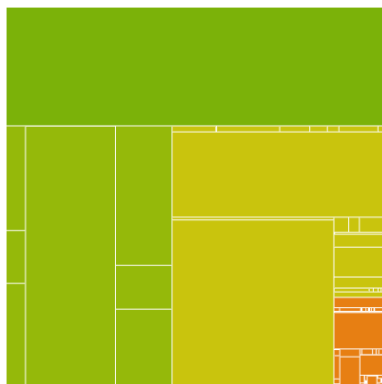
# Graham et al. replication: Evaluating the impact of inclusion criteria on the comparator cohort in ATLAS

## Inclusion Report for Truven MDCR (v779)

		Match Rate	Matches	Total	
Summary Statistics:		31.13%	56,648	182,001	
Inclusion Rule		N	% Remain	% Diff	
1. Has prior atrial fibrillation or atrial flutter diagnosis		86,995	47.80%	52.20%	
2. Has no prior treatment with comparator drug (dabigatran)		83,161	45.69%	2.11%	
3. Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)		78,222	42.98%	2.71%	
4. Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date		78,161	42.95%	0.03%	
5. Not undergoing dialysis or kidney transplant recipient		76,110	41.82%	1.13%	
6. No mitral valve disease, heart valve repair, or replacement in the prior 6 months		69,645	38.27%	3.55%	
7. No deep vein thrombosis or pulmonary embolism in the prior 6 months		59,195	32.52%	5.74%	
8. No joint replacement surgery in the prior 6 months		56,648	31.13%	1.40%	

Population Visualization

[Switch to attrition view](#)



Attrition Visualization

[Switch to intersect view](#)





# 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%.<sup>18–20</sup> Major bleeding was defined as

Table 2. International Classification of Disease, 9<sup>th</sup> 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



# Graham et al. description of the outcomes

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...and look, ischemic stroke is a ‘validated’ outcome!

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# Sidebar: just how good was that validation?

Ref 18 from Graham et al.:

## **Validating Administrative Data in Stroke Research**

David L. Tirschwell, MD; W.T. Longstreth, Jr, MD

**Background and Purpose**—Research based on administrative data has advantages, including large numbers, consistent data, and low cost. This study was designed to compare different methods of stroke classification using administrative data.

**Methods**—Administrative hospital discharge data and medical record review of 206 patients were used to evaluate 3 algorithms for classifying stroke patients. These algorithms were based on all (algorithm 1), the first 2 (algorithm 2), or the primary (algorithm 3) administrative discharge diagnosis code(s). The diagnoses after review of medical record data were considered the gold standard. Then, using a large administrative data set, we compared patients with a primary discharge diagnosis of stroke with patients with their stroke discharge diagnosis code in a nonprimary position.

**Results**—Compared with the gold standard, algorithm 1 had the highest  $\kappa$  for classifying ischemic stroke, with a sensitivity of 86%, specificity of 95%, positive predictive value of 90%, and  $\kappa=0.82$ . Algorithm 3 had the highest  $\kappa$  values for intracerebral hemorrhage and subarachnoid hemorrhage. For intracerebral hemorrhage, the sensitivity was 85%, specificity was 96%, positive predictive value was 89%, and  $\kappa=0.82$ . For subarachnoid hemorrhage, those values were 90%, 97%, 94%, and 0.88, respectively. Nonprimary position ischemic stroke patients had significantly greater comorbidity and 30-day mortality (odds ratio, 3.2) than primary position ischemic stroke patients.

**Conclusions**—Stroke classification in these administrative data were optimal using all discharge diagnoses for ischemic stroke and primary discharge diagnosis only for intracerebral and subarachnoid hemorrhage. Selecting ischemic stroke patients on the basis of primary discharge diagnosis may bias administrative samples toward more benign, unrepresentative outcomes and should be avoided. (*Stroke*. 2002;33:2465-2470.)





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**Results**—Compared with the gold standard, algorithm 1 had the highest  $\kappa$  for classifying ischemic stroke, with a sensitivity of 86%, specificity of 95%, positive predictive value of 90%, and  $\kappa=0.82$ . Algorithm 3 had the highest  $\kappa$  values for intracerebral hemorrhage and subarachnoid hemorrhage. For intracerebral hemorrhage, the sensitivity was 85%, specificity was 90%, 97%, 94% for algorithm 1, 2, 3, respectively. For subarachnoid hemorrhage, the sensitivity was 85%, specificity was 90%, 97%, 94% for algorithm 1, 2, 3, respectively. For comorbidity and stroke and primary stroke, the sensitivity was 85%, specificity was 90%, 97%, 94% for algorithm 1, 2, 3, respectively.

**Conclusions**—Stroke classification in these administrative data were optimal using all discharge diagnoses for ischemic stroke....Selecting ischemic stroke patients on the basis of primary discharge diagnosis may bias administrative samples toward more benign, unrepresentative outcomes and should be avoided.

**Conclusions-** Stroke classification in these administrative data were **optimal using all discharge diagnoses** for ischemic stroke....Selecting ischemic stroke patients on the basis of **primary discharge diagnosis may bias** administrative samples toward more benign, unrepresentative outcomes and **should be avoided**.



# Graham et al. replication: Designing the outcome cohort in ATLAS



**ATLAS**

Home  
Data Sources  
Search  
Concept Sets  
**Cohort Definitions**  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs

**Cohort #6273**

[OHDSI Europe tutorial] Graham replication: outcome cohort #1 - incident ischemic stroke, observed in inpatient setting

Definition ⓘ Concept Sets Generation Reporting Export Messages

Ischemic stroke, as defined in Graham et al, Circulation, 2015: <http://www.ncbi.nlm.nih.gov/pubmed/25359164>

**Cohort Entry Events** ⓘ

Events having any of the following criteria:

+ Add Initial Event ▾

a condition occurrence of Ischemic stroke ▾ + Add attribute... ▾

Condition Type is any of ☒ Inpatient detail - primary ☒ Inpatient header - primary ☒ Primary Condition

☒ ☒ Inpatient detail - 1st position ☒ Inpatient header - 1st position Add Import

☒ with a Visit occurrence of: ☒ Emergency Room Visit ☒ Inpatient Visit Add Import

with continuous observation of at least 0 ▾ days before and 0 ▾ days after event index date

Limit initial events to: earliest event ▾ per person.

Restrict initial events

Delete Criteria



# Graham et al. replication: Designing the outcome cohort in ATLAS

**ATLAS**

Home  
Data Sources  
Search  
Concept Sets  
**Cohort Definitions**  
Characterizations  
Cohort Pathways  
Incidence Rates  
Profiles  
Estimation  
Prediction  
Jobs

**Cohort #6273**

Events having any of the following criteria:

a condition occurrence of **Ischemic stroke** + Add

Condition Type **is any of** ☒ Inpatient detail - primary ☒ Inpatient header - primary ☒ Primary Condition

☒ Inpatient detail - 1st position ☒ Inpatient header - 1st position Add Import

☒ with a Visit occurrence of: ☒ Emergency Room Visit ☒ Inpatient Visit Add Import

with continuous observation of at least  days before and  days after event index date

Limit initial events to:  per person.

☒ Inpatient detail - 1st position ☒ Inpatient header - 1st position Add Import

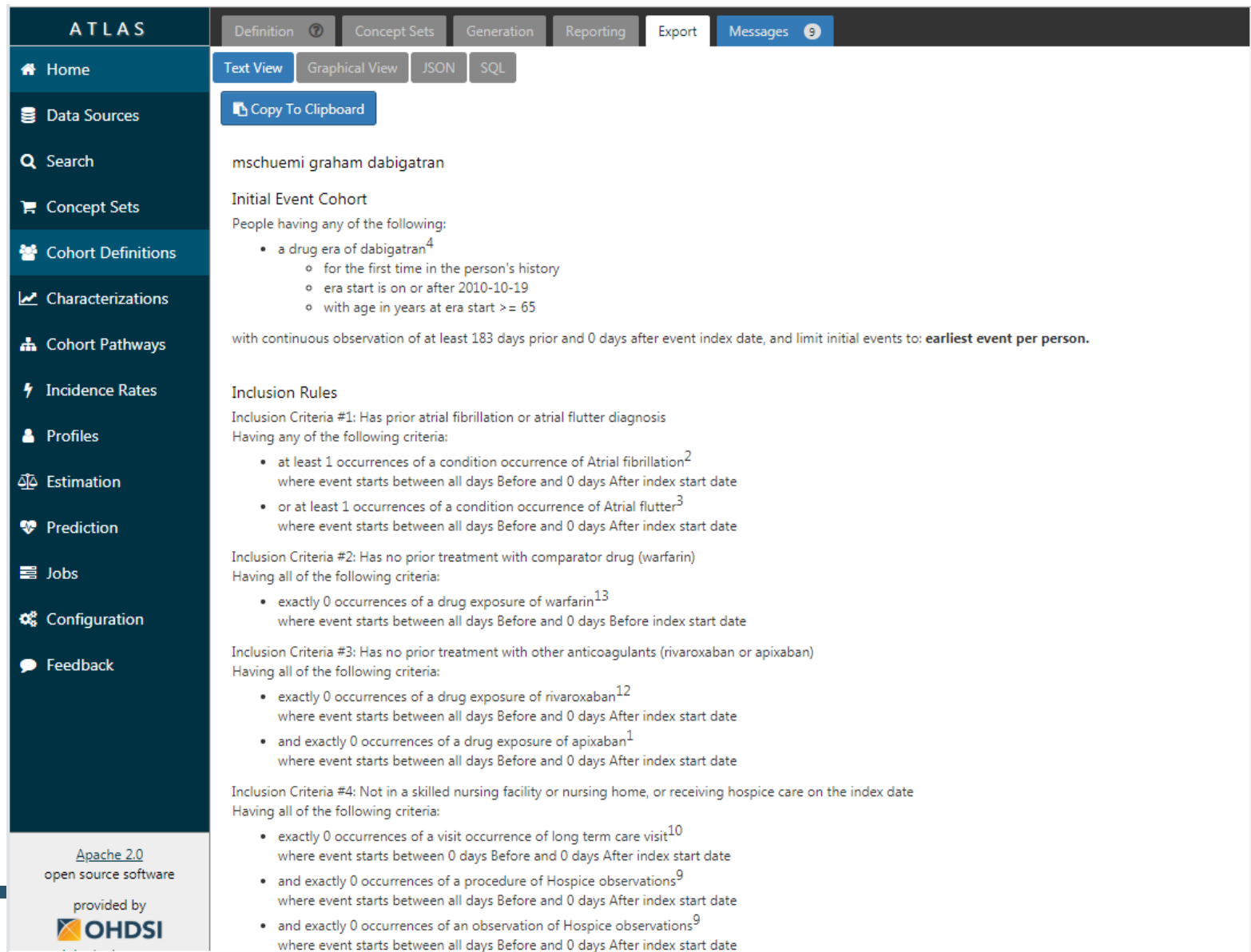
☒ with a Visit occurrence of: ☒ Emergency Room Visit ☒ Inpatient Visit Add Import

with continuous observation of at least  days before and  days after event index date

Limit initial events to:  per person.

Restrict initial events

# Graham et al. replication: Cohort exports



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Definition ⓘ Concept Sets Generation Reporting Export Messages 9

Home Data Sources Search Concept Sets **Cohort Definitions** Characterizations Cohort Pathways Incidence Rates Profiles Estimation Prediction Jobs Configuration Feedback

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Initial Event Cohort

People having any of the following:

- a drug era of dabigatran<sup>4</sup>
  - for the first time in the person's history
  - era start is on or after 2010-10-19
  - with age in years at era start >= 65

with continuous observation of at least 183 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: Has prior atrial fibrillation or atrial flutter diagnosis

Having any of the following criteria:

- at least 1 occurrences of a condition occurrence of Atrial fibrillation<sup>2</sup> where event starts between all days Before and 0 days After index start date
- or at least 1 occurrences of a condition occurrence of Atrial flutter<sup>3</sup> where event starts between all days Before and 0 days After index start date

Inclusion Criteria #2: Has no prior treatment with comparator drug (warfarin)

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of warfarin<sup>13</sup> where event starts between all days Before and 0 days Before index start date

Inclusion Criteria #3: Has no prior treatment with other anticoagulants (rivaroxaban or apixaban)

Having all of the following criteria:

- exactly 0 occurrences of a drug exposure of rivaroxaban<sup>12</sup> where event starts between all days Before and 0 days After index start date
- and exactly 0 occurrences of a drug exposure of apixaban<sup>1</sup> where event starts between all days Before and 0 days After index start date

Inclusion Criteria #4: Not in a skilled nursing facility or nursing home, or receiving hospice care on the index date

Having all of the following criteria:

- exactly 0 occurrences of a visit occurrence of long term care visit<sup>10</sup> where event starts between 0 days Before and 0 days After index start date
- and exactly 0 occurrences of a procedure of Hospice observations<sup>9</sup> where event starts between all days Before and 0 days After index start date
- and exactly 0 occurrences of an observation of Hospice observations<sup>9</sup> where event starts between all days Before and 0 days After index start date

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ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**

Prediction

Jobs

Configuration

Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

New Population Level Estimation Analysis

SpecificationUtilities

enter a description here (1000 characters max)

AllComparisonsAnalysis SettingsEvaluation Settings

Comparative Cohort Settings

Comparisons

+ Add Comparison

Show 10 entriesFilter:

Remove

Target

Comparator

Outcomes

NC Outcomes

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Showing 0 to 0 of 0 entriesPreviousNext

Effect Estimation Analysis Settings

Analysis Settings

+ Add Analysis Settings

Show 10 entriesFilter:

Remove

Description

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No data available in table

Showing 0 to 0 of 0 entriesPreviousNext

Evaluation Settings

Negative Control Outcome Cohort Definition

This expression will define the criteria for inclusion and duration of time for cohorts intended for use as negative control outcomes.  
The type of occurrence of the event when selecting from the domain.

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Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**

Prediction

Jobs

Configuration

Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

New Population Level Estimation Analysis

Specification

Utilities

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Evaluation Settings

Comparative Cohort Settings

Comparisons

+ Add Comparison

Show 10 entries

Filter:

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No data available in table					

Showing 0 to 0 of 0 entries

Previous Next

Effect Estimation Analysis Settings

Analysis Settings

+ Add Analysis Settings

Show 10 entries

Filter:

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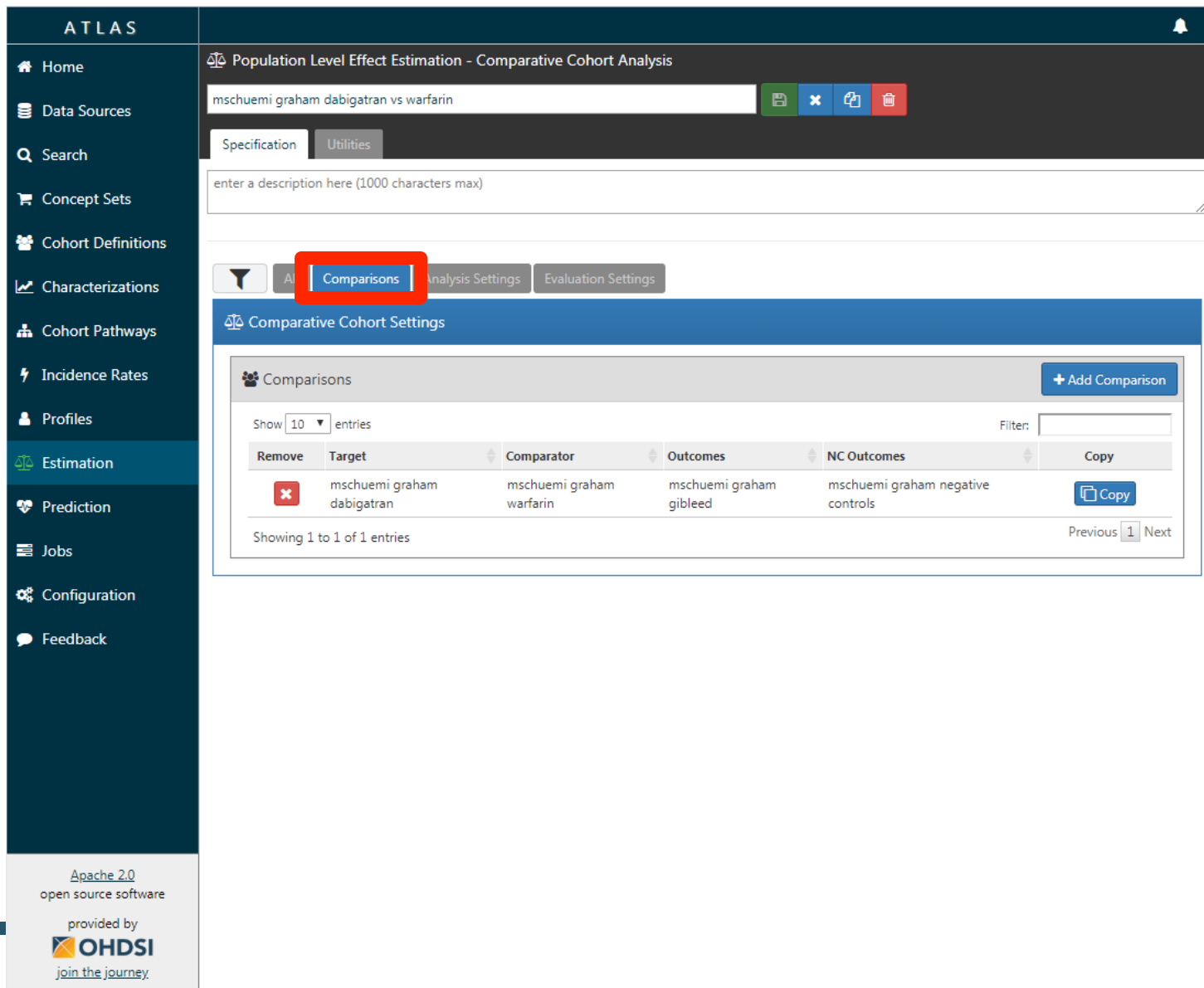
Previous Next

Evaluation Settings

Negative Control Outcome Cohort Definition

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The type of occurrence of the event when selecting from the domain.

# Graham et al. replication: Specifying the comparison



The screenshot displays the ATLAS web application interface. The left sidebar contains a navigation menu with the following items: Home, Data Sources, Search, Concept Sets, Cohort Definitions, Characterizations, Cohort Pathways, Incidence Rates, Profiles, **Estimation** (highlighted with a red arrow), Prediction, Jobs, Configuration, and Feedback. The main content area is titled 'Population Level Effect Estimation - Comparative Cohort Analysis'. It features a search bar with the text 'mschuemi graham dabigatran vs warfarin' and a 'Specification' tab. Below the search bar is a text input field for a description. The 'Comparisons' tab is selected and highlighted with a red box. The 'Comparative Cohort Settings' section shows a table of comparisons. The table has columns: Remove, Target, Comparator, Outcomes, NC Outcomes, and Copy. The first entry is: Remove (red X icon), Target (mschuemi graham dabigatran), Comparator (mschuemi graham warfarin), Outcomes (mschuemi graham gibleed), NC Outcomes (mschuemi graham negative controls), and Copy (Copy button). The table also includes a 'Show 10 entries' dropdown, a 'Filter' input, and pagination controls (Previous, 1, Next).

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Specification Utilities

enter a description here (1000 characters max)

Comparisons Analysis Settings Evaluation Settings

Comparative Cohort Settings

Comparisons + Add Comparison

Show 10 entries Filter:


Remove	Target	Comparator	Outcomes	NC Outcomes	Copy
	mschuemi graham dabigatran	mschuemi graham warfarin	mschuemi graham gibleed	mschuemi graham negative controls	Copy

Showing 1 to 1 of 1 entries Previous 1 Next

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# Graham et al. replication: Specifying the comparison



ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**


Prediction

Jobs

Configuration

Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Comparison

Add or update the target, comparator, outcome(s) cohorts and negative control outcomes

Choose your target cohort:

mschuemi graham dabigatran

Choose your comparator cohort:

mschuemi graham warfarin

Choose your outcome cohorts:

Add Outcome

Show 10 entries

ID	Name		
5348	mschuemi graham gibleed	Edit cohort	Remove
5386	graham ischemic stroke	Edit cohort	Remove

Showing 1 to 2 of 2 entries

Choose your negative control outcomes:

mschuemi graham negative controls

Covariate selection


**Please note:** If you would like to include/exclude covariates based on descendant concepts, it is most efficient to specify this as part of the analysis settings. If you plan to include/exclude descendants, define your concept sets utilizing **the ancestor concepts only**.

What concepts do you want to include in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

What concepts do you want to exclude from baseline covariates in the propensity score model? (Leave blank if you want to include everything)

mschuemi graham concepts to exclude from covariates

# Graham et al. replication: Specifying the comparison



ATLAS

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation**
- Prediction
- Jobs
- Configuration
- Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

**Comparison**  
Add or update the target, comparator, outcome(s) cohorts and negative control outcomes

Choose your target cohort:  
mschuemi graham dabigatran

Choose your comparator cohort:  
mschuemi graham warfarin

Choose your outcome cohorts:  
[Add Outcome](#)

Show 10 entries Search:

ID	Name		
5348	mschuemi graham gibleed	<a href="#">Edit cohort</a>	<a href="#">Remove</a>
5386	graham ischemic stroke	<a href="#">Edit cohort</a>	<a href="#">Remove</a>

Showing 1 to 2 of 2 entries Previous 1 Next

Choose your negative control outcomes:  
mschuemi graham negative controls

**Covariate selection**

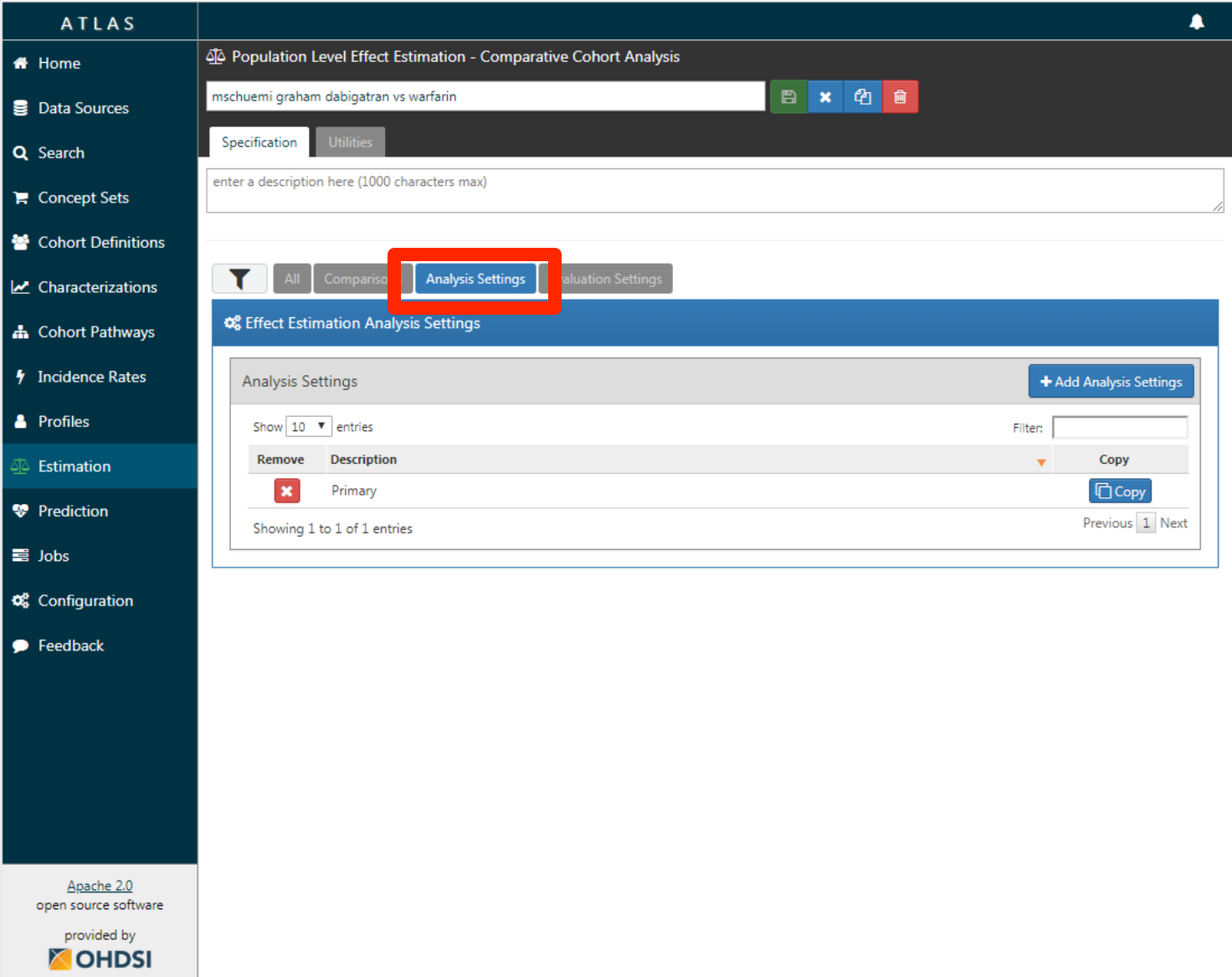
*Please note: If you would like to include/exclude covariates based on descendant concepts, it is most efficient to specify this as part of the analysis settings. If you plan to include/exclude descendants, define your concept sets utilizing the ancestor concepts only.*

What concepts do you want to include in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

What concepts do you want to exclude from baseline covariates in the propensity score model? (Leave blank if you want to include everything)

mschuemi graham concepts to exclude from covariates

# Graham et al. replication: Specifying the analysis settings



The screenshot displays the ATLAS software interface. On the left is a dark blue sidebar with a menu of options: Home, Data Sources, Search, Concept Sets, Cohort Definitions, Characterizations, Cohort Pathways, Incidence Rates, Profiles, Estimation (highlighted with a red arrow), Prediction, Jobs, Configuration, and Feedback. The main content area is titled 'Population Level Effect Estimation - Comparative Cohort Analysis'. It features a search bar containing 'mschuemi graham dabigatran vs warfarin' and tabs for 'Specification' and 'Utilities'. Below these is a text input field for a description. A row of filter tabs includes 'All', 'Comparison', 'Analysis Settings' (highlighted with a red box), and 'Evaluation Settings'. The 'Effect Estimation Analysis Settings' section is active, showing a table of analysis settings. The table has columns for 'Remove', 'Description', and 'Copy'. One entry is visible: 'Primary'. The interface also includes a 'Show 10 entries' dropdown, a 'Filter' input, and pagination controls at the bottom right.

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

Estimation

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Specification Utilities

enter a description here (1000 characters max)

All Comparison **Analysis Settings** Evaluation Settings

Effect Estimation Analysis Settings

Analysis Settings

+ Add Analysis Settings


Show 10 entries Filter:

Remove	Description	Copy
	Primary	

Showing 1 to 1 of 1 entries Previous 1 Next


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# Graham et al. replication: Specifying the analysis settings







## ATLAS

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation**
- Prediction
- Jobs
- Configuration
- Feedback

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### < Analysis Settings

Add or update the analysis settings

Analysis name:

 **All** **Study Population** Covariate Settings Time At Risk Propensity Score Adjustment Outcome Model

#### Study Population

Study start date - a calendar date specifying the minimum date that a cohort index can appear (leave blank to use all time):

Study end date - a calendar date specifying the maximum date that a cohort index can appear (leave blank to use all time). **Important:** the study end date is also used to truncate risk windows, meaning no outcomes beyond the study end date will be considered.

Should only the first exposure per subject be included?

Remove subjects that are in both the target and comparator cohort?

Restrict the analysis to the period when both exposures are observed?

The minimum required continuous observation time prior to index date for a person to be included in the cohort.

If either the target or the comparator cohort is larger than this number it will be sampled to this size. (0 for this value indicates no maximum size)

Remove subjects that have the outcome prior to the risk window start?

How many days should we look back when identifying prior outcomes?

If a subject is in multiple cohorts, should time-at-risk be censored when the new time-at-risk start to prevent overlap?

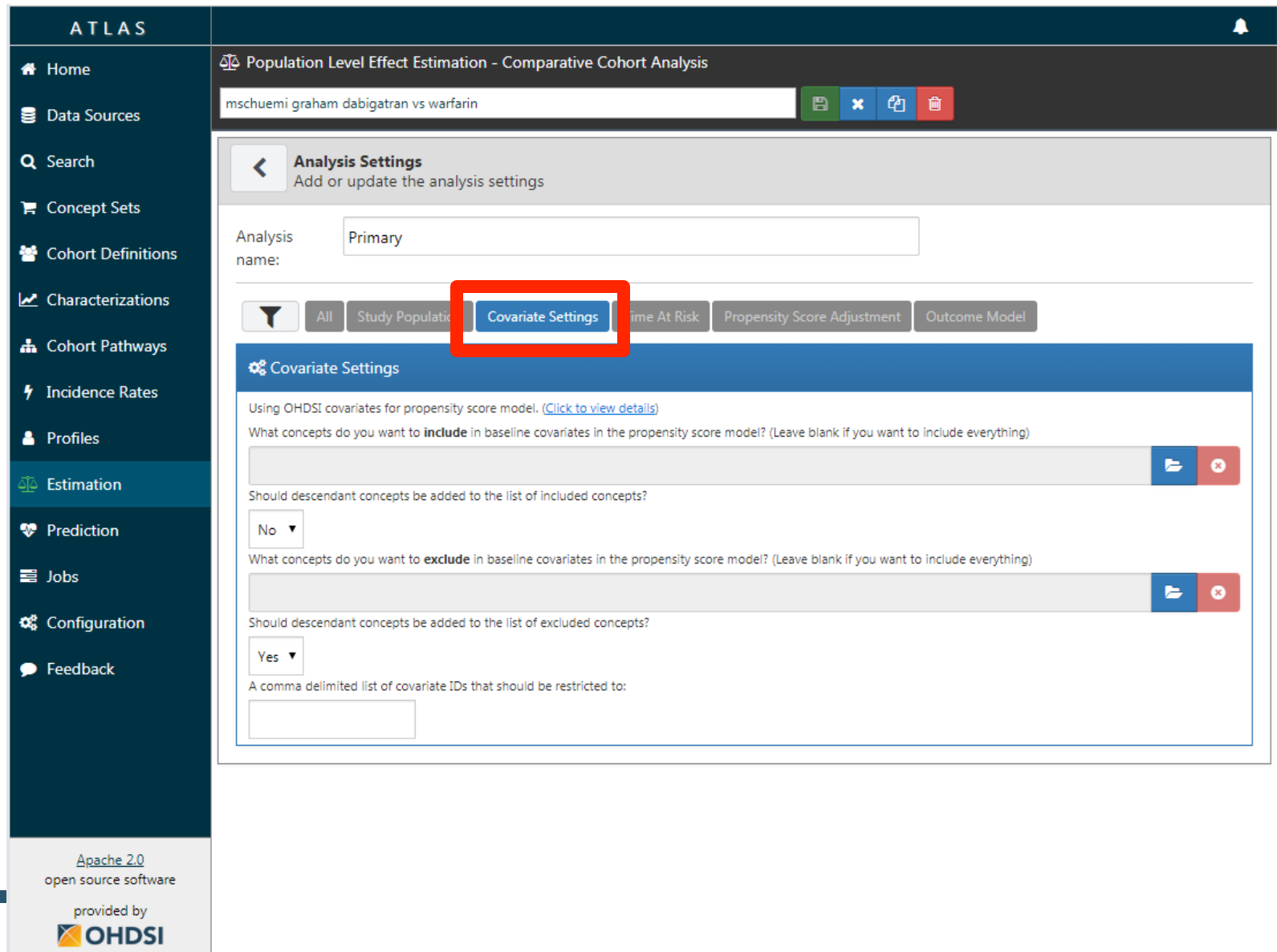


# Graham et al. replication: covariates for confounding adjustment

Claims data on chronic medical conditions, cardiovascular risk factors, risk factors for bleeding events, and healthcare utilization were collected for each patient during the 6 months preceding their cohort-qualifying prescription fill. We also collected data on prescriptions for medications used for treatment of cardiovascular disease and other chronic medical conditions, as well as potentially interacting medications that might alter warfarin or dabigatran pharmacokinetics. Finally, to the extent possible using claims data, we calculated the CHADS<sub>2</sub> score,<sup>11</sup> which predicts the risk of stroke in patients with AF, and the HAS-BLED score,<sup>12,13</sup> which predicts the risk of bleeding in patients with AF treated with warfarin.

To reduce confounding due to imbalance in study covariates, propensity score matching was used.<sup>14-16</sup> Unconditional logistic regression was used to estimate the predicted probability of patients initiating dabigatran therapy given their sociodemographic characteristics, baseline medical comorbidities, medications used during the preceding 6 months, prescriber characteristics, and other potentially relevant variables (Table 1 and

# Graham et al. replication: covariates for confounding adjustment



The screenshot displays the ATLAS software interface. On the left is a dark blue sidebar with a navigation menu. A red arrow points to the 'Estimation' option in this menu. The main content area is titled 'Population Level Effect Estimation - Comparative Cohort Analysis' and shows a search bar with the text 'mschuemi graham dabigatran vs warfarin'. Below this is the 'Analysis Settings' section, which includes a dropdown for 'Analysis name' set to 'Primary'. A row of tabs is visible, with 'Covariate Settings' highlighted and circled in red. The 'Covariate Settings' panel contains instructions about using OHDSI covariates for a propensity score model. It includes two text input fields for 'include' and 'exclude' baseline covariates, each with a file icon and a close button. Below these are two dropdown menus for 'Should descendant concepts be added to the list of included/excluded concepts?', with 'No' and 'Yes' selected respectively. At the bottom, there is a text input field for 'A comma delimited list of covariate IDs that should be restricted to:'. The footer of the interface mentions 'Apache 2.0 open source software' and 'provided by OHDSI'.

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

Estimation

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Analysis Settings  
Add or update the analysis settings

Analysis name: Primary

All Study Population **Covariate Settings** Time At Risk Propensity Score Adjustment Outcome Model

**Covariate Settings**

Using OHDSI covariates for propensity score model. ([Click to view details](#))

What concepts do you want to **include** in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

Should descendant concepts be added to the list of included concepts?

No

What concepts do you want to **exclude** in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

Should descendant concepts be added to the list of excluded concepts?

Yes


A comma delimited list of covariate IDs that should be restricted to:

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open source software

provided by  
OHDSI



# Graham et al. replication: covariates for confounding adjustment



**ATLAS**

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation**
- Prediction
- Jobs
- Configuration
- Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

**Analysis Settings**  
Add or update the analysis settings

Analysis name: Primary

**Covariate Settings**

Using OHDSI covariates for propensity score model. ([Click to view details](#))

What concepts do you want to **include** in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

Should descendant concepts be added to the list of included concepts?

No

What concepts do you want to **exclude** in baseline covariates in the propensity score model? (Leave blank if you want to include everything)

Should descendant concepts be added to the list of excluded concepts?

Yes

A comma delimited list of covariate IDs that should be restricted to:





# Graham et al. replication: covariates for confounding adjustment

- Leverages FeatureExtraction package
- Default settings create covariates for all drug and condition group concepts, and procedure, measurement, observation, and device exposure concepts during 2 lookback window
- Defaults also include demographics and 4 risk indexes

Select Covariates...

	Gender	Age	Age Groups	Race	Ethnicity	Index Year	Index Month	Prior Observation Time	Post Observation Time	Time In Cohort	Index Year & Month
Demographics	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Time bound covariates

Set the time windows for the time bound covariates in days relative to the cohort index

	Any Time Prior	Long Term	Medium Term	Short Term	End Days
Time Windows	All Time	-365	-180	-30	0

Set the time bound era covariates

Domain	Any Time Prior	Long Term (-365 days)	Medium Term (-180 days)	Short Term (-30 days)	Overlapping	Era Start		
						Long Term (-365 days)	Medium Term (-180 days)	Short Term (-30 days)
Condition	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Condition Group	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Drug	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Drug Group	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Set the time bound covariates

Domain	Any Time Prior	Long Term (-365 days)	Medium Term (-180 days)	Short Term (-30 days)	Distinct Count		
					Long Term (-365 days)	Medium Term (-180 days)	Short Term (-30 days)
Condition	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Condition - Primary Inpatient	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Drug	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Procedure	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Measurement	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Measurement - Value	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Measurement - Range Group	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Observation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Device	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
Visit - Count		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Visit - Concept Count		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			

Set the index score covariates

Index Score Type	
CHADS <sub>2</sub>	<input checked="" type="checkbox"/>
CHA <sub>2</sub> DS <sub>2</sub> VASc	<input checked="" type="checkbox"/>
DCSI	<input checked="" type="checkbox"/>
Charlson	<input checked="" type="checkbox"/>

# Graham et al. replication: specifying time-at-risk



**ATLAS**

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation**
- Prediction
- Jobs
- Configuration
- Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

**Analysis Settings**  
Add or update the analysis settings

Analysis name: Primary

**Time At Risk**

Define the time-at-risk window start, relative to target/comparator cohort entry:  
1

Add the length of exposure the start of the risk window?  
No

Define the time-at-risk window end:  
0

Add the length of exposure of the risk window?  
Yes

The minimum number of days at risk?  
1

Follow-up began on the day after the first qualifying anticoagulant prescription fill and continued until disenrollment from Medicare, occurrence of a study outcome, a gap in anticoagulant days of supply >3 days

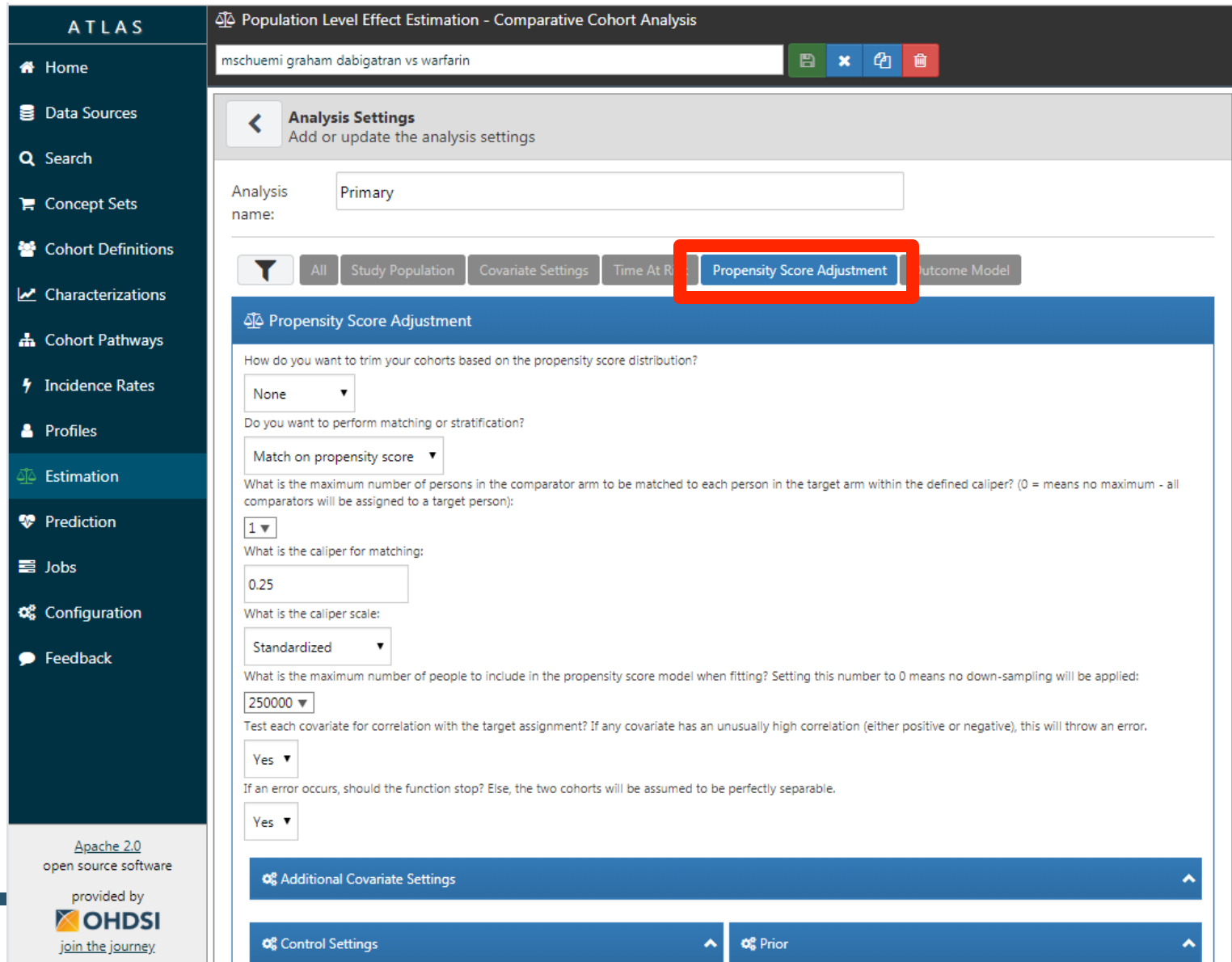
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# Graham et al. replication: specifying the propensity score model

Dabigatran users were propensity score matched to warfarin users in a 1:1 ratio with the use of a greedy matching algorithm. The balance of measured covariates between the matched cohorts was assessed with the standardized mean difference, a measure not influenced by sample size and thus useful for comparing cohorts in large observational studies.<sup>17</sup> A standardized mean difference of  $\leq 0.1$  indicates a negligible difference in the measured variables between groups.<sup>17</sup>

# Graham et al. replication: specifying the propensity score model



**ATLAS**

- Home
- Data Sources
- Search
- Concept Sets
- Cohort Definitions
- Characterizations
- Cohort Pathways
- Incidence Rates
- Profiles
- Estimation**
- Prediction
- Jobs
- Configuration
- Feedback

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Population Level Effect Estimation - Comparative Cohort Analysis

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**Analysis Settings**  
Add or update the analysis settings

Analysis name: Primary

All Study Population Covariate Settings Time At Risk **Propensity Score Adjustment** Outcome Model

**Propensity Score Adjustment**

How do you want to trim your cohorts based on the propensity score distribution?  
None

Do you want to perform matching or stratification?  
Match on propensity score

What is the maximum number of persons in the comparator arm to be matched to each person in the target arm within the defined caliper? (0 = means no maximum - all comparators will be assigned to a target person):  
1

What is the caliper for matching:  
0.25

What is the caliper scale:  
Standardized

What is the maximum number of people to include in the propensity score model when fitting? Setting this number to 0 means no down-sampling will be applied:  
250000

Test each covariate for correlation with the target assignment? If any covariate has an unusually high correlation (either positive or negative), this will throw an error.  
Yes

If an error occurs, should the function stop? Else, the two cohorts will be assumed to be perfectly separable.  
Yes

Additional Covariate Settings

Control Settings

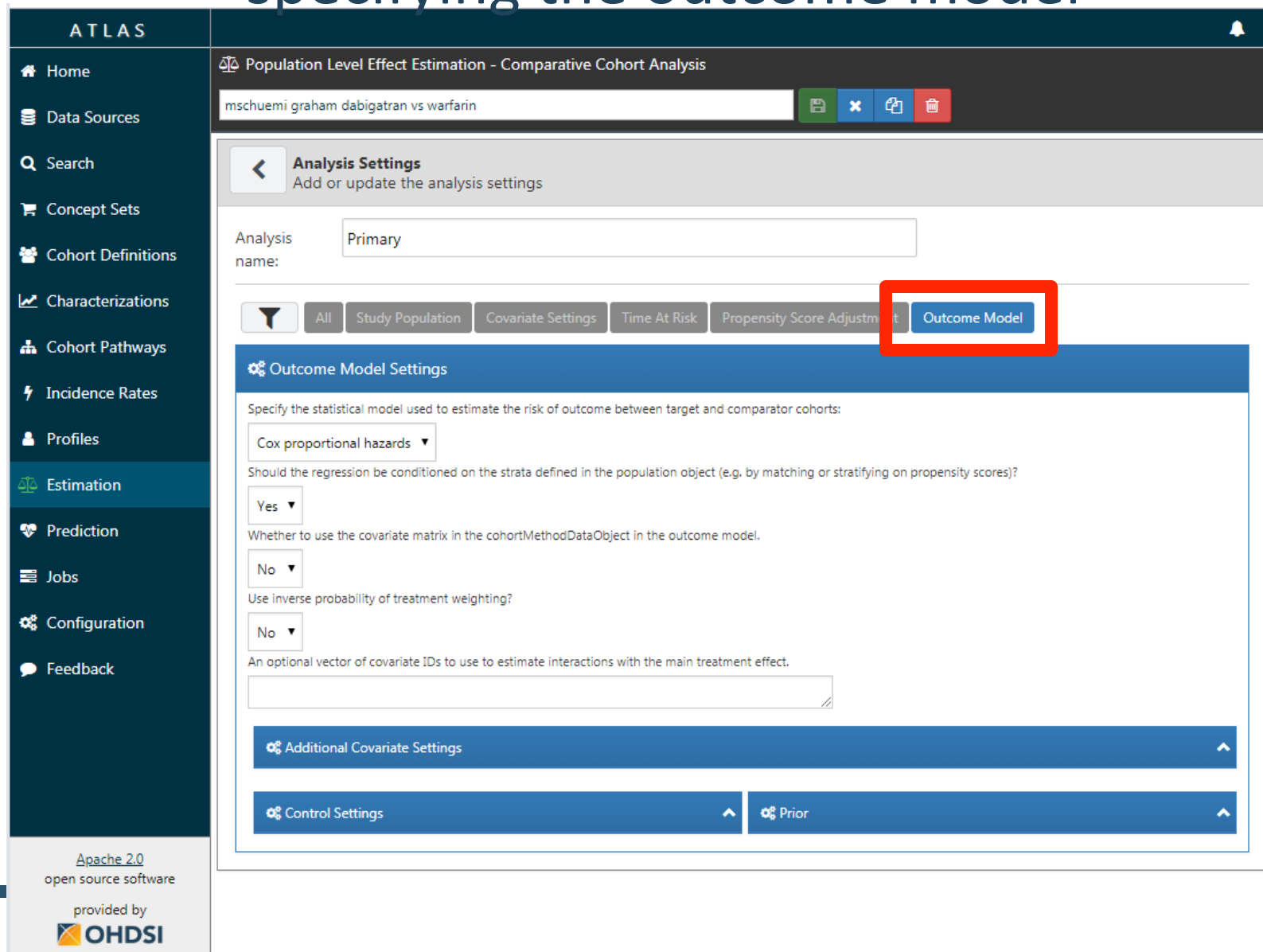
Prior



# Graham et al. replication: specifying the outcome model

Analyses were performed on the propensity score–matched cohorts, thereby accounting for the potential confounding factors shown in Table 1 and in the online-only Data Supplement. Incidence rates were estimated with the use of event counts and exposure follow-up time. Kaplan–Meier plots were generated to characterize the contour of risk over time for each outcome. Cox proportional hazards regression was used to compare time to event in dabigatran compared with warfarin (reference) cohorts.

# Graham et al. replication: specifying the outcome model



The screenshot displays the ATLAS software interface for specifying the outcome model. The left sidebar contains a navigation menu with the following items: Home, Data Sources, Search, Concept Sets, Cohort Definitions, Characterizations, Cohort Pathways, Incidence Rates, Profiles, **Estimation** (highlighted with a red arrow), Prediction, Jobs, Configuration, and Feedback. The main content area is titled 'Population Level Effect Estimation - Comparative Cohort Analysis' and shows the analysis name 'mschuemi graham dabigatran vs warfarin'. Below this, the 'Analysis Settings' section is visible, with a red box highlighting the 'Outcome Model' tab. The 'Outcome Model Settings' section includes a dropdown menu for 'Cox proportional hazards', a question about conditioning the regression on strata (answered 'Yes'), a question about using the covariate matrix (answered 'No'), a question about using inverse probability of treatment weighting (answered 'No'), and a text input field for an optional vector of covariate IDs. At the bottom, there are expandable sections for 'Additional Covariate Settings', 'Control Settings', and 'Prior'.

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Analysis Settings

Add or update the analysis settings

Analysis name: Primary

Outcome Model

Outcome Model Settings

Specify the statistical model used to estimate the risk of outcome between target and comparator cohorts:

Cox proportional hazards

Should the regression be conditioned on the strata defined in the population object (e.g. by matching or stratifying on propensity scores)?

Yes

Whether to use the covariate matrix in the cohortMethodDataObject in the outcome model.

No

Use inverse probability of treatment weighting?

No

An optional vector of covariate IDs to use to estimate interactions with the main treatment effect.

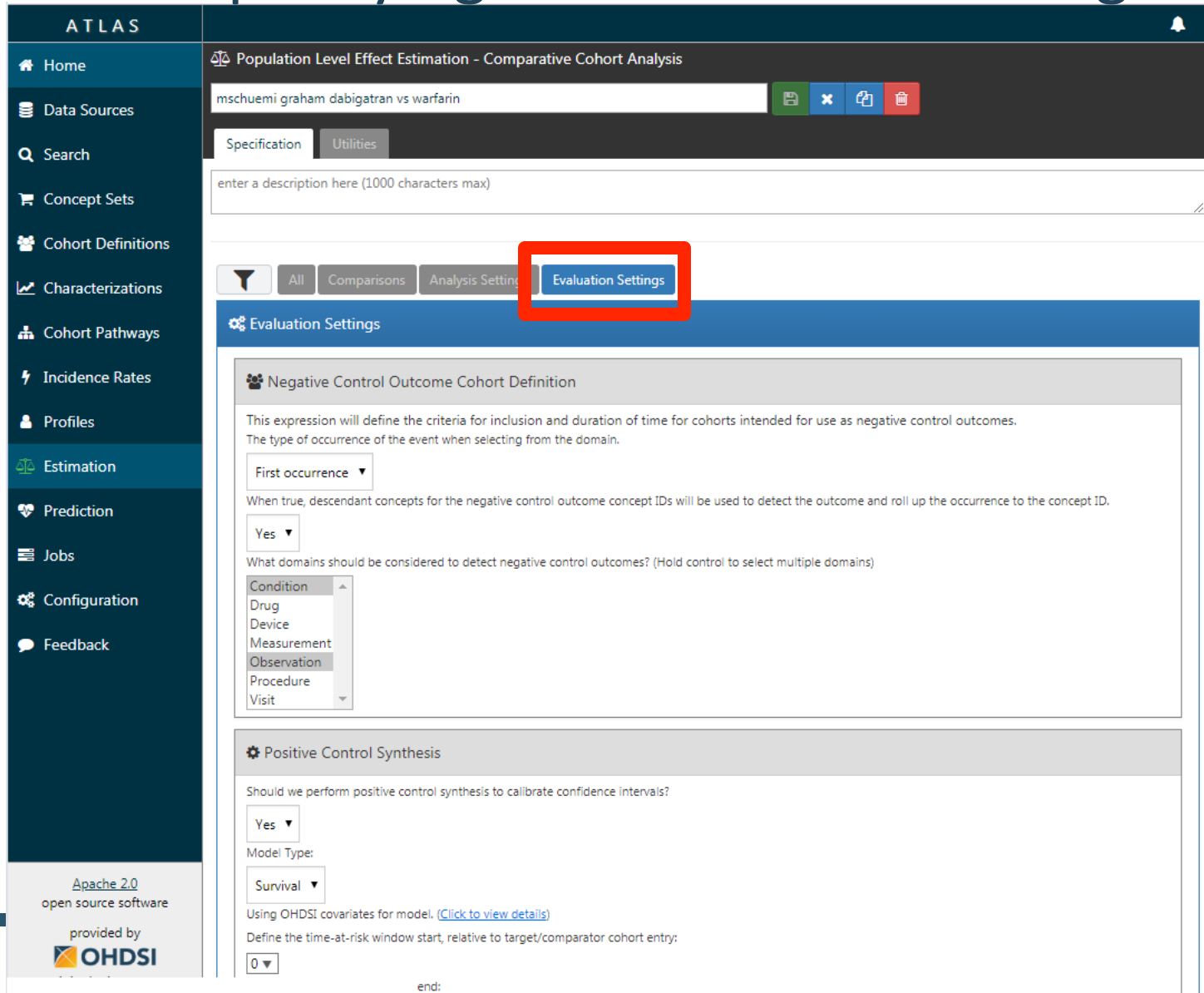
Additional Covariate Settings

Control Settings

Prior

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# Graham et al. replication: specifying the evaluation settings



The screenshot displays the ATLAS software interface. On the left is a dark blue sidebar with a navigation menu. A red arrow points to the 'Estimation' option in this menu. The main content area has a dark blue header with the title 'Population Level Effect Estimation - Comparative Cohort Analysis' and a search bar containing 'mschuemi graham dabigatran vs warfarin'. Below the header, there are tabs for 'Specification' and 'Utilities'. A text box for a description is present. A red rectangle highlights the 'Evaluation Settings' tab in the sub-navigation bar. The 'Evaluation Settings' page is divided into two sections: 'Negative Control Outcome Cohort Definition' and 'Positive Control Synthesis'. The first section includes a dropdown for 'First occurrence', a 'Yes' button, and a list of domains (Condition, Drug, Device, Measurement, Observation, Procedure, Visit) with 'Observation' selected. The second section includes a 'Yes' button, a 'Model Type' dropdown set to 'Survival', and a text box for 'Define the time-at-risk window start, relative to target/comparator cohort entry:' with a value of '0'.

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

Estimation

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

Specification Utilities

enter a description here (1000 characters max)

All Comparisons Analysis Settings Evaluation Settings

Evaluation Settings

Negative Control Outcome Cohort Definition

This expression will define the criteria for inclusion and duration of time for cohorts intended for use as negative control outcomes. The type of occurrence of the event when selecting from the domain.

First occurrence

When true, descendant concepts for the negative control outcome concept IDs will be used to detect the outcome and roll up the occurrence to the concept ID.

Yes

What domains should be considered to detect negative control outcomes? (Hold control to select multiple domains)

Condition Drug Device Measurement Observation Procedure Visit

Positive Control Synthesis

Should we perform positive control synthesis to calibrate confidence intervals?

Yes

Model Type:

Survival

Using OHDSI covariates for model. [Click to view details](#)

Define the time-at-risk window start, relative to target/comparator cohort entry:

0

end:

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# Graham et al. replication: exporting the study package for execution

ATLAS

Home

Data Sources

Search

Concept Sets

Cohort Definitions

Characterizations

Cohort Pathways

Incidence Rates

Profiles

**Estimation**

Prediction

Jobs

Configuration

Feedback

Population Level Effect Estimation - Comparative Cohort Analysis

mschuemi graham dabigatran vs warfarin

SpecificationUtilities

DownloadExport

Please click the button below to view the full study specifications. Once reviewed, scroll down to download the study package.  
[Click here to review the full study specifications](#)

### Step 1. Review Full Study Specification

Column visibilityCopyCSVShow 10 entriesFilter:

Target Cohort Name	Comparator Cohort Name	Outcome Cohort Name	Analysis Name
mschuemi graham dabigatran	mschuemi graham warfarin	mschuemi graham gibleed	Primary
mschuemi graham dabigatran	mschuemi graham warfarin	graham ischemic stroke	Primary

Showing 1 to 2 of 2 entriesPrevious1Next

### Step 2. Download the study package

Please provide a name for the study package.

Download Study Package

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